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PART 1

HETEROCYCLIC PHOTOCHEMISTRY: THE PHOTOCHEMICAL SYNTHESIS OF β-LACTAMS

PART 2

THE ^{13}C NMR SPECTRA OF NAPHTHALENE CROWN ETHER COMPLEXES: FIELD INDUCED π POLARIZATION AND CROWN ETHER CONFORMATIONAL CHANGES

By

Mark R. Johnson

A DISSERTATION

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

DOCTOR OF PHILOSOPHY

Department of Chemistry

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Mark R. Johnson

ABSTRACT

PART 1

HETEROCYCLIC PHOTOCHEMISTRY: THE PHOTOCHEMICAL SYNTHESIS OF β-LACTAMS

PART 2

THE ^{13}C NMR SPECTRA OF NAPHTHALENE CROWN ETHER COMPLEXES: FIELD INDUCED π POLARIZATION AND CROWN ETHER CONFORMATIONAL CHANGES

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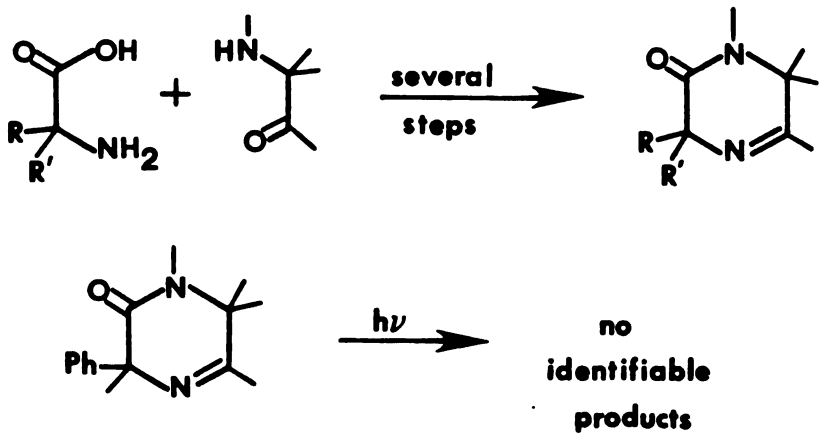
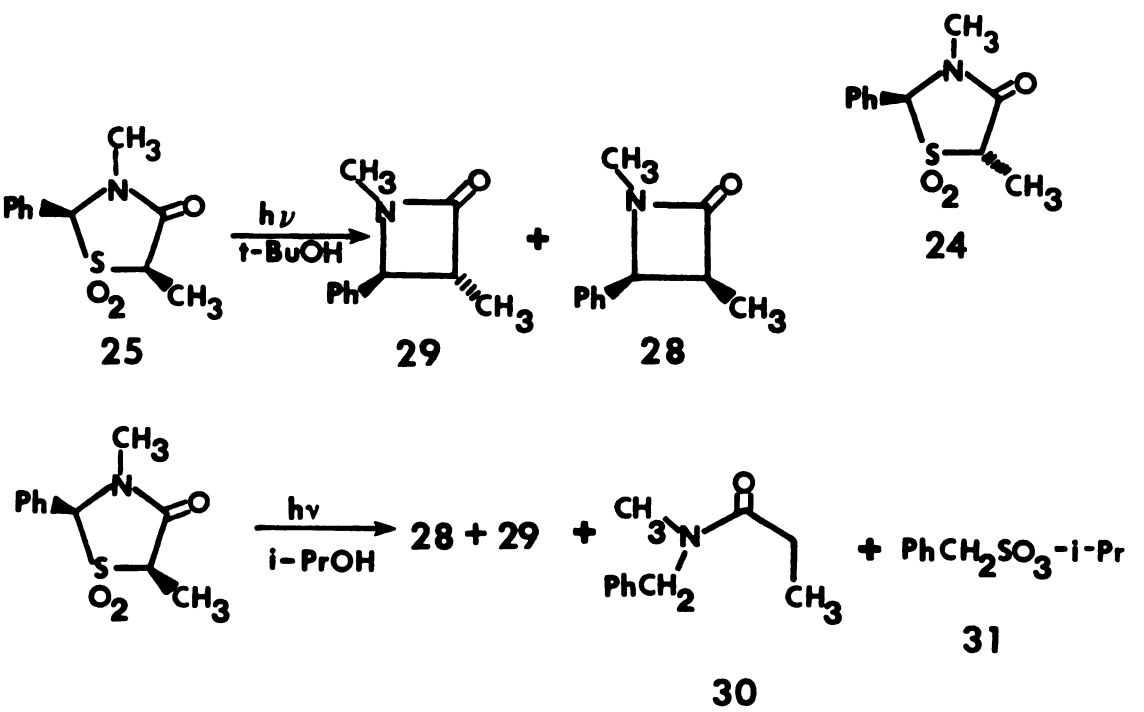
The first part of this thesis describes attempts to photochemically synthesize β-lactams. Two proposed methods were studied, one of them being successful. The first method involved a hoped for 1,3-acyl migration of a 3,6-dihydro-2(1H)-pyrazinone. A general synthesis of this little-known heterocyclic system was developed, starting from an α-amino acid and an α-aminoketone. Photolysis, however, led to slow decomposition and formation of no identifiable products.



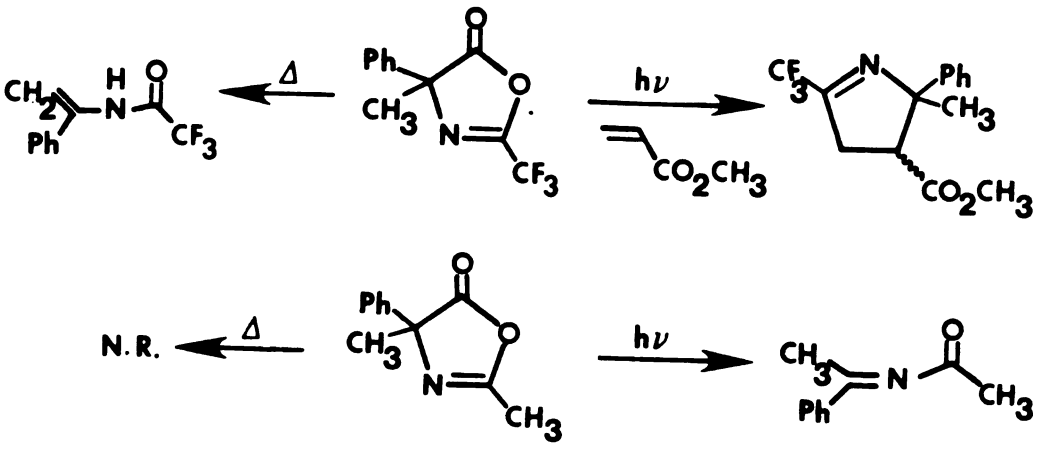
The second method involved sulfur dioxide extrusion from 1,1-dioxo-4-thiazolidinones. These were synthesized by literature methods. Stereochemical assignments for sulfones 24 and 25 were made by x-ray crystallography. An attempt to use standard NMR techniques to assign the stereochemistry of the corresponding sulfoxides resulted in completely erroneous assignments. Photolysis of cis sulfone 25 in t-butyl alcohol/acetonitrile resulted in formation of both cis and trans β-lactams, 28 and 29, with the cis isomer the major product. Photolysis of the trans sulfone also gave the β-lactams, with the trans β-lactam the major product. Photolysis in isopropanol gave reduction products 30 and 31, along with some β-lactams, indicating radical intermediates.



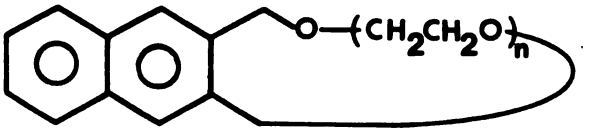
25 29 28 24

30 31

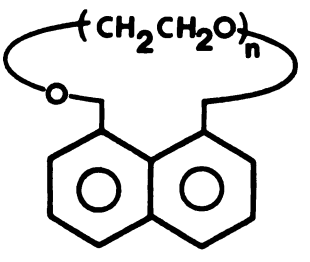
In the course of the first study, the photochemistry and thermal chemistry of 2,4,4-trisubstituted Δ^2-oxazolin-5-ones were examined, and a dramatic substituent effect of the trifluoromethyl group noted.



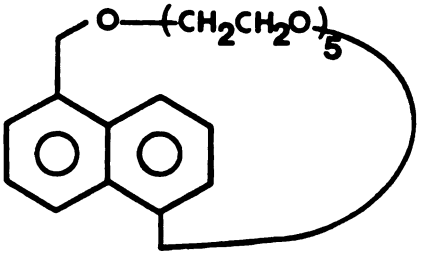
In Part 2 of this thesis the ^{13}C NMR spectra of naphthalene crown ethers 42 through 43 and their alkali and alkaline earth metal complexes were studied. The complexation induced shifts of the aromatic carbons are dependent on only the cation's charge, consistent with field induced π polarization of the naphthalene, and correlate reasonably well with INDO calculated charge density changes. The chemical shift changes of the ether carbons are cation dependent and provide information about conformational changes in the crown ring.



42-44, n=3,4,5



46-48, n=3,4,5



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ACKNOWLEDGMENTS

I would like to thank Lynn Sousa for an excellent job of directing my graduate education. No better a job could have been done. Thanks also go to the other members of the research group for their friendship and fellowship, and to my wife, Cheri, who not only patiently waited for me to finish, but typed most of this thesis.

Financial support from Michigan State University and the National Science Foundation is also gratefully acknowledged.

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HETEROCYCLIC PHOTOCHEMISTRY: THE PHOTOCHEMICAL SYNTHESIS OF β-LACTAMS

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PART 1

HETEROCYCLIC PHOTOCHEMISTRY: THE PHOTOCHEMICAL SYNTHESIS OF β-LACTAMS

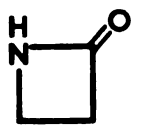
Preface

The potential usefulness of photochemistry in organic synthesis has been often noted in recent years. Despite this "potential", little use has been made of photochemistry as a synthetic tool on a laboratory scale. A variety of reasons have been suggested for this, the most common being the general unpredictability of photochemical reactions, and the sensitivity of photochemical reactions to modest changes in substitution. This apparent capriciousness is due to our difficulty in dealing with molecules on potential energy surfaces other than that of the ground state. Another principal difficulty with photoreactions is the frequent intermediacy of radicals of various sorts. A brief examination of useful laboratory synthetic reactions reveals that most of them involve ionic species rather than radical intermediates, although many industrial reactions involve radicals. With the possible exception of reactions involving transition metals, radical reactions are not very useful synthetically, on a laboratory scale.

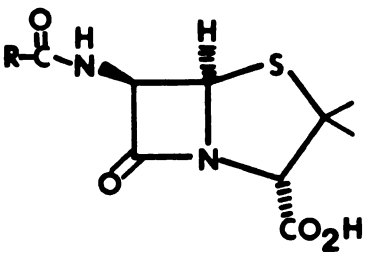
Despite these difficulties, there is at least one area in which photochemical reactions have found considerable use, the preparation of strained ring systems. In particular, four membered rings of various sorts, both carbocyclic and heterocyclic, have frequently been synthesized by photochemical means. These include bicyclobutanes,[1] cyclobutanes,[2] oxetanes,[3] and lactams. Perhaps the two most important reasons for the use of photochemical reactions in synthesizing these systems are the difficulty in using ground state reactions in making four membered rings, and the sensitivity of these strained systems to many reagents, making them unusable. In contrast, there is reason to believe

that photochemical reactions may generally prefer to give high energy ground state systems such as strained rings,[4] and these strained rings generally show no special instability under photochemical reaction conditions, mainly because they usually don't absorb light.

