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ODD-ELECTRON & BONDING IN MEDIUM-RING BICYCLIC BRIDGEHEAD RADICALS

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ODD-ELECTRON σ BONDING IN MEDIUM-RING BICYCLIC BRIDGEHEAD RADICALS

By

Liliana Crăciun

A DISSERTATION

Submitted to Michigan State University in partial fulfillment of the requirements for the degree of

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ABSTRACT

ODD-ELECTRON σ BONDING IN MEDIUM-RING BICYCLIC BRIDGEHEAD RADICALS

By

Liliana Crăciun

My research has combined multi-step organic synthesis with physical and computational studies to explore medium-ring bridgehead radicals. The results of MNDO and ab initio HF/6-31G* calculations, presented in Chapter 1, suggest that such species might show unusual stability and/or persistence, as well as interesting bridgeheadbridgehead interactions.

Description of the synthesis, kinetics, spin trapping, EPR, ENDOR and computational studies, of bicyclo[3.3.3]undec-1-yl (1-manxyl) radical, a key reference species for medium-ring bridgehead radicals, now generated in solution from manxane by H-abstraction with *tert*-butoxyl radicals, is given in Chapter 2. The exceptional persistence of this sterically open radical is unique and is attributed to the high strain of all its decomposition products. [3.3.3]Propellane has been identified among the decay products of 1-manxyl radical; its formation was rationalized by a novel ε -disproportionation. This research is extended in Chapter 3, where efforts toward the bridgehead carbon-centered radical of 1-azabicyclo[3.3.3]undecane (manxine) are described.

My synthetic work centered on developing routes and efficient precursors to atrane-like bicyclics, whose corresponding bridgehead organic radicals could provide a potentially long series of compounds for the investigation of intrabridgehead throughspace σ interactions. A modified literature procedure for the preparation of 3-(2hydroxyethyl)-1,5-pentanediol, along with the syntheses of the novel compounds, tris-2aminoethyl-methane and tris(*o*-hydroxyphenyl)methane are depicted in Chapter 4.

Chapters 5 and 6 describe additional computational work. Inspired by the hybridization change of the bridgehead carbons in manxane and manxine, associated with decreased one-bond C-H couplings, we explored the prediction, from standard quantum chemical models, of C-H couplings in a series of bi- and polycyclics. Lastly, the availability of the RHF/6-31G*//RHF/6-31G* wavefunctions and energies obtained for the set of small- and medium-ring polycyclic compounds considered in the hybridization study, led us to reexamine the performance of the Wiberg and Ibrahim/Schleyer hydrocarbon group increments in calculating heats of formation from ab initio energies.

The research described herein was motivated by the challenge of designing species that can be used to probe theories of structure and bonding. The unusual properties of the bicyclo[3.3.3] system are a consequence of the geometry and strain inherent in a bicyclic array made up entirely of eight-membered rings. Our foray in the field of medium-ring bicyclic radicals revealed unforeseen opportunities for further work in this area.

"It is not thy duty to complete the work but neither are thou free to desist of it"

Ethics of the Fathers (The Talmud) 2:21

DEDICATION

Dedicated to those courageous Romanians who lost their lives in the fight against communism during the 1989 revolution, without their sacrifice I could not have reached to this dream, and to my mentors, Ioan Voda, Dorin Breazu, Sorin Mager, and James E. Jackson, from whom not only I learned a great deal about chemistry, but also how to enjoy it.

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I like to believe that the whole world is my family, but from those closest to my heart, I want to thank Laura and Radu, whom I deprived of too many hours, my adoptive parents and Laura's grandmothers, who provided us not only with free daycare, but also with lots of love and support, and my wonderful advisor at MSU, Prof. James E. Jackson, with the regret that I could not do more and better.

TABLE OF CONTENTS

LIST OF TABLES
LIST OF FIGURES
LIST OF SCHEMES
CHAPTER 1. Odd-Electron σ Bonding in Medium-Ring Bicyclic Bridgehead Radicals: A Theoretical Investigation
1.1 An Overview of Research on Odd-Electron σ Bonds
1.2 Intrabridgehead Interactions in Medium-Ring Bicyclics10
1.2.1 Closed-Shell Interactions in Neutral Medium-Ring Bicyclics 11
1.2.2 Atranes
1.2.3 Radical Cations of Medium-Ring Bicyclic Diamines, Disulfides and Diphosphines
1.2.4 Medium-Ring Bicyclic Carbon-Centered Bridgehead Radicals
1.2.5 Bridgehead Phosphoranyl Radicals
1.2.6 Intrabridgehead Indirect Interactions via Hydrogen
1.3 Geometry, Strain and Odd-Electron σ Bonding in Medium-Ring Bicyclic Bridgehead Radicals: A Semiempirical and Ab Initio HF/6-31G* Analysis28
1.4 References
CHAPTER 2. 1-Manxyl: A Persistent Tertiary Alkyl Radical that Disproportionates via ε-Hydrogen Abstraction
2.1 Results and Discussion
2.2 Spin Trapping Studies on 1-Manxyl Radical

2.3 Kinetic Decay and Product Analysis	77
2.4 Conclusions	92
2.5 Experimental Section	92
2.6 References	103
CHAPTER 3. 5-Manxinyl Radical: A Computational and Experimental Study	107
3.1 Results and Discussion	10 8
3.2 Experimental Methods	121
3.3 References	127
CHAPTER 4. Progress Toward the Synthesis of Atrane-Like Compounds	130
4.1 3-(2-Hydroxyethyl)-1,5-Pentanediol and 3-(2-Aminoethyl)-1,5- Pentanediamine	132
4.2 tris-(o-Hydroxyphenyl)-Methane	139
4.4 Experimental Methods	143
4.5 References	152
CHAPTER 5. Correlation of Tertiary One-Bond ¹³ C- ¹ H Spin-Spin Coupling Constants with PM3 Calculated Structures in Some Bi- and Polycyclic Saturated Hydrocarbons	155
5.1 Introduction	156
5.2 Theoretical Model	162
5.3 Results and Discussion	164
5.4 Summary	183
5.5 Experimental Methods	186
5.6 References	188

CHAPTER 6. Heats of Formation of Medium-Ring Strained Cyclo- and Polycycloalkanes: Comparison of Ab Initio Group Equivalent Schemes with

the PM3 and MMX Methods		
	6.1 Results and Discussion	
	6.2 References	
APPENDIX		

LIST OF TABLES

Table 1.1	Experimental One- and Three-Electron Bond Energies
Table 1.2	MM2 Steric Energies of Lowest Energy Conformations for Some Bicyclic Hydrocarbons
Table 1.3	Heats of Some Formal Dehydrogenations
Table 1.4	Heats of Formation and Strain Energies of Some Bicyclic Hydrocarbons and Propellanes
Table 1.5	HF/6-31G* Total Energies (MNDO Heats of Formation), BDE's, Intrabridgehead Distances and Radical Stabilization Energies Relative to the <i>tert</i> -Butyl Radical in 1, 44 and 45
Table 1.6	HF/6-31G* Total Energies (MNDO Heats of Formation), BDE's, Intrabridgehead Distances and Radical Stabilization Energies Relative to the <i>tert</i> -Butyl Radical in 8 and 46-50
Table 1.7	HF/6-31G* Total Energies (MNDO Heats of Formation), BDE's, Intrabridgehead Distances and Radical Stabilization Energies Relative to the <i>tert</i> -Butyl Radical in 51-55
Table 1.8	HF/6-31G* Total Energies (MNDO Heats of Formation), BDE's, Intrabridgehead Distances and Radical Stabilization Energies Relative to the <i>tert</i> -Butyl Radical in 57-62
Table 1.9	Spin Densities (ρ) and HF/6-31G* Intrabridgehead Distances (BB) in the Carbon-Centered Bridgehead Radicals of 1, 8 and 44-62
Table 1.10	Rate Constants for Reactive Bridgehead Systems
Table 1.11	HF/6-31G* Total Energies, Strain and Bond Dissociation Energies 40

Table 2.1	Calculated Heats of Formation, Strain Energies and Bond Dissociation Energies	8
Table 2.2	INDO Predicted Hyperfine Coupling Constants (in G) for 1-Manxyl Radical 2	2
Table 2.3	UHF/6-31G* (PM3) Geometrical Parameters for 1-Manxyl Radical 2	7
Table 2.4	PM3 Atomic Cartesian Coordinates (in Å) for 1-Manxyl Radical 2	8
Table 2.5	UHF/6-31G* Atomic Cartesian Coordinates (in Å) for 1-Manxyl Radical 2	9
Table 2.6	Calculated Heats of Formation and Strain Energies	5
	CHAPTER 3	
Table 3.1	Calculated Heats of Formation, Strain Energies and Bond Dissociation Energies 114	4
	CHAPTER 5	
Table 5.1	¹³ C NMR Chemical Shifts and Experimental ${}^{1}J_{{}^{13}C-{}^{1}H}$ Couplings 160	5
Table 5.2	Experimental One-Bond C-H Spin-Spin Coupling Constants (in Hz), and Calculated % s _C Character of the C Hybrid Forming the C-H Bonds in 1-39	8
Table 5.3	Previously Reported Correlations of Experimental One-Bond C-H Coupling Constants with Hybridization, Bond Angles or Atomic Charges in Hydrocarbons 174	4
Table 5.4	Semiempirical Relationships between Experimental One-Bond C-H Couplings and Hybridization, C-H distance, C-H Bond Order, Natural Atomic Charges on Carbon and Hydrogen, or Internuclear Angles, Established by Least-Squares Analysis for the PM3 Optimized Geometries of Hydrocarbons 1-39	5
Table 5.5	Semiempirical Relationships between Experimental One-Bond C-H Coupling Constants and Hybridization, Natural Atomic Charges on Carbon and Hydrogen, or Internuclear Angles, Established by	

	Least-Squares Analysis for the HF/6-31G* Optimized Geometries of Hydrocarbons 1-39	184
	CHAPTER 6	
Table 6.1	Experimental and Calculated Heats of Formation	197
Table 6.2	Comparison of the Wiberg and Ibrahim/Schleyer Group Equivalents with those Derived from the Ab Initio Energies of Table 6.1	206
	APPENDIX	
Table 1A	PM3 and HF/6-31G* Calculated Parameters for 1-39	213

LIST OF FIGURES

Figure 1.1	Plot of pyramidalization angle, $\angle XC^{\bullet}C$, vs. $\triangle BDE$ in the bridgehead radicals of bicyclics 1, 8 and 44-62.
	CHAPTER 2
Figure 2.1	(a) EPR spectrum (9.1 GHz) of 1-manxyl radical in cyclopropane at -55 °C ($g = 2.0024$). (b) Computer simulation 56
Figure 2.2	The ENDOR spectrum of 1-manxyl radical 2 in toluene at -50 °C. Insert: the central part of the ENDOR spectrum of 2, which reveals small HFCs at 0.19 and 0.08 G.
Figure 2.3	Assignments of the hyperfine coupling constants in 1-manxyl radical 2. 62
Figure 2.4	Selected UHF/6-31G* calculated geometrical parameters and experimental hyperfine coupling constants (in G) of bridgehead radicals. Legend: $\angle CC \cdot C_{avg}$ refers to the average CC $\cdot C$ angles in degrees, obtained as $\Sigma(\angle CC \cdot C)/3$
Figure 2.5	HF/6-31G* geometry optimized structures of manxane 1, 1-manxyl 2, 1-bicyclo[2.2.2]octyl 22, and 1-adamantyl 23 radicals. Legend (C ₃ refers to the axis of symmetry): $\alpha = C_3C^*C_{\beta}$ angle, and $\theta = C_3C^*C_{\beta}H_{\beta}$ torsion angle, in degrees
Figure 2.6	EPR spectrum (9.065 GHz) of the N-alkoxyanilino radical obtained by spin trapping of 1-manxyl radical 2 with TBN $(g = 2.003)$.
Figure 2.7	Kinetics of decay of 1-manxyl radical in methylcyclopentane at 23 °C: (a) variation with time of the concentration of 1-manxyl radical 2; (b) plot of the inverse concentration of 2 against time
Figure 2.8	Mass spectra showing the EI fragmentation of: a) [3.3.3]propellane 31 (retention time 3.6 min.), and of the peaks with 3.6 min. retention time

	in the chromatograms from the analysis of decomposition products of 2 in b) neat di- <i>tert</i> -butyl peroxide, and in c) cyclopropane, which are assigned to 31.	
Figure 2.9	Mass spectra showing the EI fragmentation of: a) manxane 1 (retention time 6.4 min.), and of the peaks with 6.2 min. retention time in the GC-MS analysis of the decomposition products of 2 in b) neat di- <i>tert</i> -butyl peroxide, and in c) cyclopropane, which are assigned to manxene 30.	;
Figure 2.10	Mass spectra showing the EI fragmentation of the peaks with a) 7.22 and b) 7.41 min. retention times (see Scheme 2.2 for tentative assignments) in the chromatograms from the analysis of the decomposition products of 2 in neat di- <i>tert</i> -butyl peroxide89)
Figure 2.11	Mass spectra showing the EI fragmentation of the peaks with a) 10.4 and b) 10.6 min. retention times (see Scheme 2.2 for tentative assignments) in the chromatograms from the analysis of the decomposition products of 2 in neat di- <i>tert</i> -butyl peroxide. 90)
Figure 2.12	Mass spectra showing the EI fragmentation of the peak with 14.4 min. retention time (presumably 1-benzylmanxane) in the chromatogram that resulted from the analysis of the decomposition products of 2 in neat di- <i>tert</i> -butyl peroxide	l
	CHAPTER 3	
Figure 3.1	The EPR spectra (9.1 GHz) resulting from UV photolysis of manxine in a) di- <i>tert</i> -butyl peroxide/cyclopropane, and in b) AIBN/cyclopropane, at -90 °C.)
	CHAPTER 5	
Figure 5.1	Experimental one-bond C-H spin-spin coupling constants vs. percent s character of the C hybrid in the C-H bonding orbital obtained from NBO analysis of: a) PM3, and b) HF/6-31G* optimized geometries of 1-39.	7
Figure 5.2	Plot of experimental vs. calculated (with semiempirical relationship 29, Table 5.4) one-bond C-H spin-spin coupling constants in 1-39.	l
Figure 5.3	Experimental one-bond C-H spin-spin coupling constants in 1-39 against: a) PM3 natural atomic charge on hydrogen, $q_{\rm H}$ (61 data points, 38a is excluded from the correlation), and	

b) PM3 atomic orbital coefficient on hydrogen (61	data
points, 38a is excluded from the correlation).	

Figure 6.1	Plot of experimental heats of formation, $\Delta H_{f}(exp)$, vs.	
	calculated values, ΔH_{f} (calcd), from the HF/6-31G* group	
	equivalents evaluated in this work, for the compounds in	
	Table 6.1. Slope 1.00 was taken for the correlation line.	207

LIST OF SCHEMES

Scheme 2.1	Manxane synthesis	53
Scheme 2.2	Analysis of products from decomposition of 1-manxyl radical	87
	CHAPTER 3	
Scheme 3.1	Manxine synthesis	110
Scheme 3.2	Newcome's synthesis of 1-azoniatricyclo[3.3.3.0]undecane chloride	111
	CHAPTER 4	
Scheme 4.1	Synthesis of 3-(2-hydroxyethyl)-1,5-pentanediol	133
Scheme 4.2	Synthesis of 4-substituted tetrahydropyrans	136
Scheme 4.3	Synthesis of the tris acid chloride of methanetriacetic acid and of the tris(N-benzyl)methanetriacetamide	
Scheme 4.4	Synthesis of tris(o-hydroxyphenyl)methane	142

"Through doubting we come to questioning and through questioning we come to the truth" *Peter Abelard*

CHAPTER 1

ODD-ELECTRON σ BONDING IN MEDIUM-RING BICYCLIC BRIDGEHEAD RADICALS: A THEORETICAL INVESTIGATION

Abstract: The study of interactions and chemical reactions between two bridgehead atoms in medium-ring systems is reviewed. Intrabridgehead σ -type bonding in bicyclic carbon-centered radicals with various donors and acceptor heteroatoms is examined by semiempirical (MNDO) and ab initio (HF/6-31G*) methods. It is found that the tertiary C-H bond dissociations that yield bridgehead radicals of the symmetrical [3.3.3] bicyclics investigated are considerably lower (by 5 to 26 kcal/mol at the HF/6-31G* level) than for *tert*-butyl radical, the prototype tertiary alkyl radical. Intrabridgehead σ -bonding can amount to as much as 18 kcal/mol of the stabilization energy, with the highest values for the radicals where the opposite bridgehead site is occupied by aluminum. The computational results suggest that medium-ring bridgehead radicals might show unusual stability and/or persistence as well as interesting bridgehead-bridgehead interactions.

1.1 An Overview of Research on Odd-Electron σ Bonds

Two atoms' σ -type interactions can occur in four topological situations:



Intermolecular Intramolecular Transannular Intrabridgehead

Furthermore, these interactions can be direct or via an intervening atom, e.g. as in hydrogen bonding, and may be classified by the number of electrons involved. One- and three-electron bonds play an important role in radical and electron transfer chemistry, and in many gas-phase processes involving radical ions. Experimentally, one-electron¹ and three-electron bonds² are abundant and well-characterized. Three-electron bonding is a general concept that can be applied to many different bonding situations in both paramagnetic and diamagnetic molecules.³ Numerous examples have been reported and substantiated by experimental data and theoretical calculations; various $(R_2S \therefore SR_2)^+$ radical cations.⁴ (RS:SR)⁻ radical anions.⁵ and R_2S :SR neutral radicals^{5b,6} have been identified, as well as N: N, P: P, AS: AS, SS: SS, IOII: I, II and a wide variety ofheteronuclear X: Y two-center three-electron bonds.¹² Having an odd electron, one- and three-electron bonded species are, in general, reactive and their generation and characterization, particularly in fluid solutions, is not necessarily straightforward. In rigid matrices, however, such species can be produced in situ by radiolysis or photolysis, and the observation of reactive species can be carried out at leisure. EPR spectroscopy has

played a major role in the study of odd-electron bonded species,¹³ along with pulse radiolysis¹⁴ and mass spectrometry¹⁵.

First described by Pauling in 1931,¹⁶ odd-electron bonds owe their stability to resonance between two limiting localized Lewis structures that are mutually related by charge transfer, as shown in (1) for one-electron bonds, and in (2) and (3) for typical three-electron bonds.

$$A^{*}B^{+} \leftrightarrow A^{+}B^{*}$$
(1)

$$A^{+}B: \leftrightarrow A:B^{+}$$
 (2)

$$A^{*}B^{*} \leftrightarrow A^{*}B^{*}$$
(3)

The bond strength depends on the energy difference between the two resonance structures (i.e. the difference in ionization potential between A and B), and stabilization will be significant only if the resonating structures are of almost equal energy. Thus, Meot-Ner et al.¹⁷ observed that bonding energies in radical dimer cations of aromatic compounds are largest in symmetric associations and decrease as the difference in the ionization potentials of the neutral fragments increases. In $(C_6H_6)_2^+$ the dissociation enthalpy was measured as 17 kcal/mol, while in $C_6H_6^+ \cdot C_6F_6$ it was about 11 kcal/mol; the difference, 6 kcal/mol, is ascribed to charge transfer resonance.¹⁷

In MO theory the stability of one- and three-electron bonds is considered to arise from the fact that they possess one net bonding electron in the MO's of the AB species. The formal AB bond order is 1/2 for both one- and three-electron bonds; for a single electron, the occupancy of the bonding MO yields a bond order of 1/2, whereas for the three-electron case the bonding effect of one of the two bonding electrons is canceled by that of the antibonding electron, leaving one net bonding electron. If overlap is included, the antibonding orbital is more destabilized than the bonding orbital is stabilized, originating a distinctive bond strength dependence on overlap for three-electron bonds.¹⁸ The quantum-mechanical foundation of this unusual dependence on overlap for threeelectron-bonded systems is illustrated by the orbital splitting diagram represented below, where the symbols α , β and S represent the Hückel coulomb, resonance, and overlap integrals, respectively.



Since the advantage in magnitude of destabilization over stabilization increases with S, then under some circumstances the destabilization of a single-electron occupying the antibonding MO will outweigh the total stabilization of the two electrons occupying the bonding MO. Thus, if the maximum strength of a three-electron bond is half that of the corresponding two-electron bond, the strength of the bond falls off rapidly with increasing overlap integral. A simple mathematical evaluation from the above expressions shows the interaction associated with a three-electron bond involving two initially degenerate levels to be net destabilization occurs at even smaller overlaps. As the gap energy between initial levels is increased, the numerical advantage held by destabilization of the

antibonding MO over stabilization of the bonding MO increases. In addition, electron repulsion in the three-electron case is a problem not explicitly acknowledged in the Huckel formalism; e.g. consider H_2^{-1} which dissociates to H⁻ and H⁻.¹⁹

The bonding in many diatomic cations, including He₂⁻⁺, Ne₂⁻⁺, Kr₂⁻⁺, and Xe₂⁻⁺, involves two-center three-electron bonds and is well-characterized.²⁰ A summary of some of the available data is shown in Table 1.1; however, the focus here is on odd-electron bonding through heteroatoms in organic molecules and despite the ample observations of such species, few experimental data exist even hinting at the strengths of their odd-electron bonds, and detailed thermodynamic data are remarkably sparse.

Meot-Ner and Field²¹ obtained thermodynamic parameters for the association reactions of CO⁺ and N₂⁻⁺ radical cations and of even-electron HCO⁺ and N₂H⁺ ions with CO and N₂, by equilibrium studies in pulsed high-pressure mass spectrometry. Alder et al.²² deduced bond energies for N.: N three-electron bonds in radical cations of polycyclic diamines, from ionization energies and proton affinity measurements of the neutral amines, and from kinetic decomposition studies of the radical ions. Illies et al.^{4b-4,11b} reported gasphase measurements on the strength of iodine-iodine and sulfur-sulfur three-electron bonds, estimated from ion-molecule time-resolved equilibrium studies carried out in the high-pressure ion source of a mass spectrometer. Apart from these experimental determinations of two-center three-electron binding energies, most of the information about odd-electron bonding energies comes from theoretical studies.²³

Clark²⁴ has carried out systematic ab initio molecular orbital calculations on series of one- and three-electron bonded radical cation complexes of first- and second-row elements Li-Ar and their hydrides to address the question of whether significant σ bonding

5

Reaction	Bond Energy [*] (kcal/mol)
$H_2^{+} \rightarrow H^+ + H^-$	64.4 ^{1a}
$Li_2^{+} \rightarrow Li^+ + Li$	29.4 ^{1b}
$Na_2^{+} \rightarrow Na^+ + Na^-$	22.7 ^{1c}
$K_2^{+} \rightarrow K^+ + K^-$	18.3 ^{1d}
$\operatorname{He}_{2}^{+} \rightarrow \operatorname{He}^{+} + \operatorname{He}^{-}$	57.4 ^{2¢}
$Ne_2^{+} \rightarrow Ne^+ + Ne^-$	31.1 ^{2e}
$Ar_2^{+} \rightarrow Ar^+ + Ar^-$	28.8 ^{2e}
$Xe_2^{+} \rightarrow Xe^+ + Xe^-$	23
$F_2^{\cdot +} \rightarrow F^+ + F^-$	29.7 ²
$Cl_2^{-} \rightarrow Cl^{-} + Cl^{-}$	29.1 ^{2¢}
$Br_2 \rightarrow Br + Br$	26.2
$I_2 \rightarrow \Gamma + \Gamma$	24.3
$IBr \rightarrow Br + I$	23.1

 Table 1.1 Experimental One- and Three-Electron Bond Energies

^a From NIST Standard Reference Database 25, Structures and Properties, version 2.02, 1994, by Lias, S. G.; Liebman, J. F.; Levin, R. D. and Kafafi, S. A., unless otherwise noted.

can occur in a given situation, and to identify the factors affecting odd-electron bond dissociation energies. He found that first row elements form stronger odd-electron bonds than their second row equivalents, while hydrogen and helium form the strongest odd-electron bonds, up to 65 kcal/mol. Within a given row of the periodic table the alkali metals and the noble gases form the weakest odd-electron bonds. Asymmetric three-electron bonds are of special interest since they generally possess a lower stability than their homonuclear analogs, as a consequence of the electronegativity difference between the two atoms. Clark²⁴ proposed a general equation (4) to predict dissociation energies of both one- and three-electron bonds in unsymmetrical complexes:

$$D_{AB} = \frac{1}{2} (D_{AA} + D_{BB}) \exp(-\lambda_A \lambda_B \Delta_{IP})$$
(4)

where D_{AA} , D_{BB} and D_{AB} are the binding energies of the symmetric and unsymmetrical dimers, Δ_{IP} is the difference in the ionization potentials of A and B (the energy required to transfer an electron from one partner in the complex to the other), and λ_A and λ_B are adjustable preexponential factors characteristic of the elements involved. In preceding computational studies, $Clark^{25}$ found an analogous exponential decrease of D_{AB} in the three-electron bonded radical cation complexes of HCl, H₂S and PH₃, with increasing difference in Δ_{IP} . Also, since Δ_{IP} can only be small for charged species, $Clark^{24}$ concluded that neutral odd-electron bonded complexes should be weakly bound in the gas-phase because the charge transfer in (5) is strongly endothermic, but nevertheless, they may be stabilized in solution.

$$AB \rightarrow A^{+}B^{-}$$
 (5)

Gill and Radom²⁶ performed similar calculations on the first- and second-row ion dimers $He_{2}^{+,+}$, $(NH_{3})_{2}^{+,+}$, $(H_{2}O)_{2}^{+,+}$, $(HF)_{2}^{+,+}$, $Ne_{2}^{+,+}$, $(PH_{3})_{2}^{+,+}$, $(H_{2}S)_{2}^{+,+}$, $(HCl)_{2}^{+,+}$, and $Ar_{2}^{+,+}$, to examine whether they exist as hydrogen-bonded ions or as hemibonded species, the latter involving binding through heavy atom-heavy atom three-electron bonds. The hydrogenbonded systems are favored for all the first-row elements, while for the remaining secondrow systems, the hemibonded isomers are preferred. Gill and Radom²⁶ calculate remarkably strong three-electron hemibonds with energies greater than 41 kcal/mol. concluding that if rearrangement to hydrogen-bonded species is precluded by appropriate substitution, the hemibonded species examined should be readily observable. The calculations performed by Clark²⁴ and by Gill and Radom²⁶ were carried out at both unrestricted Hartree-Fock (UHF) and Møller-Plesset perturbation (MP) levels, and exhibited important and sometimes intriguing features: (i) high levels of ab initio theory, including in particular electron correlation, are necessary to predict accurately oddelectron bonding energies; (ii) the MP2 level is satisfactory and provides geometries and bonding energies in good agreement with higher orders of perturbation theory; (iii) puzzlingly, UHF optimized geometries of odd-electron bonded species are similar with MP2 geometries, whereas bonding energies are exceedingly underestimated; (iv) the HF error is nonsystematic and always large for three-electron bonds, while the error is smaller in the case of one-electron bonds. A nonempirical remedy for the HF bias was proposed by Hiberty et al.^{23c}; their established Uniform Mean-Field Hartree-Fock (UMHF) procedure involves orbital occupancy constraints and correction of the UHF resonance energies by nonempirical factors, and provides a routine inexpensive tool for obtaining

8

odd-electron bond energies for large molecules. The UMHF approach was tested on oneand three-electron bonded systems, and was shown to yield bonding energies in satisfactory agreement with more sophisticated calculations (up to and beyond fourth order MP perturbation theory).^{23c}

In contradiction with Clark's²⁴ theoretical results, Janssen et al.²⁷ showed that three-electron bonded phosphoranyl radicals, R_3P .. SR_n^{n-1} (n = 0,1,2), are formed despite an unfavorable balance of the ionization potentials of the two fragments involved, implying that a large number of heteronuclear three-electron bonds between a variety of elements should be experimentally accessible in solution and in the solid-phase. Also, despite the fact that theory predicts first-row three-electron complexes to be more stable than their second-row analogues, most systems studied are formed from second-row or heavier atoms. Apart from F_2^- , first-row systems are rare. Recently, evidence for H_3N .. NH_3^{-+} radicals has been presented,²⁸ but these centers were very unstable, giving NH_3^{-+} at *ca*. 140 K, presumably via the reaction:

$$H_{3}N:.NH_{3}^{**} \rightarrow NH_{3} + NH_{3}^{**}$$
(6)

In particular, cases where carbon participates in odd-electron bonding are relatively rare and poorly characterized.²⁹

Regardless of disagreements between experiment and theory, computational chemistry remains a powerful tool that, when judiciously used, can help predict or confirm daring hypotheses. In this work, intrabridgehead σ -type interactions of bicyclic carboncentered radicals with various donor and acceptor heteroatoms are examined by semiempirical and ab initio molecular orbital calculations. The results suggest that such

9

species might show unusual stability and/or persistence as well as interesting bridgeheadbridgehead interactions.

1.2 Intrabridgehead Interactions in Medium-Ring Bicyclics

Our interest in through-space perturbation of unpaired electron centers has drawn us to the rich potential of intrabridgehead chemistry.³⁰ The special structure/strain relationship in medium ring bicyclic frameworks has allowed the construction of many unusual chemical entities such as 1- and 3- electron bonds,³¹ symmetrical C-H-C hydride-bridged carbenium³² and N-H-N hydrogen-bonded ammonium cations,³³ intrabridgehead donoracceptor complexes,³⁴ hyperstable olefins,³⁵ near-planar aliphatic amines,³⁶ stabilized bridgehead carbocations,³⁷ and rapidly autoxidizable alkanes³⁸. In the following, the study of interactions and chemical reactions between two bridgehead atoms in medium-ring systems will be reviewed.

Bicyclic compounds have essentially rigid molecular frameworks and well defined structures, and thus, allow control of orbitals and bonds toward a desired alignment. The optimum chain length/ring sizes for enforcing σ -type interactions between the two bridgeheads are likely to be in the range of 3 to 5 atoms for each bridge to permit close approach of the bridgehead atoms without developing strain. Geometrical control of the intrabridgehead relationship provides an opportunity for the careful examination of fundamental questions of structure and bonding.

1.2.1 Closed-Shell Interactions in Neutral Medium-Ring Bicyclics

The strain energy³⁹ of medium-ring bicyclics is mainly due to nonbonded interactions between the bridges and torsional strain. To avoid intolerable H/H steric repulsions, bond angles are opened up, causing increased angle strain and framework rehybridization. In addition, bicyclic ring systems with large enough bridges to allow *in/out* isomerism⁴⁰ are conformationally very complex. The prediction and understanding of possible conformations is a difficult matter; the borderlines where *in,out*- and *in,in*-isomers become possible are by no means obvious and depend strongly on the bridgehead atoms and their substituents. Whereas the *out,out*-, *in,out*- and *in,in*-isomers in compounds with carbon bridgeheads are separated by high barriers, the situation is quite different for bridgehead amines where nitrogen inversion allows equilibration of the isomers.

The question of the relative thermodynamic stability of *out,out-, in,out-,* and *in,in*isomers of bicyclic hydrocarbons is amenable to molecular mechanics (MM) calculations. Saunders⁴¹ used the stochastic (or Monte Carlo) search method for 32 bicyclic hydrocarbons ranging from bicyclo[3.2.2]nonane to bicyclo[6.6.6]eicosane, to locate all isomers and predict thermodynamic preferences (see Table 1.2). As expected, *out,out*isomers are strongly preferred for systems built from small- and common-sized rings; their strain energy grows rapidly as the sizes of the constituent rings increase, reaching a maximum in the [4.4.4]system. *Out,out-*bicyclo[4.4.4]tetradecane, built entirely from tenmembered rings, has a strain energy which is more than three times that of cyclodecane⁴². Because of this high strain energy, *in,out-*isomers become preferred to *out,out* in medium-

11

ring systems. According to Saunders' calculations, the *in,out*-isomers become the most stable for several bicyclotridecanes ([4.4.3], [5.3.3], and [5.4.2]), while the *in,in*-isomer is the most stable for bicyclo[5.5.5]heptadecane.

	Steric Energy ^c (in kcal/mol)		
Compound	out,out	in,out	in,in
Bicyclo[3.2.2]nonane	24.3	81.4	-
Bicyclo[3.3.2]decane	29.9	66.8	130.2
Bicyclo[3.3.3]undecane	37.3	-	119.6
Bicyclo[4.3.3]dodecane	48.6	55.8	93.5
Bicyclo[4.4.3]tridecane	58.4	54.8	82.4
Bicyclo[4.4.4]tetradecane	68.7	56.5	71.9
Bicyclo[5.4.4]pentadecane	64.9	55.0	63.6
Bicyclo[5.5.4]hexadecane	63.8	54.8	57.1
Bicyclo[5.5.5]heptadecane	60. 8	54.2	49.8

 Table 1.2 MM2* Steric Energies of Lowest Energy Conformations for Some Bicyclic Hydrocarbons^b

^a Allinger, N. L. J. Am. Chem. Soc. 1977, 99, 8127. ^b Reproduced from ref. 41. ^c The sum of bond stretching, angle bending, torsion, and van der Waals terms, that form the force-field, is called the steric energy of a molecule; steric energy can be roughly interpreted as strain energy, and steric energy differences between stereoisomers can properly be understood as strain energy differences.

In many respects, the most interesting cases are those where all the bridges are of the same length, and especially the symmetrical [3.3.3], [4.4.4], and [5.5.5] hydrocarbons. Bicyclo[3.3.3]undecane 1 (manxane) was first prepared in 1970 as the prototype compound which comprises together three eight-membered rings.⁴³ The conformations of manxane and of all known derivatives indicate the *out,out* C_{3h} symmetry conformation to be the energy minimum, but even this arrangement is strained in contrast to the flexibility observed for most eight-membered rings. Ab initio calculations carried out at the HF/6-31G* level estimate a strain energy of 28.0 kcal/mol for manxane, in good agreement with the 27.2 kcal/mol experimental value (Table 1.4).



One structural manifestation of the strain is flattening of the bridgehead regions accompanied by widening of the angles in the bridges. X-ray structures of 1azabicyclo[3.3.3]undecane (manxine) hydrochloride 2 and bicyclo[3.3.3]undecane-1,5-diol 3 show the expected structural features.⁴⁴ The electron-diffraction data from manxane vapors also confirms both the bridgehead flattening and the C_{3h} molecular symmetry.⁴⁵

There is only limited experimental evidence concerning bicyclo[4.4.4]tetradecane and derivatives, while bicyclo[5.5.5]heptadecane is unknown. Saunders' calculations⁴¹ (Table 1.2) predict the *in,out*-isomer as the most stable for the former and the *in,in*-isomer for the latter, but clearly suggest that all isomers should be isolable. McMurry and Hodge^{32a-b} prepared *in*-bicyclo[4.4.4]tetradec-1-ene 5 in 30% yield by Ti-induced cyclization of 6-(4-oxobutyl)cyclodecanone 4 and were able to hydrogenate it slowly to *in,out*-bicyclo[4.4.4]tetradecane 6 (5 is a "hyperstable olefin", where the alkene is less strained than the corresponding alkane). In addition to 6, a small amount of an isomeric product (presumably the *out,out*-isomer, calculated to be 7.4 kcal/mol less stable than 5) was obtained in the cyclization reaction, but no further work on this material has been reported.



The symmetric monoamines 1-azabicyclo[2.2.2]octane 7 (quinuclidine),⁴⁶ manxine 8,^{36a-b,43a-b} and *out*-6H-1-azabicyclo[4.4.4]tetradecane 9 (hiddenamine),⁴⁷ form a series in which the nitrogen atom appears to be successively pyramidal *out*, essentially flat, and pyramidal *in*. Structural data on 8 and 9 have not been obtained, but the photoelectron spectrum of 8 is indicative of a flat amine,⁴⁸ and the X-ray structure of the outside protonated ion of 1,6-diazabicyclo[4.4.4]tetradecane 10,⁴⁹ a compound which should be structurally similar to 9, reveals an *in,out* conformation.



1-Azabicyclo[4.4.4]tetradec-5-ene 11 also appears to have an inwardly pyramidalized nitrogen since its photoelectron spectrum indicates a strong lone pair/ π -bond interaction, and 11 reacts rapidly with acid to form the saturated azoniapropellane salt 12.⁵⁰



In the bicyclic bridgehead diamine series: 1,4-diazabicyclo[2.2.2]octane (DABCO) 13 is out,out,⁵¹ 1,5-diazabicyclo[3.3.3]undecane 14 most likely has nearly flat nitrogens



according to its photoelectron spectrum, 5^{2} and 1,6-diazabicyclo[4.4.4]tetradecane 15 adopts an *in,in* structure established by X-ray crystallography 5^{3} .

The structure/strain situation in medium-ring bicyclic compounds forces inverting atoms like nitrogen to have inside lone pairs with interesting chemical consequences. Thus, any process that allows outside pyramidalized bridgehead atoms to planarize or pyramidalize inward brings considerable relief of strain. The most effective strain-relieving process, however, is intrabridgehead bond formation. Alder³¹ tried to estimate the thermodynamics for this process by calculating the energetics of the hypothetical dehydrogenation reaction which removes the bridgehead hydrogens from a bicyclic ring system and forms a propellane. His results (see Table 1.3) confirm once more that intrabridgehead bond formation brings relief primarily in medium-ring bicyclics.

The chemistry of propellanes has been very well reviewed.⁵⁴ In small-ring propellanes the bridgehead carbons are severely distorted from the tetrahedral geometry

15

Bicycloalkane	Dehydrogenation Product	Heat of Dehydrogenation ^b (kcal/mol)
Bicyclo[1.1.1]pentane	[1.1.1]Propellane	+39
Bicyclo[2.2.2]octane	[2.2.2]Propellane	+67
Bicyclo[3.3.3]undecane	[3.3.3]Propellane	-5
Bicyclo[4.4.4]tetradecane	[4.4.4]Propellane	-36
Bicyclo[5.5.5]heptadecane	[5.5.5]Propellane	+0.5

Table 1.3 Heats of Some Formal Dehydrogenations^a

^aOnly *out,out* isomers were considered. Reproduced from ref. 31b. ^b These results, presumably MM2 calculations, correlate reasonably well with those presented below in Table 1.4, with the exception of [2.2.2]propellane, where our calculated HF/6-31G* structure is more strained, leading to a difference in the formal heat of dehydrogenation of 24 kcal/mol between MM2 and HF/6-31G* computations.

	Heat of Formation [*]	Strain Energy ^b
Compound	(kcal/mol)	(kcal/mol)
Bicyclo[1.1.1]pentane	49.7	67.6
[1.1.1]Propellane	84	97.9
Bicyclo[2.2.2]octane	-23	9.7
[2.2.2]Propellane	68°	(96.7)
Bicyclo[3.3.3]undecane	-21.2 ^d	27.2
[3.3.3]Propellane	-28.7 ^c	(14.9)
in,out-Bicyclo[4.4.4]tetradecane	-10.5°	25.9
[4.4.4]Propellane	-43.6°	(14.8)

Table 1.4 Heats of Formation and Strain Energies of Some Bicyclic Hydrocarbons and Propellanes

^a From NIST Standard Reference Database 25, Structures and Properties, version 2.02, 1994, by Lias, S. G.; Liebman, J. F.; Levin, R. D. and Kafafi, S. A., unless otherwise noted.

^b Strain energy; from experimental (calculated) heats of formation and the Benson group equivalents (Benson, S. W. *Thermochemical Kinetics*; John Wiley: New York, 1976).

^c This work; from HF/6-31G* total energies ([2.2.2]propellane -309.80932 H; [3.3.3]propellane -427.04326 H; *in,out*-bicyclo[4.4.4]tetradecane -545.24313 H; [4.4.4]propellane -544.14676 H) and the Wiberg group equivalents (Wiberg, K. B. J. Org. Chem. **1985**, 50, 5285).

^d Parker, W.; Steele, W. V.; Stirling, W.; Watt, I. J. Chem. Thermodyn. 1975, 7, 795.

for central bond formation. The distortion is extreme in [1.1.1]propellane 16 where each bridgehead carbon is "inverted" with all four bonds to one side, while the hybridization at the bridgehead carbons in [4.4.4]propellane 18 is close to the normal $sp^{3.55}$



The bond angle distortions in propellanes lead to both strain and unusual reactivity. The strain is lower in medium-ring propellanes, where only modest distortion of the bridgehead carbons is required to permit bonding. That intrabridgehead bond formation brings strain relief in medium-ring bicyclics is reflected in the lower strain energies in propellanes 17 and 18 than in the corresponding bicyclic hydrocarbons (Table 1.4).

1.2.2 Atranes

Heterobicyclic esters of triethanolamine (TEA) are commonly known as "atranes".³⁴ This term was extended to define general structures of the type $ZE(YCH_2CH_2)_3N$, where $Y = CH_2$, O, S or NR (e.g. when Y = NR the prefix aza is inserted) and E presently extends from group 1 to group 15.⁵⁶ Qualitatively, atranes can be viewed as donor-acceptor bonded propellanes and may be differentiated with respect to the strength of this transannular dative interaction. The intrabridgehead distance in atranes is quite variable, changing from the sum of the van der Waals radii of the atoms E and N or higher, as depicted in **A**, through intermediate distances, represented by **B**, to full transannular
bonds, as shown in C.



Main group element atranes (e.g. E = B, Al, Si, P) have been the most comprehensively studied. In particular, silatranes have aroused widespread interest not only among synthetic and structural chemists but also among pharmacologists and physiologists. The discovery of the high toxicity and specific biological activity of 1arylsilatranes (e.g. 1-phenylsilatrane is about twice as toxic as strychnine or hydrocyanic acid)⁵⁷ originated an extensive search for new types of biologically active organosilicon compounds. Thus, many practically non-toxic or low toxicity silatranes display specific biological and pharmacological activity, having a broad spectrum of action with applications in health, agriculture, and industrial microbiology.⁵⁸

The most intriguing aspect of atrane structure is the existence of the transannular dative bond, which leads to hypervalent bridgehead atoms and unique physical and chemical properties. The validity of this intrabridgehead interaction was initially demonstrated by Voronkov⁵⁹ in silatranes, based on dipole moment measurements and infrared absorption spectra. Further overwhelming experimental data from X-ray crystallography,⁶⁰ XPS, infrared spectroscopy, mass spectrometry, and NMR featuring several isotopes (¹H, ¹³C, ¹⁵N, ²⁹Si, ²⁷Al, ¹¹B, ³¹P), confirmed this hypothesis.⁶¹ The

strength of the intrabridgehead bond is stereoelectronically controlled, depending on the electron-withdrawing power of Z and the steric properties of E and Y substituents.

In silatranes the N-Si internuclear distance has been found to range from 2.89 Å to 1.96 Å.⁶⁰ These distances are considerably shorter than the 3.5 Å sum of the van der Waals radii, yet they are longer than conventional N-Si covalent bonds of 1.7-1.8 Å found in tetracoordinate silicon compounds. Structural correlations have been made between the N-Si bond length and a variety of parameters. The Si atom displacement (Δ Si) out of the plane of the three oxygens is linearly dependent on the N-Si distance.⁶² Taft's polar inductive parameter, σ^* , of the substituent (R) attached to Si, as well as Si-R bond lengths, vary linearly with N-Si distance, and with ¹⁵N chemical shifts, ⁶³ The N-Si bond length decreases with increased electronegativity of R; considerable charge transfer from N to Si is observed by XPS when Si is bound to a very electronegative substituent.⁶⁴ The anticipated increase of the binding energy of N_{1s} and the decrease of that of Si_{2p} in silatranes relative to TEA and triethoxysilane, was confirmed by X-ray photoelectron measurements. In addition, the correlation between N_{1s} and Si_{2p} binding energies in silatranes with different substituents on silicon, proves the existence of the intrabridgehead interaction.⁶⁵ Voronkov et al.⁶⁶ estimated the strength of N-Si bonds in a variety of silatranes from thermochemical parameters and ionization potential data; bond energies between 7 and 22 kcal/mol were obtained, reflecting a progression with increasing electron-withdrawing power of the silicon substituent.

Azatrane chemistry is expanded considerably by the presence of the nitrogen substituents. The steric hindrance resulting from stepwise substitution of the NH

functionalities with bulky groups leads to a significant weakening of the N-Si bond in silazatranes, correlated with ²⁹Si deshielding and increases in ¹J_{Si-C} and ²J_{Si-H} for the Z substituents.⁶⁷ Verkade⁶⁸ demonstrated a gradation of hypervalent N-P interactions in phosphazatranes. The N-P distance varies from 1.9 Å to 3.2 Å depending on the apical substituent, Z, on phosphorus. Well-developed transannular N-P bonds emerge when the phosphorus lone-pair is strongly polarized by a positively charged Lewis acid and are associated with substantial upfield ³¹P chemical shifts.⁶⁹ Unusual phosphorus basicity is found in proazaphosphatranes of the type P(RNCH₂CH₂)₃N (where R = H, CH₃, CH₂Ph) producing the unexpectedly weak conjugate acids HP(RNCH₂CH₂)₃N⁺ (pK₄ ~ 27 for **20** in DMSO).⁷⁰ The flexibility of these versatile nonionic superbases with respect to transannulation gives rise to new and exciting chemistry that has valuable implications for synthesis and catalysis. Thus, the commercially available N-methyl derivative of



proazaphosphatrane 19 has found applications as a superior catalyst for aryl isocyanate trimerization,⁷¹ as well as for silvlation of hindered tertiary alcohols and phenols⁷².

1.2.3 Radical Cations of Medium-Ring Bicyclic Diamines, Disulfides and Diphosphines

Alder⁷³ has repeatedly stressed the unique chemistry of medium-ring bicyclic compounds and demonstrated the potential of the intrabridgehead situation for studying weak σ -type bonding. Thus, the persistence of medium-ring bicyclic diamine radical cations in solution was interpreted on the basis of through-space intrabridgehead interactions presumed to generate three-electron σ bonds.^{22b} The first persistent radical cation discovered by Alder et al.⁷⁴ was that of naphtho[3.3.3]diamine, **21**. Subsequently, oxidation of a wide range of medium-ring diamines in solution led to long-lived radical cations.^{22b,75} Lifetimes of more than a second in CH₃CN at 25 °C are obtained for the radical cations of [3.3.3], [4.3.3], [4.4.3], [4.4.4], [5.4.3], and [6.3.3] diamines. The perchlorate salt of the [4.4.4]diamine radical cation **22** is indefinitely stable as a crystalline solid. Vogel et al.⁷⁶ prepared **23**, a modified [3.3.3] structure whose perchlorate salt is also stable as a solid.