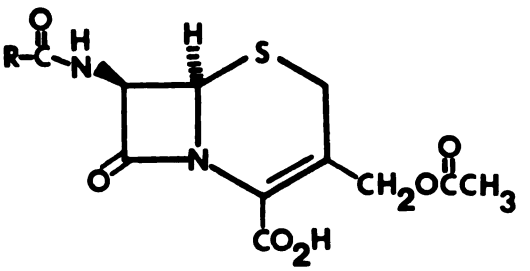
One of these ring systems, whose synthesis by photochemical means has attracted only limited attention, is the 2-azetidinone, or β-lactam ring, 1. β-Lactams are extremely important compounds, as this ring system is found in all of the penicillin, 2, and cephalosporin antibiotics, 3.[5] Currently, all of the penicillins



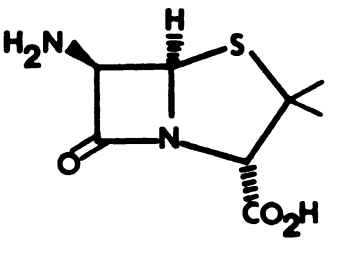
2-azetidinone 1



Penicillins 2



Cephalosporins 3



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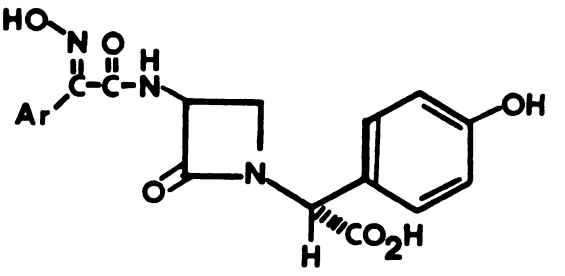
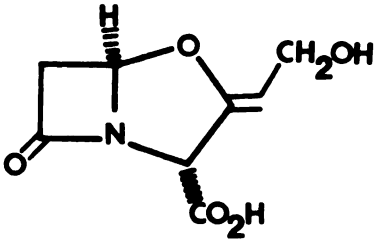
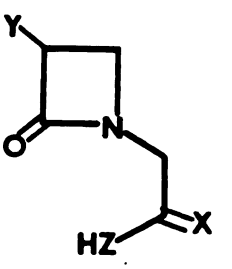
and cephalosporins in use are produced either entirely by bacteria or are synthesized from 6-amino penicillanic acid, 4, which is also made microbially. The total synthesis of the penicillins and cephalosporins is exceptionally difficult, until recently there being only one of penicillin[6] and one of cephalosporin,[7] neither of which has had much impact on the commercial production of any useful drugs.[8] Contrary to earlier opinion, the minimum structural requirement for biological activity is considerably less than the multitude of functionality surrounding the β-lactam rings of the penicillins and cephalosporins. The β-lactam is, of course, essential, but the minimum structural requirements for biological activity seem to be those described by structure 5. Some examples of compounds which show signifigant biological activity are also shown below.[9,10]



Nocardicin A



Clavulinic Acid



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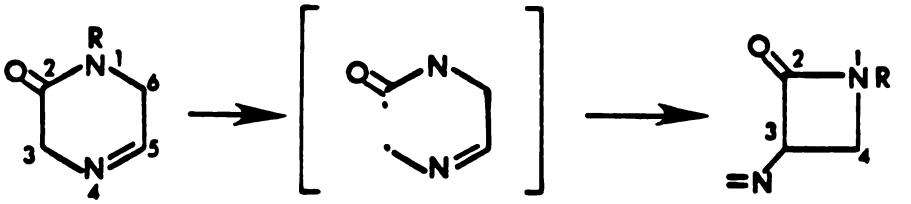
With this in mind, we have chosen to attempt to devise a practical photochemical synthesis of β-lactams, which would be applicable to the formation of biologically important compounds. A handful of other photochemical syntheses of β-lactams are known, none of which, however, have any practical importance. The most common photochemical method is the photolytic decomposition of diazo compounds, followed by either C-H bond insertion[11] or Wolf rearrangement.[12] In these cases, it is the carbene chemistry, not the photochemistry, which is of interest. Other reactions include the cyclization of substituted acrylamides,[13] and the ring contraction of 3-oxo-pyrroline 1-oxides.[14]

The two methods which we have proposed and studied illustrate the two extremes to which one might proceed. The first proposed method involved an unprecedented photochemical migration in a complex and virtually unknown heterocyclic system. The second method studied involved a simple reaction with ample precedent, using a known and readily available heterocyclic precursor of the β-lactam. Perhaps significantly, the former method was unsuccessful, and the latter successful. In the course of the first investigation the photochemistry of another heterocyclic system was explored, and an interesting substituent effect on both photolytic and thermal reactions observed. The above three investigations comprise the heterocyclic photochemistry portion of this thesis and will be discussed in the above order.

Synthesis and Photochemistry of 3,6-Dihydro-2(1H)-pyrazinones

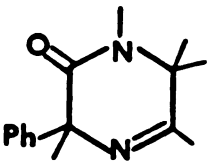
Introduction

The first proposed photochemical method for the synthesis of β-lactams involves a 1,3-acyl shift in a 3,6-dihydro-2(1H)-pyrazinone.



The proposed reaction would be analogous to that frequently observed with β,γ-unsaturated ketones.[15] Of course, our system is a very "hetero" version of this, the carbonyl group being an amide, and the double bond one between carbon and nitrogen, rather than two carbons. This makes any predictions based on β,γ-unsaturated ketones tenous. Another objection to the scheme is that the reaction involves two functional groups, an amide and an imine, which are not very reactive photochemically. While these are serious problems (hindsight is always 20/20), the scheme does have some nice features. If the reaction were to occur, the β-lactam would have a nitrogen attached to C(3), where a heteroatom substituent is generally required for biological activity. Further, the nitrogen substituent at C(3), being an imine, would be manipulable, so that one could choose any side chain amide that was desired. Hydrolysis of the imine group in the product would dispose of C(3) of the starting material and the groups attached to it, allowing a choice of substituents at C(3) which would enhance

cleavage of the C(2)-C(3) bond in the pyrazinone. These would then function as disposable photo-activating groups. Another nice feature of this scheme also involves the imine group of the product. Photochemically, acyclic imines are generally inert, due to energy dissipation by syn-anti isomerization. This would protect the β-lactam product from undergoing secondary photoreactions, a frequent problem in preparative organic photochemistry. With this in mind we chose as our initial synthetic target, 1,3,5,6,6-pentamethyl-3-phenyl-2(1H)-pyrazinone, 6. The substituents at



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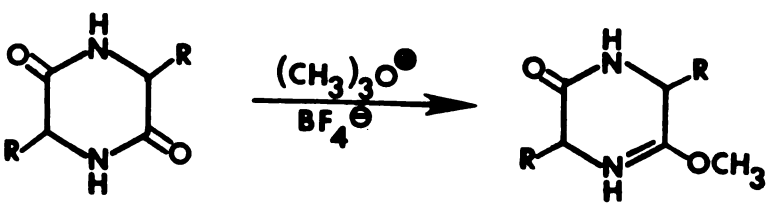
C(3) and C(5) were chosen so to enhance cleavage of the C(2)-C(3) bond, and the other methyl groups chosen so as to minimize possible photochemical hydrogen abstraction or migration reactions.

Synthesis of 3,6-Dihydro-2(1H)-pyrazinones[16]

A search of the literature revealed only one method for the synthesis of the desired heterocyclic system. This method involved O-alkylation of a diketopiperazine, and hence, was limited to the production of 5-alkoxy substituted derivatives.[17] We have developed a more general method for the synthesis of this system, which does not limit the choice of substituents on the ring. This approach



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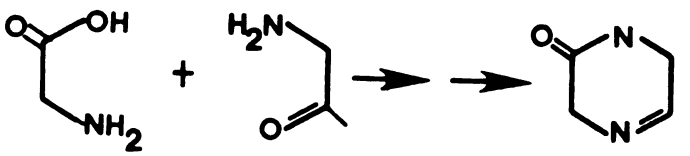
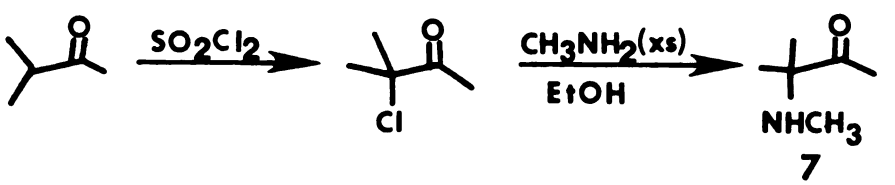
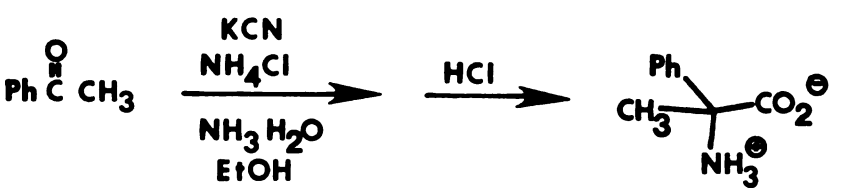
envisions the product arising from the condensation of an α-amino acid and an α-amino ketone, with formation of the amide and imine bonds as key steps. The necessary steps in this sequence are protection of the amino group and activation of the carbonyl group



of the amino acid, coupling of the activated amino acid with the amino ketone, deprotection of the remaining amino group, and condensation of the amine with the ketone. The required amino ketone, 3-methyl-3-(methylamino)-2-butanone, 7, was prepared according to literature procedures by chlorination of methyl isopropyl ketone with sulfuryl chloride,[18] followed by reaction with methylamine.[19] The required amino acid, α-phenylalanine, 8, was also prepared by literature methods, using the Strecker amino acid synthesis.[20]





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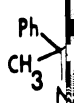
Protection and activation of α-phenylalanine was accomplished by treatment with trifluoroacetic anhydride to give the N-trifluoroacetyl amino acid, followed by cyclization using thionyl chloride to 4-methyl-4-phenyl-2-trifluoromethyloxazolin-5-one, 9, in 76% yield from α-phenylalanine.[21] Other methods for activation and protection of amino acids fail when applied to hindered α-disubstituted amino acids. Coupling of the oxazolinone and α-amino ketone were accomplished in good yield simply by mixing the two in dry acetonitrile overnight. Deprotection and cyclization were carried out in one step by treatment of a methanol solution of the coupling product 10 with dry hydrogen chloride for seven hours at 50° C. The crude product contained some starting material, and was purified by silica gel chromatography, eluting with 2% methanol in methylene chloride, which gave the pure 3,6-dihydro-2(1H)-pyrazinone 6 in 49% yield (69% based on recovered starting material, which was recycled). Higher reaction temperatures resulted in cleavage of both amide bonds of 10, giving the methyl ester of α-phenylalanine along with unreacted 10. As expected from literature reports,[21] other deprotection methods failed for this protected α-disubstituted amino acid. 10 was found to be stable to sodium hydroxide in aqueous dimethyl sulfoxide, sodium borohydride in refluxing ethanol, and even lithium aluminum hydride in refluxing tetrahydrofuran.