The first ionization energies of such medium-ring bicyclic diamines are exceptionally low, and their photoelectron spectra show two bands separated by ~ 1 eV. Alder et al.^{22b} argued that this splitting is a measure of the through-space interaction of the nitrogen lone-pair orbitals. Thus, 1,6-diaza[4.4.4]tetraundecane is oxidized at a less positive potential than N,N,N',N'-tetramethylphenylenediamine, the diamine that produces the well-known and indefinitely stable Würster's blue radical cation, 24. Furthermore, the ESR spectra of these bicyclic diamine radical cations show hyperfine coupling to two nitrogens.⁷⁷ DABCO 13 also forms an unusually persistent radical cation 25 in solution $(t_{1/2} \sim 1 \text{ s in CH}_3\text{CN at 25 °C})$ which shows two equivalent nitrogens in its ESR spectra, in contrast to the transient quinuclidin-4-yl radical 26 which does not show any spin



delocalization at nitrogen; this result was rationalized primarily by through-bond longrange electron delocalization, however, rather than a three-electron bond.⁷⁸

Alder et al.^{22b} estimated the stabilization resonance induced by three-electron bonding in radical cations of medium-ring diamines as the difference in the N⁺-H bond dissociation energies of the protonated diamine and the analogous monoamine. An energy of 11 kcal/mol was obtained for the three-electron bond in both the radical cations of [3.3.3] and [4.4.4] diamines, in agreement with a previous estimate of 14.5 kcal/mol for the three-electron bond in 27.^{22a} Further oxidation of bicyclic diamine radical cations with loss of a second electron produces stable propellane hydrazinium dications with central N^+-N^+ two-electron σ -bonds, also prepared quantitatively by alkylation of bicyclic bridgehead diamines.⁷⁹ Their reductive cleavage affords a convenient route to mediumring bicyclic diamines.^{77a} X-ray structural data for all three oxidation states of diamine 15 show progressive shortening of the N-N distance from the neutral amine to the dication.⁸⁰ Crystals of the perchlorate salt of 22 were obtained in acetonitrile by a remarkably slow one-electron transfer reaction from 15 to the diperchlorate salt of 28. The three-electron bond in 22 is perhaps one of the few established bond lengths in a three-electron case.



Medium-ring disulfides undergo facile oxidation, too, where cation formation occurs concomitantly with coupling of the two sulfur atoms.^{14a,81} Even though most thioethers are easily oxidized, only the eight- (e.g. the radical cation of 1,5-DTCO 29) and nine-membered rings give long-lived radical cations. Subsequent oxidation gives dications



having S⁺-S⁺ bonds. Cycles with a thioether group transannular to other groups with lone pair electrons undergo oxidative coupling reactions to give stable cations; evidence of $N \therefore S$ bond formation was also obtained in several aminothioethers.^{81b} Similarly, twoelectron P⁺-P⁺ bonds are found in medium-ring cyclic and bicyclic diphosphines; the X-ray structure of **30** shows a P-P distance significantly shorter than in neutral diphosphines despite the adjacent positive charges.⁸² A series of nucleophilic adducts of **30** have been described, with Y-P-P⁺ bonding. As with Verkade's atrane-type superbases, the adduct with Y = H, **31**, was very difficult to deprotonate.^{82b,83}

1.2.4 Medium-Ring Bicyclic Carbon-Centered Bridgehead Radicals

There are only two examples in the literature of intrabridgehead odd-electron bonded complexes with carbon participation: the radical cation of [3.3.3]propellane **32**,^{29a} and the 1-azabicyclo[3.3.3]tetradec-4-yl radical **33**.^{29b}



Ion **32** was generated as a transient species in CCl₄ or CBr₄ matrices by γ -radiolysis of [3.3.3]propellane at 77 K. The ESR spectrum of **32** shows strong coupling to 6 equivalent hydrogens, characteristic of C_{3h} symmetry of the radical cation. The bridgehead radical **33** was obtained by γ -irradiation of 1-azoniatricyclo[4.4.4.0^{1,6}]tetradecane tetrafluoroborate, either as the pure salt or in dilute methanol solution, at 77 K. In both media, the ESR spectrum of **33** shows a quartet of broad lines, which is assigned to hyperfine coupling to the three pseudo-equatorial equivalent hydrogens adjacent to the radical center. The spin density on nitrogen is not higher than 5%. Thus, despite the ideal structure of the bicyclo[4.4.4] system for intrabridgehead bond formation, the three-electron bonding in the neutral radical **33** is very weak, in agreement with Clark's²⁴ calculations and Harcourt's³ theoretical predictions that three-electron bonding is destroyed by too much overlap.

1.2.5 Bridgehead Phosphoranyl Radicals

Hamerlinck et al.⁸⁴ reported that X-ray irradiation of 34·BF₄ at 77 K produces phosphoranyl P^V radicals. Their structure has been proposed based on single-crystal ESR measurements, which hint at initial formation of 35, followed by an irreversible transformation to 36 with temperature increase. Also, 36 could be obtained directly from 34·BF₄ by UV laser irradiation. The evidence for the unprecedented structure of 36, where the unpaired electron is in apical position, has been disputed by Roberts.⁸⁵ He interpreted the results to be consistent with structure 37, where the odd-electron is localized in a P-N σ* molecular orbital, generating a three-electron bond between phosphorus and nitrogen, however, there is still no definite answer to this problem.



1.2.6 Intrabridgehead Indirect Interactions via Hydrogen

All of the observed indirect interactions across medium-ring bicyclic compounds involve hydrogen, as they are normally too small to accommodate anything larger. In macrobicyclic compounds, interactions via other atoms (or ions) are possible, but they will not be discussed here. The [1.1.1]cryptand, for example, can hold two hydrogens or one lithium cation, but it is certain that the interactions with the oxygen atoms are as important as the intrabridgehead bonding and no evidence of complexation other than for protons has been found in the analogous bicyclic diamines.^{31b}

Alder et al.³³ converted 13 medium-ring bicyclic diamines to inside protonated monocations, all of which have intrabridgehead hydrogen bonds, by slow, conventional proton-transfer or by redox-promoted rearrangements. X-ray structures were obtained for seven inside-protonated ions and show N-H-N distances varying from 2.47 to 2.69 Å, and N-H-N angles ranging from 180° (in **38**) to 132°.



An interesting question is whether these intrabridgehead hydrogen-bonded ions have single or double minimum potentials. On the basis of the $\delta\Delta({}^{1}\text{H},{}^{2}\text{H})$ test⁸⁵ for equilibrating and resonance structural distinction, also known as isotopic perturbation of equilibrium, all inside protonated ions have double minima structures except for the *in*[4.4.4]H⁺ ion **38**.⁸⁷ Neutron diffraction studies show the inside hydrogen atom in **38** to be central even at 20 K; the N-H-N distance in **38** (2.53 Å) is the shortest known for a linear hydrogen bond.⁸⁷ A chemical indication of the strength of these N-H-N hydrogen bonds is their resistance to deprotonation. In fact, upon treatment with strong base, **38** slowly undergoes redoxmediated loss of proton (i.e. loss from one of the CH₂ sites) rather than "simple" loss of the internal H⁺. µ-Hydrido-bridged carbocations of medium-ring systems give rise to transannular interaction by C-H-C three-center two-electron bonding.⁸⁸ They are characterized by the high field ¹H NMR chemical shift of the bridging hydrogen, anomalously low coupling constants involving this hydrogen, and very small isotope perturbation shifts. Whereas monocyclic ions, such as 40,⁸⁹ are susceptible to loss of hydrogen and rearrangement at higher temperature, in the intrabridghead situation, e.g. 41 and 42, the inside hydrogen is well enclosed in the caged structure, making escape sterically impossible and, thus, inducing kinetic stability.⁸⁸



Three-center two-electron bonds can exist in two distinct types, often referred to as "open" and "closed" geometries, although it is recognized that intermediate geometries are



possible. Sorensen and Whitworth⁹⁰ prepared a series of ions based on a bridged bicyclo[3.3.1]nonyl ring as in the general structure 41, to examine the effect of C-H-C bending on μ -hydrido bridging. When n = 5 the formal C⁺ center and the potentially bridging remote H-C group are close enough to develop a fully μ -hydrido-bridged structure; for larger sizes of the polymethylene-connecting link, one sees a gradation of structures with progressive C-H-C bending, leading for n = 8 back to a normal tertiary ion. Similarly, McMurry and Lectka⁸⁸ built a set of bicyclo[x.y.z] carbocations (x, y, z = 2 to 6) as in the general structure 42, all of which showed three-electron two-center bonding and progressive bending of the central C-H-C¹⁺ bond with decreasing ring size. Particularly, *in*-bicyclo[4.4.4]-1-tetradecyl cation 43 is one of the most stable carbocations known; 43 was obtained by protonation of bridgehead alkene 5, as well as upon a remarkable protonolysis of 6 in glacial acetic acid at 40 °C.⁹¹



The present review demonstrates the potential of intrabridgehead chemistry for studying weak σ -type interactions. When the interacting bridgeheads are of the same type, odd-electron bonding becomes a significant and easily observed phenomenon.

1.3 Geometry, Strain and Odd-Electron σ Bonding in Medium-Ring Bicyclic Bridgehead
 Radicals: A Semiempirical and Ab Initio HF/6-31G* Analysis

The unique properties of medium-ring bicyclic compounds are intimately connected with special structure/strain relationships. For example, the experimental rates of solvolysis of bridgehead derivatives correlate well with the calculated strain (steric) energy differences between substrate and the intermediate carbenium ion.⁹² Solvolysis reactions occurring at

bridgehead positions are mechanistically simple and homogeneous, since most of the potentially competing pathways are forbidden for structural reasons. The relative rates of bridgehead derivatives are dominated by steric effects and essentially independent of leaving groups or solvent. On these grounds a unified reactivity scale for solvolysis of bridgehead derivatives was proposed,^{92c} while the experimental data for solvolytic bridgehead reactivities were used to develop a revised force-field for tertiary carbenium ions.^{92e} Radical reactivities also parallel those of the corresponding bridgehead carbenium ions.^{92a-b} Bridgehead compounds provide a calibrated series of widely varving reactivities. spanning 22 orders of magnitude, which permits a general, reasonable reactivity prediction for similar substrates. Rate enhancements of larger magnitude than in typical acyclic analogs have been reported for bridgehead systems.⁹³ 1-Chlorobicyclo[3.3.3]undecane (1manxyl chloride) is ca. 10⁴ times more reactive than *tert*-butyl chloride in solvolysis reactions.^{93a} Consistent with the results of solvolysis studies and the experimental observation that manxane reacts rapidly with atmospheric oxygen to produce a mixture of bridgehead peroxides and hydroperoxides, empirical force-field calculations suggest that enhanced reactivities at these sites are due to 6.8 kcal/mol relief of strain when the bridgehead converts to a trigonal center $(sp^3 \rightarrow sp^2$ rehybridization in the transition state).^{93a} All the CCC bond angles in manxane are considerably larger than the ideal tetrahedral value and a sp^2 hybridized carbon is more readily accommodated at the bridgehead, also reducing the repulsive nonbonded interactions between the bridges.⁴⁵ The structure/reactivity relationship in manxane suggests the symmetrical [3,3,3] system as the archetypal medium-ring bicycle for studying intrabridgehead σ -type interactions.

29

Semiempirical (MNDO)⁹⁴ and ab initio (HF/6-31G^{*})⁹⁵ calculations were performed on various symmetrical [3.3.3] bicyclics and their bridgehead carbon-centered radicals, to evaluate the bridgehead C-H bond dissociation energy and the strength of potential intrabridgehead odd-electron σ -bonds in the radicals. The bond dissociation energies of the bridgehead C-H bonds in 1, 8 and 44-62 were estimated relative to the *tert*-butyl radical (see Tables 1.5 to 1.8).⁹⁶ In all cases, the calculated BDE's (Tables 1.5 to 1.8) show strikingly low values for the tertiary C-H sites, consistent with the strain relief upon bridgehead flattening discussed above.

Aliphatic carbon-centered radicals are considerably stabilized by lone pair donors or acceptors which can delocalize the unpaired electron through π -resonance as shown below.⁹⁷ In the radicals considered here the semioccupied orbital is collinear with the opposite bridgehead and their interaction occurs by σ -delocalization. The substantial shortening of the BB distance (see Tables 1.5 to 1.8) in the bridgehead radicals of 1, 8 and 44-62, may sufficiently augment contact of the two bridgeheads to form odd-electron σ bonds.

 π -Delocalization σ -Delocalization > N + > N

The C-H bond dissociation energy differences (Δ BDE's; see Tables 1.5 to 1.8) relative to *tert*-butyl radical reflect both the strain energy relief due to bridgehead flattening and the electronic stabilization by intrabridgehead σ bonding. However, the Δ BDE's of the radicals with carbon atoms in the opposite bridgehead represent

30

Table 1.5 HF/6-31G* Total Energies (MNDO Heats of Formation), BDE's, Intrabridgehead Distances and Radical Stabilization Energies Relative to the *tert*-Butyl Radical^{*} in 1, 44 and 45

R-H	TE (R-H) (ΔH _f)	BB [♭] (R-H)	TE (R [·]) (ΔH _f)	BB ^b (R [.])	ΔBDE ^c	BDE⁴	ΔBB°
	-428.17907	3.401	-427.56808	3.097	8.1	87.9	0.304
	(-21.7)	(3.357)	(-9.71)	(3.024)	(4.7)	(91.3)	(0.333)
()	-426.35559	3.012	-426.76778	2.172	22.7	73.3	0.840
44	(181.6)	(3.006)	(188.4)	(2.369)	(9.9)	(86.1)	(0.637)
() ⁻	-427.50194	3.306	-426.89565	2.491	11.9	84.1	0.815
45 ^d	(-14.8)	(3.035)	(-4.8)	(2.623)	(6.7)	(89.3)	(0.412)

^a HF/6-31G^{*} total energies (TE) are given in hartrees, 1 H = 627.5 kcal/mol; MNDO heats of formation (Δ H_d) and bond dissociation energies (BDE) are given in kcal/mol; distances are given in angströms. ^b BB is intrabridgehead distance.

[°] Stabilization energy relative to *tert*-butyl radical; from isodesmic reactions vs. *iso*butane/*tert*-butyl radical.

^d Based on relative stabilities vs. tert-butyl radical and BDE (tert-Bu-H) = 96.0 kcal/mol (ref. 96).

 $^{\circ}$ ΔBB is the difference between the intrabridghead distance of R-H and that of the corresponding bridgehead radical.

^d The carbanion calculations are done at 6-31+G* level, since a proper description of anions requires basis sets which incorporate diffuse functions. Total energies at 6-31+G* level: *iso*butane -157.31456 H; *tert*-butyl radical -156.68935 H.

R-H	TE (R-H) (ΔH _f)	BB (R-H)	TE (R [·]) (ΔH _f)	BB (R [.])	∆BDE ^ь	BDE⁵	ΔBB ^c
()	-414.42449	3.032	-413.82346	2.520	14.4	81.6	0.512
46	(-34.5)	(3.023)	(-25.2)	(2.645)	(7.4)	(88.6)	(0.378)
47	-631.61403	3.171	-631.03176	2.474	26.2	69.8	0.697
	(-30.0)	(3.128)	(-26.1)	(2.610)	(12.8)	(83.2)	(0.518)
	-444.55189	3.119	-443.55189	2.801	8.6	87.4	0.318
	(-4.0)	(3.124)	(8.1)	(2.784)	(4.6)	(91.4)	(0.340)
() Si H 48	-679.24119 (-48.0)	3.531 (3.462)	-678.64296 (-41.0)	3.012 (3.060)	16.2 (9.7)	79.8 (86.3)	0.519 (0.402)
() ↓ H 49	-730.84114 (-130.1)	3.477 (3.386)	-730.24028 (137.737)	2.930 (2.978)	14.5 (9.4)	81.5 (86.6)	0.547 (0.408)
50	-730.44256	3.739	-729.83717	3.341	11.7	84.3	0.398
	(-48.7)	(3.530)	(-39.9)	(3.146)	(7.9)	(88.1)	(0.384)

Table 1.6 HF/6-31G* Total Energies (MNDO Heats of Formation), BDE's, Intrabridgehead Distances and Radical Stabilization Energies Relative to the *tert*-Butyl Radical in 8 and 46-50^a

[•] HF/6-31G* TEs are given in hartrees,; MNDO heats of formation (ΔH_{t}) and bond dissociation energies (BDEs) are given in kcal/mol; distances are given in angströms. BB is intrabridgehead distance. ^b Stabilization energy relative to *tert*-butyl radical. BDE based on relative stabilities vs. *tert*-butyl radical and BDE (*tert*-Bu-H) = 96.0 kcal/mol (ref. 96). [°] Δ BB is the difference between the intrabridgehead distance of R-H and that of the corresponding bridgehead radical.

R-H	TE (R-H) (ΔH _f)	BB (R-H)	$TE (\mathbf{R}^{\cdot})$ (ΔH_{f})	BB (R [.])	∆BDE ^ь	BDE ^b	ΔBB ^c
°° 51	-535.65528 (-127.6)	3.238 (3.263)	-535.03929 (-112.4)	3.011 (2.967)	5.0 (1.5)	91.0 (94.5)	0.227 (0.296)
0-B;0 ()∕ 52	-522.03574 (-176.4)	2.827 (2.840)	-521.42545 (-163.92)	2.548 (2.519)	8.6 (4.2)	87.4 (91.8)	0.279 (0.321)
0-Al ^{-∗0} ()) 53	-739.23863 (-182.3)	2.996 (3.072)	-738.64586 (-176.2)	2.413 (2.633)	19.6 (10.6)	76.4 (85.4)	0.583 (0.439)
^H → ^{Si} , ^O → → → → → → → → → → → → → → → → → → →	-786.85057 (-221.7)	3.373 (3.440)	-786.24312 (-212.1)	3.033 (3.423)	10.4 (7.1)	85.6 (88.9)	0.340 (0.170)
55	-838.36592 (30.1)	3.313 (3.326)	-837.75614 (41.2)	2.957 (2.956)	14.2 (5.6)	81.8 (90.4)	0.356 (0.370)
°- ^P -0 ()) 56	-837.98495 (-196.4)	3.568 (3.505)	-837.37264 (-184.3)	3.297 (3.173)	7.3 (4.6)	88.7 (91.4)	0.271 (0.332)

Table 1.7 HF/6-31G* Total Energies (MNDO Heats of Formation), BDE's, Intrabridgehead Distances and Radical Stabilization Energies Relative to the *tert*-Butyl Radical in 51-56^a

^a HF/6-31G^{*} TEs are given in hartrees; MNDO heats of formation (ΔH_t) and BDEs are given in kcal/mol; distances are given in angströms. BB is intrabridgehead distance. ^b Stabilization energy relative to *tert*-butyl radical; from isodesmic reactions vs. *iso*butane/*tert*-butyl radical. Based on relative stabilities vs. *tert*-butyl radical and BDE (*tert*-Bu-H) = 96.0 kcal/mol (ref. 96). ^c Δ BB is the difference between the intrabridgehead distance of R-H and that of the corresponding bridgehead radical.

R-H	TE (R-H) (ΔH _f)	BB (R-H)	TE (R [•]) (ΔH _f)	BB (R [.])	∆BDE ^ь	BDE⁵	ΔBB ^c
	-476.13947	3.360	-475.52549	3.114	6.3	89.7	0.246
	(15.6)	(3.323)	(29.0)	(3.006)	(3.3)	(92.7)	(0.317)
	-462.49187	2.935	-461.88426	2.638	10.3	85.7	0.297
	(-31.0)	(2.912)	(-20.2)	(2.572)	(5.9)	(90.1)	(0.340)
HN-AI-NH NH 59	-679.67332 (-25.8)	3.129 (3.120)	-679.07967 (-20.5)	2.560 (2.676)	19.0 (11.4)	77.0 (84.6)	0.569 (0.444)
	-728.28875	3.482	-727.68399	3.109	12.1	83.9	0.373
	(-58.0)	(3.455)	(-50.0)	(3.068)	(8.7)	(87.3)	(0.387)
	-778.85268	3.406	-778.24526	3.024	10.4	85.6	0.382
	(161.9)	(3.336)	(171.271)	(2.941)	(7.3)	(88.7)	(0.395)
	-778.45020	3.610	-777.84163	3.279	9.7	86.3	0.331
	(-46.6)	(3.525)	(-36.0)	(3.177)	(6.1)	(89.9)	(0.348)

Table 1.8 HF/6-31G* Total Energies (MNDO Heats of Formation), BDE's, Intrabridgehead Distances and Radical Stabilization Energies Relative to the *tert*-Butyl Radical in 57-62*

^a HF/6-31G* TEs are given in hartrees; MNDO heats of formation (ΔH_t) and BDEs are given in kcal/mol; distances are given in angströms. BB is intrabridgehead distance. ^b Stabilization energy relative to *tert*-butyl radical; from isodesmic reactions vs. *iso*butane/*tert*-butyl radical. Based on relative stabilities vs. *tert*-butyl radical and BDE (*tert*-Bu-H) = 96.0 kcal/mol (ref. 96). ^c Δ BB is the difference between the intrabridgehead distance of R-H and that of the corresponding bridgehead radical.

exclusively the strain energy changes upon radical formation. Accordingly, if the bridgehead radicals of 1, 51 and 57 are taken as references for their set of compounds, then the difference in the relative BDE's for the other radicals can be approximated as a measure of stabilization by σ -delocalization over the opposed bridgehead. Based on Clark's²⁴ findings, the cation radical 44 and anion radical 45, where the bridgeheads are of the same type, would give best (upper limits for the one- and three-electron BDEs) charge delocalized one- and three-electron bonds (see Table 1.5).

The bridgehead C-H bond dissociation energy in manxine **8** is similar to the BDE of the bridgehead C-H bonds in 1 (Table 1.6), suggesting that there is no significant stabilization by σ -delocalization in this case. Analogously, the EPR study of the quinuclidin-4-yl radical 63 revealed very little delocalization of the unpaired spin to the nitrogen,⁹⁸ in contrast to the radical cation of 13,⁹⁹ whose EPR spectrum shows two equivalent N's. This lack of stabilization was considered to originate in the nondegeneracy of the interacting orbitals.



The bridgehead atoms are in close contact in all radicals considered in Tables 1.5-1.8; in each one, the BB distance is shorter than the sum of the van der Waals radii of the bridgehead atoms (van der Waals radii: C 1.65 Å, B 1.7 Å, N 1.55 Å, Al 2.15 Å, Si 2.10 Å, P 1.85 Å)¹⁰⁰ and may allow intrabridgehead σ -type interactions (Table 1.9). The calculated geometries of the radicals presented below show inward pyramidalization of the radical center, having the semioccupied orbital directed toward the opposite bridgehead in

		R-H	H R'				
Compound	X	BB	BB	∆BB ^b	ρ	Σr_{vdW}^{c}	
	CH (1)	3.401	3.097	0.304	0.00213	2.30	
×	B (46)	3.032	2.520	0.512	0.05324	2.35	
$\langle \rangle$	Al (47)	3.171	2.474	0.697	0.04505	3.80	
	N (8)	3.119	2.801	0.318	0.01227	2.20	
	SiH (48)	3.531	3.012	0.519	0.00115	3.75	
	P ⁺ H (49)	3.477	2.930	0.547	0.00156	3.50	
	P (50)	3.739	3.341	0.398	0.00167	3.50	
V and O	CH (51)	3.238	3.011	0.227	0.00030	2.30	
0-10	B (52)	2.827	2.548	0.279	0.01836	2.35	
())	Al (53)	2.996	2.413	0.583	0.03489	3.80	
	SiH (54)	3.373	3.033	0.340	0.00455	3.75	
	P ⁺ H (55)	3.313	2.957	0.356	0.00577	3.50	
	P (56)	3.568	3.297	0.271	0.00003	3.50	
HN_XNH	CH (57)	3.360	3.114	0.246	0.00140	2.30	
NH I	B (58)	2.935	2.638	0.297	0.01834	2.35	
$\langle \rangle \rangle /$	Al (59)	3.129	2.560	0.569	0.02774	3.80	
	SiH (60)	3.482	3.109	0.373	0.00456	3.75	
	P⁺H (61)	3.406	3.024	0.382	0.00636	3.50	
	P (62)	3.610	3.279	0.331	0.00042	3.50	
	44	3.012	2.172	0.840	0.49576	2.30	
	45	3.306	2.491	0.815	0.55237	2.30	

Table 1.9 Spin Densities^a (ρ) and HF/6-31G^{*} Intrabridgehead Distances (BB) in the Carbon-Centered Bridgehead Radicals of 1, 8 and 44-62

* Spin density at the bridgehead opposite to the radical center, calculated by NBO analysis of the HF/6-31G* wave-functions. ^b Δ BB is the difference between the intrabridghead distance of R-H and that of the corresponding bridgehead radical. ^c Sum of the van der Waals radii of the bridgehead atoms.

a favorable arrangement for σ bonding. The pyramidalization is greatest for aluminum compounds (47, 53 and 59), whose carbon-centered radicals exhibit considerably high stabilization energies relative to the *tert*-butyl radical. The calculated bridgehead spin densities (ρ) on aluminum in 47, 53 and 59 are 0.04505, 0.03489 and 0.02774 atomic units, respectively (Table 1.9). Increased spin densities on the bridgehead opposite to the radical center are calculated also for the radicals of the boron-containing compounds 46, 52 and 58, of 0.05324, 0.01836 and 0.01834 atomic units, respectively (Table 1.9).



A good linear correlation of the relative $\triangle BDE$'s with the pyramidalization angle of the radical center, $\angle XC^{\bullet}C$, is obtained for all compounds included in Tables 1.5 to 1.8,



(correlation coefficient 0.96; Figure 1.1). It is difficult, however, to separate the effects of strain energy relief from stabilization by intrabridgehead σ bonding.

As mentioned previously, the difference in the relative BDE's of the bridgehead radicals vs. the reference radicals of bicyclics 1, 51 and 57, can be viewed as an upper limit



Figure 1.1 Plot of pyramidalization angle, ∠XC·C, vs. ΔBDE in the bridgehead radicals of bicyclics 1, 8 and 44-62 (the best fit was taken for the correlation line).

for stabilization by σ -delocalization over the opposed bridgehead. Examination of Δ BDE's from Tables 1.6 to 1.8 reveals that intrabridgehead σ -bonding can amount to as much as 18.1 kcal/mol for the bridgehead radical of 47, which also exhibits considerable shrinkage of the BB distance and substantial inward pyramidalization of the radical center. The strain relief is large when Si or P is placed at the bridgehead, since due to longer Si-C and P-C bonds the methine bridgehead is more strained then in the parent hydrocarbon and one needs to "push" harder to flatten the bridgehead regions. The Δ BDE's are smaller for the compounds from Tables 1.7 and 1.8 relative to those in Table 1.6. In the bridgehead radicals of 52 and 58 it is conceivable that boron is less available for σ delocalization because of π -resonance with the lone pairs of the adjacent oxygen or nitrogen atoms, but it sure looks like aluminum (compounds 47, 53 and 59) offers good opportunities.

Parker et al.^{93a} used empirical force field calculations to predict bridgehead reactivities, in a quest to find systems significantly more reactive than *tert*-butyl chloride. Their data (Table 1.9) suggested 1-chlorobicyclo[4.4.4]tetradecane to be even more reactive than 1-manxyl chloride. Our computational results (HF/6-31G*) show 21.7 kcal/mol strain energy relief when 6 is converted to the corresponding bridgehead radical 64 (Table 1.10). Radical 64, expected to be persistent by analogy with the corresponding bridgehead cation 43, appears to be an excellent objective for experimental investigation.



UHF/6-31G* parameters: $d_1 = d_{CH} = 1.07 \text{ Å}$ $d_2 = d_{HC} = 1.93 \text{ Å}$ $\angle CCH = 104.7^\circ$ $\angle CC \cdot H = 94.3^\circ$

<u></u>		Predicted rate constants ^c				
		Bingham force field		Engler force field		
Compound	k(exp) ^b	ΔSE^{d}	k(calcd)	ΔSE^{d}	k(calcd)	
1-Bicyclo[3.3.3]undecyl Chloride	17.4	-6.77	2.9	-8.36	2.5	
1-Bicyclo[4.4.4]tetradecyl Chloride	-	-14.94	2.0×10 ³	-20.8	1.2×10 ⁵	

Table 1.10 Rate Constants for Reactive Bridgehead Systems^a

^a Reproduced from ref. 93a. ^b Experimental rate of solvolysis in 80% ethanol at 70°C; in s⁻¹. ^c Calculated from the semiempirical correlations of experimental solvolysis rates in bridgehead chlorides with strain energy differences between substrate and the intermediate carbenium ion, estimated with various force fields; in s⁻¹. ^d Strain energy difference between carbenium ion and corresponding hydrocarbon.

Table 1.11 HF/6-31G* Total Energies, Strain, and Bond Dissociation Energies^a

Compound	Total Energy ^b	ΔH_{f}^{c}	SE ^d	BDE ^e
Bicyclo[4.4.4]tetradecane 6	-545.24313	-10.5	52.7	-
1-Bicyclo[4.4.4]tetradecyl Radical 64	-544.65377	11.8	31.0	74.3

⁶ In kcal/mol; structures were fully optimized at the HF/6-31G* level, using Spartan 4.0 (Wavefunction Inc., Irvine, CA). ^b Total energies are given in hartrees, 1 H = 627.5 kcal/mol. ^c Calculated from Wiberg's group equivalents (Wiberg, K. B. J. Org. Chem. 1985, 50, 5285). The BDE estimates were used to calculate values for radical 64. ^d Strain energy; from calculated ΔH_f and Benson's group equivalents (Benson, S. W. Thermochemical Kinetics; John Wiley: New York, 1976) for 6, and from isodesmic reactions vs. *iso*butane/*tert*-butyl radical for 64. ^e Based on BDE (*tert*-Bu-H) = 96.0 kcal/mol (ref. 96).

In a letter addressed to Professor James E. Jackson, McMurry¹⁰¹ wrote that cyclic voltammetry studies on the cation 43 showed a one-electron reduction to generate a persistent radical, but no ESR work was pursued further. The bridgehead bicyclo[4.4.4]-tetradec-1-ene is "hyperstable" and we might see rapid loss of 64 by conventional β -disproportionation. Nevertheless, radical 64 provides a unique opportunity for examination of a caged H abstraction where one can address the question of single- or double-well potential for 1,6-H[•] migration.

Given the expected stability of the bridgehead radicals, significant hydrogen abstraction at other sites in these molecules seems unlikely. Hence, hydrogen abstraction from the parent compounds by *tert*-butoxyl radicals generated photolytically from di-*tert*butyl peroxide should selectively produce the bridgehead radicals. Such species promise to become new examples with unforeseen properties in the already unique chemistry of medium-ring bicyclics.

1.4 References

¹ For hydrogen and alkali radical cations see: (a) Bates, D. R.; Ledsham, K.; Stewart, A. L. *Philos. Trans. R. Soc. London* **1953**, *A246*, 215. (b) Mathur, B. P.; Rothe, E. W.; Reck, G. P.; Lightman, A. J. *Chem. Phys. Lett.* **1978**, *56*, 336. (c) Carlson, N. W.; Taylor, A. J.; Jones, K. M.; Schawlow, A. L. Phys. Rev. **1981**, *A24*, 822. (d) Leytwyler, S.; Herrman, A.; Woeste, L.; Schumacher, E. *Chem. Phys.* **1980**, *48*, 253. For other oneelectron bonded radical cations: (e) Gilbert, T. L.; Wahl, A. C. J. Chem. Phys. **1971**, *55*, 5247 and references therein. (f) Shida, T.; Kubodera, H.; Egawa, Y. Chem. Phys. Lett. **1981**, *79*, 179. (g) Wang, J. T.; Williams, F. J. Chem. Soc., Chem. Commun. **1981**, 666.

² For leading references, see: (a) Asmus, K.-D. In *Sulfur-Centered Reactive Intermediates* in *Chemistry and Biology*; Chatgilialoglu, C., Asmus, K.-D. Eds.; Plenum Press: New York and London, 1990; p 155. (b) Gilbert, B. C. In *Sulfur-Centered Reactive Intermediates in Chemistry and Biology*; Chatgilialoglu, C., Asmus, K.-D. Eds.; Plenum Press: New York and London, 1990; p 135.

³ Harcourt, R. D. Lect. Notes Chem. 1982, 30, 80.

⁴ (a) Gilbert, B. C.; Hodgeman, D. K. C.; Norman, R. D. C. J. Chem. Soc., Perkin Trans. 2 1973, 1748. (b) Illies, A. J.; Livant, P.; McKee, M. L. J. Am. Chem. Soc. 1988, 110, 7980. (c) Ekern, S.; Illies, A.; McKee, M. L.; Peschke, M. J. Am. Chem. Soc. 1993, 115, 12510. (d) Deng, Y.; Illies, A. J.; McKee, M. L.; Peschke, M. J. Am. Chem. Soc. 1995, 117, 420. (e) James, M. A.; McKee, M. L.; Illies, A. J. J. Am. Chem. Soc. 1996, 118, 7836. (f) Chaudhri, S. A.; Mohan, H.; Anklam, E.; Asmus, K.-D. J. Chem. Soc., Perkin Trans. 2 1996, 383.

⁵ (a) Symons, M. C. R. J. Chem. Soc., Perkin Trans. 2 1974, 1618. (b) Nelson, D. J.; Peterson, R. L.; Symons, M. C. R. J. Chem. Soc., Perkin Trans. 2 1977, 2005. (c) Marignier, J. L.; Belloni, J. Chem. Phys. Lett. 1980, 73, 461. (d) Marignier, J. L.; Belloni, J. J. Phys. Chem. 1981, 85, 3100. (e) Surdhar, P. S.; Armstrong, D. A. J. Phys. Chem. 1987, 91, 6532.

⁶ (a) Gilbert, B. C.; Marriott, P. R. J. Chem. Soc., Perkin Trans. 2 1979, 1425. (b) Giles, J. R. M.; Roberts, B. P. J. Chem. Soc., Perkin Trans. 2 1980, 1497. (c) Franzi, R.; Geoffroy, M.; Reddy, M. V. V. S. J. Phys. Chem. 1987, 91, 3187.

⁷ (a) Ganghi, N.; Wyatt, J. L.; Symons, M. C. R. J. Chem. Soc., Chem. Commun. 1986, 1424. (b) Alder, R. W. Acc. Chem. Res. 1983, 16, 321 and references therein. (c) Alder, R. W.; Bonifacic, M.; Asmus, K.-D. J. Chem. Soc., Perkin Trans. 2 1986, 277. (d) Dinnocenzo, J. P.; Banach, T. E. J. Am. Chem. Soc. 1988, 110, 971. (e) Gerson, F.; Knöbel, J.; Buser, U.; Vogel, E.; Zehuder, M. J. Am. Chem. Soc. 1986, 108, 3781.

⁸ (a) Lyons, A. R.; Symons, M. C. R. J. Chem. Soc., Faraday Trans. 2 1972, 68, 1589.
(b) Symons, M. C. R.; McConnachie, G. D. G. J. Chem. Soc., Chem. Commun. 1982, 851.

⁹ Hudson, R. L.; Williams, F. J. Phys. Chem. 1980, 84, 3483.

¹⁰ Nishikada, K.; Williams, F. Chem. Phys. Lett. 1975, 34, 302.

¹¹ (a) Mohan, H.; Asmus, K.-D. J. Phys. Chem. 1988, 92, 118. (b) Livant, P.; Illies, A. J. Am. Chem. Soc. 1991, 113, 1510.

¹² (a) Musker, W. K.; Hirschon, A. S.; Doi, J. T. J. Am. Chem. Soc. 1978, 100, 7754. (b) Asmus, K.-D.; Bahemenn, D.; Bonifacic, M.; Gillis, H. A. Discuss. Faraday Soc. 1977, 63, 1748. (c) Symons, M. C. R.; Petersen, R. L. J. Chem. Soc., Faraday Trans. 1978, 210. (d) Bonifacic, M.; Asmus, K.-D. J. Chem. Soc., Perkin Trans. 2 1980, 758. (e) Asmus, K.-D.; Goebl, M.; Hiller, K. O.; Mahling, S.; Moning, J. J. Chem. Soc., Perkin Trans. 2 1985, 641. (f) Raynor, J. B.; Rowland, I. J.; Symons, M. C. R. J. Chem. Soc.,

Dalton Trans. 1987, 421. (g) Symons, M. C. R.; Chanfra, H.; Alder, R. W. J. Chem. Soc., Chem. Commun. 1988, 844. (h) Breslow, R.; Brandl, M.; Hunger, J.; Turro, N.; Cassidy, K.; Krogh-Jespersen, K.; Westbrook, J. D. J. Am. Chem. Soc. 1987, 109, 7204. (i) Bobrowski, K.; Holcman, J. J. Phys. Chem. 1989, 93, 6381. (j) Abu-Raqabah, A.; Symons, M. C. R. J. Am. Chem. Soc. 1990, 112, 8614. (k) Abu-Raqabah, A.; Symons, M. C. R. J. Chem. Soc., Faraday Trans. 1990, 86, 3293. (l) Kishore, K.; Asmus, K.-D. J. Phys. Chem. 1991, 95, 7233.

¹³ (a) Williams, F.; Sprague, E. D. Acc. Chem. Res. 1982, 12, 408. (b) Shida, T.; Haselback, E.; Bally, T. Acc. Chem. Res. 1984, 17, 180-186.

¹⁴ (a) Asmus, K.-D. Acc. Chem. Res. 1979, 12, 436. (b) Asmus, K.-D.; Janata, E. In The Study of Fast Processes and Transient Species by Electron Pulse Radiolysis; Baxendale, J. H., Busi, F. Eds.; Reidel, Dordrecht, 1982.

¹⁵ Meot-Ner, M. Acc. Chem. Res. 1984, 5, 186.

¹⁶ (a) Pauling, L. J. Am. Chem. Soc. 1931, 53, 1367. (b) Pauling, L. J. Chem. Phys. 1933, 1, 56.

¹⁷ Meot-Ner, M.; Hamlet, P.; Hunter, E. P.; Field, F. H. J. Am. Chem. Soc. 1978, 100, 5466.

¹⁸ Baird, N. C. J. Chem. Educ. 1977, 54(5), 291.

¹⁹ Harcourt, R. D. J. Phys. B 1987, 20, 617.

²⁰ Gilbert, T. L.; Wahl, A. C. J. Chem. Phys. 1971, 55, 5247 and references therein. For an X-ray structure of a salt of Xe₂⁻⁺, see: Seppelt, K.; Drews, T. Angew. Chem. Int. Ed. Engl. 1997, 36, 273.

²¹ Meot-Ner, M.; Field, F. H. J. Chem. Phys. 1974, 61(9), 3742.

²² (a) Nelsen, S. F.; Alder, R. W.; Sessions, R. B.; Asmus, K.-D.; Hiller, K.-O.; Gobl, M. *J. Am. Chem. Soc.* 1980, 102, 1429. (b) Alder, R. W.; Arrowsmith, R. J.; Casson, A.; Sessions, R. B.; Heilbronner, E.; Kovač, B.; Huber, H.; Taagepera, M. *J. Am. Chem. Soc.* 1981, 103, 6137.

²³ For recent theoretical papers see: (a) McKee, M. L. J. Phys. Chem. **1992**, 96, 1675 and references therein. (b) Ekern, S.; Illies, A.; McKee, M. L. J. Am. Chem. Soc. **1993**, 115, 12510. (c) Hiberty, P. C.; Humbel, S.; Danovich, D.; Shaik, S. J. Am. Chem. Soc. **1995**, 117, 9003.

²⁴ Clark, T. J. Am. Chem. Soc. 1988, 110, 1672.

²⁵ Clark, T. J. Comput. Chem. 1983, 4, 404.

²⁶ Gill, P. M. W.; Radom, L. J. Am. Chem. Soc. 1988, 110, 4931.

²⁷ Janssen, R. A. J.; Aagaard, O. M.; van der Woerd, M. J.; Buck, H. M. Chem. Phys. Lett. **1990**, 171, 127.

²⁸ Ganghi, N.; Wyatt, J. L.; Symons, M. C. R. J. Chem. Soc., Chem. Commun. 1986, 1424.

²⁹ (a) Alder, R. W.; Sessions, R. B.; Symons, M. C. R. J. Chem. Res., Synop. 1981, 82.
(b) Symons, M. C. R.; Chandra, H.; Alder, R. W. J. Chem. Soc., Chem. Commun. 1988, 844.

³⁰ (a) Jang, S.-H.; Bertsch, R. A.; Jackson, J. E.; Kahr, B. *Mol. Cryst. Liq. Cryst.* 1992, 211, 289. (b) Jang, S.-H.; Lee, H.-I.; McCracken, J.; Jackson, J. E. *J. Am. Chem. Soc.* 1993, 115, 12623. (c) Dostal, S.; Stoudt, S. J.; Fanwick, P.; Sereatan, W. F.; Kahr, B.; Jackson, J. E. *Organometallics* 1993, 12.

³¹ For reviews on intrabridgehead chemistry, see (a) Alder, R. W. Acc. Chem. Res. 1983, 16, 321. (b) Alder, R. W. Tetrahedron 1990, 46, 683.

³² (a) McMurry, J. E.; Hodge, C. N. J. Am. Chem. Soc. 1984, 106, 6450. (b) McMurry, J. E.; Lectka, T.; Hodge, C. N. J. Am. Chem. Soc. 1989, 111, 8867. (c) Sorensen, T. S.; Whitworth, S. M. J. Am. Chem. Soc. 1990, 112, 8135.

³³ Alder, R. W.; Moss, R. E.; Sessions, R. B. J. Chem. Soc., Chem. Commun. 1983, 997.

³⁴ (a) Voronkov, M. G.; Dyakov, V. M.; Kirpichenko, S. V. J. Organomet. Chem. 1982, 233, 1. (b) Müller, E. Ph.D. Thesis, ETH, Zürich, 1982. (c) Verkade, J. Acc. Chem. Res. 1993, 26, 483. (d) Verkade, J. Coord. Chem. Rev. 1994, 137, 233.

³⁵ (a) Maier, W. F.; Schleyer, P. v. R. J. Am. Chem. Soc. 1981, 103, 1891. (b) Schleyer, P. v. R.; McEwen, A. B. J. Am. Chem. Soc. 1986, 108, 3951.

³⁶ (a) Leonard, N. J.; Coll, J. C.; Wang, A. H. J.; Missavage, R. J.; Paul, I. C. J. Am. Chem. Soc. 1971, 93, 4628. (b) Wang, A. H.; Missavage, R. J.; Byrn, S. R.; Paul, I. C. J. Am. Chem. Soc. 1972, 94, 7100.

³⁷ Saunders, M.; Jiménez-Vázquez, H. A. Chem. Rev. 1991, 91, 375.

³⁸ Korcek, S.; Chenier, J. H. B.; Howard, J. A.; Ingold, K. U. Can. J. Chem. 1972, 50, 2285.

³⁹ The strain energy is the difference between the experimental (calculated) heat of

formation of a compound and that of a hypothetically "strainless" model.

⁴⁰ Alder, R. W.; East, S. P. Chem. Rev. 1996, 96, 2097.

⁴¹ Saunders, M. J. Comput. Chem. 1989, 10, 203.

⁴² Pedley, J. B.; Naylor, R. D.; Kirby, S. B. In *Thermochemical Data of Organic Compounds*, 2nd ed., Chapman and Hall: London and New York, 1986.

⁴³ (a) Doyle, M.; Parker, W. *Tetrahedron Lett.* 1970, 42, 3619. (b) Leonard, N. J.; Coll, J. C. J. Am. Chem. Soc. 1970, 92, 6685. (c) Coll, J. C.; Crist, D. R.; Barrio, M. d. C. G.; Leonard, N. J. J. Am. Chem. Soc. 1972, 94, 7092.

⁴⁴ For the crystal structure of manxine hydrochloride see refs. 35 a-b. The crystal structure of bicyclo[3.3.3]undecane-1,5-diol is described in: Murray-Rust, P.; Murray-Rust, J.; Watt, C. I. F. *Tetrahedron* 1980, *36*, 2799.

⁴⁵ Gundersen, G.; Murray-Rust, P.; Rankin, D. W. H.; Seip, R.; Watt, C. I. F. Acta Chem. Scand. 1983, A37, 823.

⁴⁶ Wada, T.; Kishida, E.; Tomiie, Y.; Suga, H.; Seki, S.; Nitta, I. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 1317.

⁴⁷ Alder, R. W.; Arrowsmith, R. J. J. Chem. Res., Synop. 1980, 163; J. Chem. Res., Miniprint 1980, 2301.

⁴⁸ Aue, D. H.; Webb, H. M.; Bowers, M. T. J. Am. Chem. Soc. 1975, 97, 4136.

⁴⁹ Alder, R. W.; Orpen, A. G.; White, J. M.; Saunders, M. unpublished results.

⁵⁰ Alder, R. W.; Arrowsmith, R. J.; Boothby, C. St.; Heilbronner, E.; Zhong-Zhi, Y. J. Chem. Soc., Chem. Commun. 1982, 940.

⁵¹ (a) Nitta, I. Acta Crystallogr 1960, 13, 1960. For a complete X-ray crystal analysis, see ref. 45 and: (b) Weiss, G. S.; Parkes, A. S.; Nixon, E. R.; Hughes, R. E. J. Chem. Phys. 1964, 41, 3759.

⁵² For proton affinities and photoelectron spectra of bicyclic amines and diamines, including 14, see: Alder, R. W.; Arrowsmith, R. J.; Casson, A.; Sessions, R. B.; Heilbronner, E.; Kovač, B.; Huber, H.; Taagepera, M. J. Am. Chem. Soc. 1981, 103, 6137.

⁵³ For the X-ray Structure of 15, see: Alder, R. W.; Orpen, A. G.; Sessions, R. B. J. Chem. Soc., Chem. Commun. 1983, 999.

⁵⁴ Wiberg, K. B. Acc. Chem. Res. 1984, 17, 379.

⁵⁵ A single crystal X-ray analysis of [1.1.1]propellane is described in: Seiler, P. *Helv. Chim. Acta* 1990, 73, 1574. For the structure of [4.4.4]propellane by X-ray analysis, see: Ermer, O.; Gerdil, R.; Dunitz, J. D. *Helv. Chim. Acta* 1971, 54, 2476.

⁵⁶ For reviews on main group atranes, see ref. 33. For a review on metallatranes, see: Voronkov, M. G.; Baryshok, V. P. J. Organomet. Chem. 1982, 239, 199. For recent papers on transition metal atranes, see: (a) Scheer, M.; Müller, J.; Häser, M. Angew. Chem., Int. Ed. Engl. 1996, 35, 2492. (b) Schrock, R. R.; Cummins, C. C.; Wilhelm, T.; Lin, S.; Reid, S. M.; Kol, M.; Davis, W. M. Organometallics 1996, 15, 1470. (c) Duan, Z.; Verkade, J. G. Inorg. Chem. 1995, 34, 1576. (d) Zanetti, N.; Schrock, R. R.; Davis, W. M. Angew. Chem., Int. Ed. Engl. 1995, 34, 2044. (e) Scheer, M.; Schuster, K.; Budzichowski, T. A.; Chisholm, M. H.; Streib, W. E. J. Chem. Soc., Chem. Commun. 1995, 1671. (f) Laplaza, C. E.; Davis, W. M.; Cummins, C. C. Angew. Chem., Int. Ed. Engl. 1995, 34, 2042. (g) Kol, M.; Schrock, R. R.; Kempe, R.; Davis, W. M. J. Am. Chem. Soc. 1994, 116, 4382. (h) Shih, K.-Y.; Schrock, R. R.; Davis, W. M. Organometallics 1992, 11, 1452. (j) Nugent, W. A. J. Am. Chem. Soc. 1992, 114, 2768.