To demonstrate the generality of this synthetic scheme, the 3,6-dihydropyrazinone from an α-monosubstituted amino acid, alanine, was prepared, using the same α-amino ketone as before. Reaction of alanine with excess trifluoroacetic anhydride at 140° C for



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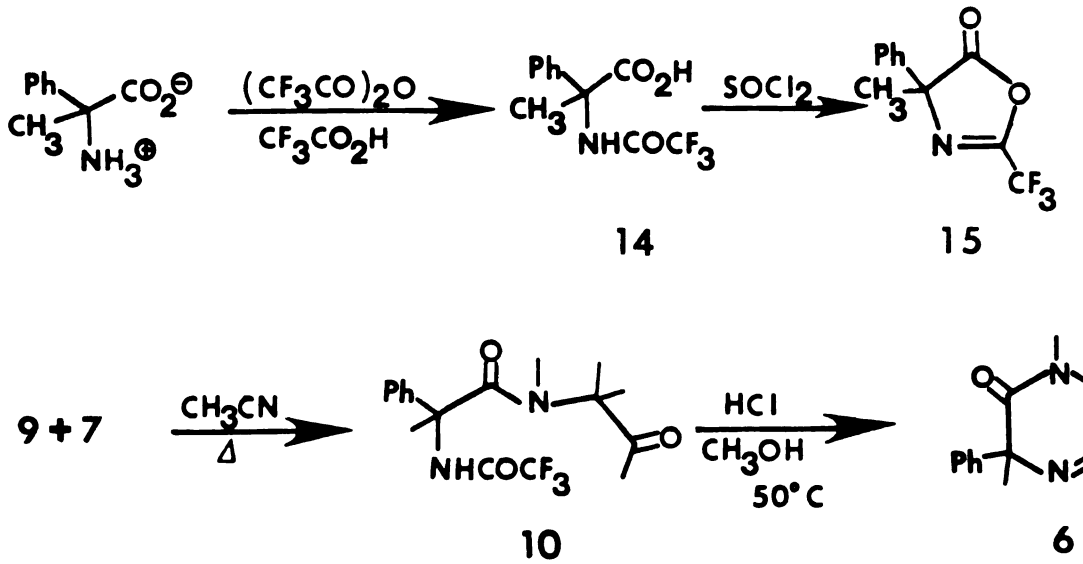
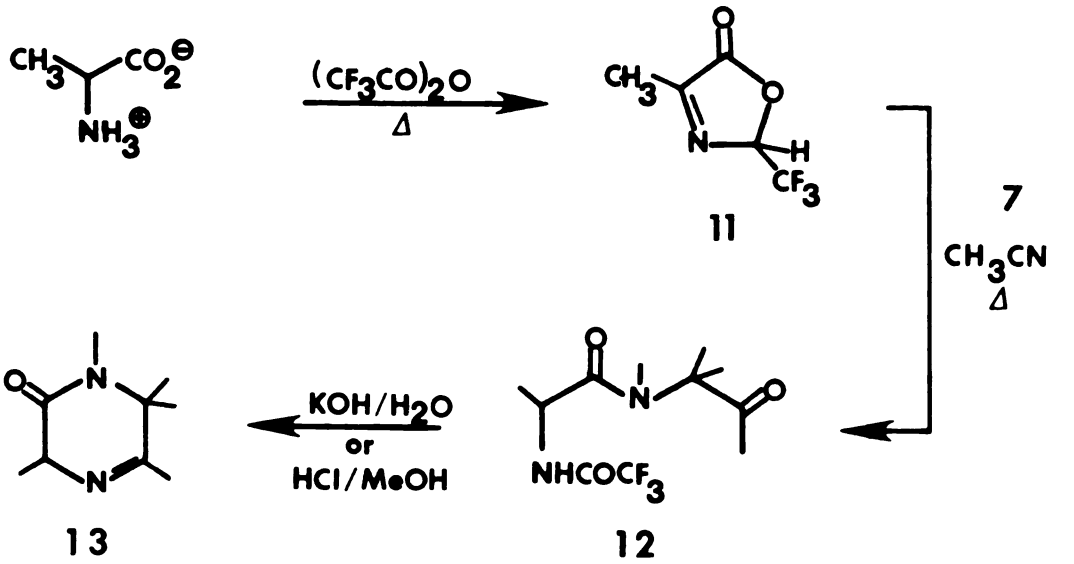
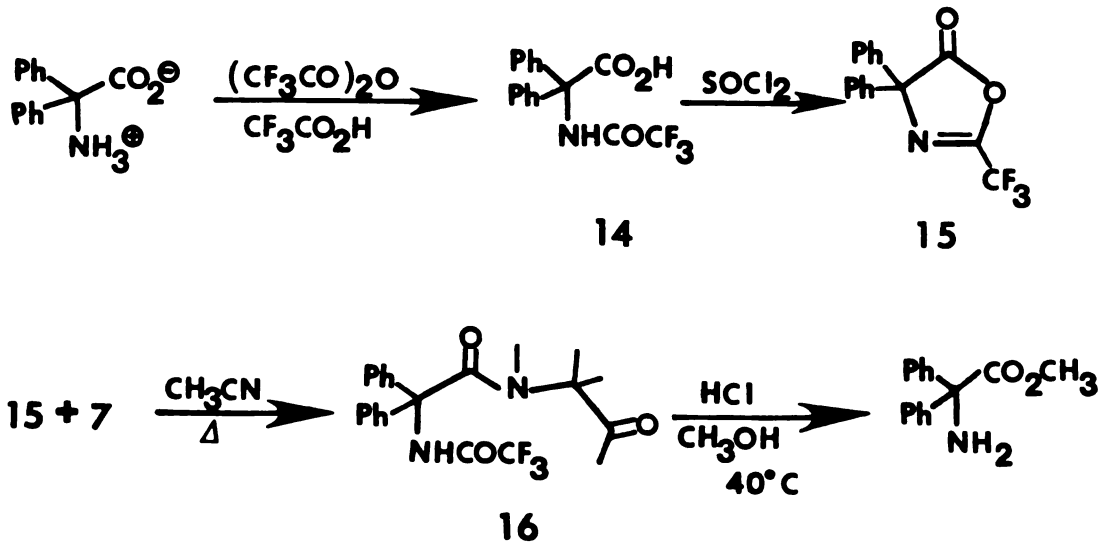


two hours gave the Δ^3-oxazolinone, 11, directly, in 57% yield.[22] In the case of 4-monosubstituted oxazolin-5-ones the Δ^3 isomer is more stable. As this isomer is less reactive than the Δ^2-oxazolinones, coupling with 7 required 15 hours in refluxing acetonitrile. The coupling product, 12, was extremely difficult to purify, and was generally deprotected without purification. Deprotection and cyclization to 13 could be affected by treatment with methanolic hydrogen chloride as before, or, more conveniently, by treatment with a mixture of aqueous potassium hydroxide and ether.

An attempt to prepare the 3,6-dihydropyrazinone from α,α-diphenylglycine and 7 was unsuccessful. Treatment of the amino acid with trifluoroacetic anhydride gave the N-trifluoroacetyl amino acid, 14,



which was cyclized as before with thionyl chloride to give the oxazolinone, 15. Coupling of the oxazolinone with 7 was effected by mixing at 50° C for 48 hours to give 16. Attempts to deprotect 16 with methanolic hydrogen chloride at 40° C gave the methyl ester of diphenylglycine along with unreacted 16. Lower temperatures resulted in no reaction.



This synthetic route to 3,6-dihydro-2(1H)-pyrazinones seems general except when extremely hindered α-disubstituted α-amino acids are used. While only one α-amino ketone was used, there is no reason to expect difficulties with others. Yields are quite good, 6 being formed in 20% yield from α-phenylalanine, and 13 in 41% yield from alanine.

Photochemistry of 1,3,5,6,6-Pentamethyl-3-phenyl-2(1H)-pyrazinone, 6

Photolysis of 6 in a variety of solvents failed to produce any detectable amounts of any β-lactam. Photolyses were conducted in acetonitrile, methanol, hexane, acetonitrile with trifluoroacetic acid, and acetonitrile with acetophenone. In each case except the last, the only materials obtained were starting material and polymeric material. Photolysis through pyrex with acetophenone afforded the pinacol of acetophenone as the only identifiable product. Decomposition of starting material under all conditions was fairly slow.

This leaves us then with the questions of what went wrong, and what can we do about it. The problem seems to be one of lack of reactivity, rather than another process going on faster than the desired reaction. In order to "heat up" the C(2)-C(3) bond even more, the attempt to synthesize the 3,3-diphenyl pyrazinone was made. As already noted this was unsuccessful.

In more general terms the failure of this method is perhaps not unexpected, and the mistake made was a strategic one. The mistake was made in attempting to try and predict the photochemical behavior of a fairly complex heterocyclic compound, with little

precedent for the desired photoreaction. Considering our relatively primitive ability for predicting photochemical reactions it is perhaps wiser to choose a well documented and common photochemical reaction to use in β-lactam synthesis. The chemistry described in the next section of this thesis was our response to our first unsuccessful method and the system and reaction chosen were based on the above considerations.

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EXPERIMENTAL

General. Proton NMR spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 237B grating spectrophotometer. Mass spectra were taken on a Hitachi Perkin-Elmer RMU-6D spectrometer. Microanalyses were performed by Instranal Laboratory, Rensselaer, N.Y. Melting points are uncorrected.

Preparation of 3-chloro-3-methyl-2-butanone[18]. Over a period of 1.5 h 65 g (0.5 Mole) of sulfuryl chloride was added to 43 g (0.5 Mole) of 3-methyl-2-butanone in an ice-cooled round bottom flask. Upon completion of the addition the solution was allowed to warm to room temperature and stirred for 48 h. The mixture was distilled directly from the reaction mixture and then redistilled to yield 35 g, 60%, of 3-chloro-3-methyl-2-butanone; NMR ($CDCl_3$) δ 1.65 (6H,s), 2.35 (3H,s); ir (liq film) 1720 (vs), 1100 (s), 1125 cm^{-1} (s).

Preparation of 3-methyl-3-methylamino-2-butanone (7)[19]. This material was prepared by a slight modification of the published procedure. The material obtained from the literature method contained an unknown contaminant, which was removed by extraction of a methylene chloride solution of the ketone with hydrochloric acid, neutralization of the extract with solid sodium hydroxide, and reextraction into methylene chloride. The extract was dried ($MgSO_4$), filtered, concentrated under reduced pressure, and redistilled to yield the desired ketone.

The ketone is stable when stored in the cold, but slowly decomposes at room temperature; NMR ($CDCl_3$) δ 1.2 (6H,s), 2.15 (3H,s), 2.20 (3H,s).

Preparation of α-phenylalanine (8)[20]. In a 2 l round bottom flask were placed, in the order mentioned, 66 g (1.0 Mole) of potassium cyanide in 100 mL of water, 59 g (1.1 Mole) of ammonium chloride in 150 mL of water, and 134 mL of aqueous ammonia (sp. gr. 0.9). The mixture was shaken and 120 g (1 Mole) of acetophenone in 300 mL of 95% ethanol was added. The flask was stoppered and heated for 5 h in a water bath maintained between 60° and 80°C. After 5 h the solution was cooled and carefully added to 800 mL of 12 M HCl in a 5 l round bottom flask which was immersed in an ice bath. The solution was diluted with 1 l of water and refluxed for 2 h. Solvent was then removed by distillation, and the solid mass taken up in 600 mL of absolute ethanol. The solution was filtered to remove inorganic salts, the salts washed with another 600 mL of ethanol, and the filtrates combined. The filtrate was then concentrated to 750 mL, 100 mL of pyridine added, and the solid product collected by filtration. The product was dried under vacuum to yield 35.5 g, 21%, of α-phenylalanine; NMR (TFAC) δ 1.9 (3H,s), 7.0 (5H,s); ir (nujol) 1590 (m), and 1670 cm^{-1} (m).

Synthesis of N-trifluoroacetyl-α-phenylalanine[21]. A solution of 11.1 g (67.3 mmol) of α-phenylalanine and 10 mL (68 mmol) of trifluoroacetic anhydride in 30 mL of trifluoroacetic acid was stirred at room temperature for 8 h under a nitrogen atmosphere. The trifluoroacetic acid and anhydride used were dried by distillation from phosphorous pentoxide. Solvent was removed under reduced pressure to yield a

brown solid which was purified by filtration through a short silica gel column (Mallinckrodt CC-7), eluting with methylene chloride. Solvent removal yielded 14.6 g, 83%, of N-trifluoroacetyl-α-phenylalanine, (mp 131.5-132.5 °C (lit.[21] 126-128°C)); NMR ($CDCl_3$) δ 2.0 (3H,s), 6.5 (2H, br. s.), 7.3 (5H,m); ir (nujol) 1710 (vs), 1550 cm^{-1}(s).

Preparation of N-trifluoroaetyl-α,α-diphenylglycine (15). To an ice bath cooled solution of 5.0 g(22 mmol) of α,α-diphenylglycine (Aldrich) in 20 mL of trifluoroacetic acid, 4.6 g (22 mmol) of trifluoroacetic anhydride was added over a period of 1 h. The solution was stirred overnight at room temperature, and then solvent removed under reduced pressure. The residue was treated with 100 mL of ether, and the unreacted starting material removed by filtration. Solvent removal from the filtrate gave a white solid which was recrystallized from chloroform/hexane to yield 4.2 g, 62%, of N-trifluoroacetyl-α,α-diphenylglycine, mp (183-185°C); ir (nujol) 3300 (m) 3250-2900 (s), 1740 (s), 1710 cm^{-1}(s).