⁵⁷ Baltkais, J. J.; Voronkov, M. G.; Zelchan, G. I. Latv. Kim. Z. 1964, N2, 102.

58 Voronkov, M. G. Top. Curr. Chem. 1979, 84, 77.

⁵⁹ Voronkov, M. G. Pure Appl. Chem. 1966, 13, 35.

⁶⁰ Structural parameters for 46 crystallographically determined silatranes are provided by: Hencsei, P.; Parkanyi, L. In *Reviews on Silicon, Germanium, Tin and Lead Compounds*; Gielen, M. Ed.; Scient. Pub. Div. Freund Pub. House: Tel-Aviv; Vol. VIII, No. 2 and 3; p 191. Also, see: Hencsei, P. *Struct. Chem.* **1991**, *2*, 21.

⁶¹ For a comprehensive review on silatranes, see ref. 33a and references therein. Also, see:
(a) Tandura, S. N.; Voronkov, M. G.; Alekseev, N. V. Top. Curr. Chem. 1986, 131, 99.
(b) Voronkov, M. G.; Baryshok, V. P.; Petukhov, L. P.; Rakhlin, V. I.; Mirskov, R. G.; Pestunovich, V. A. J. Organomet. Chem. 1988, 358, 39. (c) Lukevits, E.; Pudova, O.; Sturkovich, R. In Molecular Structure of Organosilicon Compounds; Ellis Horwood: Chichester, 1989; p 262. (d) Cervean, G.; Chuit, C.; Corrin, R. J. P.; Nayyar, N. K.; Reye, C. J. Organomet. Chem. 1990, 389, 159. (e) Chuit, C.; Corrin, R. J. P.; Reye, C.; Young, J. C. Chem. Rev. 1993, 93, 1371.

⁶² (a) Sidorkin, S. F.; Pestunovich, V. A.; Voronkov, M. G. Russ. Chem. Rev. 1980, 49, 414. (b) Greenberg, A.; Wu, G. Struct. Chem. 1990, 1, 79.

63 (a) Zhu, J.; Sun, X.; Wu, H.; Jing, L.; Chen, P.; Wu, G. Acta Chim. Sin. 1985, 43,

1151. (b) Iwamiya, J. H.; Maciel, G. E. J. Am. Chem. Soc. 1993, 115, 6835.

⁶⁴ Gray, R. C.; Hercules, D. M. Inorg. Chem. 1977, 16, 1426.

⁶⁵ (a) Gradock, S.; Ebsworth, E. A.; Muiry, J. B. J. Chem. Soc., Dalton Trans. 1975, 25.
(b) Wang, D.; Zhang, D.; Lu, K.; Wu, G. Sci. Sin., Ser. B 1982, 10, 875. (c) Wang, D.; Lu, K.; Wu, Y.; Wu, G. Chem. Bull. (Beijing) 1982, 10, 12. (d) Wang, D.-X.; Zhang, D.; Lu, K.-J.; Wu, Y.-X.; Wu, G.-L. Sci. Sin., Ser. B 1983, 26, 9.

⁶⁶ (a) Brodskaya, L. I.; Voronkov, M. G. Bull. Acad. Sci. USSR, Div. Chem. 1986, 7, 1694. (b) Voronkov, M. G.; Klyuchnikov, V. A.; Korchagina, A. N.; Danilova, T. F.; Shvets, G. N.; Baryshok, V. P.; D'yakov, V. M. Bull. Acad. Sci. USSR, Div. Chem. 1986, 9, 1976.

⁶⁷ (a) Gudat, D.; Verkade, J. G. Organometallics 1989, 8, 2772. (b) Gudat, D.; Daniels, L. M.; Verkade, J. G. J. Am. Chem. Soc. 1989, 111, 8520. (c) Gudat, D.; Daniels, L. M.; Verkade, J. G. Organometallics 1990, 9, 1464.

⁶⁸ (a) Lensink, C.; Xi, S. K.; Daniels, L. M.; Verkade, J. G. J. Am. Chem. Soc. **1989**, 111, 3478. (b) Xi, S. K.; Schmidt, H.; Lensink, C.; Kim, S.; Wintergrass, D.; Daniels, L. M.; Jacobson, R. A.; Verkade, J. G. Inorg. Chem. **1990**, 29, 2214. (c) Tang, J.-S.; Laramay, M. A. H.; Young, V.; Ringrose, S.; Jacobson, R. A.; Verkade, J. G. J. Am. Chem. Soc. **1992**, 114, 3129.

⁶⁹ (a) Millbrath, D. S.; Verkade, J. G. J. Am. Chem. Soc. 1977, 99, 6607. (b) Müller, E.; Bürgi, H.-B. Helv. Chim. Acta 1987, 70, 1061. (c) Laramay, J. G.; Verkade, J. G. J. Am. Chem. Soc. 1990, 112, 9421.

⁷⁰ (a) Laramay, M. A. H.; Verkade, J. G. Z. Anorg. Allg. Chem. 1991, 605, 163. (b) Tang, J.-S.; Verkade, J. G. Tetrahedron Lett. 1993, 34, 2903. (c) Tang, J.-S.; Verkade, J. G. J. Am. Chem. Soc. 1993, 115, 1660.

⁷¹ (a) Tang, J.-S.; Verkade, J. G. Angew. Chem., Int. Ed. Engl. 1993, 32, 896. (b) Tang, J.-S.; Mohan, T.; Verkade, J. G. J. Org. Chem. 1994, 59, 4931.

⁷² D'Sa, B. A.; Verkade, J. G. J. Am. Chem. Soc. 1996, 118, 12832.

⁷³ See refs. 30 and 39. Also, see: (a) Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215. (b) Alder, R. W.; Heilbronner, E.; Honegger, E.; McEwen, A. B.; Moss, R. E.; Olefirowicz, E.; Petillo, P. A.; Sessions, R. B.; Weisman, G. R.; White, J. M.; Yang, Z.-Z. *J. Am. Chem. Soc.* **1993**, *115*, 6580.

⁷⁴ (a) Alder, R. W.; Goode, N. C.; King, T. J.; Mellor, J. M.; Miller, B. W. J. Chem. Soc., Chem. Commun. 1976, 173. (b) Alder, R. W.; Gill, R.; Goode, N. C. J. Chem. Soc., Chem. Commun. 1976, 973.

⁷⁵ Alder, R. W.; Sessions, R. B. J. Am. Chem. Soc. 1979, 101, 3651.

⁷⁶ Gerson, F.; Knobel, J.; Buser, U.; Vogel, E.; Zehnder, M. J. Am. Chem. Soc. 1986, 108, 3781.

⁷⁷ (a) Alder, R. W.; Sessions, R. B.; Mellor, J. M.; Rawlins, M. F. J. Chem. Soc., Chem. Commun. 1977, 747. (b) Symons, M. C. R.; Smith, I. G. J. Chem. Res., Synop. 1979, 382. (c) Kirste, B.; Alder, R. W.; Sessions, R. B.; Bock, M.; Kurreck, H.; Nelsen, S. F. J. Am. Chem. Soc. 1985, 107, 2635.

⁷⁸ McKinney, T. M.; Geske, D. H. J. Am. Chem. Soc. 1965, 87, 3013.

⁷⁹ Alder, R. W.; Sessions, R. B.; Bennet, A. J.; Moss, R. E. J. Chem. Soc., Perkin Trans. 1 1982, 603.

⁸⁰ (a) Alder, R. W.; Sessions, R. B. J. Am. Chem. Soc. 1979, 101, 3651. (b) Alder, R. W.; Orpen, A. G.; White, J. M. J. Chem. Soc., Chem. Commun. 1985, 949.

⁸¹Musker, W. K. Acc. Chem. Res. 1980, 13, 200.

⁸²(a) Alder, R. W.; Ganter, C.; Harris, C. J.; Orpen, A. G. J. Chem. Soc., Chem. Commun.
1992, 1170. (b) Alder, R. W.; Ganter, C.; Harris, C. J.; Orpen, A. G. J. Chem.
Soc., Chem. Commun. 1992, 1172.

⁸³ Alder, R. W.; Ganter, C.; Harris, C. J.; Orpen, A. G. Phosphorus, Sulfur, Silicon 1993, 77, 234.

⁸⁴ Hamerlinck, J. H. H.; Schipper, P.; Buck, H. M. J. Am. Chem. Soc. 1983, 105, 385.

⁸⁵ Roberts, B. P. Tetrahedron Lett. 1983, 24, 3377.

⁸⁶ (a) Saunders, M.; Telkowski, L.; Kates, M. R. J. Am. Chem. Soc. 1977, 99, 8070. (b) Altman, L. J.; Laungani, D.; Gunnarsson, G.; Wennerstrom, H.; Forsen, S. J. Am. Chem. Soc. 1978, 100, 8264.

⁸⁷ Alder, R. W.; Moss, R. E.; Sessions, R. B. J. Chem. Soc., Chem. Commun. 1983, 1000.

⁸⁸ (a) McMurry, J. E.; Lectka, T. Acc. Chem. Res. 1992, 47. (b) McMurry, J. E.; Lectka, T. J. Am. Chem. Soc. 1993, 115, 10167.

⁸⁹ Kirchen, R. P.; Sorensen, T. S. J. Chem. Soc., Chem. Commun. 1978, 769.

⁹⁰ Sorensen, T. S.; Whitworth, S. M. J. Am. Chem. Soc. 1990, 112, 8135.

⁹¹ (a) McMurry, J. E.; Lectka, T.; Hodge, C. N. J. Am. Chem. Soc. 1989, 111, 8867. (b) McMurry, J. E.; Lectka, T. J. Am. Chem. Soc. 1990, 112, 869.

⁹² (a) Gleicher, G. J.; Schleyer, P. v. R. J. Am. Chem. Soc. 1967, 89, 583. (b) Bingham, R. C.; Schleyer, P. v. R. J. Am. Chem. Soc. 1971, 93, 3189. (c) Bentley, T. W.; Roberts, K. J. J. Org. Chem. 1985, 50, 5852. (d) Müller, P.; Blanc, J.; Mareda, J. Helv. Chim. Acta 1986, 69, 635. (e) Müller, P.; Mareda, J. Helv. Chim. Acta 1987, 70, 1017.

⁹³ (a) Parker, W.; Tranter, R. L.; Watt, C. I. F.; Chang, L. W. K.; Schleyer, P. v. R. J. Am. Chem. Soc. 1974, 96, 7121. (b) Lomas, J. S.; D'Souza, M. J.; Kevill, D. N. J. J. Am. Chem. Soc. 1995, 117, 5891.

⁹⁴ Dewar, M. J. S.; Theil, W. J. Am. Chem. Soc. 1977, 99, 4899.

95 Hariharan, P. C.; Pople, J. A. Chem. Phys. Lett. 1972, 66, 217.

⁹⁶ All structures were fully optimized employing the computer program Spartan; see: Hehre, W. J.; Huang, W. W.; Burke, L. D.; Shusterman, A. J. A *SPARTAN* Tutorial, version 4.0, Wavefunction Inc.: Irvine, CA, 1995. The BDE estimates are based upon: BDE_{tert-butyl-H} = 96.0 kcal/mol, see Gutman, D. *Acc. Chem. Res.* **1990**, *23*, 375; $\Delta H_{f,MNDO}$ (*iso*butane) = -26.8 kcal/mol; $\Delta H_{f,MNDO}$ (*tert*-butyl radical) = -10.1 kcal/mol; and the HF/6-31 G* total energies for *iso*butane -157.29898 H and *tert*-butyl radical -156.67501 H, respectively.

⁹⁷ (a) Grotewald, J.; Lissi, E. A.; Scaiano, J. C. J. Chem. Soc. B 1971, 1187. (b) Burkey, T. J.; Castelhano, A.; Griller, D.; Lossing, F. P. J. Am. Chem. Soc. 1983, 105, 4701. (c) Crans, D.; Clark, T.; Schleyer, P. v. R. Tetrahedron Lett. 1980, 21, 3681.

⁹⁸ Bank, S.; Cleveland, W. K. S.; Griller, D.; Ingold, K. U. J. Am. Chem. Soc. 1979, 101, 3409.

⁹⁹ (a) McKinney, T. M.; Geske, D. H. J. Am. Chem. Soc. 1965, 87, 3013. (b) Eastland, G. W.; Symons, M. C. R. Chem. Phys. Lett. 1977, 45, 422.

¹⁰⁰ Bondi, A. J. Phys. Chem. 1964, 68, 441.

¹⁰¹ McMurry, J. Private Communication 1988.

"When you have eliminated the impossible, whatever remains, however improbable, is the truth" A. Conan Doyle

CHAPTER 2

1-MANXYL: A PERSISTENT TERTIARY ALKYL RADICAL THAT DISPROPORTIONATES VIA ε-HYDROGEN ABSTRACTION

Abstract: Bicyclo[3.3.3]undecane (manxane) shows high bridgehead reactivity. With atmospheric oxygen it autoxidizes to form a mixture of bridgehead peroxides and hydroperoxides. 1-Manxyl chloride undergoes solvolysis ca. 10⁴ times faster than tertbutyl chloride. The enhanced reactivity at these sites is due to relief of strain when the bridgehead converts to a trigonal center, as indicated by earlier molecular mechanics and new ab initio results. The 1-manxyl radical 2 has now been generated in solution from manxane 1 by hydrogen abstraction with *tert*-butoxyl radicals. The EPR spectrum of 2, which shows anomalously low β hyperfine coupling constants, is reported here for the first time. Continuous-wave ENDOR experiments have helped to confirm the values of the hyperfine splittings. The decay of the radical is bimolecular with a rate constant of 0.5 $M^{-1}s^{-1}$ in methylcyclopentane at 23 °C; one of the decay products of 2 has been identified as the [3.3.3] propellane 31, formed presumably by an unusual ε -disproportionation. 1-Manxyl is the first example of a persistent alkyl radical whose exceptionally long lifetime arises not from steric protection, but from the high strain of all its decomposition products.

Bicyclo[3,3,3]undecane (manxane)¹ 1 was first synthesized in 1970 independently by Leonard et al.² and by Doyle et al.³ as the prototype compound which comprises together three eight-membered rings. The conformations of manxane and some of its derivatives have been studied by dynamic NMR³ and molecular mechanics⁴. Calculations point to the C_{3h} boat-chair conformation as the energy minimum, but even this arrangement is strained in contrast to the flexibility observed for most monocyclic eight-membered rings. Confirmation of the high ground strain of manxane has been provided by experimental measurements of its enthalpy of formation, $\Delta H_f(C_{11}H_{20}, g) = -21.2 \text{ kcal/mol.}^5$ One structural manifestation of the strain is a flattening of the bridgehead regions, accompanied by widening of the angles in the bridges. Bridgehead flattening in 1 has been related to increased p character in the methine C-H bond, and this hybridization change is reflected in the low value of the corresponding ${}^{1}J_{C-H}$ (120.0 Hz). X-ray structures of 1azabicyclo[3.3.3]undecane hydrochloride⁶ and bicyclo[3.3.3]undecane-1,5-diol⁷ show the expected structural features. The electron-diffraction data from manxane vapors confirmed the C_{3h} molecular symmetry.⁸ At room temperature manxane is in rapid conformational equilibrium between two degenerate forms. In a temperature dependence study of the ¹H



NMR spectrum of 1, Doyle et al.³ obtained the "frozen" spectrum, corresponding to the slow exchange between 1a and 1b, at -80 °C with $CDCl_3/CD_2Cl_2$ (1:1) as solvent, and calculated a free energy of activation for the inversion process of 11 ± 2 kcal/mol.

Our interest in through-space perturbation of unpaired electron centers⁹ has drawn us to the rich potential of interbridgehead chemistry, for which the bicyclo[3.3.3]undec-1yl, or 1-manxyl, radical 2 is a key reference species. With its 27.2 kcal/mol strain energy (SE) (Table 2.1) and high bridgehead reactivity,¹⁰ manxane 1 readily undergoes hydrogen abstraction by *tert*-butoxyl radicals to yield radical 2. Herein we present EPR, ENDOR, spin trapping, product studies, and ab initio results for the 1-manxyl radical 2.



This sterically open radical shows remarkable persistence and unexpectedly small β hydrogen hyperfine couplings.

2.1 Results and Discussion

Manxane 1 was prepared in a multistep synthesis involving double-ring expansion of the short bridge of bicyclo[3.3.1]nonan-9-one 8, following Leonard et al.², with modifications to obtain an overall optimized yield (Scheme 2.1) of 2.2%. Bicyclo[3.3.1]nonan-9-one 8 was made from cyclohexanone 3 in four steps according to the method of Foote and




Woodward¹¹. The morpholine enamine of cyclohexanone **4** was condensed with acrolein in THF to give 2-N-morpholinyl-bicyclo[3.3.1]nonan-9-one 5. The mechanism of this remarkable condensation is somewhat obscure; at some stage in the reaction the nitrogen and oxygen functions must exchange positions.^{11b} Conversion of the aminoketone to the *N*-oxide 6 by oxidation with hydrogen peroxide in methanol followed by pyrolysis at 120 °C (Cope elimination) vielded bicyclo[3.3.1]non-2-en-9-one 7, which was hydrogenated over Pd/C 10% to give 8. Ring expansion of bicyclo[3.3.1]nonan-9-one 8 with methanolic diazomethane afforded bicyclo[3.3.2]decan-9-one 9. The original experimental procedures of Leonard et al.² for conversion of 9 to 9-methylenebicyclo-[3.3.2]decane 10 and its subsequent epoxidation to 11 were replaced by a revised Wittig reaction for methylenation of sterically hindered ketones with tert-BuOK and $(C_6H_5)_3$ CH₃PBr in refluxing benzene,¹² and respectively, by epoxidation with *m*chloroperbenzoic acid in an alkaline biphasic system (NaHCO₃, H₂O/CHCl₃)¹³. The resulting 9-epoxymethylenebicyclo[3.3.2]decane 11 was cleaved by sodium azide in DMF to the hydroxyazide 12, and reduction in ethanol with hydrogen over Adams' catalyst, followed by Demianov-Tiffeneau ring expansion of the hydrochloride salt 13 yielded a 3:1 mixture of bicyclo[3.3.3]undecan-9- and 10-ones 14 and 15. Wolff-Kishner reduction of the ketone mixture afforded 1.

Manxane 1 is autoxidized by air to a mixture of bridgehead peroxides and hydroperoxides, and 1-manxyl chloride undergoes solvolysis ca. 10⁴ times faster than *tert*-butyl chloride, consistent with a molecular mechanics estimate of 6.8 kcal/mol strain relief for bridgehead conversion to a trigonal center.¹⁰ Given the enhanced reactivity of the

bridgehead sites, hydrogen atom abstraction from manxane 1 by photochemically generated *tert*-butoxyl radicals provides a convenient technique for generating the bridgehead radical 2.¹⁴

tert-BuO-O-tert-Bu
$$\xrightarrow{n_0}$$
 2 tert-BuO.

$$tert$$
-BuO[•] + Manxane (1) \rightarrow 1-Manxyl[•] (2) + $tert$ -BuOH

Reaction of 1-manxyl chloride with triethylsilyl (Et_3Si) or tri-*n*-butyl-tin (*n*-Bu₃Sn) radicals provides in principle a direct route to 2;¹⁵ the bridgehead chloride, however, is troublesome to synthesize, has never been isolated pure, and solvolyzes completely to the alcohol on exposure to air.¹⁰ This route was therefore not attempted.

Cyclopropane, with C-H bond dissociation energies (BDE's) of 106.3 kcal/mol,¹⁶ is a convenient solvent for the hydrogen abstraction procedure.¹⁴ Figure 2.1 shows the EPR spectrum obtained from photolysis of a cyclopropane solution of manxane 1 and di*tert*-butyl peroxide at -55 °C. Identical EPR spectra arise in toluene or methylcyclopentane solutions, and in neat di-*tert*-butyl peroxide. On shuttering the photolysis beam, the spectrum of 2 decays extremely slowly, i.e., the radical lifetimes are, depending on temperature and solvent, on the order of days or even weeks. The photolysis temperature can be widely varied; in cyclopropane the best EPR spectra are obtained between -60 and -40 °C, but in toluene and neat di-*tert*-butyl peroxide, room temperature gives the optimum experimental conditions. Remarkably, the EPR spectrum of 2 in frozen toluene, obtained after gradual cooling of a toluene solution of 1-manxyl radicals, displays all the features of the spectrum recorded in liquid phase.



Figure 2.1 (a) EPR spectrum (9.1 GHz) of 1-manxyl radical in cyclopropane at -55 °C (g = 2.0024). (b) Computer simulation.

We assign this EPR spectrum to 1-manxyl radical 2 on the following grounds: (1) the radical is tertiary, showing neither an α C-H hyperfine coupling constant, nor a corresponding splitting in the 2,4,6-tri-*tert*-butyl-nitrosobenzene spin trapping product (see section 2.3); (2) simulation of the spectrum (Figure 2.1) requires five different sets of three equivalent protons; (3) the radical decays via an extraordinarily slow bimolecular process, and trapping by addition of *n*-Bu₃SnH immediately after photolysis turns off production of its disproportionation products, of which one is [3.3.3]propellane (see section 2.2); (4) the known autoxidation of 1 is specific for the bridgehead site.

With 18 secondary and only 2 tertiary C-H bonds in 1, significant secondary hydrogen abstraction might be expected on statistical grounds, but no evidence for the secondary 2- and 3-manxyl radicals, 16 and 17, is seen in the EPR spectra under any



conditions. Generally, in compounds where more than one type of hydrogen atoms are present, the EPR spectrum observed belongs to that radical produced by hydrogen abstraction from the weakest bond.¹⁷ The BDEs of the C-H bonds in manxane were estimated at HF/6-31G* level from isodesmic reactions vs. *iso*butane/*tert*-butyl radical for 2, and propane/*iso*propyl radical for 16 and 17.¹⁸ Besides being the unique tertiary sites in manxane, the bridgeheads also afford the greatest strain relief upon hydrogen abstraction, resulting in BDE differences of 6.9 and 7.9 kcal/mol vs. 16 and 17, respectively (Table

Compound	Total Energy ^b	ΔH_{f}^{c}	SE ^d	ΔSE [°]	BDE
Manxane 1	-428.17907	-20.4 (-21.2) ⁸	28.0 (27.2)		
1-Manxyl Radical 2	-427.56808	14.6	19.9	-7.3	87.9
2-Manxyl Radical 16	-427.55704	21.5	24.6	-2.6	94.8
3-Manxyl Radical 17	-427.55538	22.5	25.6	-1.6	95.8

 Table 2.1 Calculated Heats of Formation, Strain Energies and Bond Dissociation

 Energies^a

^a In kcal/mol; structures were fully optimized at HF/6-31G* level, using Spartan 4.0 (Wavefunction Inc., Irvine, CA).

^bTotal energies are given in hartrees, 1 H = 627.5 kcal/mol.

^c Calculated (experimental) from Wiberg's group equivalents (Wiberg, K. B. J. Org. Chem. 1985, 50,

5285) for manxane. The BDE estimates were used to calculate heats of formation for the product radicals. ^d Strain energy; from calculated (experimental) ΔH_f and Benson's group equivalents (Benson, S. W. *Thermochemical Kinetics*; John Wiley: New York, 1976) for manxane, and from isodesmic rections vs. *iso*butane/*tert*-butyl radical for 1-manxyl radical, and propane/*iso*propyl radical for 2- and 3-manxyl radicals.

^e Defined vs. SE of manxane.

^f Based on BDE (*t*-Bu-H) = 96.0 kcal/mol (Gutman, D. Acc. Chem. Res. **1990**, 23, 375), and BDE (*iso*-Pr-H) = 98.2 kcal/mol (Russell, J. J.; Seetula, J. A.; Gutman, D. J. Am. Chem. Soc. **1988**, 110, 3092). ⁸ Ref. 5. 2.1). A recent model relating activation energies to reaction exothermicities suggests that for *tert*-butoxyl abstracting H from alkanes, barrier heights change by roughly 30-40% of reaction energy differences.¹⁹ Thus, even a fraction of the difference between Habstraction transition states would easily outweigh the 9:1 statistical factor between secondary and tertiary sites in **2**.

The experimental EPR spectrum of 2, essentially independent of temperature, can be simulated with the following hyperfine constants: $a_{\rm H} = 5.3$ G (3H), $a_{\rm H} = 2.4$ G (3H), $a_{\rm H}$ = 0.99 G (3H), $a_{\rm H}$ = 0.88 G (3H) (see Figure 2.1). The EPR simulation program employed in this work was written at MSU by Dr. Andrew S. Ichimura, for use with the non-linear least squares fitting program KINFIT.²⁰ The resonance fields were calculated to first order, and the hyperfine splitting constants and the line widths were varied until a minimum in the rms error was found between the observed and calculated spectra. The EPR spectrum of 2 was also analyzed using the computer program MATCH, kindly provided to us by Professor R. A. Jackson from University of Sussex, UK.²¹ MATCH was designed to determine accurate coupling constants and line width data for EPR spectra, based on correlation methods. The analysis is efficient even for low intensity or complex spectra; in our case MATCH produced coupling constants identical with the values determined from simulation. The procedure involves comparison of the experimental EPR spectrum with a matching "test spectrum", using a product function produced by crosscorrelation of the test spectrum with the experimental spectrum, as the optimization criterion for improvement of fit.

¹H ENDOR (*Electron Nuclear DOuble Resonance*)²² resonance measurements were performed on samples containing 2 in toluene solution, in order to confirm the values of the hyperfine couplings obtained by simulation of its experimental EPR spectrum. In the ENDOR experiment nuclear spin transitions in paramagnetic molecules are induced by means of a suitable radio frequency (RF) field and are detected by a change in the EPR signal intensity. The ENDOR spectrum consists of pairs of lines that correspond to the types of protons in the molecule, each symmetrically split from the free proton nuclear magnetic resonance frequency of 14.44 MHz by the appropriate electron nuclear hyperfine interaction. The principal advantages and improved resolving power of ENDOR over ESR are those of simplifying complex spectra and giving precise values of the hyperfine coupling constants (HFC), which can be extracted without difficulty and usually unambigously without need for computer simulations. The ENDOR studies on 2 confirmed the previously determined HFCs and revealed two more couplings at 0.19 and 0.08 G (see Figure 2.2).

The ground state conformation of 2 has C₃ symmetry, and accordingly, the maximum number of different hyperfine couplings is 7 (6 sets of 3 equivalent Hs each, and one H in the opposed bridgehead). INDO (*Intermediate Neglect of Differential Overlap*)²³ calculations performed on PM3 and UHF/6-31G* geometries of 2 (see Table 2.2) reproduce the magnitude of the smaller couplings well, but predict a β -hydrogen hyperfine of ~ 20 G, well above the largest HFC to hydrogen, $a_{\rm H}$, observed (5.3 G). The 2.4 G coupling is assigned to one set of γ -hydrogens related to the semioccupied orbital via a W arrangement that commonly leads to a strong interaction with the unpaired electron.



Figure 2.2 The ENDOR spectrum of 1-manxyl radical 2 in toluene at -50 °C. Insert: the central part of the ENDOR spectrum of 2, which reveals small HFCs at 0.19 and 0.08 G.

				<i>a</i>				ΔH_{f}^{b}
Method	1	2	3	4	5	6	7	
UHF/6-31G*	20.9	0.8	2.0	-1.0	0.9	0.2	1.2	14.6
PM3	23.5	1.1	2.7	-1.2	0.6	0.3	1.6	-14.3
ΔBB°(Å)								
+0.3	18.6	0.5	3.3	-1.3	1.3	0.3	0.6	-9.1
+0.2	20.3	0.7	3.2	-1.2	1.1	0.3	0.8	-12.0
+0.1	22.0	0.9	3.0	-1.2	0.8	0.3	1.1	-13.7
-0.1	24.8	1.4	2.2	-1.1	0.3	0.3	2.5	-13.7
-0.2	25.6	1.7	1.7	-0.9	0.1	0.2	3.8	-12.2
-0.3	25.5	2.1	1.1	-0.8	-0.2	0.2	5.9	-9.7
$\theta (C_2 C_1 C_5 C_4)^d$								
15°	27.9	2.0	2.3	-1.0	0.7	0.2	1.4	
30°	29.4	3.1	1.7	-1.0	0.5	0.0	1.4	
60°	26.7	3.0	3.0	-0.6	-0.2	0.2	3.0	
Exp.	5.3	0.88	2.4	0.99	0.08		0.19	

Table 2.2 INDO Predicted Hyperfine Coupling Constants (in G) for 1-Manxyl Radical 2^a

* Structures were fully optimized using Spartan 4.0. H's are labeled as below, in Figure 2.3.

^b Heats of formation in kcal/mol.

^c Δ BB is defined as an inward (-)/outward (+) displacement of the spin-bearing bridgehead carbon along the symmetry axis (C₃) from the BB (bridgehead-bridgehead) distance in the PM3 geometry optimized structure (3.0127 Å). A constraint is defined as the new BB distance (elongated or contracted by Δ BB), and the new structure is geometry optimized at the PM3 level.

^d Dihedral angle in degrees (1: $\theta(C_2C_1C_5C_4) = 0^\circ$; 2: $\theta(C_2C_1C_5C_4) = 0.43^\circ$); equal to $\theta(C_8C_1C_5C_6)$ and $\theta(C_9C_1C_5C_{11})$.

Figure 2.3 Assignments of the hyperfine coupling constants in 1-manxyl radical 2.

Tentative $a_{\rm H}$ assignments, based on INDO results, are: 5.3 G and 0.88 G for β -H, 2.4 G and 0.99 G for γ -H, 0.08 G for δ -H, and 0.19 G for the ϵ -H (Figure 2.3).

The β -hydrogen splitting has been rationalized in terms of a hyperconjugative mechanism, described by the familiar McConnell relationship, $a_{H\beta} = A + B \cos^2\theta$, where A is small and usually neglected, B is assumed to be $2 \times a_{H\beta}$ of the *tert*-butyl radical (≈ 50 G), and θ is the angle between the H-C-C plane and the axis of the spin bearing orbital.²⁴ Under conditions where rotation about the $C_{\alpha}(2p)$ -C $_{\beta}$ bond is rapid, the average value of $\cos^2\theta$ is 0.5 and $a_{H\beta} \approx 27$ G.²⁵ The hyperfine interactions are expected to be small for β -protons, provided that the C_{β} -H $_{\beta}$ bond lies in the nodal plane of the $C_{\alpha}(2p)$ orbital. The angular dependence of the β -proton coupling, along with the variation with temperature of the EPR HFCs and line shapes, have been commonly employed to distinguish preferred conformations and to determine rotation and ring inversion barriers of alkyl and cycloalkyl radicals.^{25,26} According to the McConnell relation, the 5.3 G β -H splitting in 2 is unexpectedly low. The analogous delocalized D_{3h} radical cations of [3.3.3]propellane, **18**,²⁷ and **1**,5-diazabicyclo[3.3.3]undecane, **19**,²⁸ show β -H couplings of 17 G and 22 G.



respectively, interpreted as reflecting nearly planar bridgeheads with θ angles of approximately 30°. The calculated structures (UHF/6-31G*) of 2 and of radical cations 18

and 19 show similar torsion angles (θ) of the β -hydrogens with the half-occupied orbital (33.3°, 31.9° and 32.6°); however, the radical center in 2 is pyramidalized *syn* to the C_{β}-H_{β} bonds, which should make hyperconjugation less effective.²⁹ The EPR spectra of bicyclo[2.2.0]hex-1-yl³⁰ 20 and 1-cubyl³¹ 21 radicals also show exceptionally low β -hydrogen HFCs (12.4 G and 6.2 G, respectively; see Figure 2.4) considering that θ is formally zero and thus optimum for overlap. The more comparable $a_{H\beta}$ values of 6.64 and 6.58 G for the localized bridgehead radicals 1-bicyclo[2.2.2]octyl 22 and 1-adamantyl 23 are attributed to pyramidal geometries at the radical sites (Figure 2.5).³²

Bridgehead radicals are strongly pyramidal with β -carbons tied back by the cage structure leaving the radical center sterically uncongested. In bridgehead radicals the orientation of the SOMO with respect to the orbitals of the β -C-H bonds is usually less favorable for overlap, and the rigid structure prevents rotation to improve it. In addition, hyperconjugative structures will contain strained "anti-Bredt" bridgehead alkene units. Thus, most bridgehead radicals have $a_{H\beta}$ values lower in magnitude than predicted by the McConnell relation, while they show large long-range HFCs.³³ For 1-manxyl radical 2, however, the UHF/6-31G* (or PM3) structure shows only modest pyramidalization and β -hydrogens that are more nearly eclipsed than those in 22 and 23 (see Figure 2.5, and Tables 2.3 to 2.5), leaving the low $a_{H\beta}$ value somewhat puzzling.

The 1-norbornyl radical 24 gives β -H HFCs of 9.81 G for H_{β -exo}, 0.49 G for H_{β -endo}, and 2.35 G for the two β -Hs from the one-carbon bridge; this set fits linearly with $\cos^2\theta$ but with a B coefficient of about a quarter of the corresponding constant for planar

64



Selected UHF/6-31G* calculated geometrical parameters and experimental hyperfine coupling constants (in G) of bridgehead radicals. Legend: $\angle CC^{\bullet}C_{\bullet\nu\mu}$ refers to the average CC angles in degrees, obtained as $\Sigma(\angle CC^{\bullet}C)/3$. Figure 2.4



Figure 2.5 HF/6-31G* geometry optimized structures of manxane 1, 1-manxyl 2, 1-bicyclo[2.2.2]octyl 22, and 1-adamantyl 23 radicals. Legend (C₃ refers to the axis of symmetry): $\alpha = C_3C^*C_\beta$ angle, and $\theta = C_3C^*C_\beta H_\beta$ torsion angle, in degrees.

Selected distances (r), b	UHF/6-31G* (PM3)	
	$r(C_1-C_2)$	1.5052 (1.4799)
	$r(C_2-C_3)$	1.5362 (1.5234)
(\mathcal{L}_3)	$r(C_1-C_5)$	3.0970 (3.0127)
⊙ ,щ	$\angle (C_2C_1C_8)$	119.3 (199.7)
	$\angle(C_1C_2C_3)$	113.7 (112.2)
c S	∠(C ₂ C ₃ C ₄)	117.0 (113.9)
G=C-C4	∠(C₅C₁C₂)	85.2 (86.8)
2	$\theta(C_3C_1C_2H_1)$	33.3 (35.5)
	$\theta(C_3C_1C_2H_2)$	97.1 (99.9)
	$\theta(C_2C_1C_5C_4)$	0.43 (7.8)

Table 2.3 UHF/6-31G* (PM3) Geometrical Parameters for 1-Manxyl Radical 2^a

^a Distances in Å, angles in degrees; C_3 refers to the three-fold axis of symmetry.

Atom	x	у	Z
H 1	-0.5784940	-2.0251974	-1.0658355
C 2	-1.0681364	-1.0356499	-1.2087390
H 3	-1.7478700	-1.1612237	-2.0752316
C 4	0.0000000	0.0000000	-1.5951783
C 5	-1.9242512	-0.7247960	0.0089550
H 6	-2.3332975	0.3067356	-0.0844577
C 7	-1.1896046	-0.8763683	1.3349257
H 8	-2.8044188	-1.3977577	0.0116290
C 9	0.0000000	0.0000000	1.4177657
H 10	-0.9012690	-1.9355879	1.4913718
H 11	-1.8711708	-0.6202584	2.1715529
C 12	-0.1641549	1.4684120	1.3349257
C 13	1.3537595	-0.5920437	1.3349257
H 14	-1.4646254	1.5135892	-1.0658355
H 15	-0.1317142	2.0943117	-2.0752316
H 16	0.0000000	0.0000000	-2.7151618
C 17	1.4309674	-0.4072083	-1.2087390
C 18	1.5898174	-1.3040524	0.0089550
H 19	2.0431194	0.5116082	-1.0658355
H 20	1.8795842	-0.9330880	-2.0752316
H 21	0.9010079	-2.1740627	-0.0844577
C 22	-0.3628309	1.4428582	-1.2087390
H 23	1.4727449	-1.3103522	2.1715529
H 24	2.1269028	0.1872721	1.4913718
H 25	0.3984259	1.9306106	2.1715529
H 26	-1.2256338	1.7483158	1.4913718
C 27	0.3344338	2.0288484	0.0089550
H 28	1.4322896	1.8673271	-0.0844577
H 29	0.1917158	3.1275767	0.0116290
H 30	2.6127030	-1.7298191	0.0116290

Table 2.4 PM3 Atomic Cartesian Coordinates (in Å) for1-Manxyl Radical 2

			_
Atom	X	y	Z
H 1	0.0000000	0.0000000	2.7009321
C 2	0.0000000	0.0000000	1.6142657
C 3	0.0593796	-1.5134558	1.2630577
C 4	1.2810014	0.8081521	1.2630577
C 5	-1.3403809	0.7053037	1.2630577
H 6	2.1405044	0.1443425	1.3266034
H 7	1.4208356	1.5340192	2.0608630
C 8	1.3544058	1.6073025	-0.0462537
H 9	-2.0389174	0.4634702	2.0608630
C 10	-2.0691677	0.3692985	-0.0462537
H 11	-1.1952565	1.7815600	1.3266034
H 12	-0.9452480	-1.9259025	1.3266034
H 13	0.6180818	-1.9974893	2.0608630
C 14	0.7147619	-1.9766011	-0.0462537
H 15	-3.0129518	0.9105534	-0.0425296
H 16	-2.3383691	-0.6826451	-0.0421622
C 17	-1.3324475	0.6885334	-1.3559473
H 18	2.2950383	2.1540161	-0.0425296
H 19	0.5779966	2.3664096	-0.0421622
C 20	1.2625112	0.8096666	-1.3559473
C 21	0.0699363	-1.4982001	-1.3559473
H 22	0.7179135	-3.0645695	-0.0425296
H 23	1.7603726	-1.6837645	-0.0421622
C 24	0.0000000	0.0000000	-1.4827090
H 25	-1.2073288	1.7641697	-1.4505304
H 26	-1.9787037	0.3868696	-2.1808085
H 27	-0.9241514	-1.9276623	-1.4505304
H 28	1.3243907	1.5201729	-2.1808085
H 29	2.1314802	0.1634926	-1.4505304
H 30	0.6543130	-1.9070424	-2.1808085

•

Table 2.5 UHF/6-31G* Atomic Cartesian Coordinates(in Å) for 1-Manxyl Radical 2

radicals.³⁴ In bicyclo[1.1.1]pent-1-yl radical 25, where the C_{β} -H_{β} bonds are basically orthogonal to the axis of the $C_{\alpha}(2p)$ orbital, $a_{H\beta}$ is 1.2 G.³⁵ Such strained small-ring bicycloalkyl radicals have been studied by EPR mostly for the assessment of through-bond (TB) and through-space (TS) interactions. Thus, the bridgehead hydrogen HFC increases steeply from 24 (2.5 G), with the odd-electron delocalized onto the bridgehead H atom through a TS mechanism, to bicyclo[2.1.1]hex-1-yl radical 25 (22.5 G),³⁶ where both TS and TB mechanisms operate, and to 26 (69.6 G), where the TB interaction is prevalent.

Bicyclo[3.3.3]undec-1-yl cation 27, prepared by Olah et al.³⁷ from 1-chloro- or 1hydroxybicyclo[3.3.3]undecane with SbF_5/SO_2Cl_2 at -78 °C, shows the same temperatureindependent behavior as 2. As observed by ¹H and ¹³C NMR the solution of 27 does not change between -135 and -30 °C, and it slowly decomposes at high temperatures. This behavior is surprising in comparison with manxane 1 or the bridgehead manxyl dication 28, where the intriguing bridge flipping process (see below) is frozen at low temperature.



Olah et al.³⁷ suggested either a rapid ring flipping in 27, faster than can be detected on the NMR time scale, or a very slow inversion of conformation due to additional strain in 27 introduced by the sp² hybridized carbon at $C_{\alpha}(2p)$. However, bridgehead planarization in 27, if anything, brings relief of strain when compared to 1, which leaves the first alternative as more probable. By analogy with 27, 2 might also undergo rapid vibrational

averaging with the net effect of reducing $a_{H\beta}$. Furthermore, it is of interest to mention that the methine protons in manxane 1 (δ 2.38 ppm; width ~ 24 Hz) and the methine proton in 1-azabicyclo[3.3.3]undecane (manxine) (δ 2.57 ppm; width ~ 18Hz) are broad multiplets with no discernable couplings.² The broad signal becomes a well-resolved septet upon addition of dipivaloylmethanatoeuropium(III) complex to manxine, as well as in manxine hydrochloride (J = 5 Hz).² The dihedral angle (ϕ) dependence of vicinal spin-spin couplings, ³J_{H-H}, is described by the Karplus relation:³⁸

$$^{3}J_{H-H} = A + B \cos \phi + C \cos 2\phi$$

Application of the Karplus equation in manxane and manxine, gives ${}^{3}J_{H-H}$ values of 10 Hz and 2.5 Hz for the methine H couplings with the adjacent β -Hs. However, the observed near equivalency of the β methylenes must be due to rapid (on the NMR time scale) equilibration of conformations.

For a radical in solution there will be a rotational motion about the C_{α} - C_{β} bond with a number of torsional states for each trough of the potential function. The observed EPR spectrum, therefore, shows a β -proton coupling constant which is an average over the torsional states.²⁶ Rotation is inhibited in 1-manxyl radical because of the cage structure, nevertheless, a full understanding of the dynamics and EPR HFCs of 2 ideally requires a complete analysis of the vibronic wave functions. The INDO method²⁴ has been applied to a large number of hydrocarbon radicals and usually, INDO calculated spin densities correlate well with experimental isotropic hyperfine splittings. In an attempt to mimic the effects of vibrational motions on the magnitude of EPR couplings in 2, we performed INDO calculations on PM3 structures of 2, which map the two low-frequency vibrations shown below. Constraints were referenced to either the BB distance or the



torsion angles $\theta(C_2C_1C_5C_4)$, $\theta(C_8C_1C_5C_6)$ and $\theta(C_9C_1C_5C_{11})$, and the new structures were geometry optimized at PM3 level. The INDO results (see Table 2.2), however, fail to provide an explanation for the reduced $a_{H\beta}$ in 2.

2.2 Spin Trapping Studies on 1-Manxyl Radical

The observation and structural elucidation of organic free radicals by EPR is limited to experimental conditions which generate detectable steady-state concentrations of the radical. A successful strategy to overcome this limitation is spin trapping, whereby short-lived free radicals may be transformed into more persistent paramagnetic species enabling EPR techniques to be applied to systems in which the concentration of the reactive radical remains below normal detection limits.³⁹ The general principle is represented by the reaction given below, where a diamagnetic compound (the "spin trap"), with a high

 $\begin{array}{rrr} R^{\cdot} &+ & ST &\rightarrow & (ST-R^{\cdot}) \\ & & spin trap & spin adduct \end{array}$

affinity for radicals, is added to the reactive radical to give a particularly persistent new

free radical (the "spin adduct"), whose concentration will build to readily detectable levels $(> 10^{-7} - 10^{-6} \text{ M})$. The success and value of the spin-trapping experiment depend upon how fast and selective is the trapping reaction, how persistent is the resulting radical, and if the identity of R⁻ can be readily discerned from the EPR spectrum of the spin adduct. Although many different unsaturated groups have been used to trap various radicals, the vast majority of investigations or applications of the spin-trapping technique depend on the use of C-nitroso compounds or nitrones, to yield relatively stable aminoxyl (or nitroxide) free radicals, which are readily detected by EPR spectroscopy. The preeminent advantage of C-nitroso-compounds over nitrones as spin traps is that in the spin adduct the scavenged radical is directly attached to the nitroxide nitrogen. As a result, the ESR



spectrum of the spin adduct is likely to reveal splittings from magnetic nuclei in the trapped radical, which facilitate its identification.

Spin trapping of the 1-manxyl radical 2 by the nitroxide method was attempted with 2,4,6-tri-*tert*-butyl-nitrosobenzene (TBN) as spin scavenger.⁴⁰ The main benefits of TBN over other spin traps are that it functions as an ambident ("bifunctional") spin trap, and that it is stable to light both in solution and in the solid state, which makes it useful for application to photoradical reactions. Thus, TBN reacts at either the N or the O atoms of the nitroso-group, depending on the steric hindrance of the attacking radicals, to give as spin adducts the corresponding nitroxide or *N*-alkoxyanilino radicals. Primary alkyl radicals react at nitrogen, secondary alkyl radicals react at both trapping sites, while tertiary alkyl radicals react exclusively at the oxygen atom. It is therefore possible to distinguish between attacking primary, secondary and tertiary alkyl radicals from the EPR spectra of the spin adducts, since nitroxides have significantly different a_N and a_H splittings than *N*-alkoxyanilino radicals. The alkoxyaminyl radicals have a lower *g*-value than the nitroxides (*ca.* 2.004 vs. 2.006) and their spectra are therefore centered at higher field positions than those of nitroxides. Splitting patterns are also significantly different; the spectra of the alkoxyaminyls show much larger splittings from the *meta*-protons of the aryl rings than do the nitroxides, but a_N is smaller. In addition, TBN is monomeric and does not dimerize.



TBN reacts with 1-manxyl radical 2 to produce a persistent *N*-alkoxyanilino radical, the EPR spectrum of which (Figure 2.6) shows the following g value and coupling constants: g = 2.003, $a_N = 9.0$ G (1N), $a_H = 1.8$ G (2H). The spin trapping experiments were performed either by adding a toluene solution of TBN to an irradiated sample of

manxane in di-*tert*-butyl-peroxide, which contained 2 in concentrations of ~ 10^{-3} - 10^{-4} M, or by UV irradiation of a solution containing manxane, TBN and di-*tert*-butyl-peroxide, directly in the cavity of a Varian E4 spectrometer. Identical EPR spectra were obtained in both cases, in agreement with the experimental observations that TBN is not a good trap for radicals other than alkyl, and it can be used successfully *in situ* when the alkyl radicals are generated by H atom abstraction from substrates with *tert*-butoxyl radicals. Irradiation of TBN itself, in solid state or in di-*tert*-butyl peroxide solution, gave no detectable EPR signal.