Anal. Calcd. for $C_{16}H_{12}F_3NO_3$: C, 59.45; H, 3.74; N, 4.33. Found: C, 59.47; H, 3.98, N, 4.35.

Preparation of 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (9)[21]. A solution of 14.6 g (60 mmol) of N-trifluoroacetyl-α-phenylalanine in 30 mL of thionyl chloride (purified by distillation from triethyl phosphite) was heated to 60°C and maintained at that temperature for one h. Excess thionyl chloride was removed at room temperature using aspirator vacuum, and the residue distilled at reduced pressure to yield 12.6 g, 92%, of 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one, (bp 52° C (0.5 mm) lit.[21] 53-57° C)

NMR ($CDCl_3$) δ 1.9 (3H,s), 7.2-7.6 (5H,m); ir (neat) 1850 (vs), 1680 (s), 1370 cm^{-1} (vs).

Preparation of 4,4-diphenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (15). A solution of 3.0 g (9.3 mmol) of N-trifluoroacetyl-α,α-diphenyl glycine in 12 mL of thionyl chloride was heated at reflux for 2 h. The solution was allowed to cool and the remaining thionyl chloride removed with aspirator vacuum. The residue was distilled under vacuum to yield 2.37 g, 84%, of 4,4-diphenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one, (bp 87°C, 0.4 mm); NMR ($CDCl_3$) δ 7.1-7.4 (m); ir (neat) 3050 (m), 1850 (vs), 1690 (s), 1370 (vs), 1225 (vs), 1170 cm^{-1} (vs); mass spectrum (70 eV) m/e (rel. intensity), 305 (<1), 209 (20), 208 (100), 180 (13), 165 (13), 152 (30), 77 (12).

Preparation of 4-methyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (11).[22] A solution of 4.32 g (54.7 mmol) of alanine in 15 ml of trifluoroacetic anhydride was refluxed in an oil bath maintained at 140°C for 2 h. The solution was allowed to cool, volatile materials removed under reduced pressure, and the residue distilled at atmospheric pressure to give a yellow liquid (bp 140°C). This material was taken up in methylene chloride, washed with saturated sodium bicarbonate, dried, and concentrated under reduced pressure to yield 4.7 g, 51%, of 4-methyl-2-trifluormethyl-Δ^2-oxazolin-5-one.

Preparation of 2-phenyl-2-trifluoroacetamido-N-methyl-N-(2-(2-methyl-3-oxo)butyl)propanamide (10). A solution of 7.7 g (31 mmol) of 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one and 3.6 g (31 mmol) of 3-methyl-3-methylamino-2-butanone in 200 mL of dry acetonitrile was stirred at room temperature for 24 h. Solvent removal under reduced

pressure gave an oil which was crystallized by addition of a little ether. Recrystallization from ether gave 8.8 g, 78%, of the desired amide, 10 (mp 108-109°C); NMR ($CDCl_3$) δ 1.30 (3H,s), 1.35 (3H,s), 2.05 (3H,s), 2.10 (3H,s), 2.50 (3H,s), 7.10 (5H,s), 8.8 (1H,br.s, removed by D_2O); ir (nujol) 3300 (m), 3050 (s), 1710 (s), 1625 cm^{-1} (m); mass spectrum (70 eV) m/e (rel. intensity), 360 (<1), 315 (21), 216 (48), 181 (20), 169 (20), 131 (32), 119 (34), 103 (47), 72 (99), 69 (100).

Anal. Calcd. for $C_{17}H_{21}F_3N_2O_3$: C, 56.98; H, 5.91; N, 7.69 Found: C, 56.70; H, 5.84; N, 7.69.

Preparation of 2,2-diphenyl-2-trifluoroacetamido-N-methyl-N-(2-(2-methyl-3-oxo)-butyl)acetamide (16). A solution of 1.93 g (6.33 mmol) of 4,4-diphenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one and 0.728 g (6.33 mmol) of 3-methyl-3-methylamino-2-butanone in 125 mL of dry acetonitrile was heated at 50°C for 42 h. Solvent was removed under reduced pressure, the residue taken up in methylene chloride, washed with 0.1 M HCl(aq), dried ($MgSO_4$), filtered, and solvent removed to yield an oil which crystallized from ether/pentane, 66%, (mp 139-141°C); ($CDCl_3$) δ 1.2 (6H,s), 2.0 (3H,s), 2.3 (3H,s), 7.0-7.4 (5H,m), 8.8 (1H,br.s); ir (nujol) 3250 (m), 1720 (s), 1660 cm^{-1} (s).

Anal. Calcd. for $C_{22}H_{23}F_3N_2O_3$: C, 62.85; H, 5:51, N, 6.66. Found: C, 62.65; H, 5.19; N, 6.55.

On one occasion the material crystallized as a monohydrate, mp 154°-156° C ($-H_2O$).

Anal. Calcd. for $C_{22}H_{25}F_3N_2O_4$: C, 60.27; H, 5.75; N, 6.39. Found: C, 60.42; H, 5.93; N, 6.38.

Preparation of 1,3,5,6,6-pentamethyl-3,6-dihydro-2(1H)-pyrazinone(13). A solution of 2.40 g (14.2 mmol) of 4-methyl-2-trifluoromethyl-Δ^3-oxazolin-5-one and 1.65 g (14.2 mmol) of 3-methyl-3-methylamino-2-butanone in 125 mL of dry acetonitrile was heated at reflux for 10 h. The solution was allowed to cool and solvent removed under reduced pressure to yield a dark oil, which consisted mainly of N-methyl-2-trifluoroacetamido-N-(2-(2-methyl-3-oxo)-butyl)propanamide, in ~85% yield (determined by NMR). This material was extremely difficult to purify and was generally used as obtained. A small amount of material was purified by column chromatography on silica gel (Silicar CC-7), eluting with methylene chloride/methanol (1/1), and had the following data, mp 78-80°C; NMR (DMSO) δ 1.2 (6H,s), 1.3 (3H,d), 1.9 (3H,s), 3.0 (3H,s), 4.6 (1H,q), 9.0 (1H,br.d).

The crude amide product was taken up in a mixture containing 75 mL each of 1 M KOH (aq) and diethyl ether, and stirred at room temperature for 13 h. The ether layer was removed, and the aqueous layer extracted four times with methylene chloride. The combined methylene chloride extracts were dried ($MgSO_4$), filtered, and solvent removed to yield an oil which crystallized on cooling in a dry ice/acetone bath. Recrystallization from hexane/chloroform afforded 0.8 g (33% based on azlactone 11) of the desired diazine; NMR ($CDCl_3$) 1.45 (6H,s), 1.50 (3H, d, J = 6 Hz), 2.05 (6H,d, J = 2 Hz), 2.90 (3H,s), 4.10 (1H,q of d, J = 6 Hz, J^1 = 2 Hz); ir (neat) 2960 (m), 1640 (vs), 1450 (s), 1380 cm^{-1} (s); mass spectrum (70 eV) m/e (rel. intensity) 169 (3.3), 168 (26), 153 (14), 127 (25), 125 (10), 111 (13), 110 (23), 99 (14), 93 (31); ^{13}C NMR ($CDCl_3$) δ 169.32 (s), 166.43 (s), 60.09 (s), 55.88 (d), 26.49 (m), 24.98 (m), 23.80 (m), 23.02 (m), 20.39 (m).

Anal. Calcd. for $C_9H_{16}NO$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.40; H, 9.25; N, 16.47.

Preparation of 1,3,5,6,6-pentamethyl-3-phenyl-3,6-dihydro-2(1H)-pyrazinone (6). A solution of 500 mg (1.39 mmol) of the keto amide 10 in 60 mL of dry methanol was treated with gaseous hydrogen chloride for a period of 7.5 h. The solution was cooled in an ice bath for the first 0.5 h, and then heated at 50°C for the remainder of the time. The solution was stirred at room temperature for another 2.5 h after the hydrogen chloride was turned off. Solvent was removed under reduced pressure to give a gummy residue, which was taken up in ∿20 mL of methanol. This solution was made basic by addition of triethylamine (pH > 12), and the triethylamine hydrochloride precipitated by addition of 80 mL of ether. The solution was chilled in an ice bath, filtered, and the filtrate dried over sodium sulfate and filtered again. Solvent removal under reduced pressure gave an oil which contained a mixture of the desired product and starting material. This material was chromatographed on silica gel (Mallinckrodt CC-7) eluting first with methylene chloride, which brought off 145 mg of starting material, and then 3% methanol/methylene chloride, which brought off 167 mg (49%) of 1,3,5,6,6-pentamethyl-3-phenyl-3,6-dihydro-2(1H)-pyrazinone. An analytical sample was prepared by recrystallization from ether/pentane, mp 98-99°C; NMR ($CDCl_3$) δ 1.2 (3H,s), 1.45 (3H,s), 1.8 (3H,s), 2.2 (3H,s), 2.9 (3H,s), 7.0-7.4 (5H,m); ir ($CHCl_3$) 2900 (s) 1680 cm^{-1} (vs); mass spectrum (70 eV) m/e (rel. intensity), 245 (16), 244 (100, 229 (24), 201 (12), 187 (20), 172 (52), 146 (78), 145 (28), 127 (10), 104 (48), 103 (26); uv (hexane), λ_{max} = 264 nm (ε = 400) 257 nm (ε = 542).

Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.55; H, 8.26; N, 11.56.

Unsuccessful attempts to deprotect 2-phenyl-2-trifluoroacetamido-N-methyl-N-(2-(2-methyl-3-oxo)-butyl)propionamide (10). Samples of 200 mg or 250 mg of 10 were submitted to each of the following conditions: a) 100 mL of 0.2 M sodium hydroxide in 9/1 dimethylsulfoxide/water at 65°C for 42 h; b) 110 mL of dimethylformamide stirred over 0.8 g of sodium hydroxide at 100°C for 40 h; c) 15 mg of sodium borohydride in 50 mL of ethanol at 65°C for 8 h; and d) 15 mg of lithium aluminum hydride in 100 mL of tetrahydrofuran at reflux for 24 h. In each case standard work-up provided only unreacted starting material.

Attempted deprotection of 2,2-diphenyl-2-trifluoroacetamido-N-methyl-N-(2-(2-methyl-3-oxo)-butyl)acetamide (16). A solution of 250 mg (0.59 mmol) of keto amide 16 in 50 mL of methanol was treated with HCl (g) continously for 8 h, with the temperature maintained at 0°C for the first 30 min and at 40°C for the remainder. The solution was allowed to cool, solvent removed under reduced pressure, the residue taken up in 10 mL of methanol, and then treated with 5 mL of triethylamine. The solution was mixed with 100 mL of ether, chilled in an ice bath, and filtered to remove the salt. Solvent removal under reduced pressure gave a residue of mainly starting material and a little methyl diphenylglycinate.

Exploratory photolyses of 6. Solutions of 6 in hexane, acetonitrile, methanol, and acetonitrile with trifluoroacetic acid were irradiated through either vycor or quartz filters, for varying time periods. Photolysis in acetonitrile with acetophenone was done through a pyrex

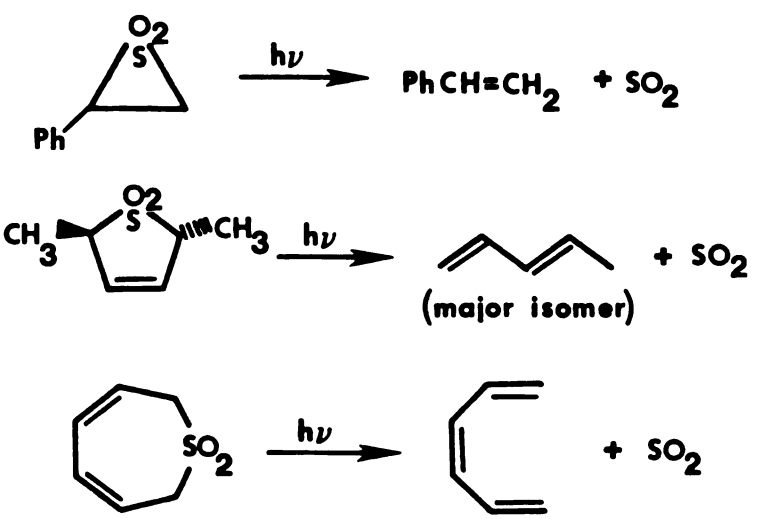
filter. In each case solvent was removed under reduced pressure, the crude photolysate was examined by NMR spectroscopy, and the residue chromatographed on silica gel. In no case was anything other than starting material or polymer obtained.

Synthesis and Chemistry of 1,1-Dioxo-4-thiazolidinones

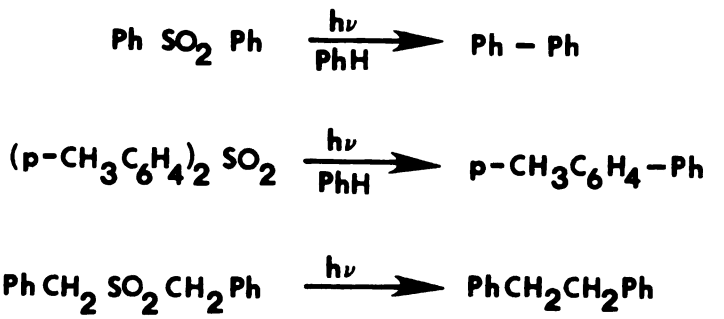
Introduction

Perhaps the most common and easily predicted photochemical reactions are those that involve extrusion of a small stable molecule. Examples include the loss of nitrogen upon photolysis of diazo compounds,[23] loss of carbon monoxide from aldehydes,[24] and extrusion of sulfur dioxide from sulfones.[25] This last reaction frequently occurs when sulfones are photolyzed, and was chosen as a suitable candidate for use in β-lactam synthesis.

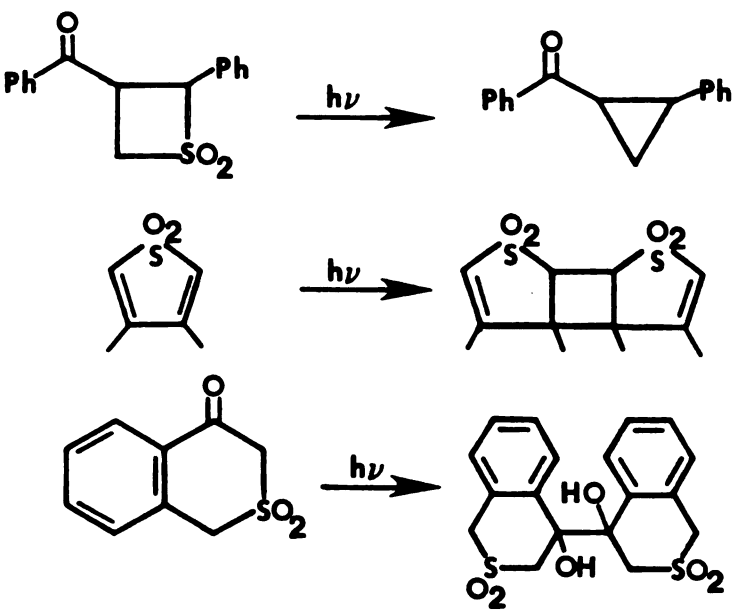
Since the sulfone functional group is not a chromophore in accessible regions of the ultraviolet spectrum, the photochemistry involves the interaction of the sulfone group with nearby excited states. Irradiation of appropriate cyclic sulfones gives loss of sulfur dioxide and olefin formation. In some instances this reaction is thought to be a concerted chelotropic reaction. Examples of this reaction include the photoreactions of episulfones,[26] sulfolenes,[27] and dihydrothiepin dioxides.[28] Irradiation of simple acyclic



benzylic or aryl sulfones also leads to sulfur dioxide loss with formation of products expected from radical intermediates.[29] More



complex sulfones can also lose sulfur dioxide photochemically.[30] There are some cases where other reaction occur, unaffected by the presence of the sulfone. These include some 2+2 cycloadditions[31] and pinacol formation.[32]

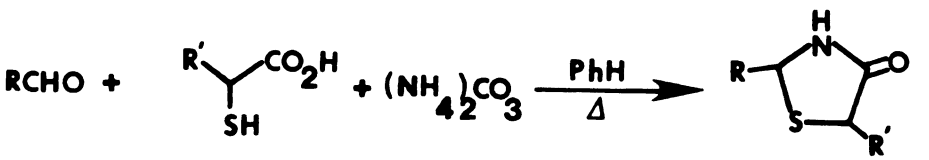


We have chosen to investigate a method involving ring contraction of a five membered ring sulfone to a β-lactam via loss of sulfur dioxide.

The system chosen for study was the 1,1-dioxo-4-thiazolidinone system. This choice was based on the desire to place the sulfone group away from the carbonyl function, which might complicate the photochemistry, and the accessibility of the ring system.

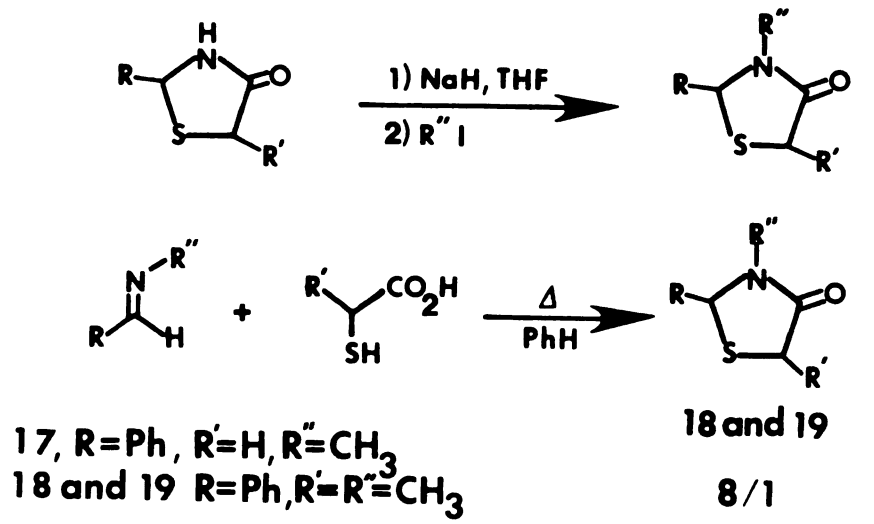
Synthesis of 1,1-Dioxo-4-thiazolidinones

The desired sulfones are readily prepared by oxidation of the corresponding sulfides.[33] The sulfides can be prepared by condensation of the appropriate aldehyde, α-thiol carboxylic acid, and ammonium carbonate, with azeotropic removal of water.[34] These

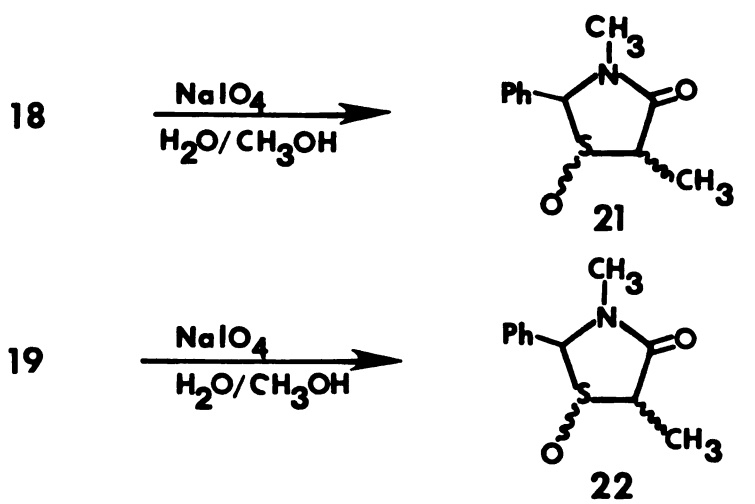


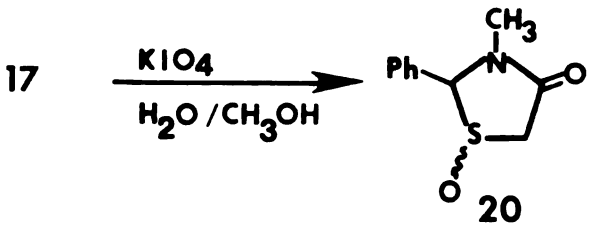
N-unsubstituted compounds can be N-alkylated with sodium hydride and the appropriate alkyl halide. Alternatively the N-substituted compound can be prepared by condensation of the pre-formed aldimine with the α-thiol carboxylic acid with azeotropic water removal.[35] Yields using this method are exceptionally good. Synthesis of 3-methyl-2-phenyl-4-thiazolidinone, 17, was achieved in better than 99% yield from benzylidene methylamine and thioglycolic acid. Condensation of benzylidene methylamine with thiolactic acid afforded the 3,5-dimethyl-2-phenyl-4-thiazolidinones, 18 and 19, in 95% yield as an 8/1 mixture of the cis and trans isomers. These same compounds may be prepared by alkylation of 5-methyl-2-phenyl-4-thiazolidinone with sodium hydride and methyl iodide. This method afforded a 1/1 mixture of the two isomers in 84% yield. Separation

was accomplished by silica gel chromatography, eluting with 1/1 ether/pentane. The stereochemical assignments for these compounds will be discussed in detail in the next section.

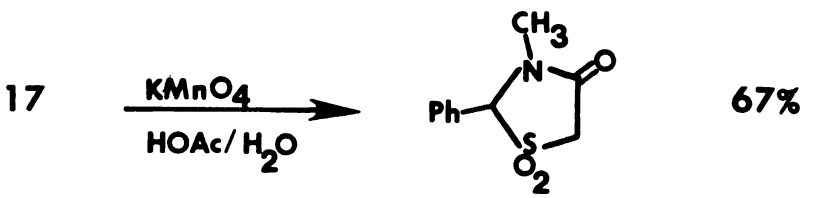


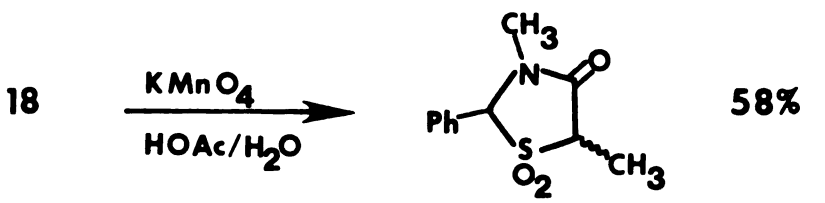
The sulfides could easily and controllably be oxidized to the corresponding sulfoxides and sulfones. The sulfoxides were prepared to assist in assigning the stereochemistry of the sulfides and sulfones. Treatment of sulfides 17, 18, and 19 with sodium periodate in aqueous methanol afforded sulfoxides 20, 21, and 22, respectively.[36]

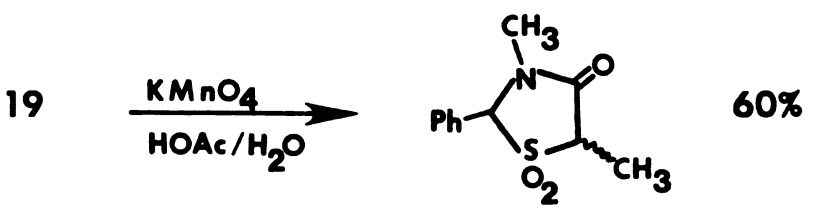




Treatment of acetic acid solutions of the same sulfides with aqueous potassium permanganate afforded the desired sulfones in good yields. A large number of other reagents also oxidize sulfides to sulfones,[37] and it is likely that one or more of these will give the sulfones in even higher yields. No attempts were made to investigate this, as the reaction with potassium permanganate was

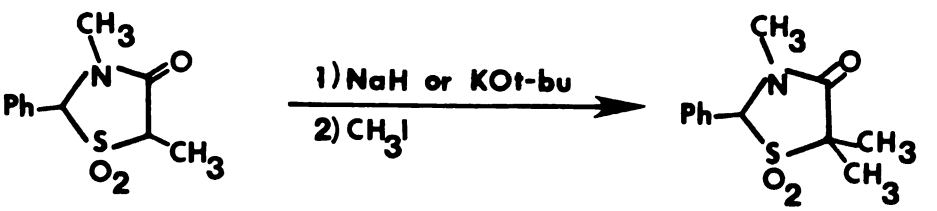






exceptionally clean and easy to work up. The epimeric sulfones 24 and 25 were easily isomerized to a 1/1 mixture of the two isomers by treatment with base, florisil, or silica gel. All attempts to separate these mixtures were unsuccessful, and it was necessary to separate the isomers at the sulfide stage.