The 1.8 G meta-H hyperfine and the absence of β -hydrogen splittings in the EPR spectrum of the TBN spin adduct of 2 indicate exclusive addition at the O atom of TBN by an unreactive tertiary radical such as 2, consistent with the observed multi-minute trapping time. The rate constant for the reaction of TBN with *tert*-butyl radical has been experimentally determined as 2.3×10^5 M⁻¹s⁻¹ at 24 °C in benzene.⁴¹ If we extrapolate this value for the reaction of TBN with 2, under the pseudo first-order conditions of the spin trapping experiment the above rate constant gives reaction times on the order of miliseconds; however, as expected, the trapping rate of 1-manxyl radical 2 by TBN is considerably slower, since it takes a few minutes for the addition of 1 to TBN to be complete. Thus, the choice of TBN as spin trap to elucidate the nature of the radical obtained on H atom abstraction from 1 is validated: the long lived radical obtained from photolysis of manxane and di-tert-butyl peroxide reacts slowly, at the O position of TBN, to yield a tert-alkyl alkoxyaminyl radical, and the significant steric effects revealed in the trapping reaction, all strongly support the assignment of the initial EPR spectrum to an inflexible, bulky alkyl radical such as 2.



Figure 2.6 EPR spectrum (9.065 GHz) of the *N*-alkoxyanilino radical obtained by spin trapping of 1-manxyl radical 2 with TBN (g = 2.003).

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2.3 Kinetic Decay and Product Analysis

The kinetics of radical disappearance for 1-manxyl radical 2 were readily obtained from spin resonance experiments due to its remarkable persistence. Photolysis of 1 and di-*tert*butyl peroxide in methylcyclopentane at room temperature (23 °C) generated 1-manxyl radical 2, whose decay was monitored by EPR. The number of electron spins present in the cavity during the EPR measurement was obtained by comparison of the area under the absorption curve with that of a reference radical. DPPH (diphenylpicrylhydrazyl) solutions of known concentration (4×10^{-4} M, 2×10^{-4} M, 1×10^{-4} M, 8×10^{-5} M, 6×10^{-5} M, and 4×10^{-5} M) in benzene were employed as standards for spin concentration determinations.⁴²



The EPR spectra of both 2 and the reference samples were recorded at 23 °C with identical microwave power levels. No saturation was observed for any of the radicals under the conditions of the experiment. However, in computing the absolute number of spins, a correction had to be applied because of different modulation amplitude and gain settings. From a consideration of the various errors involved in such a determination, a deviation of $\pm 50\%$ is usually assigned to concentration, which, nevertheless, does not change the order of magnitude of the rate constant for radical disappearance.⁴²

The areas resulting from double integration of the EPR derivative signals of DPPH solutions were plotted against DPPH concentration for calibration. The calibration curves

were validated by UV measurements of the DPPH absorption (at 327 and 520 nm), which established, as expected, a linear variation of DPPH concentration with UV absorption. The number of spins corresponding to 1-manxyl radical 2 was computed from the area of the EPR absorption curve, obtained by double integration of the derivative signal, relative to that of the standard. The plot of the inverse concentration (1/c) of 1-manxyl radical against time (τ) is linear at longer times and indicates second order kinetics in 2 (see Figure 2.7).⁴³ The rate constant for the radical disappearance, k, is calculated from the slope of the line (best linear fit of 1/c against τ) which equals 2k, and the half-life $\tau_{1/2}$, is determined as $1/(2k[1-manxyl]_0)$, where $[1-manxyl]_0$ is the initial radical concentration equal to the intercept of the line. Thus, the decay of 2 in methylcyclopentane, monitored by EPR. is second order (n = 2) with a rate constant of 0.5 $M^{-1}s^{-1}$ at 23 °C and a half-life $(\tau_{1/2})$ of 6 hours for a 5×10⁻⁵ M initial radical concentration (c;). Such exceptional persistence is unique considering the lack of steric protection around the radical center.⁴⁴ A few representative examples of persistent secondary and tertiary alkyl radicals are given below, where the long lifetime of the radicals is a consequence of steric factors.⁴⁴



Many tertiary alkyl radicals decay with first-order kinetics presumably via intramolecular hydrogen transfer or β -scissions.⁴⁵ In general, β -scission occurs readily if

78



Figure 2.7 Kinetics of decay of 1-manxyl radical in methylcyclopentane at 23 °C:
(a) variation with time of the concentration of 1-manxyl radical 2;
(b) plot of the inverse concentration of 2 against time.

the semioccupied molecular orbital can assume an eclipsed conformation with respect to the bond about to break, or if it brings considerable relief of strain, as in 3- or 4-membered ring cycloalkyl or cycloalkylmethyl radicals. In bridgehead radicals, both internal strain and the degree of steric exposure of the radical center control their reactivity. The EPR spectra of bridgehead radicals showed that they have lifetimes in solution of the same order of magnitude as other transient alkyl radicals. It is remarkable that even radicals with as much strain as 21 or 26 could be directly observed. The orientation of the semi-occupied molecular orbital (SOMO) particularly influences the rates of unimolecular reactions such as decomposition and rearrangements. Bridgehead radicals are reluctant to rearrange due to unfavorable stereoelectronic effects. Even radicals with potentially strongly exothermic ring opening processes, such as 20, 21, or 26, require harsh conditions for β -scissions to occur. Generally, in bridgehead radicals the SOMO and the orbitals of the bond to break, C_{β} - C_{γ} , are poorly aligned for overlap and considerable structural reorganization must take place during rearrangement, which kinetically is inhibited. Instead, bridgehead radicals abstract hydrogen or halogen, add to unsaturated molecules, and take part in combination reactions. Thus, facile rearrangements are not expected for 1-manxyl radical. In agreement with the finding that 2 decays by second-order processes, the combination of two 1manxyl radicals can lead to either 1,1-bimanxyl 29 by dimerization, or 1-manxene 30 and 1 by conventional β -disproportionation.

The reaction mixtures resulting from the decay of 2 were examined by GC-MS. The samples utilized for product analysis were prepared by generating 2 in high concentration in cyclopropane, toluene or neat di-*tert*-butyl peroxide, and allowing it to

80



decompose at room temperature. The radical disappearance was monitored by EPR to ensure total consumption of 2. When no more EPR signals were detected, the EPR tubes were opened to air and subjected immediately to GC-MS analysis.

The chromatograms obtained from the decay of 2 in cyclopropane or in neat ditert-butyl peroxide were essentially identical, and besides unreacted 1, showed major peaks at 150, 220, 222, 235, and 237 amu. No 1,1-bimanxyl **29** is detected in either case, but the calculated F-strain in this compound is large, *ca*. 21 kcal/mol,⁴⁶ making dimerization less exothermic ($\Delta H_{dim.} = -18.1$ kcal/mol) than for ordinary alkyl radicals. One of the 150 amu peaks in the product mixture was identified as [3.3.3]propellane **31** by independent synthesis⁴⁷ and GC-MS analysis (Figure 2.8). A second 150 amu product seen by GC-MS is tentatively assigned to 1-manxene **30**, the Bredt alkene from conventional β hydrogen disproportionation of 1 (Figure 2.9). That both these products are derived from **2** is confirmed by their absence in samples where **2** has been quenched after short photolysis times by the addition of *n*-Bu₃SnH.

The presence of **31** among the decomposition products of **2** was rationalized by a novel ε -disproportionation. This process is reminiscent of the case of halobicyclo[1.1.1]-



Figure 2.8 Mass spectra showing the EI fragmentation of a) [3.3.3]propellane **31** (retention time 3.6 min.), and of the peaks with 3.6 min. retention time in the chromatograms from the analysis of decomposition products of **2** in b) neat di-*tert*-butyl peroxide, and in c) cyclopropane, which are assigned to **31**.



Figure 2.9 Mass spectra showing the EI fragmentation of: a) manxane 1 (retention time 6.4 min.), and of the peaks with 6.2 min. retention time in the GC-MS analysis of the decomposition products of 2 in b) neat di-*tert*-butyl peroxide, and in c) cyclopropane, which are assigned to manxene 30.



pent-1-yl radicals, where evidence was found for a new γ -disproportionation process in which the γ -fluorine (or chlorine) atom was transferred from the 3-fluoro (or 3-chloro) radical to a triethylsilyl or to a second bicyclo[1.1.1]pent-1-yl radical to yield, in both cases, [1.1.1]propellane.⁴⁸ [3.3.3]Propellane was also detected in reaction mixtures after longer photolysis times, followed by quenching of 2 with *n*-Bu₃SnH; conceivably, **31** may also be formed by bridgehead H abstraction from 2 with *tert*-butoxyl radicals. The ab initio results in Table 2.6 indicate that ϵ -disproportionation is thermochemically favored over classical β -disproportionation (ΔH_{ϵ -disprop.} = -78.3 kcal/mol; ΔH_{β -disprop.} = -36.6 kcal/mol) by more than 40 kcal/mol.



The olefinic strain (OS) of manxene **30** calculated at the HF/6-31G* level is 7 kcal/mol (see Table 2.6), higher than a previous MM1 estimate of 3.9 kcal/mol.⁴⁹ OS is used to interpret and predict the stability and the reactivity of bridgehead olefins.⁵⁰

Compound	Total Energy ^b	ΔH_{f}^{c}	SE ^d
Manxane (1)	-428.17907	-20.4 (-21.2) ^e	28.0 (27.2)
1-Manxyl Radical (2)	-427.56808	14.6	19.9
1,1-Bimanxyl (29)	-855.16181	11.1	80.8
1-Manxene (30)	-426.97830	13.0	35.0
[3.3.3]Propellane (31)	-427.04326	-28.7	14.9

Table 2.6 Calculated Heats of Formation and Strain Energies^a

^a In kcal/mol; structures were fully optimized at HF/6-31G* level, using Spartan 4.0 (Wavefunction Inc., Irvine, CA).

^b Total energies are given in hartrees, 1 H = 627.5 kcal/mol.

^c Calculated (experimental) from Wiberg's group equivalents (Wiberg, K. B. J. Org. Chem. 1985, 50, 5285) for 1, 29, 30 and 31. The heat of formation for 2 was estimated from the isodesmic reaction vs. *iso*butane/*tert*-butyl radical.

^d Strain energy; from calculated (experimental) ΔH_f and Benson's group equivalents (Benson, S. W. *Thermochemical Kinetics*; John Wiley: New York, 1976) for 1, 29, 30 and 31, and from the isodesmic reaction vs. *iso*butane/*tert*-butyl radical for 2.

^e Ref. 5.

According to empirical rules deduced from comparison of OS values with experimental behavior,⁴⁹ **30** should be an isolable olefin (OS \leq 17 kcal/mol), kinetically stable at room temperature, at least long enough to allow reactions and spectroscopic measurements to be carried out. A compound can not be unambiguously identified solely on the basis of its mass spectrum and further studies to confirm the assignment of **30** are necessary. Nevertheless, the analysis of the mass spectrum attributed to **30**, hints at a compound with the manxane skeleton but with higher unsaturation. Under electron impact manxene could fragment by breaking one of the C_β-C_γ bonds from the fully saturated bridges to give the 122 and 135 amu cations by loss of either methyl or ethyl radicals, which is exactly what is observed experimentally (see Figure 2.9).

The ratio of **30** to **31** in all runs analyzed by GC-MS is relatively constant, at about 3:1, which suggests that **30** and **31** must be formed by kinetically parallel reaction pathways. Thus, while **31** is thermodynamically favored, **30** is the kinetic product. This is not surprising since **2** is sterically uncongested and does not hinder the approach of a second *tert*-butoxyl or manxyl radical to give **30**, while the bridgehead diradical-like TS en route to **31** needs more internal motion to collapse to [3.3.3]propellane. Under continuous photolysis and thus, high concentration of radicals, **30** may undergo a second H abstraction to form the allylic π -type radical **32**, which then adds intramolecularly to the double bond to form the less strained [3.3.3]propellane skeleton via **33**. Further, combination with another *tert*-butoxyl radical gives the 222 amu product (Scheme 2.2). We believe abstraction of an allylic H from **30** to be less probable because the resulting radical **34** is severely twisted, hindering allylic conjugation. Addition of *tert*-butoxyl

86



Scheme 2.2



radicals to the double bond of 30 to form 35 is also conceivable (Scheme 2.2); however, in the competition between addition to π -systems versus H atom abstraction, *tert*-butoxyl has shown almost exclusively H-abstraction,⁵¹ which makes the addition pathway less likely. Nevertheless, both 222 and 220 amu products display in their mass spectra intense peaks at 57 amu (*tert*-Bu⁺), which confirms *tert*-butoxyl incorporation (Figure 2.10).

Further H abstraction in the already substituted bridge of these two compounds and combination with *tert*-butoxyl radicals gives rise to minor products, presumably also *tert*-butoxyl ethers, which do not exhibit the molecular ions in their mass spectra,⁵² but whose fragmentation parallels that of the above compounds (highest peaks at 235 and 237 amu, respectively; see Figure 2.11).

The GC-MS analysis of the reaction mixture obtained from the decay of 2 in toluene is consistent with the above interpretation and all the compounds discussed above can be easily identified in the GC chromatogram. The most intense peak, however, in this case is dibenzyl, confirming production of benzyl radicals from toluene under H atom abstraction conditions. The benzyl radical could not be observed by EPR because of the remarkable persistence of the concomitantly produced 1-manxyl radical 2, but photolysis of di-*tert*-butyl peroxide and toluene alone yields the spectrum of benzyl radical.¹⁴ A new peak, however, appears at 14.4 min. retention time, with a molecular ion of 242 amu,


Figure 2.10 Mass spectra showing the EI fragmentation of the peaks with a) 7.22 min. and b) 7.41 min. retention times (see Scheme 2.2 for tentative assignments) in the chromatograms from the analysis of the decomposition products of 2 in neat di-*tert*-butyl peroxide.



Figure 2.11 Mass spectra showing the EI fragmentation of the peaks with a) 10.4 min. and b) 10.6 min. retention times (see Scheme 2.2 for tentative assignments) in the chromatograms from the analysis of the decomposition products of **2** in neat di-*tert*-butyl peroxide.



Figure 2.12 Mass spectra showing the EI fragmentation patterns of the peak with 14.4 min. retention time (presumably 1-benzylmanxane) in the chromatogram that resulted from the analysis of the decomposition products of 2 in ditert-butyl peroxide/toluene.

which is believed, based on appropriate fragmentation, to be 1-benzyl-manxane (Figure 2.12).

2.4 Conclusions

Surprisingly, unlike their small-ring cousins, simple bridgehead radicals of medium-ring bicycloalkanes have not been reported, although computational results suggest that such species might show unusual stability and/or persistence. Furthermore, to date, persistent alkyl radicals have depended on steric protection by bulky groups around the radical center. The 1-manxyl radical 2 is the first example of a persistent simple medium-ring alkyl radical whose exceptionally long lifetime arises not from steric protection, but from the high strain of all its decomposition products. The remarkable persistence and puzzlingly low hyperfine splittings for the β -hydrogens in 2 suggest that even such simple entities as bridgehead alkyl radicals have not yet given up all their secrets.

2.5 Experimental Section

General Methods. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Fourier-transform infrared (IR) spectra were recorded on Mattson-Galaxy FT-IR 3000 or Nicolet IR/42 spectrometers; samples were measured either as thin layers on a NaCl plate (liquids) or as KBr pellets (solids). Electron impact (EI) mass spectra were run on a Fisons VG Trio-1 MS spectrometer which operates in line with a Hewlett Packard 5890 gas chromatograph for GC-MS measurements.

High-resolution mass spectra for analysis of the decay products from 2 were carried out on a JEOL AX-505H double-focusing mass spectrometer coupled to a Hewlett-Packard 5890J gas chromatograph via a heated interface. GC separation employed a DB5MS fused-silica capillary column (30 m length \times 0.25 mm I.D. with a 0.25 µm film coating). Direct (splitless) injection was used. Helium gas flow was approximately 1 ml/min. The GC temperature program was initiated at 100 °C with an increase of 10°/min. MS conditions were as follows: interface temperature 280 °C, ion source temperature *ca*. 250 °C, electron energy was 100 eV, scan rate of the mass spectrometer was 1 s/scan over the m/z range 45-500.

Routine ¹H and ¹³C NMR spectra were obtained at 300 MHz, on Varian GEMINI 300 or VXR-300 spectrometers. All spectra were recorded at ambient temperature and are referenced to solvent signals. Peak multiplicities are abbreviated: s singlet, d doublet, t triplet, q quartet, and m multiplet. Coupling constants (*J*) are reported in Hertz. Twodimensional HMQC (¹H-detected heteronuclear Multiple Quantum Coherence) and 2D Heteronuclear *J*-Resolved experiments were performed on a Varian VXR-500 spectrometer at 25 °C.

EPR spectra were recorded with a Varian E4 X-band spectrometer equipped with a quartz Dewar insert for variable temperature operation. The temperature was controlled by passing N_2 gas through cooling coils immersed in liquid nitrogen and was measured by a thermocouple inserted into the flow Dewar immediately below the cavity. Samples were

93

prepared in 3 mm i.d. quartz EPR tubes (Wilmad), modified with quartz \rightarrow Pyrex graded seals so they could be attached to a Kontes Right Angle Hi-Vac valve with a PTFE plug. The EPR tubes were connected to a Schlenk line through the side arm of the Kontes valve, degassed, and photolyzed directly in the cavity of the spectrometer with the unfiltered light of a 500 W Oriel high-pressure Hg lamp. Absolute values of the *g* factor were obtained directly from measurements of the microwave frequency with a Microwave Inc. EIP Model 25B frequency counter and of the magnetic field with a Bruker ER 035M gaussmeter. ENDOR spectra were recorded on a Bruker ESP 300E spectrometer. The di*tert*-butyl peroxide used in the EPR experiments was purified by passing it over activated alumina to remove traces of *tert*-butyl hydroperoxide, followed by distillation at reduced pressure (b.p. 50 °C at 90 torr).

All air-sensitive reactions were performed in oven-dried glassware using regular syringe/cannula techniques. Gravity and flash column chromatography were performed on E. Merck silica gel (230-400 mesh). Starting materials and solvents were used as supplied from commercial sources or purified according to standard procedures.

Cyclohexanone Morpholine Enamine (4). Cyclohexanone (250 ml; 2.4 mol), morpholine (294 ml; 2.4 mol) and a few crystals of p-toluenesulfonic acid were refluxed in benzene (~ 1 l) until no more water was collected in the Dean-Stark trap, and GC analysis of aliquots from the reaction mixture showed total consumption of the cyclohexanone. Usually it takes about 1 day until all the water is azeotropically distilled and separated in the Dean-Stark trap, and the reaction stops. The solvent was removed by vacuum distillation and the enamine was distilled at reduced pressure to give 340.7 g (2.04 mol) of 4 (bp_{10 mm} 116-118 °C; lit.⁵³ bp_{10 mm} 117-120 °C; yield 85%). IR 1647, 1450 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.58 (t, 1H), 3.63 (t, 4H), 2.68 (t, 4H), 2.05-1.91 (m, 4H), 1.68-1.42 (m, 4H); ¹³C NMR (300 MHz, CDCl₃) δ 145.5, 100.5, 67.0, 48.4, 26,8, 24.4, 23.2, 22.8.

2-*N*-Morpholinyl-bicyclo[3.3.1]nonan-9-one (5). Cyclohexanone morpholine enamine 4 (340.7 g; 2.04 mol) was dissolved in THF (750 ml freshly distilled from Na/benzophenone) and cooled to 0 °C with stirring. Acrolein (136 ml; 2.04 mol) was added dropwise at such a rate that the temperature remained below 10 °C. The homogeneous solution was allowed to warm to room temperature and was stirred overnight. The THF was removed on the rotary evaporator, and the residue distilled at reduced pressure to give 5 (296.6 g; 1.33 mol) as a viscous pale yellow oil (bp_{1 mm} 142-147 °C; lit.¹¹ bp_{1 mm} 141-147 °C ; yield 65%). IR 1713 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.66 (t, 2H), 3.61 (t, 2H), 2.49-2.1 (m, 2H), 2.31-2.49 (m, 7H), 1.30-2.19 (m, 8H).

N-(2-Bicyclo[3.3.1]nonan-9-one) Morpholine N-Oxide (6). To 2-N-

Morpholinyl-bicyclo[3.3.1]nonan-9-one 5 (296.6 g; 1.33 mol) were added an equal volume of methanol (600 ml) and hydrogen peroxide, H_2O_2 (30% in water; 218.9 g; 1.93 mol). The solution was refluxed for two hours and allowed to cool to room temperature. As the solution was still slightly basic, additional hydrogen peroxide was added (200.6 g H_2O_2 30%; 1.77 mol) and the solution was again refluxed for two hours and then cooled to room temperature. To the homogenous reaction mixture Pd/C 10% was added slowly in batches and with vigorous stirring to destroy the excess peroxide, and the resulting suspension was stirred for several days. The palladium was filtered off and the solvent

removed on a rotary evaporator at 50 °C and water pump pressure to afford crude N-oxide 6 (310.7 g; 1.3 mol; yield 98%) as a glassy oil, which was not characterized and was used in the next step without further purification.

Bicyclo[3.3.1]non-2-en-9-one (7). The crude N-oxide 6 (310.7 g; 1.3 mol), in a flask fitted with a short path distillation head followed by an ice-cooled trap (reversed to avoid plugging) connected in series with a dry-ice trap, was further dried at 1 torr pressure for one hour. The temperature was then slowly raised to 110-120 °C (in the oil bath) with stirring of the amine N-oxide with a teflon-covered magnetic bar, at which time pyrolysis began. In one large-scale pyrolysis the temperature was raised too rapidly, causing dangerously fast decomposition and pressurization of the system, forcing the distillation head from the flask and spewing resinous material. Proper safety precautions should be taken. After about two hours, the reaction was complete, leaving a large amount of hard resin in the pyrolysis flask. The product which was collected in the traps was poured into 6 N HCl (294 ml) and extracted with ether (4×140 ml). The ether extracts were washed once with 6 N HCl, 10% Na₂CO₃ aqueous solution, and water, then dried over anhydrous MgSO₄ and filtered. The ether was removed on a rotary evaporator, leaving a semicrystalline sweet-smelling ketone. Sublimation at 80 °C and 12 torr yielded colorless crystals of 7 (45.15 g; 0.332 mol; yield 25.5%) with mp 95-96 °C (lit.^{2b} mp 98-99 °C). IR 1730 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.87 (dt, 1H), 5.53 (m, 1H), 2.80-2.32 (m, 4H), 1.98-1.40 (m, 6H); ¹³C NMR (300 MHz, CDCl₃) δ 216.5, 129.8, 126.9, 47.56, 45.4, 45.3, 36.6, 33.1, 16.8; MS (EI) m/z (relative intensity): 136 (M⁺, 77), 108 (12), 94 (10), 95 (64), 91 (23), 80 (53), 79 (100), 78 (14), 77 (33), 68 (24), 67 (53).

Bicyclo[3.3.1]nonan-9-one (8). Bicyclo[3.3.1]non-2-en-9-one 7 (45.15 g; 0.332 mol) was hydrogenated with 10% palladium on charcoal (700 mg) in methanol (200 ml), in a Parr hydrogenator at room temperature and 3 atm. The suspension was filtered, the methanol distilled on a rotary evaporator, and the residue sublimed at 80 °C and water aspirator pressure to give colorless waxy crystals of the ketone 8 (43.5 g; 0.315 mol; yield 95%) with a distinct camphor-like odor and mp 155-158 °C (lit.^{2b} 153-155 °C). IR 1725 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.40 (m, 2H), 2.08-1.96 (m, 12H); ¹³C NMR (300 MHz, CDCl₃) δ 2.40 (m, 2H), 2.08-1.96 (m, 12H); ¹³C NMR (300 MHz, CDCl₃) δ 219.3, 46.6, 34.3, 20.6; MS (EI) m/z (relative intensity): 138 (M⁺, 36), 122 (30), 93 (22), 82 (40), 81 (75), 80 (35), 79 (38), 68 (25), 67 (100), 55 (27), 41 (45).

Bicyclo[3.3.2]decan-9-one (9). A solution of *N*-methyl-*N*-nitroso-*p*toluenesulfonamide (Diazald; 134.8 g; 0.630 mol) in methanol (1350 ml) was added dropwise to a stirred solution containing bicyclo[3.3.1]nonan-9-one **8** (43.5 g; 0.315 mol), potassium hydroxide (22.4 g; 0.40 mol), water (740 ml) and methanol (130 ml) at 0 °C over a period of 6 hours. The mixture was allowed to warm gradually to 20 °C and was stirred overnight. The suspension was filtered and the filtrate was concentrated in vacuo. The filtered salt was washed with ether, the ether washes were combined with the concentrate, more ether was added, the whole organic phase was washed with water and dried over MgSO₄, filtered and the ether was removed in vacuo. The residue in etherhexane (1:19) was placed on a silica column in the same solvent and eluted to give, in first recovery, bicyclo[3.3.2]decan-9-one **9**, which after vacuum sublimation at 60 °C (10 torr) had mp 177-179 °C, lit.^{2b} mp 177-179 °C (28.73 g; 0.189 mol; yield 70%). IR 1689 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.84 (m, 1H), 2.48 (d, 2H, *J* = 6 Hz), 2.24 (m, 1H), 1.921.41 (m, 12H); ¹³C NMR (300 MHz, CDCl₃) δ 222.1, 46.6, 34.3, 31.7, 24.4, 21.5, 20.6; MS (EI) m/z (relative intensity): 152 (M⁺, 50), 110 (24), 109 (38), 108 (45), 97 (44), 96 (91), 95 (65), 82 (63), 81 (100), 68 (40), 67 (71).

9-Methylenebicyclo[3.3.2]decane (10). To a stirred suspension of potassium tert-butoxide (21.88 g; 0.195 mol) in dry benzene (380 ml; freshly distilled over Na) under nitrogen was added an equimolar amount of methyltriphenylphosphonium bromide (67.52 g; 0.189 mol), and the mixture was heated to reflux (the oil bath was preheated to 80 °C). After 15 min. most of the benzene was distilled off until the temperature of the remaining slurry reached 90 °C. Ketone 9 (28.73 g; 0.189 mol) was added at once as a saturated solution in benzene via a syringe, causing a vigorous exothermic effect and a significant rise in temperature (10-20 °C). Heating was continued for two more hours at 90-100 °C. Pentane (280 ml) and water (140 ml) were added to the cooled reaction mixture with vigorous stirring, the organic layer was decanted, the heterogeneous residue was extracted again with pentane, and the combined organic layers were washed with water and dried (MgSO₄). The solvent was removed on a rotary evaporator and the residue was distilled at reduced pressure to afford pure 9-methylenebicyclo[3.3.2]decane 10 (bp₂ 60 °C; lit.^{2b} bp_{2.5} 67-69 °C; 18.75 g; 0.125 mol; yield 66%). IR 1610 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.68 (dd, 1H, $J_{AB} = 2.7$ Hz, $J_{AX} = 2$ Hz), 4.57 (dd, 1H, $J_{BA} = 2.7$ Hz, $J_{BX} = 2$ Hz), 2.85 (m, 1H), 2.54 (m, 2H), 2. 15 (m, 1H), 1.78-1.42 (m, 12H).

9-Epoxymethylenebicyclo[3.3.2]decane (11). Solid *m*-chloroperbenzoic acid (25.7 g 85%; 0.126 mol) was slowly added in small portions to a mechanically stirred mixture of 9-methylenebicyclo[3.3.2]decane 10 (18.75 g; 0.125 mol) in CHCl₃ (1250 ml) and aqueous sodium (or potassium) bicarbonate (15.95 g NaHCO₃; 0.19 mol in 380 ml H₂O). The mixture was stirred at room temperature for 2 hours following the addition of the peracid (the consumption of peracid was tested with starch-I₂ paper) and the two phases were separated. The organic phase was washed successively with 1 N aqueous sodium hydroxide and water, dried (Na₂SO₄) and filtered. The solvent (CH₂Cl₂ can be used, too, instead of CHCl₃) was removed under reduced pressure to yield crude **11** as a mixture of diastereomers, which was further purified by sublimation (70 °C; 10 torr) to give waxy colorless crystals (15.6 g; 0.094 mol; yield 75%) with mp 96-97 °C (lit.^{2b} mp 97-98 °C). IR 2915, 2861, 1452 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.60 (dd, 2H), 2.12 (m, 1H), 2.01 (dd, 1H), 1.83 (dd, 1H), 1.78-1.46 (m, 13H); MS (EI) m/z (relative intensity): 166 (20), 148 (18), 135 (47), 123 (65), 122 (37), 109 (41), 95 (76), 93 (40), 81 (100), 67 (74), and 166 (8), 148 (22), 123 (60), 122 (39), 109 (45), 95 (84), 93 (29), 81 (100), 67 (63).

9-Azidomethylbicyclo[3.3.2]decan-9-ol (12). The epoxide 11 (15.6 g; 0.094 mol) in DMF (520 ml) was treated with sodium azide (20.2 g; 0.31 mol) and boric acid (20.2 g; 0.32 mol) at reflux for 3 hours. The solvent was removed in vacuo and the residue was partitioned between ether and water. The ether extracts were washed with water, dried (Na₂SO₄) and filtered. The solvent was removed carefully on a rotary evaporator leaving 9-azidoethylbicyclo[3.3.2]decan-9-ol 12 as an oily residue (13.8 g; 0.066 mol; yield 70%). IR 3441, 2102 cm⁻¹ (lit.^{2b} IR 3420, 2100 cm⁻¹); ¹H NMR (300 MHz, CDCl₃) δ 3.96 (s, 1H), 3.44 (d, 1H, J_{AB} = 13 Hz), 3.31 (d, 1H, J_{AB} = 13 Hz), 2.25-2.02 (m, 3H), 1.92-1.37 (m, 13H).

The Hydrochloride Salt of 9-Aminoethylbicyclo[3.3.2]decan-9-ol (13). The hydroxyazide 12 (13.8 g; 0.066 mol) in ethanol (100 ml) was shaken with hydrogen over Adams catalyst (PtO₂ × H₂O; 750 mg) at 3 atm for 2 hours at room temperature in a Parr hydrogenator. The catalyst was removed by filtration and the ethanol was distilled on a rotary evaporator. Dried ether (freshly distilled over Na/benzophenone) was added to the residue and the resulting solution was saturated with gaseous hydrogen chloride (obtained by adding dropwise concentrated H₂SO₄ to NaCl) until no more precipitate was formed. The filtered solid was recrystallized from ethanol to afford white crystals of the hydrochloride salt of 9-aminoethylbicyclo[3.3.2]decan-9-ol 13 (13.1 g; 0.059 mol; yield 90%) with mp 240-242 °C (lit.^{2b} mp 241-242 °C). IR 3225, 3195 cm⁻¹; ¹H NMR (300 MHz, D₂O) δ 3.24 (d, 1H, J_{AB} = 13 Hz), 3.04 (d, 1H, J_{AB} = 13 Hz), 2.27 (m, 1H), 2.10-1.44 (m, 15H).

Bicyclo[3.3.3]undecan-9- and -10-ones (14 and **15**). The amine hydrochloride **13** (300 mg; 1.37 mmol) in water (6 ml) containing acetic acid glacial (0.3 ml; 5.25 mmol) was treated with sodium nitrite (0.3 g; 4.35 mmol) in water (3.3 ml) dropwise at 0 °C and warmed on a steam bath for 1 hour after the addition. The suspension was cooled and extracted with ether. The ether extracts were washed with water, sodium bicarbonate solution (10%), again water, dried (Na₂SO₄) and filtered. The solvent was removed in vacuo to yield a semicrystalline white solid, which, based on its¹H NMR spectrum, was a 2.7:1 mixture of bicyclo[3.3.3]undecan-9-one **14** to bicyclo[3.3.3]undecan-10-one **15** (227.4 mg; 1.37 mmol; yield 100%). IR 1690 cm⁻¹ (lit.^{2b} IR 1690 cm⁻¹); ¹H NMR (300 MHz, CDCl₃) δ 2.84 (q, 1H, CHC=O in 14), 2.56 (m, 2H×0.73 CH₂C=O in 14 and 4H×0.23 CH₂COCH₂ in 15).

Bicyclo[3.3.3]undecane (1). The mixture of ketones 14 and 15 (227.4 mg; 1.37 mmol) in triethylene glycol (30 ml) was heated with hydrazine hydrate (4.51 g; 0.09 mol) and hydrazine dihydrochloride (1.15 g; 0.011 mol) at 130 °C for 2.5 hours. Potassium hydroxide pellets (1.70 g; 0.03 mol) were added cautiously and the temperature was raised slowly to 210 °C with distillation of hydrazine-water. The mixture was heated for a further 2.5 hours and the product, bicyclo[3.3.3]undecane 1, collected on the cool part of the condenser where it had steam distilled or sublimed. Purification by sublimation (50 °C, 10 torr) afforded white crystals of 1 (160.3 mg; 1.05 mmol; yield 77%) with mp 191 °C (sealed tube; lit.²⁶ mp 192 °C; lit.³ mp 191-193 °C); ¹H NMR (300 MHz, CDCl₃) δ 2.38 (m, 2H), 1.45-1.55 (m, 18H), in accord with previous literature^{2,3}; ¹³C NMR (300 MHz, CDCl₃) δ 30.74 (2×CH, $J_{13C-H} = 120$ Hz), 28.96 (6×CH₂, $J_{13C-H} = 124.2$ Hz), 20.1 (3×CH₂, $J_{13C-H} = 125$ Hz); MS (EI) m/z (relative intensity): 152 (M⁺, 31), 124 (27), 109 (47), 96 (100), 81 (91), 67 (85), 55 (60).

[3.3.3]Propellane (30). Our thanks go to Professor Roger Alder, who kindly provided us with [3.3.3]propellanedione, converted to [3.3.3]propellane by Kishner-Wolff reduction according to the literature procedure.⁴⁷ [3.3.3]Propellane-3,7-dione (0.15 g; 0.84 mmol) was added to a mixture of hydrazine (0.8 ml 95%), potassium hydroxide (0.7 g), and triethyleneglycol (3 ml). The slurry was refluxed at 136 °C for 2.5 hours after which the water was distilled from the reaction until the pot temperature reached 220 °C. During the distillation [3.3.3]propellane crystallized on the condenser. The product was

removed from the condenser and the distillate by washing with ether. The combined extracts were dried (Na₂SO₄) and the ether removed by distillation at room temperature to provide a white solid which was further purified by slow sublimation in vacuum to give 53 mg of the highly volatile [3.3.3]propellane **30** (0.35 mmol; yield 42%) with mp 129 °C (lit.⁴⁸ mp 130 °C); ¹H NMR (300 MHz, CDCl₃) δ 1.53 (s); ¹³C NMR (300 MHz, CDCl₃) δ 60.3, 40.3, 24.6; MS (EI) m/z (relative intensity): 150 (M⁺, 48), 122 (11), 109 (19), 108 (21), 107 (100), 94 (18), 91 (20), 79 (50).

EPR Spectra. Manxane 2 (5 mg) was dissolved in di-*tert*-butyl peroxide (30 μ l). This solution was placed in a quartz EPR tube and degassed on a vacuum line by 3 freezepump-thaw cycles. The solvent, e.g. cyclopropane (*ca*. 260 μ l), was distilled in and the tube was sealed. Experiments were also carried out with toluene or methylcyclopentane in place of cyclopropane, in which case the freshly distilled solvent was added to the EPR tube prior to the freeze-pump-thaw cycles.

ENDOR Spectra. ¹H ENDOR resonance measurements were performed on samples containing 1-manxyl radicals 2 in toluene.

Spin Trapping. Spin trapping experiments were performed by adding a solution of 3 mg 2,4,6-tri-*tert*-butyl-nitrosobenzene (TBN) in 250 μ l toluene, to an irradiated sample of 4 mg manxane 1 in 25 μ l di-*tert*-butyl-peroxide, which contains 2 in concentrations of *ca*. 10⁻³-10⁻⁴ M. Identical EPR spectra were obtained by irradiation of a solution of 4 mg manxane, 2 mg TBN and 25 μ l di-*tert*-butyl-peroxide directly in the cavity of a Varian E4 spectrometer, with light from a 500 W Oriel high-pressure Hg lamp.

2.6 References

¹ The name suggested for this compound was inspired by the similarity between the hydrocarbon structure and the official coat of arms of the Isle of Man, a tiny, independent country surrounded by Ireland, Scotland and England. Most of the inhabitants of the isle, as well as the dialect spoken, are *Manx*. The emblem, known as *triskelion*, consists of three armored legs, which seems to be "kicking at Scotland, ignoring Ireland, and kneeling to England". Nickon, A.; Silversmith, E. F. In *Organic Chemistry: The Name Game*; Pergamon Press: New York, 1987; p 122.

² (a) Leonard, N. J.; Coll, J. C. J. Am. Chem. Soc. 1970, 92, 6685. (b) Coll, J. C.; Crist, D. R.; Barrio, M. d. C. G.; Leonard, N. J. J. Am. Chem. Soc. 1972, 94, 7092.

³ Doyle, M.; Parker, W. Tetrahedron Lett. 1970, 42, 3619.

⁴ (a) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. J. Am. Chem. Soc. 1973, 95, 8005.
(b) A study of the conformational flexibility of manxane by adiabatic mapping revealed two energy minima, corresponding to the C_{3h} and C_s conformations. The C_s conformation is higher in energy by 5.7 kcal/mol, mostly due to valence angle strain. Sessions, R. B.; Osguthorpe, D. J.; Dauber-Osguthorpe, P. J. Phys. Chem. 1995, 99, 9034.

⁵ Parker, W.; Steele, W. V.; Stirling, W.; Watt, I. J. Chem. Thermodyn. 1977, 7, 795.

⁶ (a) Leonard, N. J.; Coll, J. C.; Wang, A. H. J.; Missavage, R. J.; Paul, I. C. J. Am. Chem. Soc. 1971, 93, 4628. (b) Wang, A. H.; Missavage, R. J.; Byrn, S. R.; Paul, I. C. J. Am. Chem. Soc. 1972, 94, 7100.

⁷ Murray-Rust, P.; Murray-Rust, J.; Watt, C. I. F. Tetrahedron 1980, 36, 2799.

⁸ Gundersen, G.; Murray-Rust, P.; Rankin, D. W. H.; Seip, R.; Watt, C. I. F. Acta Chem. Scand. 1983, A37, 823.

⁹ (a) Jang, S.-H.; Bertsch, R. A.; Jackson, J. E.; Kahr, B. *Mol. Cryst. Liq. Cryst.* 1992, 211, 289. (b) Jang, S.-H.; Lee, H.-I.; McCracken, J.; Jackson, J. E. *J. Am. Chem. Soc.* 1993, 115, 12623. (c) Dostal, S.; Stoudt, S. J.; Fanwick, P.; Sereatan, W. F.; Kahr, B.; Jackson, J. E. *Organometallics* 1993, 12.

¹⁰ Parker, W.; Tranter, R. L.; Parker, W.; Watt, C. I. F.; Chang, L. W. K.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1974**, *96*, 7121.

¹¹ (a) Foote, C. S.; Woodward, R. B. *Tetrahedron* 1964, 20, 687. (b)) Foote, C. S. Ph.D. Thesis, Harvard University, 1962.

¹² Fitjer, L.; Quabeck, U. Synth. Commun. 1985, 15, 855.

¹³ Anderson, W. K.; Veysoglu, T. J. Org. Chem. 1973, 38, 2267.

¹⁴ Radicals (R[·]) can be generated by ultraviolet irradiation of a static solution of di-*tert*butyl peroxide in the presence of a hydrogen donor (R-H). Krusic, P. J.; Kochi, J. K. J. Am. Chem. Soc. **1968**, 90, 7155.

¹⁵ Hudson, A.; Jackson, R. A. J. Chem. Soc., Chem. Commun. 1969, 1323.

¹⁶ McMillen, D F.; Golden, D. M. Annu. Rev. Phys. Chem. 1982, 33, 493.

¹⁷ Hudson, A.; Hussain, H. A. J. Chem. Soc. B 1969, 793.

¹⁸ HF/6-31G* total energies for: propane -118.26365 H; *iso*propyl radical -117.63614 H; *iso*butane -157.29898 H; *tert*-butyl radical -156.67501 H. Δ H_f(propane) = -25.0 kcal/mol see Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. J. Phys. Chem. Ref. Data **1988**, 17, supplement 1; Δ H_f(*iso*propyl radical) = 21.1 kcal/mol (BDE_{*isopropyl-H*} = 98.2 kcal/mol) see Russell, J. J.; Seetula, J. A.; Gutman, D. J. Am. Chem. Soc. **1988**, 110, 3092; Δ H_f(*iso*butane) = -32.3 kcal/mol and Δ H_f(*tert*-butyl radical) = 11.6 kcal/mol (BDE_{*tert*-butyl-H} = 96.0 kcalmol) see Gutman, D. Acc. Chem. Res. **1990**, 23, 375.

¹⁹ Roberts, B. P.; Steel, A. J. J. Chem. Soc., Perkin Trans 2 1994, 2155.

²⁰ Dye, J. L.; Nicely, V. A. J. Chem. Educ. 1971, 48, 443.

²¹ (a) Jackson, R. A. J. Chem. Soc, Perkin Trans 2 1983, 523. (b) Jackson, R. A. J. Magn. Reson. 1987, 75, 174. (c) Jackson, R. A. J. Chem. Soc., Perkin Trans 2 1993, 1991.

²² (a) Kurreck, H.; Kirste, B.; Lubitz, W. Angew. Chem., Int. Ed. Engl. 1984, 23, 173. (b) Kurreck, H. In Electron Nuclear Double Resonance Spectroscopy of Radicals in Solution: Application to Organic and Biological Chemistry; VCH: New York, 1988.

²³ The semiempirical MO method known as INDO has been developed by Pople, Beveridge and Dobosh and represents the lowest level of approximation on which unpaired electron distributions in free radicals can be accommodated, since the one-center exchange integrals are necessary to introduce spin exchange polarization effects. Pople, J. A.; Beveridge, D. L.; Dobosh, P. A. J. Chem. Phys. 1967, 47, 2026.

²⁴ Heller, C.; McConnell, H. M. J. Phys. Chem. 1960, 32, 1535.

²⁵ (a) Griller, D.; Ingold, K. U. J. Am. Chem. Soc. 1974, 96, 6715. (b) Kochi, J. K. Adv. Free Radical Chem. 1975, 5, 189.

²⁶ (a) Geske, D. H. Prog. Phys. Org. Chem. 1967, 4, 125. (b) Lloyd, R. V.; Wood, D. E. J. Am. Chem. Soc. 1977, 99, 8269. (c) Kemball, M. L.; Walton, J. C.; Ingold, K. U. J. Chem. Soc., Perkin Trans 2 1982, 1017. (d) MacCorquodale, F.; Walton, J. C. J. Chem. Soc., Faraday Trans 1 1988, 84, 3233. (e) Ingold, K. U.; Walton, J. C. Acc. Chem. Res. 1989, 22, 8.

²⁷ Alder, R. W.; Sessions, R. B.; Symons, M. C. R. J. Chem. Res., Synop. 1981, 82.

²⁸ Symons, M. C. R.; Chandra, H.; Alder, R. W. J. Chem. Soc., Chem. Commun. 1988, 844.

²⁹ (a) Paddon-Row, M. N.; Houk, K. N. J. Am. Chem. Soc. 1981, 103, 5046. (b) Paddon-Row, M. N.; Houk, K. N. J. Phys. Chem. 1985, 89, 3771.

³⁰ Walton, J. C. J. Chem. Soc., Perkin Trans 2 1988, 1371.

³¹ (a) Della, E. W.; Elsey, G. M.; Head, N. J.; Walton, J. C. J. Chem. Soc., Chem. Commun. 1990, 1589. (b) Della, E. W.; Head, N. J.; Mallon, P.; Walton, J. C. J. Am. Chem. Soc. 1992, 114, 10730.

³² Krusic, P. J.; Rettig, T. A.; Schleyer, P. v. R. J. Am. Chem. Soc. 1972, 94, 995.

³³ Walton, J. C. Chem. Soc. Rev. 1992, 105.

³⁴ Kawamura, T.; Matsunaga, M.; Yonezawa, T. J. Am. Chem. Soc. 1975, 97, 3234.

³⁵ Maillard, B.; Walton, J. C. J. Chem. Soc., Chem. Commun. 1983, 900.

³⁶ Kawamura, T.; Yonezawa, T. J. Chem. Soc., Chem. Commun. 1976, 948.

³⁷ Olah; G. A.; Liang, G.; Schleyer, P. v. R.; Parker, W.; Watt, C. I. F. J. Am. Chem. Soc. 1977, 99, 966.

³⁸ Karplus, M. J. Am. Chem. Soc. 1963, 85, 2870.

³⁹ (a) Lagercrantz, C. J. Phys. Chem. 1971, 75, 3466. (b) Janzen, E. G. Acc. Chem. Res. 1971, 4, 31. (c) Perkins, M. J. Adv. Phys. Org. Chem. 1980, 17, 1. (d) Janzen, E. G.; Haire, D. L. Adv. Free Rad. Chem. (Greenwich) 1990, 1, 253.

⁴⁰ (a) Terabe, S.; Konaka, R. J. Am. Chem. Soc. 1971, 93, 4306. (b) Terabe, S.; Konaka, R. J. Chem. Soc., Perkin Trans 2 1973, 369.

⁴¹ Doba, T.; Ichikawa, T.; Yoshida, H. Bull. Chem. Soc. Jpn. 1977, 50, 3158.

⁴² Weil, J. A.; Bolton, J. R.; Wertz, J. E. In Electron Paramagnetic Resonance:

Elementary Theory and Practical Applications; John Wiley: New York, 1994, p 497.

⁴³ Steinfeld, J. I.; Francisco, J. S.; Hase, W. L. In *Chemical Kinetics and Dynamics*; Prentice Hall, Inc.: Englewood Cliffs, 1989, p 8.

44 Griller, D.; Ingold, K. U. Acc. Chem. Res. 1976, 9, 13.

⁴⁵ Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; ed. P. de Mayo, Academic Press: New York, 1980, vol.1, p 161.

⁴⁶ The front strain (F-strain) in 29 is given by six CH₃-CH₃ gauche-gauche interactions, ~ 6×1.0 kcal/mol, along with twice the strain caused by bridgehead pyramidalization, 2×7.3 kcal/mol (see Table 2.5), which adds to approximately 21 kcal/mol.

⁴⁷ Weber, R. W.; Cook, J. M. Can. J. Chem. 1978, 56, 189.

⁴⁸ Adcock, W.; Binmore, G. T.; Krstic, A. R.; Walton, J. C.; Wilkie, J. J. Am. Chem. Soc. 1995, 117, 2758.

⁴⁹ Olefin Strain (OS) is defined as the difference between the strain energy of the olefin and that of its parent saturated hydrocarbon. Maier, W. F.; Schleyer, P. v. R. J. Am. Chem. Soc. 1981, 103, 1891.