The sulfones may be alkylated at C(5) by treatment with base and methyl iodide. In this way 3,5,5-trimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone, 26, was prepared in 66% yield.



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Other current work in this group has shown this general synthetic scheme to be applicable to the synthesis of 2-aryl-4-thiazolidinones and their corresponding dioxides where the aryl group is furyl, thiophenyl, p-chlorophenyl, or p-methoxyphenyl.[38] Preliminary experiments also indicate that N-alkylation with methyl chloroacetate to give the N-carbomethoxymethyl substituted compounds also works.

Stereochemistry of Substituted 4-thiazolidinones

The stereochemical assignments for the isomeric sulfones 24 and 25 are important for the determination of the mechanism of the observed photochemical reaction (see next section). The initial stereochemical assignments of the sulfones were extrapolated from the assignments made for the corresponding sulfides, assuming the

oxidation does not affect the stereochemistry. The ^{1}H NMR spectra of sulfides 18 and 19 have signals at δ 5.3 and 4.0, due to the benzylic hydrogen and C(5) hydrogen respectively. In one isomer, 19, the benzylic hydrogen appears as a singlet and the C(5) hydrogen as a quartet (J=7Hz). In the other isomer, 18, however, the benzylic hydrogen and C(5) hydrogen are coupled (confirmed by decoupling experiments) with a coupling constant of 2 Hz. This kind of long range coupling is usually associated with a W conformation.[39] The cis isomer can readily adopt this conformation whereas the trans isomer cannot (as judged from molecular models), so the isomer with the coupling, 18, was tentatively assigned the cis configuration.

Seeking confirmation of this assignment, the literature was searched for alternative methods for the assignment of stereochemistry in this system, which would be generally applicable to a variety of 2,5-disubstituted 4-thiazolidinones and their dioxides. Two methods were found, both involving sulfoxides.

Aromatic solvent induced shifts in ^{1}H NMR spectra have frequently been used to assign the stereochemistry of cyclic sulfoxides.[40] It is observed that the difference in chemical shift of a given hydrogen on going from an inert solvent (such as CCl_4) to benzene correlates with whether the hydrogen is cis or trans to the sulfoxide oxygen. Those hydrogens cis to the lone pair experience modest upfield shifts, while those cis to the oxygen show very small or no upfield shifts. The rationale for this is that the benzene prefers to associate with the positive end of the sulfur-oxygen dipole, with consequent upfield shifts for hydrogens in

that vicinity. It isn't clear why the benzene should orient itself so as to give upfield shifts, but it is always observed to do so. This method has been applied to a variety of cyclic sulfoxides, bearing, at times, a wide variety of other functional groups.

This method was then applied to sulfoxides 20, 21, and 22, with the results indicated in Table 1. The results indicate that in sulfoxide 24, the ring hydrogens are cis to each other, whereas in 25, they are trans. This interpretation is independent of the sulfoxide group stereochemistry, and also independent of any assumptions as to the kind of shift induced by the aromatic solvent. In fact, the results indicate that, in each case, including 23, the oxygen is cis to the phenyl group, if the aromatic solvent induced shift operates as usual. These assignments are in accord with those tentatively made based on the ^{1}H NMR spectra of sulfides 18 and 19. The formation of what are presumably the more sterically hindered sulfoxides in the periodate oxidations is not unprecedented, as oxidation of substituted thianes with periodate is reported to give predominately the axial sulfoxides.[41] An attempt to employ a closely related method, that of trifluoroacetic acid induced shifts in ^{1}H NMR spectra[40] was unsuccessful due to the apparent epimerization of the sulfoxides in trifluoroacetic acid.

The second method used was the lanthanide ion induced shifts in the ^{1}H NMR spectra of the same sulfoxides.[40 43] The shift of a given hydrogen may be predicted using the McConnell - Robertson equation, where r is the distance between the paramagnetic ion and the hydrogen, K is a constant depending on the particular ion used (same for all hydrogens in the same molecule), and θ is the angle made by the principal

Table 1

Aromatic Solvent Induced Shifts in Sulfoxides[a]

Sulfoxide	Hydrogen			
	PhC<u>H</u>-	$CH_3C\underline{H}$-	$C\underline{H}_3CH$-	-N-$C\underline{H}_3$
21	+19	+29	+1	+28
22	+16	+3	+22	+28
20	+20	+39 +14	—	+31

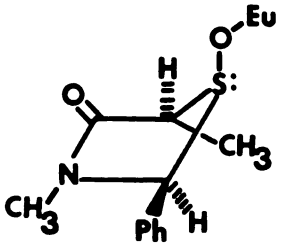
a) $\Delta\delta$ in Hz, + indicates upfield shift

magnetic axis of the complex and the lanthanide ion/hydrogen axis.[43]

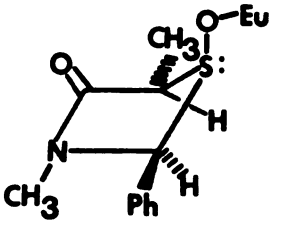
$$\Delta\delta = K\left[\frac{3\cos^2\theta - 1}{r^3}\right]$$

The principal magnetic axis is usually assumed to be the lanthanide - oxygen bond (in sulfoxides). This equation is frequently used by assuming θ to be similar for all hydrogens and using just the $1/r^3$ relationship. This is often adequate for making stereochemical assignments. Another approximation often used is to assume an average conformation of oxygen-lanthanide bond when including the angular dependence. This occasionally leads to erroneous assignments, which can be corrected by averaging the shifts predicted by the appropriate conformations.[44] This method has frequently been used, although errors have been made using the above approximations.

The shifts induced in sulfoxides 20, 21, and 22 by addition of one equivalent of $Eu(fod)_3$ are indicated in Table 2. At the crudest level of use of the McConnell-Robertson equations, these results agree with the assignments previously made. The hydrogens on the same side of the ring experience similar shifts, which are different from those on the other side of the ring. Inclusion of the angular term in calculations also predicts the same shifts for the conformations shown below,



"22"



"21"

Table 2

$Eu(fod)_3$ Induced Shifts in Sulfoxides[a]

Sulfoxide	Hydrogen			
	PhC<u>H</u>-	$CH_3C\underline{H}$-	$C\underline{H}_3CH$-	-N-C<u>H</u>$_3$
21	6.6	6.0	10.5	4.9
22	8.6	13.3	3.2	5.2
20	6.7	4.7 14.9	—	4.5

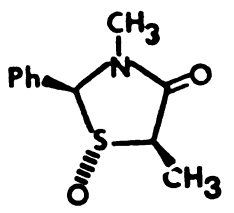
a) $\Delta\delta$ in ppm, all shifts downfield, each shift corresponds to addition of one equivalent of shift reagent

which seem to be the most reasonable choices on steric grounds. Distances and angles were measured from molecular models and all calculations were done by hand. Other conformations, including those with the europium complexed to the amide, failed to rationalize the observed shifts.

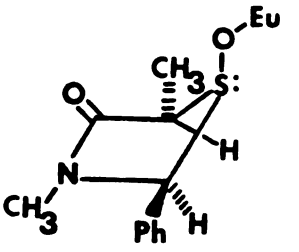
At this stage, the stereochemical assignments seemed quite certain. Nevertheless an x-ray crystal structure determination was performed on the sulfone which had been assigned the trans configuration, 25. The results, much to our surprise, indicated it was cis, not trans.[45] At this stage, several possible explanations for these seemingly contradictory, results presented themselves. The most obvious suggestion was a mix-up of samples somewhere between the sulfides and sulfoxides. This was checked by oxidizing the sulfoxides to the corresponding sulfones with potassium permanganate. In each case, the sulfone formed was exclusively the predicted one. The other most likely possibility was that the crystal used for the x-ray study was a stray crystal of the other isomer. This is not entirely unreasonable, as crystallographers choose the exceptional crystal, not the average crystal, to do their experiments with. This was checked by collecting x-ray diffraction data on another crystal of the same sulfone, from an extremely high purity sample. The data were virtually identical to those of the original crystal. This left the two least likely explanations (from our point of view at the time), that either the NMR results were all anomalous, or a single inversion of configuration occurred on oxidation of the sulfoxide to the sulfone, which would appear to be extremely unlikely.

This question was settled by having the crystal structure

determined for one of the sulfoxides. The x-ray crystal structure determination was performed on a crystal of what had been previously assigned as the trans sulfoxide, 22. This sample was carefully recrystallized, and after removal of several crystals for the x-ray study, the remainder checked by ^{1}H NMR with and without shift reagent to insure it was indeed the "trans" isomer. Once again, the results of the x-ray crystal structure determination indicated that the phenyl and methyl groups were not trans, but cis, and that the sulfoxide oxygen was trans to both of them, 22.[45]



22



22a

By now, it was abundantly clear that the NMR results were anomalous. A variety of explanations and rationalizations can be offered. For the europium induced shift experiments, one possibility, which had earlier not seemed very likely based on McConnell-Robertson calculations, was that the europium might prefer to complex with the amide rather than the sulfoxide. This was checked by doing a competition experiment, in which dimethyl sulfoxide and dimethyl formamide competed for the shift reagent. It was found that addition of one equivalent of dimethyl sulfoxide to a sample containing one equivalent each of dimethyl formamide and Eu(fod)$_3$ reduced the shift of the amide to about one half of its original value. This result suggests that for sulfoxides 20, 21, and 22, an averaging of shifts due to the europium complexed with the amide and with the sulfoxide might give rise to the

observed shifts. In fact, the calculations give a reasonably good fit to the observed shifts, which is a little better than that from the initially assigned configuration, with the europium exclusively complexed to the sulfoxide, (Table 3). A similar combination was tried to explain the shifts of the other sulfoxide isomer, assuming the phenyl and methyl groups were trans rather than cis. However, no simple combination of amide complexation and sulfoxide complexation (for both possible isomers) was able to reproduce the observed shifts. It is quite likely that some reasonable linear combination of conformations and sites of complexation does agree with the observed shifts, but an exhaustive search is not practical.

The matter of the aromatic solvent induced shifts is somewhat more difficult to explain. One possibility is that the sulfoxides are too hindered for the normal approach of the solvent, such that opposite results are obtained in some undefined way. There is at least one report in the literature of anomalous results of this sort which have been attributed to steric interference.[46] The C(5) and C(6) hydrogens in the phthalimido penicillin sulfoxide 26, both show relatively large upfield shifts on changing solvents from deuterochloroform to deuterobenzene. This was attributed to interference to approach of the solvent to the β face by the large phthalimido group. However, the method has been applied to the dihydrobenzothiophene oxide isomers, 27, which closely resemble the thiazolidinones sterically.[47] The stereochemical assignments in this case are in agreement with those based on trifluoroacetic acid induced shifts in the ^{1}H NMR spectra.

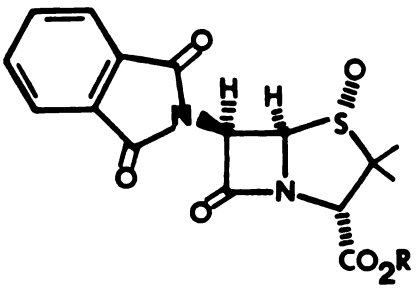
Table 3

Calculated and Observed $Eu(fod)_3$ Induced Shift Ratios[a]

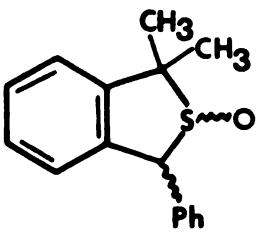
hydrogen	"22"	Configuration 22a	22[b]	50% each of 22a and 22	observed
-CHPh	3.2	-8.5	0.90	3.7	2.7
-CHCH$_3$	6.8	-8.5	1.85	4.9	4.1
-CHCH$_3$	1.0	1.0	1.0	1.0	1.0
-N-CH$_3$	3.4	-0.01	0.91	1.2	1.6

a) All shifts adjusted to a relative shift of 1.0 for CHCH$_3$

b) Same configuration as 22a except europium complexed to amide oxygen



26



27

While it is perhaps, not unusual that the aromatic solvent effect should be influenced by steric factors, it is unusual for these factors to result in different shifts for hydrogens cis to each other, and for directly opposing results to be obtained with the hydrogens trans to each other.