⁵⁰ McEwen, A. B.; Schleyer, P. v. R. J. Am. Chem. Soc. 1986, 108, 3951.

⁵¹ (a) Walling, C.; Thaler, W. J. Am. Chem. Soc. 1961, 83, 3877. (b) Erben-Russ, M.; Michel, C.; Bors, W.; Saran, M. J. Phys. Chem. 1987, 91, 2362.

⁵² In a single run, the compound with the highest mass fragment at 237 amu exhibited a very weak peak at 292 amu, which most probably is the molecular ion. Such a compound would result from the 222 amu product by substitution of a H for a *tert*-butoxyl group.

⁵³ Hünig, S.; Benzing, E.; Lücke, E. Chem. Ber. 1957, 90, 2833.

CHAPTER 3

5-MANXINYL RADICAL: A COMPUTATIONAL AND EXPERIMENTAL STUDY

Abstract: A modified literature procedure for the preparation of 1-azabicyclo[3.3.3]undecane (manxine) is described. Our attempts to produce 1-azabicyclo[3.3.3]undec-5-yl radical by bridgehead H-abstraction from the amine with *tert*-butoxyl radicals, or by γ irradiation either of manxine in adamantane matrix, or of 1-azoniatricyclo[3.3.3.0]undecane bromide or tetrafluoroborate salts, are presented. In view of the exceptional persistence of 1-manxyl radicals, a logical subsequent target of our study appears to be the bridgehead radical of 1-azabicyclo[3.3.3]undecane (manxine), where the effect of through-space σ interactions with the opposite nitrogen atom are to be probed. The synthesis of manxine 1 described herein represents a modified but efficient route to this compound, based on the original published procedure of Leonard et al.¹;



however, the preparation and characterization of the corresponding bridgehead radical, 5manxinyl 2, remain an unachieved goal. EPR investigations aiming to produce 2 by Habstraction from 1, or by γ -irradiation either of manxine 1 in an adamantane matrix, or of 1-azoniatricyclo[3.3.3.0]undecane bromide or tetrafluoroborate salts, failed to reveal evidence for the 5-manxinyl radical.

3.1 Results and Discussion

1-Azabicyclo[3.3.3]undecane 1 (manxine) was prepared following the procedure of Leonard et al.¹ from 1-azoniatricyclo[3.3.3.0]undecane bromide 3 by reduction with sodium and liquid ammonia (Scheme 5.1). The 1-azoniapropellane salt 3 was readily accessible employing the convenient synthesis of Šorm and Beránek². Several modifications were introduced, however, in the synthesis of tris(2-carboethoxyethyl)- nitromethane 10 and its reduction to 5,5-bis(2-carboethoxyethyl)-2-pyrrolidone 9. The triethyl ester 10 was obtained by an alternative route which involves a one pot threefold Michael addition of nitromethane to ethyl acrylate in high yield,³ instead of going through the sequential synthesis of tris(2-cyanoethyl)nitromethane, hydrolysis of the trinitrile and esterification of the triacid, as in the method of Šorm and Beránek². Subsequently, reduction of 10 to the pyrrolidone 9 was successfully achieved under moderate pressures (60 psi) at 80 °C with 30% Pd/C as catalyst, whereas initially, drastic reaction conditions (1500 psi and 110 °C) were employed for this chemical transformation. The activated T-1 Raney nickel catalyst, ⁴ commonly used in hydrogenations carried out at low pressures (\geq 60 °C), failed in our hands to reduce 10 to 9.

A similar six-step route to 1-azoniatricyclo[3.3.3.0]undecane chloride was developed by Newcome et al.⁵ (Scheme 5.2). In an attempt to reduce the number of steps for preparation of **3**, we converted **10** to tris(3-hydroxypropyl)aminomethane in one step by lithium aluminum hydride reduction; the experimental yield, however, was moderate (35%) and we made no efforts to improve it further.

NMR analysis of manxine in CH_2Cl_2 : $CHCl_3$ (1:1) revealed a "frozen spectrum" near -80 °C, a temperature in close agreement with that found for manxane.¹ Both ¹³C and ¹H NMR spectra of 1 indicate the unusual nature of the methine carbon and proton. The one-bond C-H coupling constant was estimated as 121 ± 5 Hz for the bridgehead C-H bond in manxine hydrochloride.¹ Overlap of signals in the off-resonance decoupled spectra of 1 precluded accurate measurement of the C-H direct couplings at the time of its first synthesis. We obtained the values of the C-H coupling constants in 1 from its 2D

109



Scheme 3.1



Scheme 3.2

Heteronuclear J-Resolved⁶ spectrum taken in CDCl₃ at ambient temperature, finding an even lower bridgehead C-H coupling, 120 Hz, for the free amine then for its hydrochloride.

The flattening of the bridgehead regions of the bicyclo[3.3.3] system is confirmed by X-ray crystallographic studies on manxine hydrochloride.⁷ In the crystal, the manxinium cation possesses C₃ symmetry with each of the three constituent eight-membered rings in boat-chair conformation. The internal strain is obvious from the angles obtained by X-ray analysis: 117-120° for the CCC angles in the methylene bridges and 114-116° for the bridgehead CCC and CNC angles.

112

in the UV spectrum of 1, reflects a reduction in the energy difference between the ground state and the excited state, where nitrogen is expected to approach coplanar bonding.¹ Analogously, the ease of oxidation of 1 (the oxidation peak potential appears at 0.38 V in aqueous alkaline solution compared to 0.73 V for triethylamine) arises from relief of angular strain that accompanies formation of the sp² hybridized aminium radical.⁹

Other spectroscopic and photophysical studies on manxine 1 include reports of its fluorescence spectrum and adiabatic ionization potential,^{9,10} of the two-photon resonanceenhanced multiphoton ionization (REMPI) spectrum for the lowest excited electronic state of 1,¹¹ as well as flash photolysis studies of 1 in acetonitrile solution at 248 nm, where the resultant transient spectra were assigned as the absorption of the solvated aminium radical cation of 1^{12} .

Aliphatic carbon-centered radicals are significantly stabilized by lone pair donors or acceptors which can delocalize the unpaired electron.¹³ Despite such additional stabilization by π -delocalization over the N atom in 11, the BDE estimates (HF/6-31G*) of the methine C-H and methylenic C-H bonds next to nitrogen in 1 (Table 3.1), point to the tertiary site in 1 as the one which affords the greatest strain relief upon H-abstraction.



Compound	Total Energy ^b	ΔH_{f}^{c}	SE ^d	∆SE [•]	BDE ^r
Manxine 1	-444.16223	1.5 (-19.2)	28.5 (7.8)		
5-Manxinyl Radical 2	-443.93979	36. 8 (-2.7)	19.9 (7.1)	-8.6 (-0.7)	87.4 (95.3)
2-Manxinyl Radical 11	-443.54295	42.4 (4.0)	23.3 (5.3)	-5.2 (-2.5)	93.0 (95.7)
1-Manxinium-5-yl Radical 12 ⁸	-443.93979	(178.2)		-6.0 (7.2)	90.0 (88.8)
1-Manxinium Radical Cation 13	-443.95605	(154.3)		-18.8 (-8.7)	

 Table 3.1 Calculated Heats of Formation, Strain Energies and Bond Dissociation

 Energies*

^a In kcal/mol; structures were fully optimized at HF/6-31G* (MNDO) level, using Spartan 4.0

(Wavefunction Inc., Irvine, CA).

^b Total energies are given in hartrees, 1 H = 627.5 kcal/mol.

^e Heat of formation; calculated from isodesmic reactions vs. trimethylamine, pentane, *iso*butane and ethane. The BDE estimates were used to calculate heats of formation for the product radicals.

^d Strain energy; from calculated ΔH_f and Benson's group equivalents (Benson, S. W. *Thermochemical Kinetics*; John Wiley: New York, 1976) for manxine 1, and from isodesmic rections vs. *isobutane/tert*butyl radical for 2 and 12, vs. propane/*iso*propyl radical for 11, and vs. trimethylamine/trimethylammonium radical cation for 13.

[•] Defined vs. SE of manxine 1.

^f Based on BDE (t-Bu-H) = 96.0 kcal/mol (Gutman, D. Acc. Chem. Res. 1990, 23, 375), and BDE (iso-Pr-H) = 98.2 kcal/mol (Russell, J. J.; Seetula, J. A.; Gutman, D. J. Am. Chem. Soc. 1988, 110, 3092). ^b HE/6-31 G^{*} total energy for protonated manying: -AAA 55A25 H: MNDO heat of formation for protonated

⁸ HF/6-31G* total energy for protonated manxine: -444.55425 H; MNDO heat of formation for protonated manxine: 165.5 kcal/mol.

Bridgehead H-abstraction in the protonated manxine would yield radical 12, where delocalization of the unpaired electron over the opposite bridgehead is precluded by protonation. The strain energy relief calculated for this process is slightly lower (6.0 kcal/mol; Table 3.1) than upon formation of 2 (8.6 kcal/mol; Table 3.1). In view of the puzzlingly low β -hyperfines in 1-manxyl radical, it seems of interest to examine the manxinium radical cation 13, too. Flash photolysis of 1 in CH₃CN with a KrF excimer laser at 248 nm produced transient spectra with first-order decay, assigned to the aminium radical 13.¹² The lifetime reported for the radical cation 12, of 4.6 µs, is lower than for the radical cations of DABCO, 12 µs, triethylamine, 14 µs, or quinuclidine, 6.3 µs.





Quinuclidine

DABCO

The reversibility of the electrochemical oxidation of amines is also a measure of the radical cation lifetime and it has been used as a test to recommend which aminium radicals might be good candidates for EPR studies. This strategy led to the discovery of the exceptionally persistent 9-*tert*-butylazabicyclo[3.3.1]nonane radical cation 14, whose stability is based on stereoelectronic grounds.¹⁴ Rapid loss of a C_{α} -H proton from tertiary amine radical cation, leading to an easily oxidized aminoalkyl radical and hence very rapid destruction, is usually responsible for their decay,¹⁴ whereas in 14 the α -H is constrained to lie in the nodal plane of the formal charge-bearing p-orbital at nitrogen, which results in a dramatic increase in the radical cation lifetime. However, the cyclic voltammetry oxidation wave of

1 is irreversible,⁹ which does not leave much hope for the observation of 13 by EPR. By analogy with the EPR studies on the radical cations of quinuclidine 15¹⁵ and 1,3,6,8-



tetraazatricyclo[4.4.1.1^{3,8}]dodecane 16,¹⁶ we attempted to produce 13 by one-electron chemical oxidation of 1 with tris(*p*-bromophenyl)aminium hexachloroantimonate in butyronitrile at -100 °C, but no EPR spectra were obtained. It is almost certain that 13 is formed under these conditions, but most likely it reacts so fast that it can not reach detectable concentrations. Aminium radicals are frequently formed in high-energy ionizing irradiation of appropriate amine precursors, however, this is an "overkill" method and generally not a clean source of radicals.¹⁷ We irradiated manxine in chloroform with ⁶⁰Co γ -rays at 77 K to obtain a strong but unresolved EPR signal, circa 80 G wide.

As mentioned previously, aminium radicals' lifetimes are principally controlled by their rates of deprotonation, although in several instances they appear to decompose by C-C bond cleavage. In highly acidic media the deprotonation rate is decreased and the lifetime of the aminium radicals increases appreciably to allow detection by EPR spectroscopy. Thermal or photolytic decomposition of *N*-haloamines in highly acidic media has successfully generated aminium radicals.¹⁷ UV photolysis of the appropriate amine Cl₂ adducts in CF₃SO₃H at 0 to -50 °C produced bridgehead aminium radicals 17, 18 and 19, and readily allowed their characterization by EPR.¹⁸ This alternate method appears as a conceivable route to produce 13 in high enough concentration that would allow detection by EPR and remains to be tested in future work.



We tried several methods to prepare the bridgehead carbon-centered radical 2, however, all attempts to generate 2 in solution or in matrix have been unsuccessful. It has been shown that impurities added to a solid adamantane matrix undergo selective radiation damage to give trapped free radicals which exhibit solution-like, isotropic EPR spectra at room temperature.¹⁹ X-rays irradiation of aliphatic amines in adamantane matrix cleanly afford α -aminoalkyl radicals. The size of the amine is limited to that which can replace an adamantane molecule in the adamantane crystal lattice without crowding for isotropic spectra to be obtained. In the case of tertiary amines, triethylamine gives a good spectrum but upon addition of only one more carbon atom (e.g. diethyl-n-propylamine) an isotropic spectrum is not obtained. The radicals diffuse only very slowly through the adamantane matrix and typically exhibit half-lives of 10 h at room temperature. Incorporation of the amine was accomplished in this study by dissolving adamantane in the desired amine followed by evaporation or by precipitation and filtration. Manxine 2 is slightly larger than adamantane, by ca. 10%, but since both molecules are globular, very close in shape and size, we assumed that 1 might be sufficiently flexible to fold into the volume of an

adamantane molecule and attempted to generate it in the matrix. We irradiated solid samples of 10% manxine (by weight) in adamantane at 77 K in a 60 Co γ -ray source with doses of *ca*. 1 Mrad to get, however, unresolved weak EPR signals.

The analogous 1-azabicyclo[4.4.4]tetradec-6-yl radical 20 was formed by γ irradiation of 1-azoniatricyclo[4.4.4.0]tetradecane tetrafluoroborate, either as the pure salt or in dilute frozen CD₃OD solution.²⁰ The EPR spectrum of 20 showed a broad quartet of lines ($a_{H\beta} = 24$ G) with no significant coupling to nitrogen. Our similar experiments on 1azoniatricyclo[3.3.3.0]undecane tetrafluoroborate 21 or bromide 3, resulted in strong but featureless EPR spectra from the pure salts. γ -Irradiation of 21 or 3 in dilute frozen CD₃OD solutions produced a strong septet of broad lines (6.5 G), while the matrix developed an intense purple color which disappeared above 150 K. However, the control probe of pure CD₃OD yielded upon γ -irradiation identical EPR signals, which we believe are due to trapped electrons in the γ -irradiated methanol- d_4 .²¹



We also attempted to produce 2 by H-abstraction from 1 with *tert*-butoxyl radicals. UV photolysis of cyclopropane (250 μ l) solutions of 2 (5 mg) and di-*tert*-butyl peroxide (25 μ l) yielded unresolved, featureless EPR spectra, with widths of circa 30 G (Figure 3.1a). The reactions of amines with photolytically produced *tert*-butoxyl radicals

have been shown previously to occur by H-abstraction at the carbon adjacent to nitrogen and are several orders of magnitude faster than in typical hydrocarbon substrates. This technique, which is perfectly satisfactory for radical generation,²² was equally unsuccessful for Griller et al.²³, who meant to characterize by EPR the α -aminoalkyls resulted by Habstraction from a variety of amines. They concluded that the large number of hyperfine interactions coupled with the general absence of sharp spectral lines preclude easy detection of these radicals. In other cases, however, α -aminoalkyl radicals generated by Habstraction were unambiguously characterized by EPR.²⁴

Azobisisobutyronitrile (AIBN), which decomposes thermally or photolytically to generate 2-cyano-2-propyl radicals,²⁵ was also employed in reaction with 1. UV photolysis of a solution of manxine 1 (5 mg) and AIBN (20 mg) in cyclopropane (250 µl) directly in the cavity of a Varian E4 spectrometer afforded a weak transient EPR spectrum (Figure 3.1b) which could be resolved into a triplet (1:1:1; $a_N = 11.5$ G) and a doublet (1:1; $a_H = 3$ G). The assignment of this spectrum is by no means obvious, since 2 should exhibit a much larger hyperfine to the geminal hydrogen, while 13 should display at least a quartet due to coupling with the β -hydrogens. In the control experiment, photolysis of AIBN alone in cyclopropane, generated, as expected, the EPR spectrum of the persistent 2-cyano*iso*propyl radical, which is not observed when manxine is present.

Generation of the bridgehead carbon-centered radical 2 proved to be much more difficult than we initially expected. Our efforts to produce it under a variety of conditions were fruitless, but by no means did we use up all the methods developed for making aminoalkyl radicals. Besides adamantane, matrices such as SF_{6} , ²⁶ GeCl₄, ²⁷ camphane, ²⁸

119



Figure 3.1 The EPR spectra (9.1 GHz) resulting from UV photolysis of manxine in a) di-*tert*-butyl peroxide/cyclopropane, and in b) AIBN/cyclopropane, at -90 °C.

urea inclusion compounds,²⁹ silica gel³⁰ and others, have been used to trap rapidly reorienting free radicals. Radiolytic generation of radicals,³⁰ as well as other chemical and photochemical means, have been successful in particular cases to allow explicit EPR studies. Ultimately, we can at least hope that the knowledge acquired will help us in future endeavors.

3.2 Experimental Methods

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Fourier-transform infrared (IR) spectra were recorded on a Nicolet IR/42 spectrometer. Electron impact (EI) mass spectra were run on a Fisons VG Trio-1 MS spectrometer which operates in line with a Hewlett Packard 5890 gas chromatograph for GC-MS measurements. Routine ¹H and ¹³C NMR spectra were obtained at 300 MHz, on Varian GEMINI 300 or VXR-300 spectrometers. All spectra were recorded at ambient temperature and are referenced to solvent signals. 2D Heteronuclear *J*-Resolved experiments were performed on a Varian VXR-500 spectrometer at 25 °C. γ -Irradiation experiments were performed on a US Nuclear Corporation variable flux γ -irradiator, model E-0117-M-1, by exposing samples inserted in a Dewar flask filled with liquid N₂ and placed in the cavity areas, to doses of circa 1 Mrad of γ -rays.

tris(2-Carboethoxyethyl)nitromethane (10). To a stirred solution of nitromethane (15.3 g; 0.25 mol), Triton B (40% benzyltrimethylammonium hydroxide in water; 1 ml) and dimethoxyethane (40 ml) was added dropwise ethyl acrylate (75 g; 0.75 mol) over 30 min at a rate such that a temperature of 72-78 °C was maintained. Additional Triton B was added twice when the temperature started to decrease; then stirring was continued for an additional 45 min. After concentration in vacuo, the residue was dissolved in CHCl₃ (250 ml), washed with 0.5 N HCl (100 ml), and then brine (3×80 ml), dried over anhydrous MgSO₄, filtered and concentrated in vacuo to afford the crude triester, which was column chromatographed on silica gel eluting with EtOAc/hexane (1:5) to give triester **10** as a light yellow oil (72.2 g; 0.2 mol; yield 80%). IR 2984, 1734, 1541, 1188 cm⁻¹ (lit.³ IR 1738, 1542 cm⁻¹); ¹H NMR (300 MHz, CDCl₃) δ 4.08 (q, 6H), 2.24 (m, 12H), 1.20 (t, 9H), in accord with previous reports³; ¹³C NMR (300 MHz, CDCl₃) δ 171.58, 91.81, 60.83, 30.09, 28.55, 13.99.

5,5-bis(2-Carboethoxyethyl)-2-pyrrolidone (9). The experimental procedure used is based on the reduction of the analogous tris(2-carboethoxymethyl)nitromethane.³¹ The triester **10** (72.2 g; 0.2 mol) in methanol (120 ml) was hydrogenated over 30% Pd/C (1.3 g) in a stainless steel autoclave at 60 psi and 80 °C for 12 hours. The reaction product was filtered to remove the catalyst, diluted with ethanol, shaken with activated charcoal and filtered. The filtrate was taken to dryness under reduced pressure to give crude 5,5-bis(2-carboethoxyethyl)-2-pyrrolidone 9 (55.9 g; 0.196 mol; yield 98 %) as an oil which crystallized upon standing in the refrigerator (mp 45 °C; lit.² mp 46 °C), and was used in the next step without further purification. IR 2980, 1732, 1691, 1305, 1186 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.34 (s, 1H), 4.25 (q, 4H), 2.48-2.32 (m, 6H), 2.00-1.94 (m,

6H), 1.26 (t, 6H); ¹³C NMR (300 MHz, CDCl₃) δ 177.33, 173.05, 60.68, 60.61, 34.53, 30.19, 30.14, 28.93, 14.05.

8-(2-Carboethoxyethyl)-3,5-dioxopyrrolizidine (8). Pyrrolidone **9** (55.9 g; 0.196 mol) was heated on an oil bath at 205-210 °C and 12 torr for 5 hours. The solidified reaction product was triturated with ether, the undissolved portion filtered off and recrystallized from ethanol/diethyl ether to afford pure 8-(2-carboethoxyethyl)-3,5dioxopyrrolizidine **8** (37.5 g; 0.157 mol; yield 80%). mp 95-96 °C (lit.² 103 °C); ¹H NMR (300 MHz, CDCl₃) δ 4.13 (q, 2H), 2.90-1.90 (m, 12H), 1.25 (t, 3H).

8-(3-Hydroxypropyl)-pyrrolizidine (7) and 2,2-bis-(3-Hydroxypropyl)-

pyrrolidine (6). A solution of 8 (37.5 g; 0.157 mol) in THF (200 ml; freshly distilled over Na/benzophenone) was added in the course of 7 hours to a suspension of LiAlH₄ (19 g; 0.5 mol) in THF (600 ml) maintaining the reaction temperature at 70-80 °C. The reaction mixture was then refluxed for 2 more hours and allowed to stand overnight. The excess LiAlH₄ was carefully decomposed with water (24 ml) under stirring and cooling. Aqueous sodium hydroxide (36 g NaOH in 180 ml H₂O) were than added dropwise at 30-40 °C to decompose the reaction complex. The resultant white precipitate was filtered and the THF solution was taken to dryness under reduced pressure and subjected to fractional distillation. 8-(3-Hydroxypropyl)-pyrrolizidine 7 was collected at 140-160 °C and 15 torr (lit.² bp_{12 mm} 130-150 °C; 13.26 g; 78.5 mmol; 50%). ¹H NMR (300 MHz, CDCl₃) δ 3.53 (t, 2H), 3.04-2.86 (m, 2H), 2.60-2.49 (m, 2H), 1.82-1.54 (m, 13H); ¹³C NMR (300 MHz, CDCl₃) δ 72.57, 63.37, 55.28, 40.56, 38.23, 27.27, 24.62. A higher boiling fraction was

collected at 170-175 °C and 1.5 torr (lit.² bp_{0.6 mm} 165-180 °C) which yielded 2,2-bis-(3-hydroxypropyl)pyrrolidine 6 as a viscous colorless oil (8.5 g; 45.5 mmol; yield 29%).¹H NMR (300 MHz, CDCl₃) δ 4.20 (s, broad, 1H), 3.51 (m, 4H), 2.92 (t, 2H), 1.82-1.38 (m, 14H); ¹³C NMR (300 MHz, CDCl₃) δ 63.71, 62.89, 45.41, 36.98, 35.94, 27.69, 25.81.

8-(3-Bromopropyl)-pyrrolizidine Hydrobromide (5). 8-(3-Hydroxypropyl)pyrrolizidine 7 (13.26 g; 78.5 mmol) and a solution of HBr 31% in glacial acetic acid (40 ml) were placed in a high-pressure reactor and heated to 100 °C in an oven for 11 hours. The reaction mixture was worked up by driving off the acid under reduced pressure, diluting the residue with water, extracting with ether and taking the aqueous solution to dryness to yield 5 (mp 123 °C; lit.² mp 123 °C; 23.3 g; 74.6 mmol; yield 95%).

2,2-bis-(3-Bromopropyl)-pyrrolidine Hydrobromide (4) The pyrrolidine derivative 6 (8.5 g; 45.5 mmol) and a solution of 31% HBr in glacial acetic acid (80 ml) were placed in a high-pressure reactor and heated to 100°C in an oven for 14 hours. The reaction mixture was worked up by driving off the acid under reduced pressure, diluting the residue with water, extracted with ether and taking the water layer to dryness to afford to 4 (mp 95°C; lit.² mp 95-96 °C; 16.4 g; 43.2 mmol; yield 95%).

1-Azoniatricyclo[3.3.3.0]undecane Bromide (3). (a) A solution of 5 (23.3 g; 74.6 mmol) in water (600 ml) was poured under vigorous stirring over freshly precipitated silver oxide prepared from silver nitrate (37 g; 0.218 mmol) and sodium hydroxide (8.9 g). The reaction mixture was stirred for 30 minutes, allowed to stand overnight, filtered, the filtrate taken to the boil, again filtered and treated with a calculated amount of picric acid

124
(17.1 g; 74.6 mmol). The picrate precipitated as yellow needles, was recrystallized from 70% ethanol and triturated with water and 48% aqueous HBr. The liberated picric acid was extracted with ether, the aqueous solution was filtered with active charcoal and taken to dryness under reduced pressure or precipitated with THF to yield 1-azoniatricyclo-[3.3.3.0]undecane bromide **3** as white prisms (16.6 g; 71.6 mmol; yield 96%). (b) A solution of the hydrobromide **4** (16.4 g; 43.2 mmol) in water (450 ml) was poured over freshly prepared silver oxide from AgNO₃ (33 g; 194 mmol) and NaOH (7.9 g). The resulting mixture was stirred for one hour and allowed to stand overnight. The precipitated AgBr was filtered off, the filtrate was briefly taken to the boil and filtered again. The aqueous solution of 1-azoniatricyclo[3.3.3.0]undecane hydroxide was either converted to the picrate as described previously, or transformed directly into the bromide by neutralization with aqueous HBr. The aqueous solution was shaken with ether, filtered over charcoal and taken to dryness under reduced pressure or precipitated with THF to afford **3** (9.6 g; 41.5 mmol; yield 96%).

1-Azoniatricyclo[3.3.3.0]undecane picrate: mp 319°C (lit.² mp 318 °C); ¹H NMR (300 MHz, CDCl₃) δ 9.03 (s, 2H). 3.76 (t, 6H), 2.14 (m, 6H), 2.05 (q, 6H), 1.22 (s, 1H).

1-Azoniatricyclo[3.3.3.0]undecane bromide **3**: mp > 275 °C (lit.² mp > 350 °C); ¹H NMR (300 MHz, D₂O) δ 3.26 (t, 6H), 2.58 (m, 6H), 2.03 (q, 6H); ¹³C NMR (300 MHz, D₂O, TMSP Sodium) δ 93.64, 64.56 (t), 37.35, 23.29.

1-Azoniatricyclo[3.3.3.0]undecane Tetrafluoroborate (20). 1-Azoniatricyclo-[3.3.3.0]undecane tetrafluoroborate was prepared either from 1-azoniatricyclo[3.3.3.0]undecane bromide 3 reacted in aqueous solution with a stoichiometric amount of NaBF₄, or from 1-azoniatricyclo[3.3.3.0]undecane picrate reacted with a calculated amount of 48% aqueous HBF₄. The tetrafluoroborate salt 18 was isolated from the reaction mixture by concentration in vacuo and coprecipitation with diethyl ether. Recrystallization from ethanol afforded pure 20, mp > 275 °C. ¹H NMR (300 MHz, CDCl₃) δ 3.57 (t, 6H), 1.86 (m, 12H); ¹³C NMR (300 MHz, D2O, TMSP Sodium) δ 96.89, 67.14 (t), 39.51, 25.74.

Manxine (1). 1-Azoniatricyclo[3.3.3.0]undecane bromide 3 (1 g; 4.3 mmol) was added to liquid ammonia (circa 50 ml) in a well-stirred, cooled flask, and small pieces of freshly cut sodium metal were added. Fresh sodium was added as the blue color disappeared, and the addition was continued until the blue color persisted. The reaction vessel was allowed to warm to room temperature and the ammonia evaporated slowly. Water and ether were carefully added and the ether layer was washed, dried over Na₂SO₄, filtered and evaporated to dryness. The crystalline residue was sublimed at 30 °C and 15 mm to give manxine 1 as a white volatile solid (260 mg; 1.7 mmol; yield 40%). mp 150-152 °C (lit.^{1b} mp 150-152 °C); ¹H NMR (300 MHz, CD₃CN) δ 2.72 (t, 6H), 2.53 (septet, 1H), 1.59-1.43 (m, 12H); ¹³C NMR (300 MHz, CD₃CN) δ 49.54 (3×NCH₂, J_{13C-H} = 134.4 Hz), 31.99 (<u>C</u>H, J_{13C-H} =120.8 Hz), 28.21 (3×NCH₂<u>C</u>H₂, J_{13C-H} = 123.9 Hz), 24.28 ($3 \times \text{NCH}_2\text{CH}_2$, $J_{13C-H} = 123.9 \text{ Hz}$); MS (EI) m/z (relative intensity): 153 (M⁺, 39), 138 (17), 124 (50), 110 (26), 97 (34), 96 (58), 84 (17), 83 (31), 82 (100), 69 (25), 58 (17), 55 (22), 43 (25), 42 (50), 41 (62).

Manxinium Tetrafluoroborate (21). Manxine 1 (15 mg; 0.1 mmol) was dissolved in 48% aqueous HBF₄ (20 μ l) diluted with water (0.5 ml). Diethyl ether was

added and the resulting white precipitate was filtered to afford pure manxinium

tetrafluoroborate 21, mp > 225 °C with decomposition (15.7 mg; 0.065 mmol; yield 65%).

¹H NMR (300 MHz, CDCl₃) δ 8.72 (s, broad, 1H), 3.28 (m, 6H), 2.58 (septet, 1H), 1.87

(m, 6H), 1.65 (m, 6H); ¹³C NMR (300 MHz, CDCl₃) δ 49.93 (J_{13C-H} = 140 Hz), 28.09

 $(J_{13C-H} = 123 \text{ Hz}), 26.48 (J_{13C-H} = 125 \text{ Hz}), 18.54 (J_{13C-H} = 126 \text{ Hz}).$

3.3 References

- ¹ (a) Leonard, N. J.; Coll, J. C. J. Am. Chem. Soc. 1970, 92, 6685. (b) Coll, J. C.; Crist, D. R.; Barrio, M. d. C. G.; Leonard, N. J. J. Am. Chem. Soc. 1972, 94, 7092.
- ² Šorm, F.; Beránek, J. Collect. Czech. Chem. Commun. 1954, 19, 298.

³ Weis, C. D.; Newkome, G. R. J. Org. Chem. 1990, 55, 5801.

⁴ Dominguez, X. A.; Lopez, I. C.; Franco, R. J. Org. Chem. 1961, 26, 1625.

⁵ Newkome, G. R.; Moorefield, C. N.; Theriot, K. J. J. Org. Chem. 1988, 53, 5552.

⁶ Bax, A. Two-Dimensional Nuclear Magnetic Resonance in Liquids; Delft University Press: Delft, Holland, 1982; p 99.

⁷ (a) Leonard, N. J.; Coll, J. C.; Wang, A. H.-J.; Missavage, R. J.; Paul, I. C. J. Am. Chem. Soc. 1971, 93, 4628. (b) Wang, A. H.-J.; Missavage, R. J.; Byrn, S. R.; Paul, I. C. J. Am. Chem. Soc. 1972, 94, 7100.

⁸ Aue, D. H.; Webb, H. M.; Bowers, M. T. J. Am. Chem. Soc. 1975, 97, 4136.

⁹ Smith, J. R. L.; Masheder, D. J. Chem. Soc., Perkin Trans 2 1976, 47.

¹⁰ Halpern, A. M. J. Am. Chem. Soc. 1974, 96, 7655.

¹¹ Weber, A. M.; Acharya, A.; Parker, D. H. J. Phys. Chem. 1984, 88, 6087.

¹² Halpern, A.; Forsyth, D. A.; Nosowitz, M. J. Phys. Chem. 1986, 90, 2677.

¹³ (a) Crans, D.; Clark, T.; Schleyer, P. v. R. *Tetrahedron Lett.* **1980**, *21*, 3681. (b) Griller, D.; Lossing, F. P. J. Am. Chem. Soc. **1981**, *103*, 1586. (c) Burkey, T. J.; Castelhano, A.; Griller, D.; Lossing, F. P. J. Am. Chem. Soc. **1983**, *105*, 4701.

¹⁴ Nelsen, S. F.; Kessel, C. R. J. Chem. Soc., Chem. Commun. 1977, 490.

¹⁵ Dinnocenzo, J. P.; Banach, T. E. J. Am. Chem. Soc. 1988, 110, 971.

¹⁶ Nelsen, S. F.; Buschek, J. M. J. Am. Chem. Soc. 1974, 96, 6424.

¹⁷ (a) Danen, W. C.; Neugebauer, F. A. Angew. Chem., Int. Ed. Engl. 1975, 14, 783. (b) Chow, Y. L.; Danen, W. C.; Nelsen, S. F.; Rosenblatt, D. H. Chem. Rev. 1978, 78, 243.

¹⁸ Danen, W. C.; Rickard, R. C. J. Am. Chem. Soc. 1975, 97, 2303.

¹⁹ (a) Wood, D. E.; Lloyd, R. V. J. Chem. Phys. 1970, 52, 3840. (b) Wood, D. E.; Lloyd, R. V. J. Chem. Phys. 1970, 53, 3832.

²⁰ Symons, M. C. R.; Chandra, H.; Alder, R. W. J. Chem. Soc., Chem. Commun. 1988, 844.

²¹ Bonin, M. A.; Takeda, K.; Williams, F. J. Chem. Phys. 1969, 50, 5423.

²² Griller, D. Magn. Reson. Rev. 1979, 5, 1.

²³ Griller, D.; Howard, J. A.; Marriott, P. R.; Scaiano, J. C. J. Am. Chem. Soc. 1981, 103, 619.

²⁴ Danen, W. C.; West, C. T. J. Am. Chem. Soc. 1974, 96, 2447.

²⁵ Engel, P. S. Chem. Rev. 1980, 80, 99.

²⁶ Fessenden, R. W.; Schuler, R. H. J. Chem. Phys. 1966, 45, 1845.

²⁷ Roncin, J.; Debuyst, R. J. Phys. Chem. 1969, 51, 577.

²⁸ Bennett, J. E. Mol. Spectr. Proc. Conf. 1968, 313.

²⁹ Griffith, O. H. J. Chem. Phys. 1965, 42, 2651.

³⁰ Wardman, P.; Smith, D. R. Can. J. Chem. 1971, 49, 1869.

³¹ Butler, D. E. Eur. Pat. Appl. EP 95,278 (Cl. C07D207/267); CA 100: P138947.

CHAPTER 4

PROGRESS TOWARD THE SYNTHESIS OF ATRANE-LIKE COMPOUNDS

Abstract: A modified literature procedure for the preparation of 3-(2-hydroxyethyl)-1,5pentanediol (1), along with the syntheses of the novel compounds, 3-(2-aminoethyl)-1,5diaminopentane (2) and tris(o-hydroxyphenyl)methane (3), as potential precursors to atrane-like bicylics, are described. Our preliminary attempts to cyclize 1 were unsuccessful so far, resulting in polymeric materials or 4-substituted tetrahydropyrans (6 and 7). Derivatization of 1 led to the novel tris(N-benzyl)methanetriacetamide (12). In view of the predicted properties for the heterocyclic medium-ring bridgehead radicals studied computationally in section 1.3, atrane-like radicals emerge as good candidates for examination of organic radical σ -type interactions with heteroelements and promise the requisite geometrical stability and intrabridgehead distances appropriate for this work.



Atranes¹ are typically derived from the condensation reaction of N(CH₂CH₂Y)₃, where Y is usually OH or NH₂, with an appropriate heteroelement halide, orthoester or triamine. Despite the ease of synthesis of atranes, atrane-like compounds with carbon at the bridgehead have not been reported. Herein, synthetic efforts centered on developing routes and efficient precursors to carbatranes, whose corresponding carbon-centered bridgehead radicals could provide a potentially interesting series of compounds to probe the effects of positioning heteroatoms at the bridgehead opposite to the radical center, are presented. For conceptual simplicity, these compounds are named as trisubstituted methanes - i.e. 1: tris(2-hydroxyethyl)methane (THEM); 2: tris(2-aminoethyl)methane (TAEM), and 3: tris(*o*-hydroxyphenyl)methane (THPM). Use of the known THEM 1 to



make atrane-like bicyclics was unsuccessful so far, resulting in polymeric materials or tetrahydropyrans. The syntheses of the novel TAEM 2 and THPM 3, aimed to favor the desired atrane-like bicyclics with respect to the polymers, were accomplished. Thus, as observed previously for similar compounds, usage of the N-alkylated derivatives of 2 should sterically hinder polymerization, while the rigidity of 3 promises to prefer entropically the monomeric compounds as regards to the polymers. Future syntheses of atrane-like compounds will undoubtedly take advantage of these potential precursors toward novel medium-ring bicyclics.

4.1 3-(2-Hydroxyethyl)-1,5-pentanediol and 3-(2-Aminoethyl)-1,5-pentanediamine

3-(2-Hydroxyethyl)-1,5-pentanediol 1 (THEM) was synthesized by reduction of triethyl methanetriacetate 4 (3-ethoxycarbonylmethyl-glutaric acid diethyl ester) with lithium aluminum hydride in THF (Scheme 4.1). Paul and Tchelitcheff² and Nasielski et al.³ report yields of 70% and 50%, respectively, for this reaction. Wetzel and Kenyon⁴ reduced 4 to THEM 1 with LiBH₄ in 47% yield, while Lukeš et al.⁵ obtained 87% yield for the LiAlH₄ reduction of trimethyl methanetriacetate. In order to improve the above experimental yields, the aluminum alkoxide obtained by hydride transfer from LiAlH₄ to the ester groups in 4, was hydrolyzed at 0 °C followed by addition of aqueous NaOH at 30-40 °C to transform the aluminum hydroxide into an easily filterable granular precipitate.⁶ This modification of the published procedure gave almost quantitative yields in THEM from 4.



S

Scheme 4.1

The Na metal reduction of triethyl methanetriacetate 4 in ethanol, reported by Walton⁷ to produce 1 in 80% yield, was unsuccessful in our hands. Other reducing systems such as NaBH₄/LiCl⁸ and NaBH₄/AlCl₃⁹ employed with 4, and BH₃·THF¹⁰ used with methanetriacetic acid, yielded only partially reduced products.

Triethyl methanetriacetate 4 was obtained based on previously published methods, by Michael addition of the diethylmalonate anion to diethylglutaconate 5.³⁻⁴ The diethyl glutaconate employed in the synthesis of 4 was prepared either from Na diethylmalonate and chloroform by the method of Kohler and Reid¹¹, with moderate yields (50%), or from Na diethylmalonate and diethyl ethoxymethylenemalonate,¹² available commercially, with experimental yields which consistently exceeded the literature values (80%).

Previous reports showed that bicyclic ortho esters can be synthesized by directly reacting a triol with strong organic acids such as trifluoroacetic acid, di- and trichloroacetic acid, or 3,5-dinitrobenzoic acid.¹³ The difference in the experimental behavior of acids having electron attracting groups from other weaker acids, which give only mixtures of ordinary esters, was rationalized on the basis of dissimilarities in equilibria or in rates.^{13,14} As illustrated below for the general reaction of 2-hydroxymethyl-2-methyl-1,3-propanediol with RCOOH, which renders stable bicyclic[2.2.2] ortho esters, when R is a strong electron-attracting group, the concentration of intermediate A would be increased.¹³ The relative rate of reaction of B with water to regenerate A as compared to the rate of cyclization to product is critical. An electron-attracting R group could inductively increase the positive charge on the carbon atom of B and in this way facilitate intramolecular attack by the third hydroxyl to yield the orthoester. By analogy, the



condensation of THEM 1 with trifluoroacetic acid was attempted under similar experimental conditions. The product of the reaction, however, was identified as the novel 4-substituted tetrahydropyran 6 instead of the desired [3.3.3] bicyclic. Thus, as noticed also in other reactions employing 1, cyclization to the strainless tetrahydropyranic ring can become a major impediment to the desired derivatization of 1. Formation of 6 can be easily understood considering the leaving group aptitudes of trifluoroacetate anion and the favorable six-membered ring closure in which -OH displaces CF₃COO⁻ instead of adding to the OCOCF₃ (Scheme 4.2). The resulting 4-(2-hydroxyethyl)-tetrahydropyran is esterified to form ultimately trifluoroacetate 6. Analogously, reaction of 1 with the dimethylformamide dimethyl ketal, HC(OCH₃)₂N(CH₃)₂, afforded 4-(2-hydroxyethyl)tetrahydropyrane 7, a compound whose synthesis was previously reported.^{5,15} but which. to our knowledge, has not been characterized prior to our work. In a selective spin decoupling experiment¹⁶ the ¹H-¹H splitting patterns in 6 were established (see experimental part).

In addition, THEM 1 reacted with trimethylborate, tris(dimethylamino)borane, tris(dimethylamino)phosphine or tris(dimethylamino)silane under a variety of experimental

135





Scheme 4.2

conditions (longer or shorter reaction times, slower or concomitant additions of reactants, high dilutions) to form insoluble oligomeric/polymeric materials. Such polymers might be able to undergo pyrolytic breakdown to yield the bicyclic orthoesters, ¹⁶ but we found that heating (up to 220 °C) under high vacuum (10^{-5} torr) did not produce any sublimable monomeric compounds. Apparently, the bicyclic carbaboratrane forms when reaction of 1 with B(OCH₃)₂ or B(N(CH₃)₂)₃ is carried out in pyridine, as shown by the decay of the ¹H NMR signals of 1 and the growth of new triplet signals, presumably due to the monomer. However, we failed to isolate this compound from the reaction mixture.

THEM 1 was also converted into the novel TAEM 2 via the reaction sequence presented below, which follows a modified procedure for synthesis of alicyclic primary



polyamines from the corresponding alcohols.¹⁷ Reaction of 1 with *p*-toluenesulfonyl chloride in pyridine at 0 °C for 30 minutes affords the *p*-toluenesulfonic triester 8 as a white solid. Any increase in the reaction temperature or contact time allows monocyclization to compete with simple substitution, leading, once again, to tetrahydropyrans as major products. Subsequently, the *p*-toluenesulfonic triester 8 reacts with sodium azide in DMSO to produce the triazide 9, which is used without further

Scheme 4.3



purification for catalytic reduction to 3-(2-aminoethyl)-1,5-pentanediamine 2.

N-Substituted tris(aminoethyl)methanes are also accessible via the acid trichloride of methanetriacetic acid 11¹⁸ (3-chlorocarbonylmethyl-pentanedioyl chloride) obtained from 10 by reaction with thionyl chloride (Scheme 4.3). Methanetriacetic acid 10 was either isolated during the synthesis of 4 as the product resulted the hydrolysis and decarboxylation of the tetraester intermediate or obtained by saponification of 4. Conversion of the acid chloride 11 into tris(*N*-benzyl)methane-triacetamide 12 was accomplished by reacting 11 with benzylamine in acetonitrile at -15 °C, once again, to avoid nucleophilic substitution with subsequent condensation to piperidin-2,6-dione which is likely to occur at higher temperature. Further reduction of the triamide was not attempted, but it should easily render the corresponding triamines.

In principle, TAEM 2 and its *N*-alkyl derivatives could provide access to mediumring bicyclics just as tris(2-aminoethyl)amine, "tren", can be used to make azatranes.^{1b-1c} It is expected that the bulkiness of the *N*-substituent will reduce the nucleophilicity of the amine functionalities and hinder polymerization.

4.2 tris(o-Hydroxyphenyl)methane

In our quest for a better ligand to form carbatranes we sought to synthesize the more rigid tris(o-hydroxyphenyl)methane (THMP) 3 by analogy with the tetradentate tripod ligand tris(o-hydroxyphenyl)amine 15,¹⁹ which does not easily form transannulated structures, probably owing to reduced flexibility of the bridges imposed by the benzo rings.²⁰

Phosphite 16 shows a bicycloundecane framework; no significant $N \cdots P$ interaction is present, as illustrated by a N-P distance of 3.14 Å in the crystal.²¹ The phosphate 17



has probably a structure very similar to 16, with no or very little N…P interaction, as judged from the chemical shift of the protons *ortho* to the N-atom of the ligand.²¹ The boron complex 18, however, shows an transannular N \rightarrow B dative bond of 1.68 Å in a strained tricyclo-[3.3.3.0]undecane chelating system.²¹ The complex reacts with nitrogen bases such as pyridine, quinuclidine and others, to form adducts in which the intramolecular N \rightarrow B bond is replaced by one between B and the external nucleophile (see below the adduct with Py, 19). In solution, this nucleophilic displacement, studied by



temperature-dependent ¹H NMR spectroscopy, is reversible.²² Analogous complexes with Al show a central $N \rightarrow Al$ dative bond, where Al is 5-coordinate in an approximately

trigonal-bipyramidal environment, in which the 3 donor O-atoms of the ligand occupy the equatorial and the N-atom one of the axial position; the remaining apical position is occupied by an external nucleophile (OH⁻, pyridine or an O-atom of a second unit; see the dimer **20** obtained by high vacuum sublimation, at 400 °C and 0.05 torr, of the corresponding pyridine adduct).²³

tris(o-Hydroxyphenyl)methane²⁴ **3** was prepared from tris(o-methoxyphenyl)methane **14** by ether cleavage with trimethylsilyl iodide (Scheme 4.4).²⁵ Addition of the Grignard reagent of o-bromoanisole to methyl o-methoxybenzoate produced carbinol **13**,²⁶ which was further reduced by treatment with refluxing ethanol/HCl^{26b} to afford tris(omethoxyphenyl)methane **14**.

Verkade^{1b} has suggested, based on NMR monitoring and molecular modeling of the possible intermediates, that generation of atranes occurs by transannular bond formation at an initial stage of the reaction, followed by successive stepwise substitution and ring closure. The precursors proposed here toward atrane-like compounds lack this stabilization by dative-bond formation, which, along with facile polymerization due to their high functionality, might be the reason why 3-(2-hydroxyethyl)-1,5-pentanediol 1, for example, did not succed to make carbatranes. The less flexible THPM **3**, however, promises to overcome this insufficiency and appears to be a reasonable candidate for assembly of novel atrane-like bicyclics.

Scheme 4.4





4.3 Experimental Methods

Diethyl Glutaconate (5). (a) From diethyl malonate and chloroform: diethyl malonate (32 g; 0.2 mol) was added slowly from a dropping funnel to a solution of sodium (11.5 g; 0.5 mol) in absolute ethanol (400 ml), followed, while the mixture was still hot, by rapid addition of chloroform (16.3 g, 0.13 mol) without losing control of the reaction. The solution boils so vigorously that it was usually necessary to use a double-jacketed coiled condensor, whereas cooling the liquid or adding the chloroform more slowly greatly diminished the yield. The liquid was allowed to stand overnight, when a mixture of the sodium derivative of the ester of dicarboxyglutaconic acid and sodium chloride separated. Water (500 ml) was added under stirring, followed by removal of ethanol on a rotary evaporator. Hydrochloric acid 5% (110 ml) was added and the reaction mixture was extracted with diethyl ether $(4 \times 100 \text{ ml})$. The ether was vacuum distilled and the free ester was hydrolyzed and cleaved by boiling it with aqueous alcoholic hydrochloric acid (30 ml EtOH 95%; 30 ml H_2O ; 30 ml HCl conc.) until solubilization was complete. The glutaconic acid, isolated by evaporating this solution under diminished pressure, was dried by azeotropic removal of water with toluene and esterified by refluxing it for 5 hours with absolute ethanol (50 ml) and concentrated H_2SO_4 (0.6 ml). The ethanol was vacuum distilled, cold water was added (200 ml) and the reaction mixture was extracted with ether $(4\times50 \text{ ml})$. The ether extracts were washed with cold water, dried over Mg₂SO₄ and filtered. The solvent was removed on a rotary evaporator and the oily residue subjected to vacuum distillation. The fraction collected at 90-93 °C and 2.3 torr contained pure diethyl

glutaconate 5 (Lit.¹² bp_{0.5} 84-87 °C; 9.3 g; 0.05 mol; yield 50%). (b) From diethyl malonate and diethyl ethoxymethylenemalonate: diethyl malonate (32 g; 0.2 mol) was added dropwise to a solution of sodium (4.6 g; 0.2 mol) in absolute ethanol (160 ml), followed by dropwise addition of diethyl ethoxymethylenemalonate (43.2 g; 0.2 mol). After the mildly exothermic reaction was complete, the reaction mixture was allowed to stand at room temperature for 24 hours, during which time the solution solidified. A mixture of glacial acetic acid (30 ml), concentrated hydrochloric acid (20 ml), and water (200 ml) was added, and the solution was extracted with ether. The ether was removed from the extract in vacuo, and the liquid residue was refluxed with dilute hydrochloric acid (60 ml HCl 18%) for 24 hours. The water and the other volatile materials were removed in vacuo, the residue was dissolved in absolute ethanol, dried with MgSO4, filtered, and again concentrated in vacuo. Absolute ethanol (60 ml) and concentrated sulfuric acid (1 ml) were added and the solution was refluxed overnight. The reaction mixture was processed as in part a, to afford after vacuum distillation pure 5 (14.9 g; 0.08 mol; yield 80%). ¹H NMR (300 MHz, CDCl₃) δ 6.95 (dt, 1H, J_{AB} = 15.7 Hz, J_{AC} = 7.2 Hz), 5.87 (dt, 1H, $J_{AB} = 15.7$ Hz, $J_{AC} = 1.5$ Hz), 4.16 (quintet, 4H, $J_{AB} = 7.2$ Hz), 3.20 (dd, 2H, $J_{AB} =$ 7.2, $J_{AC} = 1.5$ Hz), 1.27 (t, 3H, $J_{AB} = 7.2$ Hz), 1.25 (t, 3H, $J_{AB} = 7.2$ Hz), in accord with previous literature reports²⁸.

Triethyl Methanetriacetate (4). To absolute ethanol (80 ml) was added with cooling sodium (1.86 g; 0.081 mol). When reaction of sodium was complete, diethylmalonate (14.3 g; 0.088 mol) was added dropwise, followed by freshly distilled diethyl glutaconate (14.9 g; 0.08 mol). The reaction mixture was heated at reflux for 6

hours, cooled and the solvent was distilled. Cold water was added (45 ml), followed by concentrated HCl (6 ml). The solution was ether extracted, the solvent was removed in vacuo and an aliquot of the oily residue was subjected to NMR analysis, confirming the identity of the tetraester intermediate (C₂H₅CO₂CH₂)₂CH-CH(CO₂C₂H₅)₂: ¹H NMR (300 MHz, CDCl₃) δ 4.15 (q, 4H), 4.08 (q, 4H), 3.70 (d, 1H), 2.98 (sextet, 1H), 2.62-2.38 (m, 4H), 1.22 (t, 6H), 1.18 (t, 6H), in accord with previous literature reports³. Ethanol (20 ml), water (20 ml) and concentrated HCl (20 ml) were added, and the biphasic mixture was refluxed for 2 days when solubilization was complete. The volatile materials were removed on a rotary evaporator, the resulting oil was throughly dried by heating it at 40 °C under vacuum, and esterifed by refluxing it with ethanol (55 ml) and concentrated H_2SO_4 (0.9 ml) for 6 hours. Most of the ethanol was vacuum distilled, the ester was extracted with ether, the ether extracts were washed with aqueous KHCO₃ (10%) and cold water, and dried over MgSO4. The ether was removed in vacuo and the resulting oil was vacuum distilled. The fraction collected at 148 °C and 3 torr contained pure triethyl methanetriacetate 4 (Lit.²⁹ bp₁₄ 172-173 °C, bp₁₉ 200-205 °C; 17.7 g; 0.056 mol; yield 70%). IR 2984, 1734, 1377, 1159, 1030 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.11 (a, 6H, J = 7.1 Hz), 2.73 (heptet, 1H, J = 6.6 Hz), 2.43 (d, 6H, J = 6.6 Hz), 1.22 (t, 9H, J = 7.1Hz), in accord with previous literature reports³⁻⁴; ¹³C NMR (300 MHz, CDCl₃) δ 171.76, 60.28, 37.60, 28.62, 14.01; MS (EI) m/z (relative intensity); 230 (M⁺, 13), 229 (100), 201 (23), 200 (43), 187 (14), 173 (13), 154 (40), 141 (60), 126 (14), 113 (65), 85 (13).

3-(2-Hydroxyethyl)-1,5-pentanediol (1). Triethyl methanetriacetate **4** (17.7 g; 0.056 mol) in anhydrous THF (184 ml; freshly distilled over Na/benzophenone) was added

slowly to a suspension of lithium aluminum hydride (13.3 g; 0.35 mol) in THF (370 ml; freshly distilled over Na/benzophenone) under nitrogen, at 0 °C. The reaction mixture was stirred for 15 hours at 40 °C and then cooled with ice to 0 °C. Water (11 ml) was added dropwise with cooling to destroy the excess of LiAlH₄, followed by gentle heating to 40 °C and addition of aqueous sodium hydroxide (22 ml NaOH_{ao} 15%). The white suspension was stirred for 3 more hours and filtered. The filtrate was concentrated in vacuo and subjected to vacuum distillation to give quantitatively pure 3-(2-hydroxyethyl)-1.5-pentanediol 1 (bp₂ 190-192 °C, lit.² bp₂ 189-190 °C; 8.1 g; 0.055 mol; 98% yield). IR 3338, 2931, 1433, 1376, 1055, 1011, 668 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.54 (t, 3H, J = 6.5 Hz), 3.70 (q, 6H, J = 7 Hz), 2.15 (heptet, 1H, J = 7 Hz), 1.41 (q, 6H, J = 7Hz), in accord with ref. 7; ¹H NMR (300 MHz, D_2O) δ 3.45 (t, 6H), 1.44 (heptet, 1H), 1.36 (g, 6H), in accord with ref. 4; ¹H NMR (300 MHz, CD₃OD) δ 3.49 (t, 6H), 1.58 (heptet, 1H), 1.43 (q, 6H); ¹H NMR (300 MHz, Py-d₅) δ 6.12 (s, 3H), 4.18 (t, 6H), 2.51 (heptet, 1H), 2.12 (q, 6H); 13 C NMR (300 MHz, CDCl₃) δ 57.66, 33.68, 21.78; 13 C NMR (300 MHz, CD₃OD) δ 60.84, 37.82, 29.43; MS (CI) m/z (relative intensity): 149 ([M+1]⁺, 60), 133 (8), 131 (20), 129 (12), 125 910), 123 (13), 121 (17), 119 (15), 113 (13), 111 (17), 109 (42), 107 (33), 105 (25).

4-(2-Trifluoroacetoxyethyl)-tetrahydropyran (6). A mixture of triol 1 (0.5 g; 3.4 mmol) and trifluoroacetic acid (0.39 g; 3.4 mmol) in benzene was refluxed for 2 days. The solvent was removed on a rotary evaporator and the remaining oily residue was distilled at room temperature to afford pure 6 (0.65 g; 2.9 mmol; yield 75%) as a colorless liquid. IR 2931, 2762, 1786, 1220, 1166, 1094 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.50 (t, 2H, CF₃COOC<u>H₂</u>, J = 6.4 Hz), 3.98 (dd, 2H, <u>H₂,6e</u>, $J_{2e-2a} = 12$ Hz, $J_{2e-3e} = 4$ Hz, $J_{2e-3a} = 2$ Hz), 3.39 (td, 2H, H_{2,6a}, $J_{2a-2e} = 12$ Hz, $J_{2a-3a} = 12$ Hz, $J_{2a-3e} = 2$ Hz), 1.69 (q, 2H, CF₃COOCH₂C<u>H₂</u>, J = 6 Hz), 1.7-1.6 (m, 1H, H_{4a}), 1.62 (apparent dd, 2H, H_{3,5e}, $J_{3e-3a} = 12$ Hz, $J_{3e-2a} = 2$ Hz, $J_{3e-2e} = 4$ Hz), 1.33 (qd, 2H, H_{3,5a}, $J_{3a-3e} = 12$ Hz, $J_{3a-2a} = 12$ Hz, $J_{3a-4a} = 12$ Hz, $J_{3a-2e} = 2$ Hz); ¹³C NMR (300 MHz, CDCl₃) δ 157.41 (q, $J_{C-F} = 42$ Hz, CF₃COO), 114.42 (q, $J_{C-F} = 285$ Hz, <u>C</u>F₃), 67.64 (O<u>C</u>H₂), 65.64 (CF₃COO<u>C</u>H₂), 34.78 (CF₃COOCH₂<u>C</u>H₂), 32.43 (OCH₂<u>C</u>H₂), 31.53 (OCH₂CH₂<u>C</u>); MS (EI) m/z (relative intensity): 226 (M⁺, 16), 83 (99), 82 (18), 81 (20), 79 (36), 70 (56), 69 (99), 68 (27), 67 (88), 55 (100), 54 (97), 53 (20), 45 (43), 43 (23), 41 (68), 39 (34).

4-(2-Hydroxyethyl)-tetrahydropyran (7). A mixture of triol 1 (0.5 g; 3.4 mmol) and dimethylformamide dimethyl ketal (0.41 g; 3.4 mmol) in benzene was refluxed for 2 days. The solvent was removed on a rotary evaporator and the remaining oily residue was distilled at room temperature to afford pure 7 (bp₂ 106 °C, lit.⁵ bp₂ 104-106 °C; 0.3 g; 2.3 mmol; yield 68%) as a colorless liquid. IR 3394, 2925, 2849, 1442, 1092, 1055, 1016 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.91 (dd, 2H, H_{2,6e}), 3.63 (t, 2H, HOCH₂), 3.34 (td, 2H, H_{2,6e}), 1.95 (s, 1H, O<u>H</u>), 1.72-1.6 (m, 1H, H₃), 1.56 (apparent dd, 2H, H_{3,5e}), 1.47 (q, 2H, HOCH₂CH₂), 1.25 (qd, 2H, H_{3,5a}); ¹³C NMR (300 MHz, CDCl₃) δ 67.96 (O<u>C</u>H₂), 59.84 (HO<u>C</u>H₂), 39.56 (HOCH₂CH₂), 32.98 (OCH₂CH₂), 31.44 (OCH₂CH₂CH); MS (EI) m/z (relative intensity): 130 (M⁺, 10), 112 (11), 100 (15), 83 (100), 67 (68), 55 (80).

tris(Tosylhydroxyethyl)methane (8). 3-(2-Hydroxyethyl)-1,5-pentanediol 1 (120 mg; 0.8 mmol) was dissolved in pyridine (0.5 ml) and cooled to 0 °C. Tosyl chloride (560 mg; 3 mmol) was added in small portions and the reaction mixture was stirred at 0 °C for half an hour and filtered. The precipitate was dissolved in chloroform, washed with water, aqueous HCl 10%, again water, dried over Na₂SO₄ and filtered. Evaporation of the solvent gave tris(tosylhydroxyethyl)methane **8** as a white solid (474 mg; 0.78 mmol; yield 98%). ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, 6H), 7.34 (d, 6H), 3.90 (t, 6H), 2.42 (s, 9H), 1.63 (heptet, 1H), 1.50 (q, 6H).

3-(2-Azidoethyl)-1,5-pentanediazide (9). tris(Tosylhydroxyethyl)methane 8 (474 mg; 0.78 mmol) and sodium azide (mg; mmol) were dissolved in dimethyl sulfoxide and stirred under argon at 135 °C for 16 hours. After cooling, the mixture was poured into water and extracted with ether. The ethereal solution was dried over Na₂SO₄, filtered, treated with activated charcoal and filtered again. Upon evaporation of the solvent the 3-(2-azidoethyl)-1,5-pentanediazide 9 was obtained as a colorless oil (87 mg; 0.39 mmol; yield 50%) which was used immediately in the reduction step to obtain the triamine. IR 2097 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.32 (t, 6H, J = 6.9 Hz), 1.78 (heptet, 1H, J = 6.9 Hz), 1.57 (q, 6H, J = 6.9 Hz).

3-(2-Aminoethyl)-1,5-pentanediamine (2). 3-(2-Azidoethyl)-1,5-pentanediazide 9 (87 mg; 0.39 mmol) was reduced in a Parr hydrogenator with H₂ and PtO₂ (5 mg) in ethanol (2 ml) at 3 atm and room temperature for 6 hours. The catalyst was filtered and the solvent was removed by vacuum distillation to give 3-(2-aminoethyl)-1,5pentanediamine 2 as a colorless oil (42 mg; 0.29 mmol; yield 75%). ¹H NMR (300 MHz, CDCl₃) δ 2.69 (t, 6H, J = 7.3 Hz), 1.56 (s, broad, 7H), 1.41 (q, 6H, J = 7.3 Hz).

Methanetriacetic Acid (10). Triethyl methanetriacetate 4 (5.5 g; 20 mmol) was hydrolyzed by refluxing it with water (5 ml), concentrated HCl (5 ml) and ethanol 95% (5

ml) for 14 hours. The volatile materials were distilled in vacuo to afford an oil which was further dried by azeotropic removal of water with benzene. The resulting solid was recrystallized from ether to give methanetriacetic acid 10 (mp 112.5-113 °C, lit.^{29a} 113.5-114.5 °C; 3.4 g; 18 mmol; 90% yield). ¹H NMR (300 MHz, DMSO- d_6) δ 12.17 (s, 3H), 2.44 (heptet, 1H, J = 6 Hz), 2.31 (d, 6H, J = 6.1 Hz), in accord with ref. 3.

Acid Trichloride of Methanetriacetic Acid (11). Methanetriacetic acid 10 (3.4 g; 18 mmol) was heated with excess thionyl chloride (10.7 g; 90 mmol) for 30 minutes at 60 °C. The unreacted SOCl₂ is distilled and the remaining residue was recrystallized from cyclohexane to afford the acid trichloride of methanetriacetic acid 11 (mp 58-60 °C, lit.^{18a} 55-60 °C; 1.8 g; 7.4 mmol; 41%).¹H NMR (300 MHz, CDCl₃) δ 3.14 (d, 6H, *J* = 6.3 Hz), 3.70 (heptet, 1H, *J* = 6.3 Hz); ¹³C NMR (300 MHz, CDCl₃) δ 57.66, 33.68, 21.78.

tris(*N*-Benzyl)methanetriacetamide (12). The acid trichloride of methanetriacetic acid 11 (100 mg; 0.4 mmol) was dissolved in anhydrous acetonitrile (25 ml; freshly distilled over CaH₂) and cooled to 0 °C with ice. Benzylamine (340 mg; 3.17 mmol) was added under stirring and the resulting precipitate was recrystallized from methanol to afford tris(*N*-benzyl)methanetriacetamide 12 (mp > 265 °C; 146 mg; 0.32 mmol; yield 80%). IR 3282, 3069, 1641, 1549, 1454, 744, 695. ¹H NMR (300 MHz, CD₃OD) δ 7.22-7.43 (m, 15H), 4.44 (d, 6H), 3.98 (s, 6H), 2.25 (heptet, 1H); MS (EI) m/z (relative intensity): 457 (M⁺, 14), 176 (25), 149 (15), 107 (11), 106 (57), 105 (10), 92 (13), 91 (100).

tris(o-Methoxyphenyl)methanol (13). Magnesium turnings (4.2 g; 173 mmol) and a crystal of iodine were placed in a thoroughly dried flask under argon. Diethyl ether

(50 ml; freshly distilled over Na/benzophenone) and a small quantity of bromoanisole (2.8 g; 15 mmol) were added into the flask. The flask was gently warmed to initiate the reaction and a crystal of iodine was added if necessary. The onset of the reaction was accompanied by the disappearance of the iodine color, the development of cloudiness and bubbles being released from the metal surface. When the reaction was progressing well, sufficient ether (250 ml) was added to cover the magnesium and the stirrer was set in motion. The remainder of the bromoanisole (25.7 g; 0.137 mmol) was added dropwise at such a rate that the reaction proceeds smoothly. When the solution commenced to cool and only a small amount of metal remains, methyl o-methoxybenzenoate ester (12.6 g; 76 mmol) was added to the well-stirred solution at such a rate that the mixture refluxed gently. The flask was cooled in a pan of cold water during the addition. After the addition was complete, the mixture was refluxed on a steam-bath for one hour, cooled in an ice-salt bath and then poured slowly with constant stirring into a mixture of cracked ice (~ 20 G) and sulfuric acid 2M (15 ml). The resulting white precipitate was filtered, washed with water, dried and recrystallized from benzene:hexane (1:1) to give tris(o-methoxyphenyl)methanol 13 (mp 180 °C, lit.^{26a} 181 °C; 20 g; 57 mmol; yield 75%). IR 3530, 2936, 1596, 1487, 1460, 1438, 1246, 1027, 755 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.25-7.12 and 6.90-6.82 (m, 12H), 5.42 (s, 1H), 3.43 (s, 9H), in accord with ref. 26d; ¹³C NMR (300 MHz, CDCl₃) δ 157.42, 133.63, 129.71, 128.17, 120.11, 112.38, 80.28, 55.59; MS(EI) m/z (relative intensity): 350 (M⁺, 13), 243 (44), 215 (11), 136 (14), 135 (100), 121 (19), 77 (23).

tris(*o*-Methoxyphenyl)methane (14). tris(*o*-Methoxyphenyl)methanol 13 (20 g; 57 mmol) was dissolved in boiling ethanol (400 ml). Concentrated HCl (60 ml) was added and the solution was refluxed until the violet color disappears. Upon cooling the solution, the tris(*o*-methoxyphenyl)methane 14 crystallized out as white fine crystals. (mp 136 °C, lit.^{25b} 136-137 °C; 18.7 g; 56 mmol; 98%). IR 3068, 3009, 2933, 2835, 1587, 1489, 1460, 1437, 1288, 1220, 1163, 1107, 1030, 754 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.12-7.22 (m, 3H), 6.86-6.69 (m, 9H), 6.50 (s, 1H), 3.66 (s, 9H), in accord with previous literature reports³⁰; ¹³C NMR (300 MHz, CDCl₃) δ 157.30, 132.54, 129.62, 126.98, 119.91, 110.72, 55.75, 36.93; MS(EI) m/z (relative intensity): 335 (25), 334 (M⁺, 97), 319 (16), 303 (39), 227 (15), 226 (16), 195 (17), 181 (20), 165 (19), 152 (15), 121 (100), 107 (39), 91 (52).

tris(*o*-Hydroxyphenyl)methane (3). To a stirred solution of tris(*o*-methoxyphenyl)methane 14 (18.7 g; 56 mmol) in chloroform (360 ml; freshly distilled over P_2O_3) under argon was added neat trimethylsilyl iodide (74 g; 370 mmol; freshly distilled) via a dry syringe. The reaction was heated at 60 °C on an oil bath for 24 hours. At the completion of the reaction the excess trimethylsilyl iodide was destroyed and the intermediate trimethylsilyl ethers formed during the reaction were hydrolyzed to the alcohols by pouring the reaction mixture into methanol (90 ml). The volatile components were removed at reduced pressure and the residue was further purified by column chromatography on silica gel (ether:hexane 2:1) and recrystallized from benzene to give tris(*o*-hydroxyphenyl)methane 3. (mp 193-194 °C; 8.2 g; 28 mmol; yield 50%). IR 3344, 3060, 3009, 2883, 2746, 2623, 1612, 1500, 1454, 1394, 1327, 1269, 1180, 1089, 831, 761 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.02 and 6.82-6.68 (m, 12H), 5.93 (s, 1H), 4.74 (s, 3H); ¹³C NMR (300 MHz, CDCl₃) δ 153.45, 129.76, 128.52, 127.24, 121.22, 116.29; MS (EI) m/z (relative intensity): 292 (M⁺, 25), 199 (25), 197 (40), 181 (100), 152 (15), 115 (14).

4.4 References

¹ (a) Voronkov, M. G.; Dyakov, V. M.; Kirpichenko, S. V. J. Organomet. Chem. 1982, 233, 1 (b) Verkade, J. Acc. Chem. Res. 1993, 26, 483. (c) Verkade, J. Coord. Chem. Rev. 1994, 137, 233.

² Paul, R.; Tchelitcheff, S. Comptes Rendus Acad. Sc. Paris. 1951, 323, 1939.

³ Nasielski, J.; Chao, S.-H.; Nasielski-Hinkens, R. Bull. Soc. Chem. Belg. 1989, 98, 375.

⁴ Wetzel, R. B.; Kenyon, G. L. J. Am. Chem. Soc. 1974, 96, 5189.

⁵ Lukeš, R.; Štrouf, O.; Ferles, M. Collect. Czech. Chem. Commun. 1957, 22, 1173.

⁶ Nenițescu, C. D. In General Chemistry; Ed. Didactica și Pedagogica: Bucharest, 1978, p 888.

⁷ Walton, J. C. J. Chem. Soc., Perkin Trans 2 1983, 1043.

⁸ Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. J. Org. Chem. 1987, 52, 1252.

⁹ Brown, H. C.; Subba Rao, B. C. J. Am. Chem. Soc. 1956, 78, 2582.

¹⁰ Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. J. Org. Chem. 1973, 38, 2786.

¹¹ Kohler, E. P.; Reid, G. H. J. Am. Chem. Soc. 1925, 47, 2803.

¹² Schaeffer, H. J.; Baker, B. R. J. Org. Chem. 1958, 23, 626.

¹³ Barnes, R. A.; Doyle, G.; Hoffman, J. A. J. Org. Chem. 1962, 27, 90.

¹⁴ (a) Pittman, C. U. Jr.; McManus, S. P.; Larsen, J. W. Chem. Rev. 1972, 72, 357. (b) Guthrie, J. P. Can. J. Chem. 1976, 54, 202. (c) Pindur, U.; Müller, J.; Flo, C.; Witzel, H.

Chem. Soc. Rev. 1987, 16, 75.

¹⁵ Prelog, V.; Kohlbach, D.; Cerkovnikov, E.; Režek, A.; Piantanida, M. Justus Liebigs Ann. Chem. 1937, 532, 69.

¹⁶ Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. In *Spectrometric Identification of Organic Compounds*; John Wiley & Sons: New York, 1991, p 198.

¹⁷ Fleischer, E. B.; Gebala, A. E.; Levey, A.; Tasker, P. A. J. Org. Chem. 1971, 36, 3042.

¹⁸ (a) Stetter, H.; Stark, H. Chem. Ber. 1959, 92, 732. (b) Font, J.; Lopez, F.; Serratosa, F. Tetrahedron Lett. 1972, 25, 2589.

¹⁹ Frye, C. L.; Vincent, G. A.; Hauschildt, G. L. J. Am. Chem. Soc. 1966, 88, 2727.

²⁰ Correspondence with professor Edgar Müller is gratefully acknowledged. Müller, E. Ph.D. Thesis, ETH, Zürich, 1982.

²¹ Müller, E.; Bürgi, H.-B. Helv. Chim. Acta 1987, 70, 1063.

²² Müller, E.; Bürgi, H.-B. Helv. Chim. Acta 1987, 70, 499.

²³ Müller, E.; Bürgi, H.-B. Helv. Chim. Acta 1987, 70, 520.

²⁴ In Chemical Abstracts, tris(o-hydroxyphenyl)methane **3** is mentioned twice, as being identified among the hydrolysis products of phenol-formaldehyde novolac resins (ref. 24b), and produced from formaldehyde and phenol in methanolic sodium methoxide (ref. 24a), respectively. Neither of the two citations explicitly refers to isolation or synthesis of **3**. (a) Ulsperger, E.; Richter, L.; Mainas, F. Ger. (East) 46,455, CA 71:8820d. (b) Jaroslav, R. Sb. *Prednasek, "MAKROTEST 1973"* **1973**, *1*, 191 (CA 80:121401s). In Beilstein, however, there is no reference regarding compound **3**.

²⁵ Jung, M. E.; Lyster, M. A. J. Org. Chem. 1977, 42, 3761.

²⁶ (a) Baeyer, A.; Villiger, V. Chem. Ber. 1902, 25, 3013. (b) Lund, H. J. Am. Chem. Soc. 1927, 49, 1346. (c) Bachmann, W. E.; Hetzner, H. P. Org. Synth. Coll. Vol. 3 1955, 839. (d) Rufanov, K. A.; Kazennova, N. B.; Churakov, A. V.; Lemenovskii, D. A.; Kuz'mina, L. G. J. Organomet. Chem. 1995, 485, 173.

²⁷ Müller, E.; Bürgi, H.-B. Acta Crystallogr. 1989, C45, 1403.

²⁸ Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. J. Org. Chem. 1982, 47, 4059.

²⁹ (a) Ingold, C. K.; Thorpe, J. F. J. Chem. Soc. 1921, 119, 501. (b) Dreifuss, M. H.;

Ingold, C. K. J. Chem. Soc. 1923, 123, 2964.

³⁰ Huszthy, P.; Lempert, K.; Simig, G.; Tamas, J.; Hegedus-Vajda, J. J. Chem. Soc., Miniprint 1985, 7, 2524.

CHAPTER 5

CORRELATION OF ¹³C-¹H COUPLING CONSTANTS WITH ELECTRONIC STRUCTURE IN BI- AND POLYCYCLOALKANES: A PM3 AND HF/6-31G* ANALYSIS

Abstract: Müller-Pritchard type (${}^{1}J_{{}^{13}C^{-1}H} = a \times \% s_{C}$) and related expressions are explored for the prediction, from standard quantum chemical models, of one-bond C-H spin-spin coupling constants, in a series of bi- and polycyclics. Correlations of experimental ${}^{1}J_{{}^{13}C-{}^{1}H}$ with quantities computed from NBO analyses of PM3 and HF/6-31G* wavefunctions//geometries are critically examined for 39 aliphatic hydrocarbons (>150 C-H sites; J range >100 Hz). Experimental vs. calculated coupling constants are best fit when the model includes contributions from atomic charges ($q_{\rm H}$ and $q_{\rm C}$) along with s-character at carbon (% s_C). The proposed semiempirical formula (equation 29) estimates ${}^{1}J_{{}^{13}C-{}^{1}H}$ with a 3.8 Hz average deviation from experimental values (62 data points, s.d. = 4.8 Hz). Previously used geometrical measures of hybridization are also discussed. The relationships obtained can be employed to easily predict one-bond C-H coupling constants at tertiary sites in polycyclic saturated hydrocarbons with experimentally useful accuracy. By using common computational chemistry methods for a large data set, we offer both a predictive tool for the practicing chemist, and insights into the validity of hybridizationbased interpretations of coupling.

5.1 Introduction

Our interest in bicyclo[3.3.3]undecane (manxane), which exhibits unusually high bridgehead reactivity and whose bridgehead radical we have investigated by EPR and ab initio computations,¹ turned our attention to the use of one-bond C-H spin-spin coupling constants, ${}^{1}J_{{}^{13}C^{-1}H}$, as a physical property characteristic of hybridization effects on carbon. The bridgehead flattening seen in the bicyclo[3.3.3]undecane system has been related to increased p character in the bridgehead C-H bond, and this hybridization change is reflected in the low value of the corresponding ${}^{1}J_{{}^{13}C^{-1}H}$ (120.0 Hz for the methine C in manxane). Historically, experimental ${}^{1}J_{{}^{13}C^{-1}H}$ values have been interpreted in terms of the hybridization of the carbon orbitals in C-H bonds. Modern quantum chemical tools now allow easy access to self-consistent geometrical and structural data, even for fairly large molecules. This work describes a search for a simple expression relating experimental tertiary ¹J_{C-H} values over a wide range of compounds to the hybridizations obtained from routine semiempirical and ab initio calculations. The results present both a broader test of the simple notion that hybridization determines C-H coupling, and a predictive tool that may help confirm structural assignments for unknown compounds.

Much of the early interest in one-bond C-H spin-spin coupling constants has centered around theoretical models relating observed ${}^{1}J_{{}^{13}C-{}^{1}H}$ values to hybridization or, more specifically, to the fractional s character of the carbon hybrid orbital. The interpretation of the mechanism of spin-spin coupling is based on three types of electronmediated interactions: a) a Fermi contact interaction between the electron and nuclear spins; b) a magnetic dipolar interaction between the electron and nuclear spins, and c) an orbital interaction between the magnetic field produced by the orbital motion of the electrons and the nuclear magnetic dipole.² It is generally accepted that couplings involving H are dominated by the Fermi contact interaction,³ a quantity that depends on the close approach of an electron to the nucleus and accordingly, is a measure of the density of the bonding electrons at the nuclei. Since only s-orbitals have non-zero values at the nucleus and can therefore contribute to the contact interaction, the magnitude of the Fermi term is a measure of the s character of the bond at the two nuclei.

Based on the idea that the contact term is predominantly responsible for the C-H interactions, Müller and Pritchard⁴ proposed a linear relationship (1) between ${}^{1}J_{{}^{13}C-{}^{1}H}$ and the fraction of s character, s_c, in the carbon hybrid orbital bonding to hydrogen. This equation has been used in its original form or in modified versions to make quantitative predictions for nuclear spin couplings and to test theoretical models of molecular systems.

$${}^{1}J_{13}_{C^{-1}H} = 500 s_{C}$$
 (Hz) (1)

Hybridization arguments are based largely upon valence-bond (VB) or molecular orbital (MO) developments from Ramsey's second-order perturbation formula² for the Fermi contact term, using the average excitation energy (ΔE) approximation, AEE.⁵ Though such empirical assumptions have been criticized,⁶ the procedure is justified by its success in describing qualitative features of spin-spin coupling constants. Mathematical difficulties associated with the choice of a suitable algorithm for computing the ground state VB wavefunction in large molecules renders the VB method less satisfactory than the MO approach.⁷ For these reasons, recent calculations of spin-spin couplings have been mainly carried out on LCAO-MO wavefunctions using SOS (sum-over-states),^{6b,8} FPT (finite perturbation)⁹ and SCP (self-consistent perturbation) methods.¹⁰ Theory has become indeed very successful in reproducing the experimental nuclear spin-spin coupling constants between directly bonded nuclei in simple molecules. Spin-spin coupling is a subtle phenomenon, however, and considerable computational effort is required to achieve quantitative agreement with experiments even for small systems.¹¹ For larger molecules of interest it is therefore more convenient to approach prediction of ${}^{1}J_{1^{3}C^{-1}H}$ via a semiempirical strategy.

Equation 2 shows one of the several equivalent forms which results from a SOS MO treatment of the contact interaction in which the average ΔE is invoked.⁸ In this expression *h* is the Planck constant, μ_B is the Bohr magneton, γ_C and γ_H are the nuclear magnetogyric ratios, $s_C^2(0)$ is the orbital density of a carbon 2s orbital at the C nucleus, $s_H^2(0)$ is the orbital density of a hydrogen 1s orbital at the H nucleus, and $P_{s_Cs_H}$ is the carbon 2s-hydrogen 1s element of the bond-order matrix.

$${}^{1}J_{{}^{13}C^{-1}H} = (4/3)^{2} h \ \mu_{\rm B}^{2} \gamma_{\rm C} \gamma_{\rm H} (\Delta E)^{-1} \ {}^{2}s_{\rm C}^{2}(0) \ {}^{2}s_{\rm H}^{2}(0) \ {}^{2}s_{\rm C}^{s}{}^{8}s_{\rm H}$$
(2)

Interpretation of ${}^{1}J_{{}^{13}C^{-1}H}$ in terms of hybridization, or carbon s character, is based on the evaluation of the bond-order component $P_{S_{C}S_{H}}^{2}$, and effectively assumes the factor $(\Delta E)^{-1} s_{C}^{2}(0) s_{H}^{2}(0)$ to be constant. If valence molecular orbitals (MO) are constructed from atomic orbitals $1s_{H}$, $2s_{C}$ and $2p_{C}$, and overlap integrals are neglected, the $P_{S_{C}S_{H}}$ term is directly proportional to a \times b, where a and b represent atomic orbital coefficients for $1s_{H}$ and $2s_{C}$ in the C-H bonding MO, Ψ_{b} (3).

$$\Psi_{b} = a (1s_{H}) + b (2s_{C}) + c (2p_{C})$$
(3)

According to Müller and Pritchard, if all other contributing terms are neglected, under the assumptions of perfect pairing and AEE, the coupling constant can be written as:

$$J_{13_{C_{-}}I_{H}} = J_{o} a^{2} b^{2}$$
(4)

where J_o is a constant to be determined empirically. In addition, normalization of the MO (again, ignoring overlap) requires $a^2+b^2+c^2 = 1$, and spⁿ hybridization at carbon implies that $b^2 = c^2/n$. Using the symbol % s_C for the percent s character of the carbon atomic orbital in the C-H bond (% s_C = 100 s_C), it follows that:

%
$$s_{\rm C} = 100 b^2 / (b^2 + c^2) = 100 b^2 / (1 - a^2) = 100 {}^{1}J_{1^3 {\rm C}_{-1}{\rm H}} / J_{\rm o} a^2 (1 - a^2)$$
 (5)

The well known relationship of Müller and Pritchard (1) is derived from this semiempirical equation for $a^2(1-a^2) = 0.25$, the value for a pure covalent bond, and $J_o = 2000$, as determined from the formal sp³ hybridization and the observed value of 125 Hz for ${}^{1}J_{{}^{13}C^{-1}H}$ in methane.^{4,12} Despite the drastic approximations involved, the linear correlation of ${}^{1}J_{{}^{13}C^{-1}H}$ with % s_C provides an example of good agreement between experiment and theory, especially for small data sets where hybridization has been crudely estimated as spⁿ (n = 1, 2, 3), based on simple coordination numbers.¹³

The interpretation of this relation has been the subject of much controversy, since substitution may cause large changes in the couplings, in which case the exact correlations can not be foreseen. It is commonly thought that difficulties concerning the linear dependence of ${}^{1}J_{{}^{13}C-{}^{1}H}$ on hybridization are only encountered when dealing with the effects of heteroatoms. Karabatsos and Orzech¹⁴ pointed out that the contact term is not adequate to explain their observations on the coupling constants for compounds having

heteroatoms; in the case of hydrocarbons, however, the other contributing terms (spindipolar and orbital) are small or relatively constant and the criterion might still be applicable. Factors of possible importance in determining spin-spin coupling constants other then changes in hybridization have been extensively discussed in the literature: orbital electronegativities,¹⁵ effective nuclear charge,¹⁶ bond polarity,¹⁷ and excitation energy;¹⁸ in hydrocarbons, where these factors are not expected to vary sharply from molecule to molecule, the simple model of Müller and Pritchard (MP) is generally regarded as valid.

Other correlations dealing with hybridization have been proposed in the literature. Maksić et al.¹⁹ introduced a modified relationship of the ${}^{1}J_{13_{C-1}H}$ dependence on the % s_C character by including the C-H bond overlap, as calculated by the maximum overlap method (MOM). Similar studies have been published by Newton et al.²⁰ and Figeys et al.²¹, which estimate a linear dependence between the directly bonded C-H spin-spin coupling constant and the percent s character in the C-H bonding hybrid, calculated from INDO molecular orbitals via a localized molecular orbital procedure (LMO). In a recent study of bridgehead C-H bonds in a series of polycyclic hydrocarbons, Kovaček et al.²² found an analogous linear dependence between ${}^{1}J_{{}^{13}C_{-}^{1}H}$ and % s_c, calculated from AM1 optimized geometries by using the LMO method of Trindle and Sinanoglu. Gil²³ argued that ${}^{1}J_{{}^{13}C^{-1}H}$ couplings should be proportional to $(\% s_{C})^{3/2}$ as a result of orbital delocalization effects, and that this proportionality should replace the previous linear correlations which involve large additive constants; however, despite the reduction of the additivity constant, his suggestion showed no improvement over previously established
empirical correlations of ${}^{1}J_{{}^{13}C_{-}{}^{1}H}$ with % s_C.²² Hu and Zhan²⁴ used the maximum bond order hybrid orbital (MBOHO) procedure to examine the basic relations proposed by Müller and Pritchard,⁴ by Maksić et al.¹⁹ and by Gil²³, and concluded that better agreement with experiment is obtained for hydrocarbons vs. heterosubstituted hydrocarbons, while best results in both cases are attained when using the relationship derived by Maksić et al.¹⁹, in which bond overlap is replaced by bond order. Subsequently, starting from a further theoretical analysis of the Fermi contact coupling interaction with inclusion of ionic terms to the C-H bond, Zhan and Hu²⁵ proposed a novel generalized relationship for calculation of ${}^{1}J_{{}^{13}C_{-}{}^{1}H}$, which includes contributions from hybrid orbitals and net atomic charges, and is suitable for both hydrocarbons and heterosubstituted hydrocarbons. Nevertheless, the optimal form of the relationship between ${}^{1}J_{{}^{13}C^{-1}H}$ and hybridization at carbon depends upon the compounds investigated, the particular definition of percent s character and the method of calculation (localization of ab initio or semiempirical molecular orbitals into hybrid atomic orbitals,²⁶ or construction of bonding orbitals from hybrid atomic orbitals²⁷).

One-bond coupling constants serve as probes of steric strain and angle distortions, since bond angles and hybridization are closely related. Accordingly, correlations of ${}^{1}J_{{}^{13}C^{-1}H}$ coupling constants have been explored with geometrical surrogates for hybridization, such as internuclear CCC bond angles, $\theta_{CCC}^{av} = (\Sigma \angle CCC^{\circ})/3$,²⁸ and the sum of internuclear bond angle distortions, $\Sigma \Delta \theta_{CCC} = \Sigma (109.5^{\circ} - \angle CCC^{\circ})$.²⁹ Müller and Pritchard¹² also suggested a dependence of ${}^{1}J_{{}^{13}C^{-1}H}$ values on interorbital rather than internuclear angles, since bent bonds are frequently found in organic compounds³⁰. Mislow³¹ used this approach to express the relationship between one-bond ¹³C-¹H coupling constants and interorbital bond angles. Tokita et al.³² correlated ¹J_{13C-1H} with the strain energy calculated by the Allinger force-field method; in this case, however, the data comprise only rings from cyclopropane to cyclohexane, and no correlation was found for other systems³³.

Generally, the correlations described above employ parameters derived from experimental geometries, when available. In some cases, geometries assuming standard bond lengths¹⁹ or optimized by molecular mechanics or semiempirical methods (INDO^{20,21}, AM1²²) were considered. The need to restrict the correlations to a given fragment type, and to be consistent with regard to geometries for the compounds under study, led us to reevaluate the MP type relationships for strained aliphatic hydrocarbons, where previous methods gave less satisfactory results. With the ready availability of wavefunctions for geometry optimized structures from which hybridization information can be directly drawn, it seems appropriate to seek a correlation by which C-H coupling constants at tertiary sites can be predicted from easily obtained computational results for compounds of nontrivial size.

5.2 Theoretical Model

Optimized geometries of compounds 1-39 were obtained by using the semiempirical $PM3^{34}$ and the ab initio $HF/6-31G^{*35}$ methods. All calculations were carried out employing the computer program SPARTAN.³⁶

Reported average errors in PM3 calculated molecular geometries are 0.036 Å for bond lengths (average errors of 0.009 Å and 0.017 Å for C-H and C-C bonds, respectively), 3.9° for bond angles and 14.9° for torsion angles.³⁷ In general, the PM3 method is an improvement over previous semiempirical methods (MNDO³⁸, AM1³⁹). Errors in bond angles and torsion angles are slightly higher than for the AM1 method (average errors 3.3° for bond angles and 12.5° for torsion angles), but bond lengths are significantly better reproduced by PM3 calculations (AM1 average error in bond lengths is 0.050 Å, with average errors of 0.014 Å and 0.017 Å for C-H and C-C bonds, respectively).³⁷ Since optimized geometries are used to compute carbon atom hybridizations, upon which C-H bond distances depend, the PM3 method was chosen for study. The good agreement between HF/6-31G* calculated and experimental geometries of systems incorporating small strained rings suggests the application of this moderately large polarized basis set⁴⁰ as a comparison model for the performance and reliability of the essentially minimal basis set-based semiempirical PM3 method.

Hybridizations of carbon atoms and atomic charges in 1-39 were computed from PM3 and HF/6-31G* wavefunctions using the Natural Bond Orbital (NBO) analysis⁴¹ as implemented in the SPARTAN package. This method makes use of the first-order reduced density matrix of the wavefunction, which is converted into a localized form corresponding to a conventional valence structure description of the molecule, dubbed the "natural Lewis structure".⁴¹ With the density matrix transformed in a basis of atomic orbitals, the program forms for each pair of atoms the two-center density matrix and the associated matrix depleted of any lone-pair eigenvectors, searching for bond vectors

whose occupancy exceeds a preset pair threshold. If there is a simple bond between two atoms, the depleted matrix is expected to have a unique eigenvector with double occupancy, which is decomposed into normalized hybrid contributions from each atom. Hybrids from each center participating in different bonds are symmetrically orthogonalized to remove intraatomic overlap. The set of localized electron pairs found in this way constitutes the "natural Lewis structure" to describe the system. The resulting natural hybrids agree well with hybrids determined by other methods and with known trends such as those summarized in Bent's rule.^{26a} The natural atomic charges and hybridizations are calculated based on occupancies (natural populations) of the natural atomic orbitals (NAO) on each atom. The NAO's are the orthonormal atomic orbitals of maximum occupancy for the given wavefunction and are obtained as eigenfunctions of the first-order density matrix. In a study on compounds spanning a wide range of ionic character, Reed et al.⁴² found computed natural charges to be in good agreement with empirical measures of charge and ionic character. The NBO analysis is applicable at any level of ab initio or semiempirical theory and is computationally efficient, the effort required being modest as compared to that for calculation of the wavefunction.

5.3 Results and Discussion

The ¹³C NMR chemical shifts and one-bond carbon-hydrogen coupling constants measured experimentally in this work for bicyclo[3.3.1]nonane **36**, bicyclo[3.3.2]decane **37** and bicyclo[3.3.3]undecane **39** are presented in Table 5.1. The data show, as expected,

a decrease in the coupling between the bridgehead C and its attached H with successive lengthening of the variable bridge and accordingly, flattening of the bridgehead region.

The series of compounds considered in this study, which provides experimental ${}^{1}J_{{}^{13}C-{}^{1}H}$ values ranging from 120 Hz to 215 Hz, was obtained by a systematic literature search for small and medium ring saturated bicyclics with reported one-bond C-H coupling constants, and substantially augmented with other polycyclic saturated hydrocarbons. In addition, this work includes all similar compounds referenced in previous studies.

Table 5.2 lists the experimental ${}^{1}J_{{}^{13}C^{-1}H}$ values for compounds 1-39, together with the percent s character % s_c in the C-H bonding hybrids computed by NBO analysis for PM3 and HF/6-31G* optimized geometries. The expected increase in C-H bond % sc with decreasing ring size is well reproduced and is particularly evident if closely related compounds are compared. Also, enhanced C-H bond p character accompanied by wide CCC angles is associated with reduced experimental ${}^{1}J_{{}^{13}C^{-1}H}$ couplings. Selected PM3 and HF/6-31G* geometrical parameters and atomic charges for the bridgehead sites in 1-**39** are included in the Appendix (Table 1A). The changes in the PM3 geometries of 1-39 vs. the corresponding ab initio HF/6-31G* geometries are significant only regarding C-H bond lengths, which are shorter at the ab initio level (without d-type functions, included in the 6-31G* basis set, bonds to heavy elements are consistently too $long)^{43}$ and correlate surprisingly poorly with the semiempirical values (the correlation coefficient, R, for a linear fit of PM3 vs. HF/6-31G* C-H bond lengths is 0.8). Correlation of hybridization with C-H bond length is better for the PM3 method (R = 0.97) than for the ab initio HF/6- $31G^*$ method (R = 0.85). The atomic orbital coefficients on C and H are more polarized

Compound	Carbon	δ (ppm)	¹ J _{13C-1H} (Hz)
Bicyclo[3.3.1]nonane 36 ^a			
	1 2 3	27.9 31.6 22.5	129.4 127.4 125.6
	9	35.0	128.3
Bicyclo[3.3.2]decane 37° N ⁹			
	1	33.7 32.9	125.2 123.4
	3	22.8	124.3
	9	30.4	125.3
Bicyclo[3.3.3]undecane 39°			
	1	30.7	120.0
	2	28.9	124.2
V ¹ 2	د	20.1	125.0

Table 5.1 ¹³C NMR Chemical Shifts and Experimental ${}^{1}J_{{}^{13}C^{-1}H}$ Coupling Constants

[•] The ¹³C NMR spectrum of **36** is in agreement with previous literature reports (see ref. 62). ^b The ¹³C NMR signals of **37** are attributed to the corresponding carbons based on proton assignments and H/C correlations from the 2D HMQC spectrum of **37**. ^c The individual assignments of the ¹³C peaks of **39** are based on the relative intensities of the signals and their multiplicity in the off-resonance proton decoupled spectrum of **39**.

at the HF/6-31G* level of calculation, most likely due to inclusion of d-type functions in the 6-31G* basis set. Regardless of bond length differences, the PM3 and HF/6-31G* hybridizations of the carbon hybrids in the C-H bonding orbitals in this work correlate extremely well (% s_{C,PM3} = $1.09 \times$ % s_{C,HF/6-31G} + 3.22, R = 0.996). Bond angles, θ_{CCC}^{av} and θ_{HCC}^{av} , change only slightly from PM3 geometries to HF ab initio optimized geometries (the slopes of plots of PM3 bond angles vs. HF/6-31G* bond angles are 0.98 for θ_{CCC}^{av} and 1.03 for θ_{HCC}^{av} , with R values of 0.99, respectively).