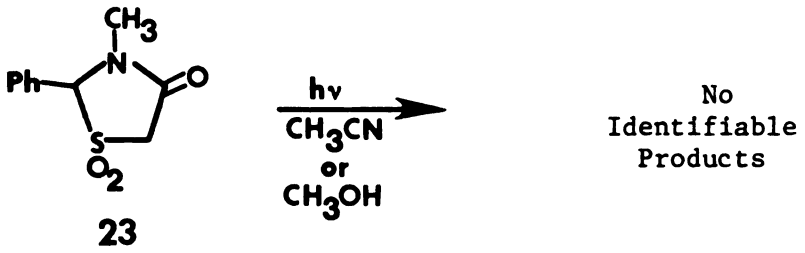
The question of the stereochemistry of the sulfides 18 and 19 is still somewhat puzzling. By analogy with the sulfoxide and sulfone assignments, sulfide 18 would be assigned the trans configuration, and 19 the cis configuration. The alternative assignments would require that each oxidation occur with a single inversion of configuration at carbon, an unreasonable suggestion. This leaves the question of the "W" coupling in the ^{1}H NMR spectrum of 18, a question for which no obvious answer presents itself.

The most important feature of these results is the ability of standard NMR techniques, of three different kinds, to all produce completely misleading predictions of the stereochemistry of the thiazolidinones. In each case, each experiment gave exactly the results expected for a different isomer. While some of these results can be rationalized, others are still left unexplained.

The most important lesson to be learned from this relates to whether one can use these methods, at all, for assigning stereochemistry in all but the simplest molecules. If it had not been for the x-ray crystal structure determination, there is no way we could have or would have made the correct stereochemical assignments. This is not a caution pertaining to the care necessary in interpreting results, but a caution pertaining to the applicability of the method for molecules with more than one functional group or modest steric requirements.

Photolysis and Thermolysis of 1,1-Dioxo-4-thiazolidinones: Results

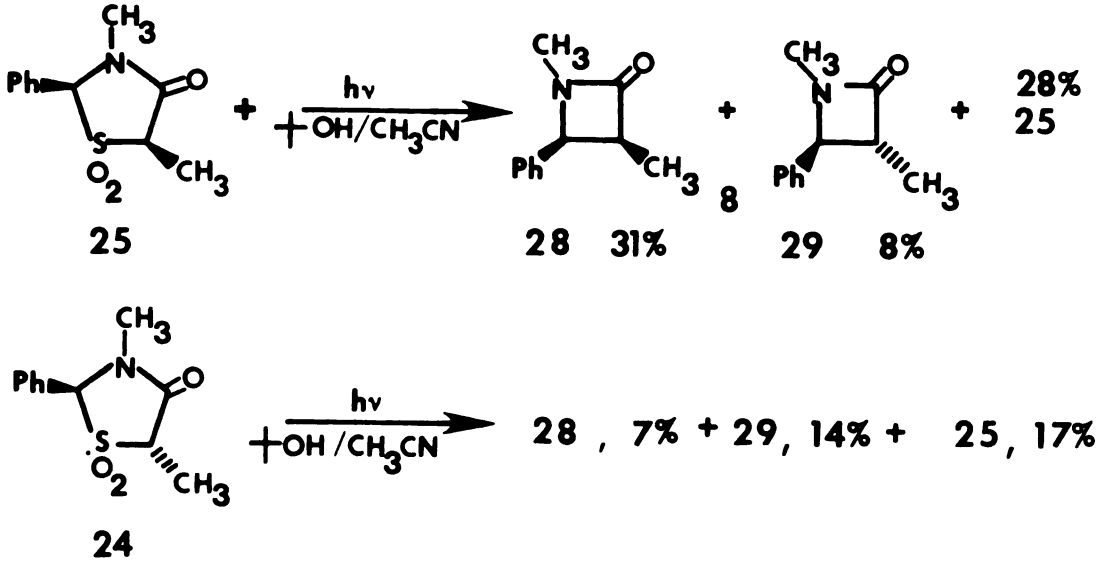
Irradiation of 3-methyl-1,1-dioxo-2-phenyl-4-thiazolidinone, 23, in methanol or acetonitrile leads to rapid decomposition, but no identifiable products were obtained. We then turned to the



23

more highly substituted 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinones, 24 and 25. Photolysis of the cis isomer, 25, in a mixture of t-butyl alcohol and acetonitrile resulted in formation of the isomeric β-lactams, cis and trans 1,3-dimethyl-4-phenyl-2-azetidinone, 28 and 29. The cis β-lactam was obtained in 31% yield, the trans isomer in 8% yield, and 28% of starting material recovered unchanged. The combined yield of β-lactams based on recovered starting material

was 55%. Photolysis of the trans sulfone, 24, in the same solvent system also afforded β-lactams 28 and 29. In this case the trans



lactam was the major product, 14% with a 7% yield of the cis lactam. The recovered sulfone, 21%, however, was completely cis. The products were identified by comparison of their ^{1}H NMR spectra to those reported in the literature.[48] The appropriate carbonyl stretching frequency was observed in the infrared spectra. Yields were determined by adding known amounts of a reference material to the NMR samples.

When the cis sulfone 25 was photolyzed in isopropanol, two additional products were formed. They were identified as N-benzyl-N-methyl propionamide, 30, and isopropyl benzenemethanesulfonate, 31. The sulfonate was identified by comparison of its NMR and infrared spectra to those reported in the literature.[49] The amide 30 was identified from its NMR spectra, which was similar to that reported for N-methyl-N-benzylacetamide, with appropriate changes.[50] These photolyses were also done in several different mixtures of isopropanol and t-butyl alcohol, and the yields for the products of these reactions are summarized in Table 4. Photolysis of the trans sulfone in

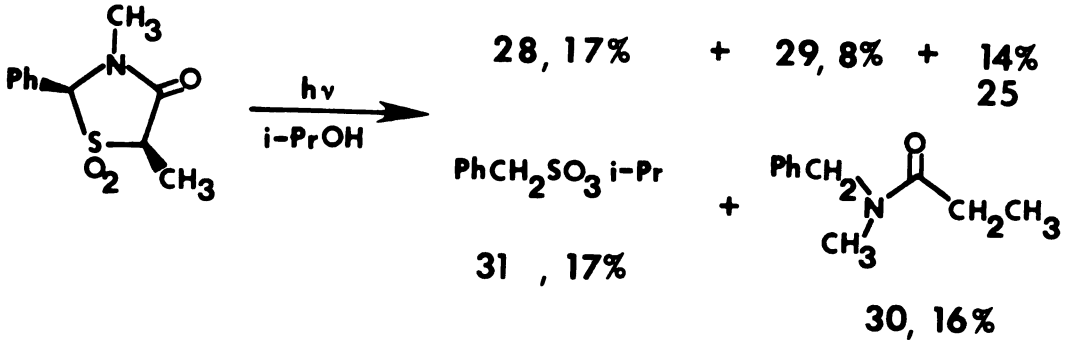
Table 4

Yields from photolysis of cis sulfone 25 in different solvents[a]

Solvent	Product					
	28	29	30	31	recovered 25	Total
i-PrOH	17	8	16	17	14	73
i-PrOH/t-BuOH 1 / 1	10	5	10	13	7	45
i-PrOH/t-BuOH 1 / 7	14	7	9	9	27	66
CH_3CN/t-BuOH 1 / 7	31	8	—	—	28	66

a) All yields are per cents based on initial amounts of starting material, with all experiments carried out under exactly the same conditions except for solvent.

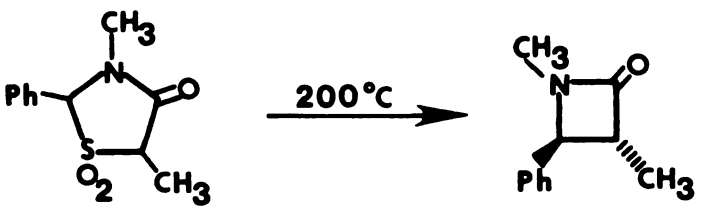
isopropanol also afforded reduction product 30.



Several attempts to sensitize and quench the photoreaction were made. Irradiation of the cis sulfone in acetone or in acetonitrile with acetophenone present through a pyrex filter gave only starting material. Attempts to quench the photo decomposition of 25 with piperylene in both isopropanol and the t-butyl alcohol/acetonitrile mixture were unsuccessful, although the photolysates were much messier in these cases.

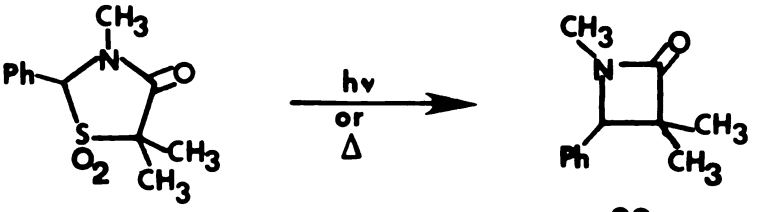
Irradiation of the β-lactams in t-butyl alcohol/acetonitrile resulted in decomposition. The trans β-lactam gave none of the cis isomer, but the cis β-lactam gave a small amount of the trans β-lactam. No reduction products were formed on photolysis of the trans β-lactam in isopropanol.

Thermolysis of sulfones 24 and 25 also leads to β-lactams. When either sulfone isomer is heated at 200° C, the trans β-lactam 29 is formed in good yield.



24 or 25

Photolysis and thermolysis of 3,5,5-trimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone, 26, gives 1,3,3-trimethyl-4-phenyl-2-azetidinone, 32.[51] The photochemical reaction gives the β-lactam in only 10% yield, while the thermal reaction gives a 66% yield, based on unreacted starting material.



26 32

The photochemistry of sulfide 19 was also briefly examined. Photolysis of the cis sulfide in acetonitrile resulted in formation of some of the trans isomer. As desulfurization with ring contraction by photolysis of sulfides in triethyl phosphite has been reported,[52] these results suggested use of this method. Photolysis of the cis sulfide in triethyl phosphite or triethyl phosphite/acetonitrile (1/1) gave only mixtures of the two isomeric sulfides, with very slow decomposition.

Photolysis and Thermolysis of 1,1-Dioxo-4-thiazolidinones: Discussion

The data do not allow a complete description of the mechanism of the photochemical reaction, but some possibilities can be ruled out. The failure to sensitize or quench the reaction suggests reaction occurs from the excited singlet state. The mechanism of the reaction could in principle be either a concerted expulsion of sulfur dioxide with concurrent bond formation between carbons two and five, or a stepwise process involving radical or ionic intermediates,

or a combination of concerted and stepwise processes. For a concerted process, orbital symmetry predicts that the process would occur with retention of configuration at both carbons two and five, assuming sulfur dioxide to be a linear leaving group.[53] For the other extreme of free diradical intermediates we would expect to find mainly the trans β-lactam, whose formation would be suppressed by addition of a radical trap. Neither of these descriptions fit the data, but some combinations or modifications of the two will.