In previous studies of empirical relationships between ${}^{1}J_{13_{C-1}H}$ and hybridization or bond angles (summarized in Table 5.3), the choice of compounds was arbitrary and those with large deviations of calculated vs. experimental ${}^{1}J_{{}^{13}C-{}^{1}H}$ couplings, such as strained polycyclics, were generally excluded, obviating meaningful comparisons between different correlations. Most studies used both experimental and calculated geometries (employing INDO^{19-21,23}, CNDO/2²⁴⁻²⁵, AM1²² or MM^{29a,32} methods) based on standard bond lengths and bond angles, which could be a source of systematic deviations, too. Thus, the "problem" cases (bicyclobutane, cyclopropane) encountered by Szalontai^{29a} when studying the relation of ${}^{1}J_{{}^{13}C_{-}{}^{1}H}$ with $\Sigma\Delta\theta_{CCC}$, the sum of internuclear angle distortions (equation 14, Table 5.3), were also problematic for the molecular mechanics based calculations of the 1980's.⁴⁴ Conformational averaging was also ignored in most cases. Hybridization parameters were extracted with different methods (MOM¹⁹, LMO^{20,21,23}, MBOHO^{24,25}); most gave the same general picture,^{26,27} but some (e.g. the MOM procedure) gave unsatisfactory results for highly strained cyclopropane ring compounds. Among previously reported MP type relationships (equations 6-10, Table

No.	Compound	${}^{1}J_{13}C^{-1}H$	% s _C PM3	% s _C HF/6-31G*	Symmetry⁵
1a		215°	41.2	34.9	C,
2a		212 ^d	41.2	34.9	C _{2v}
3	\land	210°	42.5	36.4	C _{2v}
1b		209°	41.1	34.9	C.
4	\diamondsuit	205 ^f	40.4	33.8	C _{2v}
5 a * ⁸		200.3 ^h	40.45	33.65	C,
6a		190 ⁱ	39.7	32.5	C ₂
7 a	\bigtriangledown	189 ⁱ	39.9	33.9	C,
8a		185 ^k	38.1	32.2	C _{2v}
9		179.7 ¹	39.4	33.6	D_{3h}
10		179 ^h	37.2	30.7	C _{2h}
11	\square	178.1 ^h	37.0	31.0	C.

Table 5.2 Experimental One-Bond C-H Spin-Spin Coupling Constants (in Hz), as	nd
Calculated % s_C Character of the C Hybrid Forming the C-H Bonds in 1-39	

1 2 a	A	175 ^m	36.3	30.3	C _{3v}
1 3a		174 ⁿ	36.1	30.3	C _{2v}
14a	di la constante da la constant	171°	36.1	30.1	C _{2v}
1c		171°	35.5	29.3	C,
13b	\Diamond	171 ^k	35.9	29.8	C _{2v}
15 a		169 ^p	35.5	29.2	C,
16	A	167.8 ^q	36.8	30.3	D_{3h}
1 4b	B	166 ¹	35.3	29.2	C _{2v}
8b	\triangle	166 ^h	35.7	29.6	C _{2v}
17a	A	166 ¹	33.8	27.6	C,
1d		166°	36.6	30.4	C,
18*	\bigcirc	165.7 ^r	34.6	28.7	C,
19a	R	165 ^s	33.9	27.6	C,
20a	V\$	164 ¹	33.8	27.6	C _{2v}

2b		163 ^d	36.4	30.3	C _{2v}
17b	A	161 ¹	33.8	27.7	C,
21*	\bigcirc	160°	32.9	26.95	Cı
7c	\bigtriangledown	158.8 ^h	35.9	29.8	C.
22a	\bigcirc	157.9 ^t	36.7	30.7	C _{3v}
23a	团	157 ^k	36.5	30.8	C _{2v}
24	Ð	154.5 ^u	36.5	30.8	D_{4h}
5b	\square	154.2°	34.0	28.2	C.
15b	A	152 ⁿ	34.6	28.5	C _s
23b	A	152 ^k	35.2	29.3	C _{2v}
25	Δ	151.8 ^m	34.5	28.5	C _{2v}
22b	\Diamond	148.8 ^q	34.1	28.3	C _{3v}
12b	Δ	148 ^j	33.0	27.3	$C_{3\nu}$
26		148 [°]	34.5	28.8	D_{5h}

27		147.9 ^q	32.5	27.8	D _{2d}
23c	E	146 ^k	33.4	27.5	C_{2v}
6b		145 ^f	31.9	26.4	C ₂
28	A	144.9 ^q	32.3	26.5	C,
13c	\bigotimes	144 ^k	32.7	26.9	C _{2v}
29		141.0 ^w	31.8	26.3	C _{2v}
30	K.	137.0 ^p	30.1	24.5	C_{3h}
14c	A	137 ¹	30.2	24.5	C _{2v}
17c	A	136.2 ¹	29.8	24.3	C,
31*	A	136 ^f	31.0	25	C ₂
32*	\bigcirc	135 ^x	29.6	24.1	C ₁
33	A	134.3°	29.1	24.0	$\mathbf{D}_{3\mathbf{h}}$
19b	R	134.2 ^p	29.5	24.2	C,
34*		133.7 ^y	29.9	24.5	C,

-

35	Ð	133.4 ^t	29.2	23.8	Tď
20b	N.	133 ¹	29.8	24.2	C _{2v}
36*		129.4 ^z	28.1	22.8	C _{2v}
37*	A	125.2 ^z	26.8	21.5	C,
38a*	\bigcirc	122.4ªª	25.7	21.9	C ₃
39*	A	120.0 ^z	26.5	21.0	C_{3h}
38b*	\bigcirc	111.2 ^x	25.2	20.1	C ₃

* For several compounds considered here, various literature reports present different values for the onebond carbon-hydrogen coupling constants; in such cases the most recent literature reference was considered.

^b Symmetry of lowest energy geometry.

^e Christl, M. Chem. Ber. 1975, 108, 2781.

^d Christl, M.; Brüntrup, G. Chem. Ber. 1974, 107, 3908.

^e Andrews, G. D.; Baldwin, J. E. J. Am. Chem. Soc. 1977, 99, 4851.

^f Withrich, K.; Meiboom, S.; Snyder, L. C. J. Chem. Phys. 1970, 52, 230.

⁸ Star * means it may need conformational averaging, even if they are nondegenerate.

^h Della, E. W.; Hine, P. T.; Patney, H. K. J. Org. Chem. 1977, 42, 17.

ⁱChristl, M.; Herzog, C. Chem. Ber. 1986, 119, 3067.

^j Christl, M.; Leininger, H.; Mattauch, B. Spectros. Int. J. 1983, 2, 184.

^k Figeys, H. P.; Geerlings, P.; Raeymaekers, P.; Van Lommen, G.; Defay, N. Tetrahedron 1975, 31, 1731.

¹ Katz, T. J.; Acton, N. J. Am. Chem. Soc. 1973, 95, 2738.

^m Olah, G. A.; White, A. M. J. Am. Chem. Soc. 1969, 91, 3954.

ⁿ Hamlin, J. E.; Toyne, K. J. J. Chem. Soc., Perkin Trans 1 1981, 2731.

^o Gunther, H.; Herrig, W.; Seel, H.; Tobias, S. J. Org. Chem. 1980, 45, 4329.

^p Christl, M.; Herbert, R. Org. Magn. Reson. 1979, 12, 150.

^q Lazzaretti, P.; Malagoli, M.; Zanasi, R.; Della, E. W.; Lochert, I. J.; Giribet, C. G.; Ruiz de Azna, M.

C.; Contreras, R. H. J. Chem. Soc., Faraday Trans 1995, 91, 4031.

^r Shustov, G. V.; Denisenko, S. N.; Chervin, I. I.; Asfandiarov, N. L.; Kostyanovsky, R. G. Tetrahedron 1985, 41, 5719.

^a De Meijere, A.; Schallner, O.; Weitemeyer, C.; Spielmann, W. Chem. Ber. 1979, 112, 908.

^t Della, E. W.; Cotsaris, E.; Hine, P. T.; Pigou, P. E. Aust. J. Chem. 1981, 34, 913.

- * Maruyama, K.; Muraoka, M.; Naruta, Y. J. Org. Chem. 1981, 46, 983.
- ⁹ Kovaček, D.; Maksić, Z. B.; Elbel, S.; Kudnig, J. J. Mol. Struct. 1994, 304, 247.

^m McMurry, J. E.; Lectka, T.; Hodge, C. N. J. Am. Chem. Soc. 1989, 111, 8867.

5.3) the reduced slope and positive intercept of equation 10 are strikingly different. This correlation, based on 7 data points,²² appears to be the exception rather than the rule, since the methods of calculation used are no different than those utilized in other studies (AM1 optimized geometries; hybrids estimated from AM1 wavefunctions by the LMO procedure of Trindle and Sinanoglu)²². Thus, some of the correlations presented in Table 5.3 are based on too few compounds to be of general use. Furthermore, in light of Gil's²³ finding that residual delocalization makes excitation energy dependent on carbon coordination number, it is arguably inappropriate to directly include primary, secondary and tertiary C-H sites in the same correlation, which all previous studies have done. Instead, we have focused this initial effort on prediction of tertiary C-H coupling constants for the widest possible range of hydrocarbons. The highly strained small-ring compounds included in this series provide a supplementary test for the adequacy of methods of calculation used, and extend the established relationships to more general use.

The basic MP type relationships are reexamined for the hydrocarbons listed in Table 5.2. The PM3 correlations established by least-squares analysis⁴⁵ are presented in Table 5.4. In comparison with the original relationship of Müller and Pritchard³ (1) we

^u Axenrod, T.; Liang, B.; Bashir-Hasheuri, A.; Dave, P. R.; Reddy, D. S. Magn. Reson. Chem. 1991, 29, 88.

^v Eaton, P. E.; Or, Y. S.; Branca, S. J. J. Am. Chem. Soc. 1981, 103, 2134.

^{*} Schneider, H. J.; Heiske, D.; Hoppen, W.; Thomas, F. Tetrahedron 1977, 33, 1769.

² This work.

Table 5.4 Semiempirical Relationships between Experimental One-Bond C-H Couplings and Hybridization, C-H Distance, C-H Bond Order, Natural Atomic Charges on Carbon and Hydrogen, or Internuclear Angles, Established by Least-Squares Analysis for the PM3 Optimized Geometries of Hydrocarbons 1-39^a

Semiempirical relationships	Eq. No.	s.d. ^b
${}^{1}J_{13} = 4.66 (\% s_{C})$	(19)	8.3
${}^{1}J_{{}^{13}C^{-1}H} = 5.60 (\% s_{C}) - 32.70$	(20)	7.4
${}^{1}J_{{}^{13}C^{-1}H} = 0.18 (\% s_{C})^{2} - 6.594 (\% s_{C}) + 170.98$	(21)	6.5
${}^{1}J_{13C-1}H} = 0.65 (\% s_{C})^{3/2} + 29.14$	(22)	7.0
${}^{1}J_{13C-1} = 15.5 (\% s_{C}) / (2 + 0.2 d_{C-H} + 0.6 d_{C-H}^{2}) - 20$	(23) ^c	7.6
${}^{1}J_{{}^{13}C^{-1}H} = 5.99 (\% s_{C}) / (0.2 + P_{C^{-H}}^{2}) - 21.39$	(24) ^d	6.9
${}^{1}J_{{}^{13}C^{-1}H} = -360.11 \ q_{\rm C} + 120.27$	(25)	14.4
${}^{1}J_{{}^{13}C^{-1}H} = 869.73 \ q_{\rm H} + 75.63$	(26)	8.3
${}^{1}J_{13} = -2666.15 q_{\rm H} q_{\rm C} + 128.56$	(27)	10.5
${}^{1}J_{{}^{13}C^{-1}H} = 3.24 (\% s_{C}) - 2.87 (\% s_{C}) q_{C} + 187.01 q_{H} + 19.05$	(28)	5.4
${}^{1}J_{{}^{13}C^{-1}H} = 3.79 (\% s_{C}) - 2239.27 q_{H} q_{C} + 137.17 q_{C} - 83.80 q_{H} + 26.51$	(29)	4.8
${}^{1}J_{{}^{13}C^{-1}H} = 2.64 \ \theta_{HCC}^{av} - 157.20$	(30)	7.8
${}^{1}J_{{}^{13}C^{-1}H} = -1.95 \ \theta_{CCC}^{av} + 344.65$	(31)	6.3
${}^{1}J_{{}^{13}C^{-1}H} = 131.25 + 0.66 \Sigma \Delta \theta_{\rm ccc} - 6.35 \times 10^{-5} (\Sigma \Delta \theta_{\rm ccc})^{2}$	(32)	6.3
${}^{1}J_{{}^{13}C^{-1}H} = 893.01 \ q_{\rm H} + 74.27$	(33) ^e	4.7
${}^{1}J_{13_{C_{-}}1_{H}} = -2284.54 a_{1s_{H}} + 1694.31$	(34) ^e	4.7

^a Correlations 19-32 include all 62 independent data points from Table 5.2. ^b One-bond C-H coupling constants and standard deviations (s.d.) are given in Hz. $^{\circ}d_{c-H}$ is C-H bond distance in Å. Based on equation 14 (Table 5.3) and the reported linear dependence of S_{C-H} on d_{C-H} (ref. 44), the denominator in

found, as have others before us, that better concordance between experimental and calculated ${}^{1}J_{{}^{13}C^{-1}H}$ values is obtained when a constant term, usually negative, is added to (1), (see equations 19 and 20, Table 5.4). This constant term is generally considered to originate in the deficiencies of AEE approach and the assumption of Fermi contact term predominance.⁴⁶ Maksić et al.¹⁹ suggest that the constant term results from the ionic character of C-H bonds, a point examined (and discarded) by Müller and Pritchard⁴ themselves. The plot of ${}^{1}J_{{}^{13}C^{-1}H}$ vs. percent s character shows a slight curvature (Figure 5.1), and accordingly, the correlation is improved if a second order expression is considered (equation 21, Table 5.4). There is no justification for such an empirical fit, but with so many approximations already inherent in the method, the enhanced predictive power of a better fit, however nonphysical, is worthy of exploration. Since the semiempirical PM3 method may introduce errors, we have also used the ab initio HF/6-31G* model to see whether the agreement between ${}^{1}J_{{}^{13}C^{-1}H}$ and % s_C can be refined by a higher level calculation. No improvement was found in the correlation of ${}^{1}J_{13}_{C_{-}1_{H}}$ with percent s character determined from the HF/6-31G* wavefunctions of 1-39 (equations 20 and 36, Figure 5.1), which suggests that the deviations from linearity seen in subsequent correlations are not an artifact of the PM3 method.⁴⁷ The difference between experimental and calculated ${}^{1}J_{{}^{13}C^{-1}H}$ is especially high when the carbon atom at the tertiary site is contained in at least two 3- or 4-membered rings. It is very probable that these deviations occur as a result of breakdown of the AEE approximation in strained rings.

The relationship proposed by Gil²³ was also investigated (equation 22, Table 5.4),

Table 5.4 Semiempirical Relationships between Experimental One-Bond C-H Couplings and Hybridization, C-H Distance, C-H Bond Order, Natural Atomic Charges on Carbon and Hydrogen, or Internuclear Angles, Established by Least-Squares Analysis for the PM3 Optimized Geometries of Hydrocarbons 1-39^a

Semiempirical relationships	Eq. No.	s.d. ^b
${}^{1}J_{13C^{-1}H} = 4.66 (\% s_{C})$	(19)	8.3
${}^{1}J_{13_{C}-{}^{1}H} = 5.60 (\% s_{C}) - 32.70$	(20)	7.4
${}^{1}J_{{}^{13}C^{-1}H} = 0.18 (\% s_{C})^{2} - 6.594 (\% s_{C}) + 170.98$	(21)	6.5
${}^{1}J_{13C-1}H = 0.65 (\% s_{C})^{3/2} + 29.14$	(22)	7.0
${}^{1}J_{13C-{}^{1}H} = 15.5 (\% s_{C}) / (2 + 0.2 d_{C-H} + 0.6 d_{C-H}^{2}) - 20$	(23) ^c	7.6
${}^{1}J_{13C^{-1}H} = 5.99 (\% s_{C}) / (0.2 + P_{C^{-H}}^{2}) - 21.39$	(24) ^d	6.9
${}^{1}J_{13} = -360.11 \ q_{C} + 120.27$	(25)	14.4
${}^{1}J_{{}^{13}C^{-1}H} = 869.73 \ q_{\rm H} + 75.63$	(26)	8.3
${}^{1}J_{{}^{13}C^{-1}H} = -2666.15 \ q_{\rm H} \ q_{\rm C} + 128.56$	(27)	10.5
${}^{1}J_{{}^{13}C^{-1}H} = 3.24 (\% s_{C}) - 2.87 (\% s_{C}) q_{C} + 187.01 q_{H} + 19.05$	(28)	5.4
${}^{1}J_{{}^{13}C^{-1}H} = 3.79 (\% s_{C}) - 2239.27 q_{H} q_{C} + 137.17 q_{C} - 83.80 q_{H} + 26.51$	(29)	4.8
${}^{1}J_{{}^{13}C^{-1}H} = 2.64 \ \theta_{HCC}^{av} - 157,20$	(30)	7.8
${}^{1}J_{{}^{13}C^{-1}H} = -1.95 \ \theta_{CCC}^{av} + 344.65$	(31)	6.3
${}^{1}J_{{}^{13}C^{-1}H} = 131.25 + 0.66 \Sigma \Delta \theta_{CCC} - 6.35 \times 10^{-5} (\Sigma \Delta \theta_{CCC})^{2}$	(32)	6.3
${}^{1}J_{13} = 893.01 \ q_{\rm H} + 74.27$	(33) ^e	4.7
${}^{1}J_{13_{C_{-}}1_{H}} = -2284.54 a_{1s_{H}} + 1694.31$	(34)°	4.7

[•] Correlations 19-32 include all 62 independent data points from Table 5.2. ^b One-bond C-H coupling constants and standard deviations (s.d.) are given in Hz. ^c d_{C-H} is C-H bond distance in Å. Based on equation 14 (Table 5.3) and the reported linear dependence of S_{C-H} on d_{C-H} (ref. 44), the denominator in equation 23 was approximated as a second-order polynomial regression in d_{C-H}. ^d P_{C-H} is Mulliken C-H bond order. ^e Equations 33-34 use only 61 independent data points; **38a** is excluded.



Figure 5.1 Experimental one-bond C-H spin-spin coupling constants vs. percent s character of the C hybrid in the C-H bonding orbital obtained from NBO analysis of: a) PM3, and b) HF/6-31G* wavefunctions for optimized geometries of 1-39.

and even though it gives a smaller s.d. (7.0 Hz) than the linear correlation of ${}^{1}J_{{}^{13}C^{-1}H}$ with % s_C (s.d. = 7.4 Hz), the result in the present case can not be explained on the basis of the variation of AEE with carbon coordination number, which is constant in 1-39.

The Spartan software does not explicitly report overlap integrals, so we examined the basic relationship of Maksic et al.¹⁹ (equation 14, Table 5.3) for **1-39** by replacing bond overlap with either C-H distance (overlap is a nearly linear function of distance in the range of interest⁴⁸) or C-H bond order (NBO-derived), as proposed by Zhan and Hu^{26b} (equation 15, Table 5.3). The relations obtained (equations 23 and 24, Table 5.4) do not show significant improvement over the simple linear dependence of ¹J_{13C-1H} with % s_C.

The best correlations are obtained by including the atomic charges $q_{\rm C}$ and $q_{\rm H}$ calculated by natural population analysis for carbon and hydrogen atoms (equations 28-29, Table 5.4). The calculated charges agree well with Bent's rule,⁴⁹ which states that atomic s character concentrates in orbitals directed toward electropositive substituents. Thus, small-ring compounds, where the distorted geometries cause the ring C atoms to rehybridize in such a manner as to augment the s character in the C-H bond, show increased C-H bond ionicity.

Previously, Guillen and Gasteiger⁵⁰ used the iterative partial equalization of orbital electronegativity method (PEOE) for calculating atomic partial charges in hydrocarbons with 3- and 4-membered rings and established a linear correlation between ${}^{1}J_{{}^{13}C-{}^{1}H}$ and the product of carbon and hydrogen charges (equation 17, Table 5.3). The PEOE procedure reproduces surprisingly well small trends in the coupling constants, even though hybridization states, calculated from substitution patterns, are taken to be artificially equal

for distinct compounds, as for example 4, 5a and 11. Zhan and Hu²⁵ introduced a generalized relationship suitable for hydrocarbons and molecules with $-I^+$ and $-I^$ substituents, in which the s character of the hybrids and the net atomic charges on C and H are involved for calculation of ${}^{1}J_{{}^{13}C^{-1}H}$ (equation 18, Table 5.3). Such a correlation applied to compounds 1-39, gives a much lower s.d. as compared to equations 19-24, which indicates that while hybridization is important in the study of one-bond C-H spinspin coupling constants, the ionic contribution to bridgehead C-H bonds can not be neglected. Various forms of a possible semiempirical relationship of ${}^{1}J_{{}^{13}C_{-}{}^{1}H}$ vs. hybridization, $q_{\rm H}$, and $q_{\rm C}$, have been tested, among which equation 29 gave the lowest standard deviation. In their treatment of the Fermi contact contribution to spin coupling between directly bonded atoms, using electron pair theory, Karplus⁵¹ and Grant and Litchman¹⁶ showed that besides hybridization, ${}^{1}J_{{}^{13}C^{-1}H}$ values depend also on the effective nuclear charge, which is a function of the C-H bond covalency. Our results show that ionic contributions to bridgehead C-H bonds significantly refine the classical MP relationships between ${}^{1}J_{{}^{13}C^{-1}H}$ and % s_C, in which case bond ionicity can not be ignored.

Interestingly, the best single-parameter correlations are the PM3 $q_{\rm H}$ or the PM3 atomic orbital coefficient on H, $a_{1S_{\rm H}}$ (or a, see equation 3), and experimental ${}^{1}J_{{}^{13}C{}^{-1}H}$ (equations 33-34, Table 5.4).⁵² If **38a** (the *in*-C-H bond of bicyclo[4.4.4]tetradecane) is excluded from the correlations,⁵³ linear relationships are obtained via least-squares analysis with standard deviations of only 4.7 Hz (Figure 5.3).

The polarization of C-H bonds was also considered, as the atomic orbital coefficients for C and H (a, b and c) are given by NBO analysis. The correlation of

 ${}^{1}J_{{}^{13}C^{-1}H}$ with % s_C and a_{1s_H}, as given in equation (5), did not bring any improvement over previously discussed relationships. A possible semiempirical relationship of ${}^{1}J_{{}^{13}C^{-1}H}$ with C-H bond order was also explored, but no improvement over those involving only hybridization and atomic charges was obtained.

The relationship between one-bond carbon-hydrogen spin-spin coupling constants and calculated bond angles has been investigated for the compounds under study, too (equations 30-32, Table 5.4). Average CCC and HCC angles, θ_{CCC}^{av} and θ_{HCC}^{av} ($\theta_{HCC}^{av} = (\Sigma \angle HCC^{\circ})/3$), were considered for the general case of three substituents attached to a methine carbon; again, conformational averaging was included where necessary. The PM3 empirical relationships established via least-squares analysis are recorded in Table 5.4, and show similar standard deviations for plots of ${}^{1}J_{{}^{13}C^{-1}H}$ vs. the average CCC angles, θ_{CCC}^{av} , or the sum of internuclear angle distortions, $\Sigma \Delta \theta_{CCC}$.

It is recognized that bent bonds³⁰ are frequently found in organic compounds and internuclear bonds do not always correspond to bond paths,⁵⁴ defined as the path of maximum charge density between the bonded atoms. Hybridization is more closely related to interorbital rather than internuclear angles. A simple analysis of the correlation of ${}^{1}J_{13}{}_{C^{-1}H}$ with bond path angles vs. internuclear angles in methine systems with C_{3v} symmetry, supports this idea and allows for a qualitative estimate of the amount of bond bending. Thus, we converted the corresponding hybridization, spⁿ, at carbons with local C_{3v} symmetry into interorbital angles, θ^{o}_{CCC} , using Coulson's relation:⁵⁵

$$\theta_{\rm CCC}^{\circ} = \arccos\left(-\frac{1}{n}\right) \tag{9}$$

The results show improved correlation of ${}^{1}J_{{}^{13}C^{-1}H}$ with θ°_{CCC} (s.d. is 4.4 Hz for PM3



Figure 5.2Plot of experimental vs. calculated (with semiempirical relationship 29,
Table 5.4) one-bond C-H spin-spin coupling constants in 1-39.





geometries and 4.2 Hz for HF/6-31G* geometries) compared with θ_{CCC} (s.d. is 5.1 Hz for PM3 geometries and 4.8 Hz for HF/6-31G* geometries).⁵⁴

A similar analysis was performed for the HF/6-31G* optimized geometries of 1-39. The relationships obtained are presented in Table 5.5 and, analogously with the PM3 results, show that inclusion of C and H atomic charges improve considerably the simple correlation of ${}^{1}J_{}{}^{13}C_{}{}^{-1}H}$ with hybridization. Nevertheless, the 6-31G* results are less correlated with experiment than those from the PM3 method, in accord with the conclusion of Edison et al.^{6b} that better agreement with experimental values is obtained for calculated nuclear spin-spin coupling constants when using modest levels of MO theory. More disturbing are the HF/6-31G* natural atomic charges on hydrogen and carbon in 1-39, whose oscillating behavior and poor correlation with PM3 charges is surprising. The discrepancy of the H and C atomic charges in 38a vs. other bridgehead sites with similar hybridization at carbon, however, is reduced at the HF/6-31G* level of calculation.

5.4 Summary

(1) The experimental values of ¹³C NMR chemical shifts and one-bond carbon-hydrogen coupling constants in bicyclo[3.3.1]nonane **36**, bicyclo[3.3.2]decane **37**, and bicyclo[3.3.3]undecane **39** are reported. (2) Semiempirical relationships of experimental ${}^{1}J_{13}_{C-1}$ with % s_C, q_{H} and q_{C} , $a_{1s_{H}}^{av}$, θ_{CCC}^{av} , θ_{HCC}^{av} , and $\Sigma \Delta \theta_{CCC}^{av}$, are examined for compounds **1-39**, and show reasonable agreement of calculated vs. experimental ${}^{1}J_{13}_{C-1}$ values (Tables 5.4 and 5.5). The PM3 model shows real promise; the computations

Table 5.5 Semiempirical Relationships between Experimental One-Bond C-H Coupling Constants and Hybridization, Natural Atomic Charges on Carbon and Hydrogen, or Internuclear Angles, Established by Least-Squares Analysis for the HF/6-31G* Optimized Geometries of Hydrocarbons 1-39^a

Semiempirical relationships	Eq. No.	s.d. ^b
${}^{1}J_{13C-1}H} = 5.62 (\% s_{C})$	(35)	8.0
${}^{1}J_{13}C^{-1}H} = 6.12 (\% s_{C}) - 14.47$	(36)	7.8
${}^{1}J_{{}^{13}C^{-1}H} = 0.17 (\% s_{C})^{2} - 3.58 (\% s_{C}) + 120.12$	(37)	7.3
${}^{1}J_{13}C^{-1}H} = 0.77 (\% s_{C})^{3/2} + 41.73$	(38)	7.4
${}^{1}J_{{}^{13}C^{-1}H} = -24.03 ~(\% s_{\rm C}) q_{\rm C} - 4.28$	(39)	6.0
${}^{1}J_{{}^{13}C^{-1}H} = 1.47 (\% s_{C}) - 19.35 (\% s_{C}) q_{C} - 144.70 q_{H} + 19.29$	(40)	5.5
${}^{1}J_{{}^{13}C^{-1}H} = 6.19 (\% s_{C}) - 1296.56 q_{H} q_{C} - 287.87 q_{C} - 480.79 q_{H} - 46.16$	5 (41)	5.6
${}^{1}J_{{}^{13}C^{-1}H} = -1.92 \ \theta^{av}_{CCC} + 341.88$	(42)	6.4
${}^{1}J_{{}^{13}C^{-1}H} = 131.98 + 0.65 \Sigma \Delta \theta_{\rm ccc} - 1.59 \times 10^{-4} (\Sigma \Delta \theta_{\rm ccc})^{2}$	(43)	6.4

[•] Correlations 35-43 include all 62 independent data points from Table 5.2. ^b One-bond C-H coupling constants and standard deviations (s.d.) are given in Hz.

required for PM3 geometry optimization of 1-39 and NBO analysis are modest and can be carried out with readily available electronic structure packages. Correlation of experimental ${}^{1}J_{{}^{13}C_{-}{}^{1}H}$ with PM3 hybridization is considerably improved by inclusion of natural atomic charges on C and H (equations 28-29) to give best fits of experimental vs. calculated ${}^{1}J_{{}^{13}C_{-}^{1}H}$ coupling constants (s.d. = 4.8 Hz for equation 29; 62 data points). Such an empirical relation is useful for predicting ${}^{1}J_{{}^{13}C_{-}{}^{1}H}$ for hypothetical compounds for comparison to experiment, but offers little physical insight into the coupling mechanisms. However, surprisingly good single-parameter linear correlations of ${}^{1}J_{13}_{C-1_{H}}$ with PM3 q_{H} (equation 33; 61 data points, s.d. = 4.7 Hz), or $a_{1S_{H}}$ (equation 34; 61 data points, s.d. = 4.7 Hz), are found for 1-39, when the distant outliner 38a is removed. (3) That ${}^{1}J_{{}^{13}C^{-1}H}$ depends on carbon orbital hybridization is part of the canon of organic chemistry. Numerous equations have been previously proposed based on modest data sets and various measures of hybridization. However, in most cases the choice of compounds was arbitrary and their geometries inconsistent, while the correlations established gave less satisfactory results for strained polycyclics. On the basis of the comparison between various MP type relationships and the critical evaluation of their performance for our wide range of compounds, we conclude that ionic contributions to C-H bonds are important, at least in bridgehead C-H sites, for a suitable correlation of experimental C-H couplings with carbon orbital hybridization. The relationships obtained, particularly equation 29, which includes natural atomic charges along with hybridization at carbon, can be used to easily predict one-bond C-H coupling constants at tertiary sites in polycyclic saturated hydrocarbons with experimentally useful accuracy. Equations 33-34 offer simplified, more

physically understandable alternatives for predictions of ${}^{1}J_{{}^{13}C-{}^{1}H}$ values from modest computational data; however, their use is limited by the poor performance of the PM3 model in situations like **38a** and similar cases should be treated with caution. (4) The overall agreement of calculated with experimental data confirms that the Fermi contact interaction, as modulated by hybridization, is the dominant factor in determining the magnitude of the coupling between directly bonded carbon and hydrogen atoms. The polarity of C-H bonds, however, can not be ignored even in hydrocarbons.

5.5 Experimental Methods

Bicyclo[3.3.1]nonane **36** was synthesized from bicyclo[3.3.1]nonan-9-one⁵⁷ by Clemmensen reduction with amalgamated zinc and hydrochloric acid.⁵⁸ Ring expansion of bicyclo[3.3.1]nonan-9-one with methanolic diazomethane gave bicyclo[3.3.2]decan-9one⁵⁹, which was reduced under Wolff-Kishner conditions to afford bicyclo[3.3.2]decane **37**⁶⁰. Bicyclo[3.3.3]undecane **39** was prepared from bicyclo[3.3.1]nona-9-one by a modified synthesis following Leonard et al.⁶¹ Physical and spectroscopic data of **36**, **37** and **39** were in agreement with those reported in the literature.

Bicyclo[3.3.1]nonane (36). Zinc metal (7.5 g 20-30 mesh) was added to mercuric chloride (15 ml HgCl₂ 10%) and the resulting suspension was stirred for an hour, decanted and washed with water. Bicyclononanone (500 mg; 3.6 mmol) and concentrated hydrochloric acid (10 ml) were added to the freshly prepared amalgamated zinc, and the reaction mixture was refluxed for half an hour, cooled, extracted with pentane and dried

over Na₂SO₄. The pentane was removed on a rotary evaporator, and the solid residue was sublimed to afford pure bicyclo[3.3.1]nonane **36** (178 mg; 1.44 mmol; 40 % yield); mp 144-146 °C (lit.⁵⁸ 145-146 °C); ¹H NMR (300 MHz, CDCl₃) δ 1.78-1.94 (m, 4H), 1.6-1.68 (m, 8H), 1.45-1.55 (m, 4H), in accord with previous reports⁶²; ¹³C NMR (300 MHz, CDCl₃) δ 35.01, 31.59, 27.89, 22.52, in accord with previous reports⁶³; MS(EI) m/z C₉H₁₆ 124 (M⁺), 109, 96, 81 (base), 67, 55, 41.

Bicyclo[3.3.2]decane (37). Bicyclononane (200 mg; 1.3 mmol) was added to a solution obtained from sodium (70 mg), diethylene glycol (3.2 ml) and hydrazine hydrate (84 mg 100% NH₂NH₂ × H₂O), and the reaction mixture was refluxed for one hour, cooled, diluted with water (5 ml), and extracted with pentane. The pentane extracts were dried over Na₂SO₄, filtered, the solvent was vacuum distilled and the solid residue was purified by sublimation to give bicyclo[3.3.2]decane **37** (90 mg; 0.65 mmol; yield 50%); mp 177-179 °C (lit.⁵⁹ 177-178 °C); ¹H NMR (300 MHz, CDCl₃) δ 2.25-2.35 (m, 2H), 1.41-1.75 (m, 16H), in agreement with refs. 59-60; ¹³C NMR (300 MHz, CDCl₃) δ 33.67, 32.87, 30.36, 22.78; MS(EI) m/z C₁₀H₁₈ 138 (M⁺), 123, 110, 95, 81, 67 (base), 55, 41, 39.

Bicyclo[3.3.3]undecane (39). See chapter 2 for experimental details: mp 191 °C (lit.⁶¹ 192 °C); ¹H NMR (300 MHz, CDCl₃) δ 2.38 (m, 2H), 1.41-1.55 (m, 18H), in agreement with ref. 61; ¹³C NMR (300 MHz, CDCl₃) δ 30.74, 28.96, 20.1; MS(EI) m/z C₁₁H₂₀ 152 (M⁺), 124, 109, 96, 81, 67, 55.

Melting points were measured with a Thomas Hoover capillary melting point apparatus and were uncorrected. ¹H and ¹³C NMR spectra were recorded on a Varian FT- NMR 300 MHz at ambient temperature, and were referenced to solvent signals. Mass spectra were obtained using a VG Trio-1 GC-MS spectrometer. The ¹³C NMR spectrum of bicyclo[3.3.2]decane **37** is reported here for the first time, and assignments to the corresponding carbons are made based on the HMQC (¹H-detected heteronuclear Multiple Quantum Coherence)⁶⁴ spectrum of **37**, which reveals all the crosspeaks from the secondary and tertiary carbons to the respective protons. Overlap of signals in the offresonance decoupled spectra of **36** and **37** did not allow accurate measurement of the C-H direct couplings and thus, they were obtained from the corresponding 2D Heteronuclear *J*-Resolved spectra⁶⁵, which showed contour peaks at each carbon in accordance with the number of protons directly connected. The ¹³C-¹H spin-spin coupling constants in bicyclo[3.3.3]undecane **39** were determined from the off-resonance proton decoupled spectrum of **39**. All 2D NMR spectra were recorded on a Varian VXR 500 MHz spectrometer at 25 °C.

5.6 References

- ¹ Crăciun, L.; Jackson, J. E. J. Am. Chem. Soc. 1996, 118, 12232.
- ² Ramsey, N. F. Phys. Rev. 1953, 91, 303.
- ³ Fermi, E. Z. Phys. 1930, 60, 320.
- ⁴ Müller, N.; Pritchard, D. E. J. Chem. Phys. 1959, 31, 768.
- ⁵ McConnell, H. M. J. Chem. Phys. 1956, 24, 460.
- ⁶ (a) Gil, V. M. S. J. Magn. Reson. 1973, 11, 268. (b) Edison, A. S.; Markley, J. L.;

Weinhold, F. J. Phys. Chem. 1993, 97, 11657.

⁷ Ando, I.; Webb, G. A. *Theory of NMR Parameters*; Academic Press: London, 1983; p 88.

⁸ Pople, J. A.; Santry, D. P. Mol. Phys. 1963, 8, 1.

⁹ Pople, J. A.; McIver, J. W.; Ostlund, N. S. J. Chem. Phys. 1968, 49, 2960.

¹⁰ Blizzard, A. C.; Santry, D. P. J. Chem. Phys. 1971, 55, 950.

¹¹ Kowaleski, J.; Laaksonen, A. Theoretical Models of Chemical Bonding; Springer-Verlag: Berlin, 1991; p 487.

¹² Müller, N.; Pritchard, D. E. J. Chem. Phys. 1959, 31, 1471.

¹³ In fact, rigorous sp³ hybridization at carbon is not required even for methane, as the C 2s and 2p orbitals differ in their energies and may participate to different extents in the bonding orbital combinations with symmetry adapted H 1s orbitals.

¹⁴ Karabatsos, G. J.; Orzech, C. E. J. Am. Chem. Soc. 1964, 86, 3574.

¹⁵ Considine, W. J. J. Chem. Phys. 1965, 42, 1130.

¹⁶ Grant, D. M.; Litchman, W. M. J. Am. Chem. Soc. 1965, 87, 3994.

¹⁷ Brown, T. L.; Puckett, J. C. J. Chem. Phys. 1966, 44, 2238.

¹⁸ (a) Saika, A. J. Chem. Phys. 1966, 45, 2715. (b) Cyr, N.; Cyr, T. J. R. J. Chem. Phys. 1967, 47, 3082.

¹⁹ Maksić, Z. B.; Eckert-Maksić, M.; Randić, M. Theoret. Chim. Acta 1971, 22, 70.

²⁰ Newton, M. D.; Schulman, J. M.; Manus, M. M. J. Am. Chem. Soc. 1974, 96, 17.

²¹ (a) Figeys, H. P.; Geerlings, P.; Raeymaekers, P.; Van Lommen, G.; Defay, N. *Tetrahedron* 1975, 31, 1731. (b) Van Alsenoy, C.; Figeys, H. P.; Geerlings, P. *Theoret. Chim. Acta* 1980, 55, 87.

²² Kovaček, D.; Maksić, Z. B.; Elbel, S.; Kudnig, J. J. Molec. Struct. 1994, 304, 247.

²³ Gil, V. M. S. Theor. Chim. Acta 1989, 76, 291.

²⁴ Hu, Z.-M.; Zhan, C.-G Theor. Chim. Acta 1993, 84, 521.

²⁵ Zhan, C.-G.; Hu, Z.-M Magn. Reson. Chem. 1994, 32, 465.

²⁶ (a) Foster, J. P.; Weinhold, F. J. Am. Chem. Soc. 1980, 102, 7211. (b) Zhan, C.-G. and Hu, Z.-M. Theor. Chim. Acta 1993, 84, 511.

²⁷ Randić, M.; Maksić, Z. B. Chem. Rev. 1972, 72, 43.

²⁸ (a) Foote, S. C. *Tetrahedron Lett.* **1963**, *9*, 579. (b) Laszlo, P.; Schleyer, P. v. R. J. Am. Chem. Soc. **1964**, *86*, 1171. (c) Baum, M. W.; Guenzi, A.; Johnson, C. A.; Mislow, K. Tetrahedron Lett. **1982**, *23*, 31.

²⁹ (a) Szalontai, G. *Tetrahedron* 1983, 29, 1783. (b) Zhao, C. Y.; Xiao, T.; Xu, X. F.; You, X. Z. *Chem. J. Chin. Univ.* 1996, 17, 769.

³⁰ Wiberg, K. B. Acc. Chem. Res. 1996, 29, 229.

³¹ Mislow, K. Tetrahedron Lett. 1964, 22, 1415.

³² Tokita, K.; Kondo, S.; Takeda, M. J. Chem. Res. (S) 1980, 63.

³³ Werstiuk, K. B.; Taillefer, R.; Bell, R. A.; Sayer, B. Can. J. Chem. 1973, 51, 3011.

³⁴ Stewart, J. J. P. J. Comput. Chem. 1989, 10, 209.

³⁵ Hariharan, P. C.; Pople, J. A. Chem. Phys. Lett. 1972, 66, 217.

³⁶ Hehre, W. J.; Huang, W. W.; Burke, L. D.; Shusterman, A. J. A SPARTAN Tutorial, version 4.0, Wavefunction Inc.: Irvine, CA, 1995.

³⁷ Stewart, J. J. P. J. Comput. Chem. 1989, 10, 221.

³⁸ Dewar, M. J. S.; Thiel, W. J. Am. Chem. Soc. 1977, 99, 4899.

³⁹ Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. J. Am. Chem. Soc. 1985, 107, 9.

⁴⁰ Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. J. Chem. Phys. **1982**, 77, 3654.

⁴¹ Reed, A. E.; Curtiss, L. A.; Weinhold, F. Chem. Rev. 1988, 88, 899.

42 Reed, A. E.; Weinstock, R. B.; Weinhold, F. J. Chem. Phys. 1985, 83, 735.

⁴³ Hehre, W. J. Practical Strategies for Electronic Structure Calculations; Wavefunction

³⁸ Dewar, M. J. S.; Thiel, W. J. Am. Chem. Soc. 1977, 99, 4899.

³⁹ Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. J. Am. Chem. Soc. 1985, 107, 9.

⁴⁰ Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654.

⁴¹ Reed, A. E.; Curtiss, L. A.; Weinhold, F. Chem. Rev. 1988, 88, 899.

42 Reed, A. E.; Weinstock, R. B.; Weinhold, F. J. Chem. Phys. 1985, 83, 735.

⁴³ Hehre, W. J. *Practical Strategies for Electronic Structure Calculations*; Wavefunction Inc.: Irvine, CA, 1995; p 23.

⁴⁴ Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. J. Am. Chem. Soc. 1973, 95, 8005.

⁴⁵ Program used for least-squares analysis: Curve Fitter, version 4.0, written at MSU by David C. Young for use with MS-DOS computers.

⁴⁶ Duijneveldt, F. B. v.; Gil, V. M. S.; Murrell, J. N. Theoret. Chim. Acta 1966, 4, 85.

⁴⁷ Edison et al.^{6b} also found better performance for a less complete basis set (3-21G) than for $6-31G^*$ in their more rigorous analysis.

48 Maksić, Z. B.; Randić, M. J. Am. Chem. Soc. 1970, 92, 424.

49 Bent, H. A. Chem. Rev. 1961, 61, 275.

⁵⁰ Guillen, M. A.; Gasteiger, J. Tetrahedron 1983, 39, 1331.

⁵¹ Karplus, M.; Grant, D. M. Proc. Natl. Acad. U.S.A. 1959, 45, 1269.

⁵² The linear correlation of C-H couplings (61 data points; **38a** is excluded) with the PM3 atomic orbital coefficient on carbon, $b_{2s_{\rm C}}$ (or b, see equation 3) gives a standard deviation of 4.9 Hz.

⁵³ The PM3 $q_{\rm C}$ and $q_{\rm H}$ values for the *in*-C-H bond in bicyclo[4.4.4]tetradecane **38a** are calculated much higher than for other bridgehead sites with similar hybridization at carbon, while at the HF/6-31G* level of calculation this discrepancy is considerably reduced. Similarly, *in*-[3^{4,10}][7]metacyclophane (see Pascal, R. A. Jr.; Grossman, R. B.; Van Engen, D. J. Am. Chem. Soc. **1987**, 109, 6878), a compound not formally included in our series

average CCC bond path angle. For 1-39 the second-order correlation of ${}^{1}J_{{}^{13}C^{-1}H}$ with average CCC interorbital angles derived from PM3 hybridizations by using Coulson's relation, gives a s.d. of 5.9 Hz.

⁵⁷ Foote, C. S.; Woodward, R. B. Tetrahedron 1964, 20, 687.

⁵⁸ Cope, A. C.; Synerholm, M. E. J. Am. Chem. Soc. 1950, 72, 5228.

⁵⁹ Bingham, A. C.; Schleyer, P. v. R. J. Org. Chem. 1971, 36, 1198.

⁶⁰ Doyle, M.; Hafter, R.; Parker, W. J. Chem. Soc., Perkin Trans 1 1977, 364.

⁶¹ Leonard, N. J.; Coll, J. C. J. Am. Chem. Soc. 1970, 92, 6685.

⁶² Schleyer, P. v. R.; Isele, P. R.; Bingham, R. C. J. Org. Chem. 1968, 33, 1239.

63 Heumann, A.; Kolshorn, H. Tetrahedron 1975, 31, 1571.

⁶⁴ Bax, A.; Griffey, R. H.; Hawkins, B. L. J. Magn. Reson. 1983, 55, 301.

⁶⁵ Bax, A. Two-Dimensional Nuclear Magnetic Resonance in Liquids; Delft University Press: Delft, Holland, 1982; p 99.

CHAPTER 6

HEATS OF FORMATION OF MEDIUM-RING STRAINED CYCLO- AND POLYCYCLOALKANES: COMPARISON OF AB INITIO GROUP EQUIVALENT SCHEMES WITH THE PM3 AND MMX METHODS

Abstract: Optimized structures and energies were calculated for 57 small- and mediumring strained polycyclic aliphatic hydrocarbons using ab initio HF/3-21G and HF/6-31G^{*} as well as PM3 (semiempirical) and MMX (force field) methods. Best fit CH₂, CH and C group increments relating ab initio energies to heats of formation were derived. The ab initio increments deviate little from those previously reported by Wiberg and by Ibrahim and Schleyer, yielding the expected conclusion that the intrinsically isodesmic group increment approach extends efficiently to medium-ring strained systems. For the present data set, the standard deviation between experimental and calculated heats of formation is 1.8 kcal/mol, and the correlation coefficient is 0.9994 for the RHF/6-31G^{*}//RHF/6-31G^{*} calculation. Less successful results are obtained from the HF/3-21G, PM3 and MMX data. As expected, systems with fused small rings are especially problematic for the latter methods. In the course of the study of hybridization and ¹³C-¹H NMR coupling constants described in chapter 5, ¹ we recently obtained RHF/6-31G*//RHF/6-31G* wavefunctions and energies for a large number of small- and medium-ring strained polycyclic hydrocarbons. Roughly half of this number have had experimental heats of formation reported. It was of interest to examine the performance of the Wiberg² and Ibrahim/Schleyer³ (IS) hydrocarbon group increments in calculating heats of formation from ab initio energies for these compounds, as most previous work has focused on unstrained or small-ring systems. This paper provides such an analysis for 57 hydrocarbons, of which several were beyond the range of practical computational tools when the above papers appeared. The new best fit for the CH₂, CH and C fragments are essentially unchanged from those previously reported, yielding the expected conclusion that the intrinsically isodesmic group increment approach extends effectively to mediumring strained systems.

6.1 Results and Discussion

The heat of formation of a compound is a useful characteristic, traditionally determined from combustion measurements. However, the accumulation of computational data at a consistent level for a wide variety of molecules and their correlation with experimental results allow an evaluation of their heats of formation from ab initio energies, as well. Molecular mechanics or semiempirical methods are not as generally useful, since the former method needs good experimental data, not always available, for parametrization,⁴

while the latter approximates minimal basis set calculations which frequently handle strained small-ring compounds unevenly⁵. Conversion of ab initio calculated energies to heats of formation is commonly done by the use of isodesmic comparisons with closely related compounds of known thermochemistry, such that errors due to inadequacies of basis set or electron correlation treatment largely cancel out.⁶ As was pointed out by Wiberg¹, group equivalent schemes can be viewed as a subset of isodesmic reactions in which the substitution levels of all C sites are maintained constant. Thus, Wiberg² and subsequently, Ibrahim and Schleyer³, empirically determined sets of group and atom equivalents, which, when subtracted from a compound's ab initio energy, yield its heat of formation, ΔH_f (calcd). Accordingly, ΔH_f (calcd) (in kcal/mol) is expressed as the difference between the molecule's total energy and the summed increments of the component groups, as shown by the following relation:

$$\Delta H_{f}(\text{calcd}) = 627.5 (E_{T} - \sum_{i} n_{i} E_{i})$$

where E_T is the ab initio total energy, *n* represents the number of atoms or groups of each sort, and E is the corresponding atom or group equivalent. Following these reports, simplified schemes with reduced number of parameters have been proposed,⁷ and individualized atom or group parameters were developed for particular classes of compounds⁸. Bond/group equivalents have also been derived for alkanes from density functional calculations.⁹ In a series of recent articles, Allinger et al.¹⁰ outlined an alternative method which combines bond energy with group increments, while it includes terms to explicitly account for statistical mechanical effects of populating a molecule's

higher energy conformations and low-lying vibrational states, as well as its translational and rotational motions.

The present work confirms that group equivalent-based heats of formation can be calculated with an accuracy close to that from experiments (see Table 6.1). In addition, strain energies have been determined for all compounds recorded in Table 6.1.¹¹ The wide variety of small- and medium-ring strained hydrocarbons provide a stringent test of the method.

Experimental heats of formation, $\Delta H_f(exp)$, and calculated RHF/3-21G¹² and RHF/6-31 G^{*13} total energies for the compounds considered in this study are listed in Table 6.1. The calculated values refer only to the lowest energy conformation, although in several cases the compounds exist as a Boltzmann distribution of different conformational isomers with somewhat different energies. A least squares fit¹⁴ of experimental vs. calculated heats of formation with the increments for CH₂, CH and C groups as adjustable parameters yielded ΔH_f (calcd) values at the 3-21G and 6-31G* basis-set levels as listed in Table 1, along with the group increments in Table 6.2. For a range of $\Delta H_f(exp)$ from -60 to +150 kcal/mol, the standard deviation of experimental vs. calculated heats of formation is 1.8 kcal/mol for the RHF/6-31G*/RHF/6-31G* calculation (Table 6.2; Figure 6.1). The thermochemical measurements recently reported for a variety of spirocyclopropanated cyclopropane and cyclobutane derivatives¹⁵ allowed to establish unambiguously an equivalent for the quaternary carbon atom, which was not available from the work of Ibrahim and Schleyer³, while Wiberg's^{2a} value for this parameter is based only on neopentane and spiropentane.
			MMX	PM3	HF/3-	21G	HF/6-	31G*
Alkane (Symmetry) ^b	Structure	ΔH _f (exp) ^c (SE) ^d	ΔH _f (calcd) (SE)	ΔH _f (calcd)	Total Energy	ΔH _f (calcd) [°]	Total Energy	∆H _f (calcd) ^e
Cyclopropane* (D_{3h})		12.7±0.2 (27.6)	13.4 (28.8)	16.3	-116.401206	20.1	-117.058865	12.3
Cyclobutane* (D_{2d})		6.8±0.2 (26.6)	6.0 (26.6)	-3.8	-155.230510	8.7	-156.095751	5.5
Cyclopentane* (C _s)		-18.7±0.2 (6.1)	-18.3 (8.1)	-23.9	-194.088471	-20.8	-195.163580	-20.6
Cyclohexane* (D_{3d})		-29.5±0.1 (0.2)	-29.5 (2.6)	-31.0	-232.916905	-31.7	-234.208007	-32.1
Cycloheptane (C2)		-28.3±0.1 (6.4)	-28.2 (9.7)	-30.9	-271.722111	-28.0	-273.230360	-29.7
Cyclooctane (C _s)		-29.7±0.2 (9.9)	-29.5 (14.1)	-34.3	-310.532278	-27.4	-312.256501	-29.7
Cyclononane (D_3)		-31.9±0.4 ^f (12.7)	-31.9 (17.5)	-39.9	-349.345859	-29.0	-351.283877	-30.5
Cyclodecane (C_{2h})		-36.9±0.4 ^f (12.6)	-37.2 (17.9)	-47.4	-388.162367	-32.4	-390.316828	-34.8

Table 6.1 Experimental and Calculated Heats of Formation^{*}

Cycloundecane (C ₁)		-43.1±0.4 ^f (11.4)	-43.9 (17.0)	-54.7	-426.982780	-38.2	-429.351470	40.1
Cyclododecane (D4)		-55.0±0.5 ^f (4.4)	-52.9 (13.8)	-63.2	-465.811876	-49.5	-468.393830	-50.3
Bicyclo[1.1.0]butane* (C ₂ v)	\diamondsuit	51.9±0.2 (65.6)	44.8 (59.2)	69.2	-153.986638	73.2	-154.871767	55.6
Spiropentane* (D_{2d})	X	44.2±0.2 (63.5)	44.0 (64.3)	43.1	-192.821140	49.3	-193.917759	43.1
Bicyclo[2.1.0]pentane* (C ₅)	\bigcirc	37.4±0.3 [₿] (56.1)	35.9 (56.0)	37.8	-192.839862	46.7	-193.926966	37.3
Bicyclopropyl (C _{2h})	\mathbf{X}	31±1 (54.6)	36.7 (63.0)	36.1	-231.653125	45.4	-232.962273	31.6
Spiro[2.3]hexane $(C_{2\nu})$	$\hat{\mathbf{X}}$	29.9±0.4 ⁱ (54.2)	29.5 (55.3)	21.0	-231.660193	31.8	-232.965043	29.8
Bicyclo[2.2.0]hexane* (C ₂ v)		29.8±0.4 ^h (53.4)	26.8 (52.0)	12.1	-231.674413	32.0	-232.965545	29.5
Bicyclo[3.1.0]hexane (<i>C</i> ₃)	\Diamond	9.2±0.1 (32.8)	8.6 (34.4)	8.1	-231.704539	13.1	-233.001065	7.2

Tetracyclo- [4.1.0.0 ²⁴ .0 ^{3,5}]heptane (C ₄)	Q	88.4±0.4 ⁱ (104.8)	106.0 (124.4)	107.6	-268.078925	110.1	-269.603620	92.0
Quadricyclane (C2v)		80±1 (96.4)	93.4 (111.7)	86.3	-268.105603	93.3	-269.618223	82.9
<i>trans</i> -Tricyclo- [4.1.0.0 ^{2,4}]heptane (<i>C</i> ₂)		35.7±0.4 ^k (58.2)	53.4 (78.6)	41.2	-269.319879	47.4	-270.836304	36.5
Nortricyclane (C2v)	$\langle \rangle$	20±1 (42.5)	19.5 (44.2)	26.0	-269.365435	18.8	-270.867714	16.8
Dispiro[2.1.2.0]- heptane $(C_{2\nu})$	\triangleleft	72.3±0.8™ (96.1)	76.0 (101.3)	70.9	-269.240599	78.9	-270.776457	74.1
<i>cis</i> -Bicyclo[4.1.0]- heptane (<i>C</i> ₁)	\Diamond	0.5±0.5 (29.1)	1.2 (32.8)	1.2	-270.523448	8.2	-272.036765	1.2
Bicyclo[2.2.1]heptane* (norbornane) (C2v)	$\overline{\langle}$	-12.4±0.7 ^l (16.2)	-12.8 (18.1)	-13.7	-270.566556	-18.9	-272.061199	-14.1
Cubane* (<i>O</i> _h)	Ð	149±1 (164.2)	148.9 (164.9)	113.8	-305.695899	143.3	-307.393906	149.5

Dispiro[2.0.2.2]octane (Cか)	R	53.0 <u>4</u> 0.2 ⁱ (81.7)	56.6 (87.5)	46.9	-308.089744	55.0	-309.833037	54.9
Dispiro[2.1.2.1]octane (D_{2h})	F	52.4±0.3 ⁱ (81.1)	69.4 (100.4)	46.2	-308.089281	55.3	-309.833541	54.6
<i>cis</i> -Bicyclo[5.1.0]- octane (<i>C</i> ^s)	\bigcirc	-3.8±0.7 ⁿ (29.7)	-4.1 (33.2)	-3.0	-309.341191	4.0	-311.070361	-3.4
<i>cis</i> -Bicyclo[4.2.0]- octane (<i>C</i> ₁)	\bigcirc	-6.1±1.0 ⁿ (27.4)	-5.7 (31.0)	-15.8	-309.355659	-5.1	-311.075766	-6.8
<i>trans</i> -Bicyclo[3.3.0]- octane (C_{2h})	$\widehat{\boldsymbol{B}}$	-15.9±0.6" (17.6)	-15.7 (21.0)	-18.8	-309.374421	-16.9	-311.089849	-15.7
<i>cis</i> -Bicyclo[3.3.0]- octane $(C_{2^{\gamma}})$	8	-22.3±0.5" (11.2)	-22.5 (14.2)	-31.6	-309.388361	-25.6	-311.102607	-23.7

Bicyclo[2.2.2]octane* (D _{3h})	\mathcal{A}	-23.7±0.3 ¹ (9.8)	-22.7 (14.0)	-27.8	-309.392615	-28.3	-311.103597	-24.3
Homocubane (C ₂ v)	H	97±2 (117.2)	95.1 (116.9)	75.4	-344.595378	87.9	-346.504485	96.5
Trispiro[2.0.0.2.1.1]- nonane (C_2)	XX	106.6±0.2 ⁱ (134.8)	108.0 (138.3)	98.7	-345.660210	108.3	-347.635240	107.8
Trispiro[2.0.2.0.2.0]- nonane (C_{3h})		105.9±0.3 ⁱ (134.1)	109.2 (139.5)	99.5	-345.659306	108.9	-347.635101	104.9
<i>cis</i> -Bicyclo[6.1.0]- nonane (<i>C</i> ₁)	\bigcirc	-5.5±0.2 (33.0)	-7.7 (35.4)	-6.5	-348.154941	2.3	-350.099963	-5.6
<i>trans</i> -Bicyclo[6.1.0]- nonane (<i>C</i> ₂)	\bigcirc	-6.0±0.3 (32.5)	-5.7 (37.3)	-3.0	-348.149560	5.7	-350.094372	-2.1
<i>cis</i> -Bicyclo[4.3.0]- nonane (<i>C</i> ₁) (<i>cis</i> -hydrindane)	8	-30.0±0.5 (8.5)	-28.8 (13.7)	-36.0	-348.212878	-34.0	-350.141748	-31.8

Bicyclo[3.3.1]nonane (C2v)	4	-30.5±0.6° (8.0)	-30.5 (12.0)	-35.0	-348.212098	-33.6	-350.141641	-31.8
<i>trans</i> -Bicyclo[4.3.0]- nonane (<i>C</i> ₂) (<i>trans</i> -hydrindane)	8	-31.0±0.5 (7.5)	-26.5 (16.0)	-34.8	-348.213299	-34.3	-350.143605	-33.0
<i>endo</i> -Tricyclo- [5.2.1.0 ^{2,6}]decane (4,7-methano-1H- octahydroindene) (<i>C</i> ₃)	- Ch	-14.4±0.9' (22.9)	-12.5 (28.8)	-20.1	-385.859451	-19.3	-387.993144	-12.7
Protoadamantane (C1)		-20.5±0.6 (16.8)	-20.7 (20.6)	-25.1	-385.873803	-28.3	-388.007233	-21.5
all-cis-Tricyclo- [5.2.1.0 ^{4,10}]decane (perhydrotriquinacene) (C_3)	(-24.5±0.9° (12.8)	-22.1 (19.3)	-35.0	-385.875738	-29.6	-388.010690	-23.7
Adamantane (<i>T</i> _d)		-31.8±0.3 (5.5)	-31.5 (9.8)	-34.6	-385.893381	-40.6	-388.026477	-33.6

					6.50	200 157347	-25.2
Bicyclo[3.3.2]decane (C1)	-25.3±1.7° (18.1)	-25.2 (23.0)	-28.3	-387.008489	. .4. .	1.01.000-	
<i>cis</i> -Bicyclo[5.3.0]- decane (<i>C</i> ,)	$\bigcup_{(12.3)} \frac{-31.1\pm1.2^{n}}{(12.3)}$	-31.2 (17.0)	-38.3	-387.023012	-33.4	-389.170598	-33.5
<i>trans</i> -Bicyclo[5.3.0]- decane (<i>C</i> ₁)	-31.4±1.4 ⁴ (12.0)	-32.5 (15.8)	-37.7	-387.021414	-32.4	-389.168432	-32.2
Spiro[4.5]decane (C ₁)	-34.7±0.5 ^r (9.4)	-36.8 (12.3)	-42.3	-387.032669	-48.6	-389.175059	-36.4
<i>cis</i> -Decaline (<i>C</i> ₂)	-40.4±0.5 (3.0)	-41.0 (7.2)	-42.7	-387.038933	-43.4	-389.183574	-41.7
<i>trans</i> -Decaline (<i>C</i> _{2h})	CCCCCCCCCCCCC	-43.8 (4.5)	-44.5	-387.043547	-46.3	-389.189065	-45.1

icyclo[3.3.3]undecane nanxane) 34)	A	-21.3±0.5° (27.1)	-24.3 (29.7)	-30.3	-425.811986	-19.6	-428.179071	-22.4
oiro[5.5]undecane	\otimes	-45.0±0.6 [°] (4.0)	-46.3 (8.6)	-47.3	-425.857442	-57.2	-428.215349	-45.3
etraspiro- .0.2.0.2.0.2.0]- odecane)4/)	\mathcal{H}	106.6±0.5 ⁱ (144.2)	116.2 (157.4)	100.2	-460.947636	102.1	-463.566502	106.6
icyclohexyl 2n)	\mathcal{O}	-52.2±0.7 (1.1)	-52.0 (7.8)	-54.0	-464.675788	-52.7	-467.251138	-51.3
ongressane liamantane)) _{3d})		-34.9 <u>+</u> 0.6 ^t (10.0)	-34.3 (16.3)	-38.5	-538.871299	-50.5	-541.848097	-37.1
ans-transoid-trans- erhydroanthracene 22)	8	-52.7±1.5 ^u (4.4)	-52.0 (12.3)	-53.1	-541.158059	-53.4	-544.158403	-50.8

-58.1±0.9 -58.1 -57.9 -541.168676 -60.1 -544.170009 -58.1 (1.0) (6.3) (6.3) -541.168676 -60.1 -544.170009 -58.1	 kailmol; total energies in hartrees, 1 H = 627.5 kcal/mol. All structures were fully optimized using Spartan 4.0 (Wavefunction is included in the original Wiberg's regression analysis for deriving group equivalents (ref. 2) are marked with •. fubration. e Database 25, Structures and Properties, version 2.02, January 1994, by Lias, S. G.; Liebman, J. F.; Levin, R. D.; Kafafi, S. S. all Alf and Benson's group equivalents (Benson, S. W. <i>Thermochemical Kinetics,</i> John Wiley: New York, 1976). e Database 25, Structures and Properties, version 2.02, January 1994, by Lias, S. G.; Liebman, J. F.; Levin, R. D.; Kafafi, S. S. and Alf, and Benson's group equivalents (Benson, S. W. <i>Thermochemical Kinetics,</i> John Wiley: New York, 1976). end Alf and Benson's group equivalents (Benson, S. W. <i>Thermochemical Kinetics,</i> John Wiley: New York, 1976). mated heat of vaporization or sublimation from vapor pressure measurements. Cox, J. D.; Pilcher, G. <i>Thermochemistry of mapunds,</i> Academic Press. New York, 1970. ogenation to oycloperature. See rth. Kozhushkov, S. L; Belov, V. N.; Verevkin, S. P.; de Meijere, A. J. Am. <i>Chem. Soc.</i> 1982, 104, 5679. ogenation to 13.5 -cyclophatrineer. Chnstl, M.; Brunn, E.; Roth, W. R.; Lennartz, HW. <i>Ternbedron</i> 1989, 45, 2905. S. M.; Kolesov, V. P.; Kuznetsova, T. S.; Kokoreva, O. V.; Kozhushkov, S. L; Zefirov, N. S. Russ. J. Phys. <i>Chem.</i> 1993, 67, 2130. M.; Kolson, V. P.; Kuznetsova, T. S.; Kokoreva, O. V.; Kozhushkov, S. L; Zefirov, N. S. Russ. J. Phys. <i>Chem.</i> 1993, 67, 215. Chean. <i>Brit.</i>, 134. S. M.; Kolesov, V. P.; Kuznetsova, T. S.; Kokoreva, O. V.; Kozhushkov, S. L; Zefirov, N. S. Russ. J. Phys. <i>Chem.</i> 1993, 67, 219. S. M.; Kolesov, V. P.; Kuznetsova, T. S.; Kokoreva, O. V.; Kozhushkov, S. L; Zefirov, N. S. Russ. J. Phys. <i>Chem.</i> 1993, 67, 219. S. M.; Kolesov, V. P.; Kuznetsova, T. S.; Kokoreva, O. V.; Kozhushkov, S. L; Zefirov, N. S. Russ. J. Phys. <i>Chem.</i> 1993, 67, 219.
-58.1±0.9 (1.0)	al energies in in the original 5, Structures a Benson's grou ats analysis (so of vaporization cademic Press of vaporization cademic Press of vaporization cademic Press (so of vaporization cademic Press (so of vaporization cademic Press (so of vaporization cademic Press (so of vaporization cademic Press (so of vaporization contention of vaporization (so of vaporization) (so of vaporization (so of vaporization) (so of vaporizatio
\bigotimes	Kin kcal/mol; to pounds included in y conformation. rence Database 2 imental ΔH _f and n group equivale: n estimated heat of <i>ic Compounds</i> , A hydrogenation to <i>ic Compounds</i> , A hydrogenation to <i>it</i> , C.; Kozhushko isomerization to <i>i</i> , Shary-Tehrany, <i>ic Watt</i> , I. <i>J. Chen</i> de, H.; McKerve de, H.; Mc
<i>trans-cisoid-trans-</i> Perhydroanthracene (C ₂)	 Heats of formation at 298 Inc., Irvine, CA). The complexity of lowest energy by Symmetry of lowest energy of symmetry of lowest energy from NIST Standard Refe A., unless otherwise noted. ^d Strain energy, from experident of This work; calculated from the energy from experident of the strain energy, from experident of the stimated from its heat of heat of form its heat of heat of the stimated from its heat of heat of heat of heat of heat of the stimated from its heat of heat of heat of the stimated from its heat of heat of the stimated from its heat of heat of the stimated from its heat of the stimated from stimated from stimated from stimated from stimated from stimated from stimated stin stimated from stimated stin stin stin stimated stimated stin

Table 6.2	Comparison of the Wiberg and Ibrahim/Schleyer Group Equivalents with	th
	Those Derived from the Ab Initio Energies of Table 6.1	

		Group	o equivalents	in hartrees		
Group	Wi	berg ^a	Ibrahim	/Schleyer ^b	This work	(via Table 1)
	HF/3-21G	HF/6-31G*	HF/3-21G	HF/6-31G*	HF/3-21G	HF/6-31G*
CH ₂	-38.81054	-39.02662	-38.81150	-39.02684	-38.81108	-39.02614
СН	-38.24087	-38.45350	-38.23954	-38.45338	-38.24054	-38.45402
С	-37.65633	-37.87895	-	-	-37.65544	-37.88182
s.d. ^c	7.3	2.3	7.5 ^d	2.5 ^d	6.7	1.8

^a Ref. 2b. ^b Ref. 3.

° Standard deviation (in kcal/mol) of experimental vs. calculated heats of formation for the present data

set (Table 6.1). ^d Standard deviations are based only on compounds with CH₂ and CH groups; spiranes were excluded from correlations since Ibrahim/Schleyer do not provide an equivalent for the quaternary C atom.



Figure 6.1 Plot of experimental heats of formation, $\Delta H_{f}(exp)$, vs. calculated values, $\Delta H_{f}(calcd)$, from the HF/6-31G* group equivalents evaluated in this work, for the compounds in Table 6.1. Slope 1.00 was taken for the correlation line.

The equivalents derived in this work for the CH_2 , CH and C fragments (see Table 6.2) are essentially unchanged from those previously reported, supporting the consensus that errors due to incompleteness in basis set, correlation treatment, and vibrational contributions, scale linearly with the numbers of each group. They are absorbed in the group parameters, to yield calculated heats of formation of accuracy comparable to experimental measurements. The ΔH_f (calcd) values derived for the 3-21G basis set show large errors especially in the case of cyclopropane derivatives, where the flexibility afforded by inclusion of polarization functions into the basis set is essential for a proper description of these compounds.

Analogous values for the semiempirical PM3 method¹⁶ are included in Table 6.1 for comparison and the resulting heats of formation show, as expected, unacceptably large errors; the standard deviation for the best linear fit between PM3 calculated and experimental heats of formation for the compounds listed in Table 1 is 8.0 kcal/mol. The MMX method, derived from Allinger's¹⁷ MM2 force field, was also employed to compute heats of formation for the compounds included in Table 6.1.¹⁸ Usually, MM reproduces well the thermodynamic properties of hydrocarbons; e.g., the new MM4 force field applied to 56 alkanes and cycloalkanes, excluding small rings, calculate ΔH_f with a standard deviation of 0.4 kcal/mol vs. experimental values.¹⁹ However, the MMX results in Table 6.1 show that although most compounds have MMX calculated heats of formation within experimental accuracy, in some cases there are large discrepancies between experiment and calculation (5 compounds in Table 6.1 have MMX ΔH_f (calcd) in error vs. ΔH_f (exp) by more than 10 kcal/mol). Thus, the performance of the MMX

method,²⁰ although much better than that of PM3 or HF/3-21G models, is not entirely consistent, leaving the ab initio $HF/6-31G^*$ group equivalent scheme as the most reliable when compared to experiment.

The estimates of the enthalpies of formation using the 6-31G* basis-set are uniformly quite good. Hence, the group equivalents at the 6-31G* level successfully predict heats of formation of both small and medium-ring strained hydrocarbons from ab initio energies, in rather good agreement with experimental measurements. The new group equivalents yield a modest improvement over those of Wiberg² and Ibrahim and Schleyer³. The essential message, however, is that Wiberg's original set is quite adequate as expected and the principal enhancement offered herein is an updated estimate of the quaternary carbon equivalent. Predictably, the equivalents at the unpolarized 3-21G basis set level cannot be used safely for strained compounds since polarization functions are known to be needed to properly describe small ring carbocyclics. Such calculations can be used when experimental results are unavailable, or as an independent check when an experimental result is in question.

6.2 References

¹ Crăciun, L.; J. E. Jackson, J. E. submitted to J. Phys. Chem. 1997.

² (a) Wiberg, K. B. J. Comput. Chem. 1984, 5, 197. (b) Wiberg, K. B. J. Org. Chem. 1985, 50, 5285.

³ Ibrahim, M. R.; Schleyer, P. v. R. J. Comput. Chem. 1985, 6, 157.

⁴ Burkert, U.; Allinger, N. L. Molecular Mechanics, ACS Monograph 177, 1982.

⁵ Dewar, M. J. S.; Thiel, W. J. Am. Chem. Soc. 1977, 99, 4907.

⁶ (a) Hehre, W. J.; Ditchfield, R.; Radom, L.; Pople, J. A. J. Am. Chem. Soc. **1970**, 92, 4796 and subsequent papers. (b) For an example of the use of homodesmic reactions to calculate the heats of formation of 15 representative strained and unstrained medium-sized hydrocarbons, see: Disch, R. L.; Schulman, J. M.; Sabio, M. L. J. Am. Chem. Soc. **1985**, 107, 1904.

⁷ (a) Yala, Z. J. Mol. Struct.: THEOCHEM. 1990, 207, 217. (b) Castro, E. A. J. Mol. Struct.: THEOCHEM. 1994, 304, 93. (c) Herndon, W. C. Chem. Phys. Lett. 1995, 234, 82. (d) Smith, D. W. J. Chem. Soc., Faraday Trans. 1996, 92, 1141.

⁸ Schulman, J. M.; Peck, R. C.; Disch, R. L. J. Am. Chem. Soc. 1989, 111, 5675.

⁹ Allinger, N. L.; Sakakibara, K.; Labanowski, J. J. Phys. Chem. 1995, 99, 9603.

¹⁰ (a) Allinger, N. L.; Schmitz, L. R.; Motoc, I.; Bender, C.; Labanowski, J. K. J. Phys. Org. Chem. 1990, 3, 732. (b) Allinger, N. L.; Schmitz, L. R.; Motoc, I.; Bender, C.; Labanowski, J. K. J. Am. Chem. Soc. 1992, 114, 2880. (c) Allinger, N. L.; Schmitz, L. R.; Motoc, I.; Bender, C.; Labanowski, J. K. J. Comput. Chem. 1992, 13, 838. (d) Schmitz, L. R.; Motoc, I.; Bender, C.; Labanowski, J. K.; Allinger, N. L. J. Phys. Org. Chem. 1992, 5, 225. (e) Liu, R.; Allinger, N. L. J. Phys. Org. Chem. 1993, 6, 551.

¹¹ Strain energy is the difference between the experimental (calculated) heat of formation of a compound and that of a hypothetically "strainless" model, calculated here from Benson's group equivalents (see Benson, S. W. *Thermochemical Kinetics*; John Wiley: New York, 1976).

¹² Binkley, J. S.; Pople, J. A.; Hehre, W. J. J. Am. Chem. Soc. 1980, 102, 939.

¹³ Hariharan, P. C.; Pople, J. A. Chem. Phys. Lett. 1972, 66, 217.

¹⁴ The analysis was done with Microsoft Excel version 5.0 employing the function LINEST, which uses the "least-squares" method to calculate simple or multiple linear regressions that best fit the input data.

¹⁵ Beckhaus, H.-D.; Rüchardt, C.; Kozhushkov, S. I.; Belov, V. N.; Verevkin, S.P.; de Meijere, A. J. Am. Chem. Soc. 1995, 117, 11854.

¹⁶ Stewart, J. J. P. J. Comput. Chem. 1989, 10, 209.

¹⁷ Allinger, N. L. J. Am. Chem. Soc. 1977, 99, 8127.

¹⁸ The MMX calculations were done using the interactive molecular modeling program

¹⁷ Allinger, N. L. J. Am. Chem. Soc. 1977, 99, 8127.

¹⁸ The MMX calculations were done using the interactive molecular modeling program PCMODEL version 4.0 (Serena Software, Bloomington, IN).

¹⁹ Allinger, N. L.; Chen, K.; Lii, J.-H. J. Comput. Chem. 1996, 17, 642.

²⁰ The best linear fit of $\Delta H_f(exp)$ vs. $\Delta H_f(calcd)$ gives a s.d. of 4.2 kcal/mol for the compounds listed in Table 6.1.

APPENDIX

	Iculated Parameters for 1-39 ^a
i	G* Cal
ייי קווע	16-0/111
PM3 an	
Table 1A	

								PM3					
No.	Compound	J _{exp}	% s _c	dc.H	B.O.	pc	Ън	qc dc	Чн	θ^{av}_{ccc}	$\Sigma \Delta \theta_{ccc}$	θ ^{av} HCC	$\Sigma \Delta \theta_{HCC}$
1a		215	41.2	1.0809	0.94972	0.758	0.6522	-0.204252	0.145387	71.67	113.49	136.03	-79.59
2a	$\overline{\checkmark}$	212	41.2	1.0807	0.95017	0.7578	0.6525	-0.201667	0.144582	71.38	114.36	136.19	-80.07
ŝ	\triangleleft	210	42.5	1.0772	0.94821	0.7604	0.6494	-0.195956	0.152956	68.04	124.38	139.21	-89.13
1b	A	209	41.1	1.0807	0.95	0.7575	0.6528	-0.195714	0.143787	71.52	113.94	136.09	-79.77
4	\Diamond	205	40.4	1.0832	0.9521	0.756	0.6546	-0.210323	0.139142	73.00	109.5	134.2	-74.1
5a*		200.3	40.45	1.0831	0.951175	0.7558	0.6548	-0.1986	0.138793	73.03	109.41	134.34	-74.52
6 a		190	39.7	1.0851	0.95216	0.7538	0.6571	-0.203034	0.131949	74.21	105.87	132.79	-69.87
7a	\triangleright	189	39.9	1.0815	0.954	0.7532	0.6577	-0.17706	0.131031	78.09	94.23	132.79	-69.87

-53.94	-65.16	-49.8	-48.69	-51.33	-40.26	-26.5	-39.09	-35.79
127.48	131.22	126.1	125.73	126.61	122.92	122.75	122.53	121.43
73.8	88.5	69.36	67.62	71.07	55.17	54.51	53.58	49.74
84.9	80	86.38	86.96	85.81	91.11	91.33	91.64	92.92
0.119653	0.125831	0.116459	0.112637	0.116012	0.109108	0.10922	0.109451	0.107875
-0.130058	-0.125831	-0.138128	-0.163004	-0.139106	-0.143582	-0.146581	-0.104796	-0.135451
0.6624	0.6598	0.6636	0.6649	0.6638	0.6667	0.6666	0.6667	0.6674
0.7491	0.7514	0.7481	0.747	0.7479	0.7453	0.7454	0.7453	0.7447
0.9594	0.95675	0.95852	0.96099	0.96008	0.96338	0.96313	0.96388	0.96303
1.0871	1.0827	1.0903	1.0908	1.0883	1.0933	1.0935	1.0947	1.0963
38.1	39.4	37.2	37.0	37.7	36.3	36.1	36.1	35.5
185	179.7	179	178.1	177.2	175	174	171	171
$\overline{\mathbb{A}}$	<		\triangle	\triangleright	J			
88	6	10	11	7b	12a	13a	14a	1c

-37.98	-35.61	-53.28	-33.9	-35.4	-23.19	-37.02	-30.69	-25.5
122.16	121.37	127.26	120.8	121.3	117.23	121.84	119.73	118
55.14	50.34	67.05	46.77	49.2	35.1	52.77	42.84	36.3
91.12	92.72	87.15	93.91	93.1	97.8	91.91	95.22	97.4
0.108357	0.105705	0.100197	0.105377	0.108638	0.09858	0.109605	0.100032	0.096797
-0.09562	-0.156576	-0.109247	-0.139075	-0.123456	-0.146806	-0.045928	-0.140413	-0.143878
0.6672	0.6680	0.669	0.6682	0.6674	0.6714	0.667	0.6702	0.6714
0.7449	0.7442	0.7433	0.744	0.7447	0.7411	0.7451	0.7422	0.7411
0.96401	0.96329	0.95804	0.96425	0.96367	0.96547	0.96299	0.96563	0.96568
1.0953	1.0957	1.0861	1.0969	1.0956	1.1021	1.0943	1.0996	1.1021
35.9	35.5	36.8	35.3	35.7	33.8	36.6	34.6	33.9
171	169	167.8	166	166	166	166	165.7	165
	Z	4				A	\Diamond	\square
13b	15a	16	14b	8 b	17a	1d	18*	19a

	-												
20a	A	164	33.8	1.1019	0.96607	0.7411	0.6714	-0.145323	0.096877	97.52	35.94	117.89	-25.17
2b	$\overline{4}$	163	36.4	1.0952	0.96372	0.7442	0.668	-0.07682	0.106603	92.42	51.24	121.5	-36
17b		161	33.8	1.1026	0.96484	0.7417	0.6708	-0.146069	0.098769	97.74	35.28	117.3	-23.4
21*	\Diamond	160	32.9	1.1054	0.96834	0.7386	0.6742	-0.128902	0.089865	100.1	28.2	115.85	-19.05
7с	\triangleright	158.8	35.9	1.0899	0.96458	0.7415	0.6709	-0.08703	0.096951	92.51	50.97	123.33	-41.49
22a	$\langle \rangle$	157.9	36.7	1.0875	0.96237	0.7443	0.6678	-0.129055	0.104496	89.09	61.23	125.91	-49.23
23a	B	157	36.5	1.0882	0.96289	0.7436	0.6686	-0.110768	0.102413	89.67	59.49	125.49	-47.97
24		154.5	36.5	1.0877	0.96316	0.7433	0.669	-0.101533	0.101533	06	58.5	125.26	-47.28
Sb		154.2	34.0	1.1045	0.9669	0.7386	0.6742	-0.055235	0.090241	9.66	29.7	115.76	-18.78
15b	R	152	34.6	1.0940	0.96514	0.739	0.6737	-0.06131	0.089977	95.95	40.65	120.82	-33.96

23b	H	152	35.2	1.0919	0.9658	0.7404	0.6721	-0.097991	0.093658	94.42	45.24	121.98	-37.44
25	$\overline{\mathcal{A}}$	151.8	34.5	1.0946	0.96562	0.7387	0.674	-0.099057	0.088723	96.11	40.17	120.73	-33.69
22b	\diamond	148.8	34.1	1.0958	0.96747	0.7383	0.6745	-0.103804	0.087207	96.57	38.79	120.21	-32.13
12b	J	148	33.0	1.0999	0.96858	0.7369	0.676	-0.100152	0.085769	101.1	25.2	116.92	-22.26
26		148	34.5	1.0945	0.96699	0.7395	0.6732	-0.091326	0.091326	96	40.5	120.71	-33.63
27		147.9	32.5	1.1080	0.96447	0.7369	0.6761	-0.113116	0.082807	98.73	32.31	118	-25.5
23c	B	146	33.4	1.0989	0.96782	0.7377	0.6752	-0.085668	0.087579	96.66	28.62	117.58	-24.24
6b		145	31.9	1.1118	0.9684	0.7335	0.6797	-0.040729	0.075994	104.78	14.16	111.6	-6.3
28	4	144.9	32.3	1.1028	0.96925	0.7343	0.6788	-0.087807	0.076365	101.72	23.34	116.28	-20.34

13 c	$\langle \rangle$	144	32.7	1.1009	0.96999	0.7362	0.6767	-0.030055	0.084048	101.97	22.59	116.21	-20.13
29	$\overline{\mathcal{A}}$	141	31.8	1.1043	0.97014	0.7338	0.6794	-0.085209	0.076328	103.53	17.91	114.91	-16.23
30	NJ	137	30.1	1.1107	0.97019	0.7316	0.6817	0.028676	0.071569	107.7	5.4	111.19	-5.07
14c		137	30.2	1.1107	0.9709	0.7319	0.6814	-0.021768	0.0724	107.52	5.94	111.35	-5.55
17c		136.2	29.8	1.1118	0.97079	0.7307	0.6827	-0.006528	0.06886	108.13	4.11	110.76	-3.78
31*	A	136	31.0	1.1068	0.97167	0.7319	0.6815	-0.086521	0.069885	104.66	14.52	113.77	-12.81
32*	\bigcirc	135	29.6	1.1109	0.97442	0.7299	0.6836	-0.082864	0.057674	107.78	5.16	110.82	-3.96
33	$\overline{\mathcal{A}}$	134.3	29.1	1.1146	0.97247	0.7285	0.685	-0.072741	0.062191	109.22	0.84	109.73	-0.69
19b	β	134.2	29.5	1.1130	0.97158	0.7297	0.6838	-0.040039	0.065711	108.65	2.55	110.28	-2.34
34*	$\overline{\langle}$	133.7	29.9	1.1112	0.97224	0.73	0.6834	-0.076853	0.065929	107.54	5.88	111.34	-5.52

75.06	134.52 -	114	71.5	0.24342	-0.256818	0.6078	0.7941	0.92944	1.0696	34.9	215	Z	1a
$\Delta \theta_{HCC}$		$\Sigma \Delta \theta_{ccc}$	θ_{ccc}^{av}	문	d c	Ън	pc	B.O.	d _{c-H}	% s _c	J _{exp}	Compound	No.
					F/6-31G*	H							
21.12	102.46	-17.94	115.48	0.043311	-0.061201	0.6924	0.7215	0.97863	1.1202	25.2	111.2	\bigcirc	38b'
13.11	105.13	-11.82	113.44	0.047412	-0.06418	0.6907	0.7231	0.97638	1.1201	26.5	120.0	A	39*
12.12	105.46	-10.98	113.16	0.114347	-0.146906	0.6641	0.7476	0.94956	1.1150	25.7	122.4	$ \bigcirc $	38a *
11.79	105.57	-10.71	113.07	0.049169	-0.06128	0.6901	0.7237	0.97511	1.1208	26.8	125.2	A	37*
1.68	107.94	-4.38	110.96	0.056823	-0.070346	0.6871	0.7265	0.97315	1.1178	28.1	129.4		36*
3.75	110.75 -3	4.05	108.15	0.068559	-0.005208	0.6828	0.7306	0.97079	1.1118	29.8	133		20b
.15	109.53 (0.15	109.41	0.060811	-0.072792	0.6855	0.7281	0.97233	1.1148	29.0	133.4		35

2a	$\overline{\checkmark}$	212	34.9	1.0693	0.93195	0.7932	0.609	-0.253664	0.242007	71.08	115.26	134.27	-74.31
e	\triangleleft	210	36.4	1.0678	0.92708	0.7946	0.6072	-0.256051	0.245399	67.74	125.28	138.6	-87.3
1b	A	209	34.9	1.0699	0.92871	0.7928	0.6094	-0.234109	0.240671	70.7	116.4	134.54	-75.12
4	\Diamond	205	33.8	1.07	0.9333	0.7911	0.6117	-0.246773	0.236424	73.1	109.2	130.59	-63.27
5a*		200.3	33.65	1.07085	0.93456	0.79125	0.61145	-0.24749	0.23713	72.91	109.77	130.7	-63.6
6a		190	32.5	1.072	0.93773	0.7894	0.6139	-0.24213	0.23291	74.11	106.17	127.34	-53.52
7 a	\triangleright	189	33.9	1.0727	0.93535	0.7916	0.6111	-0.244359	0.237868	77.47	96.09	132.74	-69.72
88	$\overline{\mathbb{A}}$	185	32.2	1.0736	0.93645	0.7904	0.6126	-0.241484	0.24549	84.83	74.01	127.1	-52.8
6	<≺	179.7	33.6	1.0738	0.9295	0.7901	0.613	-0.235334	0.235334	80	88.5	130.62	-63.36
10		179	30.7	1.0758	0.93701	0.7888	0.6146	-0.241435	0.230784	86.75	68.25	124.93	-46.29

6 -47.58	48	-38.1	5 -38.85	9 -38.07	ł2 -32.76	1 -36.63	12 -31.26	2 -53.16
125.3	125.5	122.2	122.4	122.1	120.4	121.7	119.9	127.2
68.07	69.57	54.69	55.17	53.88	48.72	52.08	47.97	66.9
86.81	86.31	91.27	91.11	91.54	93.26	92.14	93.51	87.2
0.229207	0.235085	0.240866	0.24017	0.243737	0.236183	0.244112	0.236009	0.217635
-0.23952	-0.245298	-0.249974	-0.244656	-0.241086	-0.25272	-0.240606	-0.257511	-0.207638
0.6157	0.6142	0.6132	0.6132	0.6125	0.6151	0.6125	0.6149	0.618
0.7880	0.7891	0.7899	0.7899	0.7905	0.7885	0.7905	0.7886	0.7862
0.94059	0.94107	0.94661	0.94097	0.94211	0.94245	0.94086	0.9452	0.94217
1.0754	1.0747	1.0745	1.0756	1.0745	1.076	1.0752	1.0761	1.0822
31	31.6	30.3	30.3	30.1	29.3	29.8	29.2	30.3
178.1	177.2	175	174	171	171	171	169	167.8
\bigcirc	\triangleright	J			A		Z	Ą
11	7b	12a	13a	14a	1c	13b	15a	16

-32.19	-31.44	-22.2	-33.54	-28.92	-22.5	-22.26	-32.67	-22.68
120.23	119.98	116.9	120.68	119.14	117.0	116.92	120.39	117.06
46.38	47.19	34.47	50.4	42.63	34.65	34.41	48.91	34.86
94.04	93.77	98.01	92.7	95.29	97.95	98.03	93.2	97.88
0.239842	0.24549	0.23388	0.239533	0.234394	0.23428	0.233907	0.236233	0.237055
-0.243015	-0.249765	-0.250069	-0.230399	-0.245476	-0.251418	-0.245473	-0.228438	-0.252515
0.6139	0.6126	0.6167	0.6141	0.616	0.6164	0.6166	0.6155	0.6153
0.7894	0.7904	0.7872	0.7892	0.7877	0.7874	0.7873	0.7881	0.7883
0.94289	0.94055	0.94789	0.94116	0.94846	0.94853	0.94928	0.94498	0.94685
1.0765	1.0757	1.0779	1.0762	1.0763	1.0779	1.0778	1.0767	1.0771
29.2	29.6	27.6	30.4	28.7	27.6	27.6	30.3	27.7
166	166	166	166	165.7	165	164	163	161
	$\overline{\mathbf{A}}$			\Diamond	\square		$\overline{4}$	
14b	8b	17a	1d	18*	19a	20a	2b	17b

21*	\bigcirc	160	26.95	1.07745	0.95373	0.7863	0.6178	-0.24754	0.232582	100.36	27.42	115.08	-16.74
7c	\triangleright	158.8	29.8	1.08	0.94741	0.7863	0.6178	-0.219619	0.226734	93.55	47.85	122.67	-39.51
22a	$\langle \rangle$	157.9	30.7	1.0801	0.94129	0.7869	0.6171	-0.21711	0.227161	88.81	62.07	126.1	-49.8
23a	B	157	30.8	1.0807	0.93854	0.7861	0.6181	-0.218015	0.224647	89.17	60.99	125.82	-48.96
24	Ð	154.5	30.8	1.081	0.93507	0.7863	0.6179	-0.22539	0.22539	06	58.5	125.27	-47.31
Sb		154.2	28.2	1.08	0.95178	0.7863	0.6179	-0.229629	0.231101	<u> </u>	28.65	115.17	-17.01
15b		152	28.5	1.0819	0.94983	0.787	0.6169	-0.22724	0.228467	96.49	39.03	120.43	-32.79
23b	H	152	29.3	1.0816	0.94323	0.7868	0.6172	-0.232165	0.229232	93.8	47.1	121.76	-36.78
25	Ą	151.8	28.5	1.0823	0.95197	0.7859	0.6183	-0.225583	0.2251	96.64	38.58	120.36	-32.58
22b	\diamond	148.8	28.3	1.0825	0.95199	0.7845	0.6201	-0.231733	0.22169	97.22	36.84	119.8	-30.9

12b	J	148	27.3	1.0818	0.95437	0.7879	0.6159	-0.243347	0.236383	101.73	23.31	116.41	-20.73
26		148	28.8	1.0821	0.94373	0.7865	0.6176	-0.230164	0.230164	96	40.5	120.72	-33.66
27		147.9	27.8	1.0845	0.94922	0.7855	0.6189	-0.232217	0.223115	97.43	36.21	119.51	-30.03
23 c	B	146	27.5	1.0825	0.9469	0.7876	0.6162	-0.240674	0.235951	100.25	27.75	117.2	-23.1
6b		145	26.4	1.0832	0.95616	0.7844	0.6203	-0.230748	0.226047	104.92	13.74	111.22	-5.16
28	$\overline{\mathcal{A}}$	144.9	26.5	1.0844	0.95772	0.7844	0.6203	-0.227417	0.223034	102.35	21.45	115.81	-18.93
13c		144	26.9	1.0817	0.95272	0.7892	0.6141	-0.254138	0.242884	102.63	20.61	115.67	-18.51
29	$\overline{\mathcal{A}}$	141	26.3	1.0838	0.95746	0.7863	0.6179	-0.239337	0.231883	103.86	16.92	114.63	-15.39
30		137	24.5	1.0846	0.95576	0.789	0.6144	-0.240937	0.240853	107.97	4.59	110.93	-4.29

14c		137	24.5	1.0853	0.95626	0.7878	0.616	-0.249355	0.238561	107.83 5.01	111.07	4.71
17c		136.2	24.3	1.0853	0.95726	0.7878	0.6159	-0.24172	0.237976	108.34 3.48	110.56	-3.18
31*	A	136	25	1.0853	0.96119	0.7833	0.6216	-0.230766	0.222406	105.78 11.16	112.84	-10.02
32*	\bigcirc	135	24.1	1.08625	0.95751	0.78305	0.62195	-0.23418	0.222745	107.3 6.6	111.12	-4.86
33	$\overline{\langle}$	134.3	24	1.0865	0.96005	0.7853	0.6191	-0.240146	0.23114	109.22 0.84	109.72	-0.66
19b	R	134.2	24.2	1.0859	0.95871	0.7866	0.6175	-0.241403	0.234631	108.77 2.19	110.16	-1.98
34*	4	133.7	24.5	1.0857	0.96182	0.785	0.6195	-0.242177	0.230364	107.71 5.37	111.19	-5.07
35		133.4	23.8	1.0872	0.96096	0.7851	0.6194	-0.239144	0.230241	109.35 0.45	109.6	-0.3
20b		133	24.2	1.0851	0.95648	0.788	0.6157	-0.243219	0.239332	108.51 2.97	110.41	-2.73

5.4	13.41	11.37	16.59	27.45
107.7	105.03	105.71	103.97	100.35
-5.07	-12.06	-10.38	-14.61	-22.02
111.19	113.52	112.96	114.37	116.84
0.228941	0.229051	0.197921	0.227384	0.232216
-0.23861	-0.240724	-0.234185	-0.241307	-0.250803
0.6207	0.6215	0.6312	0.6224	0.6211
0.7841	0.7835	0.7756	0.7827	0.7838
0.96242	0.96533	0.95055	0.96868	0.97149
1.0879	1.0878	1.0751	1.0868	1.0837
22.8	21.5	21.9	21	20.1
129.4	125.2	122.4	120.0	111.2
L.		\mathcal{O}	R	\bigcirc
36*	37*	38a*	39*	38b*

NBO analysis; d_{CH} is the C-H distance in Å; B.O. is the C-H bond order from the Mulliken atom-atom bond order matrix; p_C and p_H are polarization coefficients on C and H from NBO analysis; q_c and q_H are natural atomic charges on C and H; θ^{av} and θ^{av} are average ^a J_{exp} represents the experimental one-bond ¹³C-¹H spin-spin coupling constant; % s_c is percent s-character of the carbon hybrid from internuclear $\angle CCC$ and $\angle HCC$ distortions in degrees, defined as $\Sigma(109.5^{\circ} - \angle CCC^{\circ})$ and $\Sigma(109.5^{\circ} - \angle HCC^{\circ})$, respectively; and * \angle CCC and \angle HCC angles in degrees, defined as ($\Sigma \angle$ CCC°)/3 and ($\Sigma \angle$ HCC°)/3; $\Sigma \Delta \theta_{ccc}$ and $\Sigma \Delta \theta_{Hcc}$ represent the sum of means it may need conformational averaging, even if they are nondegenerate.