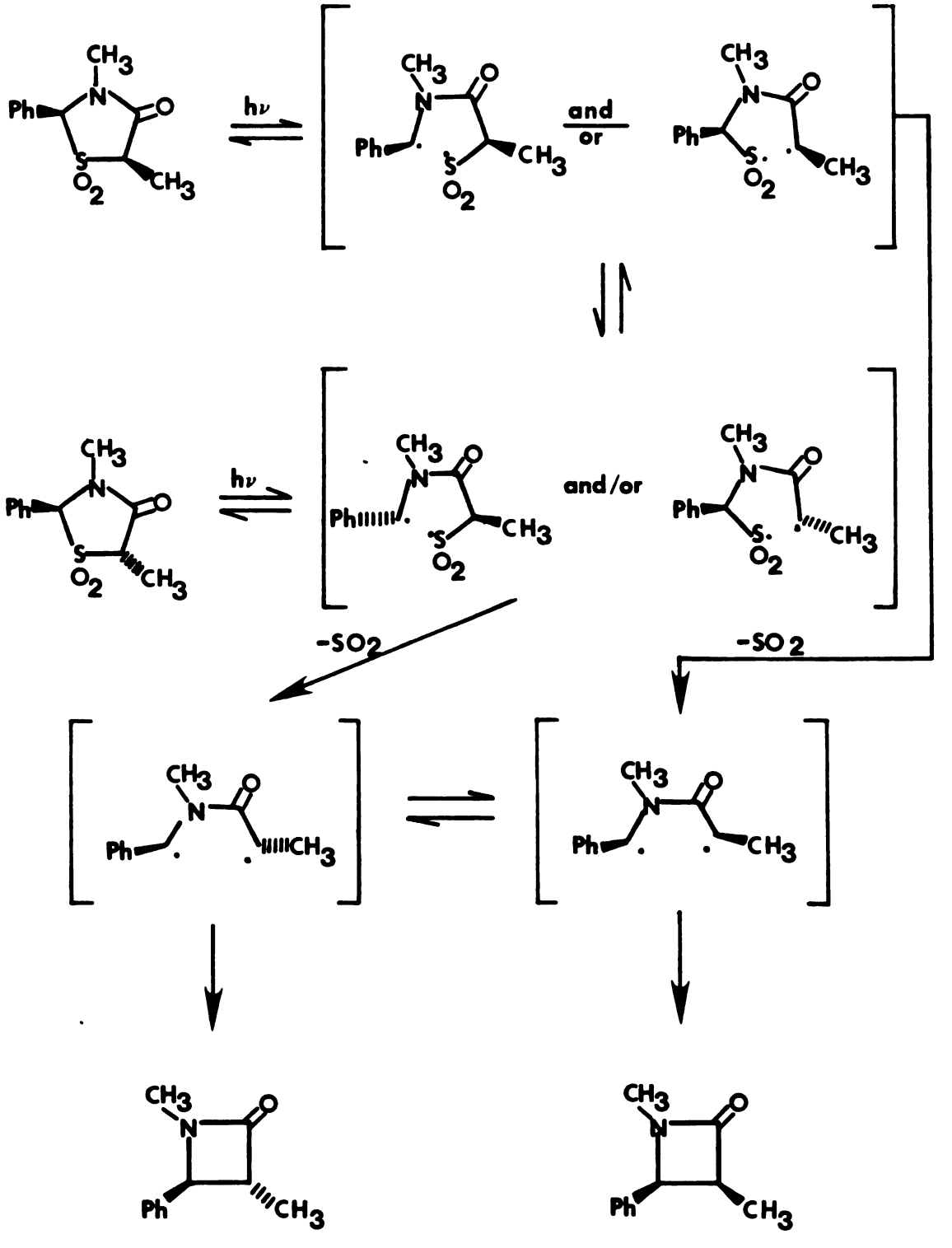
The observation that both sulfone isomers give β-lactams in which the major, but not exclusive product has retained its stereochemistry, rules out long-lived equilibrating diradicals. The formation of both β-lactam isomers from each sulfone isomer does not rule out all or some concerted sulfur dioxide expulsion, as the product lactams could photochemically interconvert (not very likely at a fast rate) or the sulfones could interconvert. It was observed that the recovered sulfone from photolysis of the trans isomer was all cis. The fact that the lactams formed in this photolysis are mostly trans eliminates the possibility that the lactams arose mainly from the cis sulfone.

The formation of reduction products upon photolysis of both sulfones in isopropanol implies the intermediacy of radicals. This does not, however, require that the radicals are intermediates in the formation of β-lactams, although it does seem likely. The fact that some β-lactams are still formed in isopropanol requires either contribution from a concerted mechanism, or the intermediacy of short-lived diradicals.

Perhaps the most likely description is shown in Scheme 1. Photolysis of either sulfone results in cleavage to a diradical, which can either reclose to the sulfone, lose sulfur dioxide, rotate and reclose to the alternate sulfone, or rotate and then lose sulfur dioxide. The diradicals from sulfur dioxide loss can then either close to the β-lactam or rotate and then close to the other β-lactam isomer. For this scheme to work, isomerization of the diradicals must be slow compared to the rate of closure to β-lactams, or the stereoselectivity wouldn't be observed. The difficulty with this scheme is that it predicts increasing stereoselectivity when radical traps are present. In fact, little difference is observed. This objection may be circumvented by postulating an alternate pathway for inversion of stereochemistry, one that doesn't involve the above diradicals. Such a pathway might be isomerization of the β-lactams photochemically, or a hydrogen abstraction recombination in isopropanol.

Whatever the details of the reaction, the important feature is the predominant formation of the cis 3,4-disubstituted β-lactam. This is the stereochemistry required for biological activity in nearly all of the penicillin and cephalosporin antibiotics. The yield of cis 1,3-dimethyl-4-phenyl-2-azetidinone from benzylidene methylamine and thiolactic acid is 21%. Clearly, a sequence that could be used to provide biologically active β-lactams in comparable yields would be extremely useful. The next question is then will the photoreaction be applicable to thiazolidinone dioxides with the proper substituents for biological activity,

Scheme 1



or groups which can be changed into the necessary functional groups. The substituents necessary for this include a carboxymethyl group on nitrogen, a heteroatom substituent at C(5) of the thiazolidinone, and a manipulable substituent at C(2). Initial work towards that objective has been done. Preliminary work suggests that the photoreaction still proceeds with a carbomethoxymethyl substituent on nitrogen. Other work in this group has shown that the photoreaction proceeds nicely with 2-furyl, 2-thiophenyl, and p-chlorophenyl substituents at C(2), rather than phenyl. The stereochemical results are still as seen for the phenyl substituted case, and furyl and thiophenyl groups are manipulable into other functional groups. Thermolysis of thiazolidinone dioxides also offers an attractive route to β-lactams, when trans disubstituted β-lactams are desired.

EXPERIMENTAL

General. In addition to the instruments and methods described in the preceding experimental section, the following methods and instruments were used. All photolyses were done with a Hanovia 450-W medium pressure mercury arc lamp, and all solutions for photolysis were purged with argon for at least 15 minutes before and during the entire photolysis. Organic solutions were dried with either sodium sulfate or magnesium sulfate and some analyses were done by Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

Preparation of 5-methyl-2-phenyl-4-thiazolidinone. A solution of 10.0 g (94.3 mmol) of benzaldehyde, 10.0 g (94.3 mmol) of thiolactic acid, and 5.0 g (52 mmol) of powdered ammonium carbonate in 250 mL of benzene was heated for 7 h at reflux with removal of water via a Dean Stark trap. The solution was allowed to cool, washed with water containing 20 mL of concentrated aqueous ammonia, and solvent removed under reduced pressure to yield a white solid which was recrystallized from chloroform/hexane to yield 10.1 g, 56%, of 5-methyl-2-phenyl-4-thiazolidinone (mp 126-127°C) having the following spectral data; NMR ($CDCl_3$) δ 1.55 (3H,d, J = 7 Hz), 3.95 (1H,q, J = 7 Hz), 5.60 (1H,br s), 6.7 (1H,br) 7.2 (5H,s); ir ($CHCl_3$) 1690 cm^{-1}(vs); mass spectrum (70 eV) m/e (rel. intensity) 193 (67), 132 (44), 106 (100), 104 (42).

Anal. Calcd. for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.46; H, 5.68; N, 7.25.

Preparation of 3-methyl-2-phenyl-4-thiazolidinone (17).[35] A solution of 10 g (84 mmol) of benzylidene methylamine and 7.73 g (84 mmol) of mercaptoacetic acid in 250 mL of benzene was refluxed for 4 h with removal of water via a Dean Stark trap. The solution was allowed to cool and solvent removed under reduced pressure to yield 16.1 g, 99% of 3-methyl-2-phenyl-4-thiazolidinone as a slightly yellow oil which had the following spectral properties: NMR ($CDCl_3$) δ 2.65 (3H,s), 3.70 (2H,br s), 5.45 (1H,m), 7.20 (5H,s); ir (neat) 1680 cm^{-1}(vs).

Preparation of cis and trans 3,5-dimethyl-2-phenyl-4-thiazolidinone, (18) and (19). A slurry of 0.36 g (15.6 mmol) of sodium hydride in dry tetrahydrofuran was prepared by washing 0.72 g of 50% sodium hydride oil dispersion three times with dry pentane, and then adding 30 mL of tetrahydrofuran. To this a solution of 2.83 g (14.7 mmol) of 5-methyl-2-phenyl-4-thiazolidinone in 70 mL of tetrahydrofuran was added dropwise over a period of 1.5 h. Then a solution of 2.10 g (14.8 mmol) of methyl iodide in 30 mL of tetrahydrofuran was added dropwise over a period of 1 h and stirring continued at room temperature for another 16 h. The reaction mixture was poured into methylene chloride and water, saturated salt solution added, the organic layer removed, dried filtered, and concentrated under reduced pressure to yield a yellow oil containing both cis and trans 3,5-dimethyl-2-phenyl-4-thiazolidinone. These were separated by chromatography on silica gel, eluting with ether/pentane (1:1). The trans isomer eluted first, 0.90 g, (mp 64-65°C) 30%, and had the following spectral data: NMR ($CDCl_3$) δ 1.55 (3H,d, J = 7Hz), 2.7 (3H,s), 4.0 (q of d, J = 7Hz, J' = 2Hz), 5.35 (1H,d, J = 2Hz), 7.2 (5H,s); ir ($CHCl_3$) 1670 cm^{-1}(s); mass spectrum (70 eV) m/e (rel. intensity) 207 (72), 150 (25), 130 (71), 120 (48), 118 (100), 91 (20), 77 (28).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76. Found: C, 63.82; H, 6.38, N, 6.77.

Following 0.59 g, 20%, of a mixture of the two isomers, 1.02 g, 34%, of the cis isomer (mp 70-71°C) with the following spectral data was obtained: NMR ($CDCl_3$) δ 1.55 (3H,d, J = 7Hz),, 2.60 (3H,s), 3.85 (1H,q, J = 7Hz),5.30 (1H,s), 7.2 (5H,s); ir ($CHCl_3$) 1670 cm^{-1}(s); mass spectrum (70 eV) m/e (rel. intensity) 207 (74), 150 (25), 130 (69), 120 (47), 118 (100), 91 (20), 77 (28).

Preparation of cis and trans 3,5-dimethyl-2-phenyl-4-thiazolidinone, (18) and (19). A solution of 10 g (84 mmol) of benzylidene methylamine and 8.9 g (84 mmol) of thiolactic acid in 250 mL of benzene was refluxed for 4 h with azeotropic water removal with a Dean Stark trap. The solution was allowed to cool and solvent removed under reduced pressure to yield 16.6 g, 95%, of an 8/1 mixture of cis and trans 3,5-dimethyl-2-phenyl-4-thiazolidinone, respectively, which was pure (only the two isomers) by ^1H NMR.

Preparation of 3-methyl-1-oxo-2-phenyl-4-thiazolidinone, (20). A slurry of 0.711 g (3.09 mmol) of potassium periodate in 25 mL of water was chilled in an ice bath, and a solution of 0.597 g (3.09 mmol) of 3-methyl-2-phenyl-4-thiazolidinone in 20 mL of methanol added. The suspension was stirred at 0°C for 8 h, and the bath allowed to melt over another 16 h. The suspension was poured into methylene chloride and water, the organic layer removed, dried, filtered and concentrated under reduced pressure to yield a yellow oil which slowly crystallized on standing. Recrystallization from chloroform/hexane afforded 0.30 g, 46%, of crystalline 3-methyl-1-oxo-2-phenyl-4-thiazolidinone (mp 124-125°C)

which had the following spectral properties: NMR ($CDCl_3$) δ 2.95 (3H,s), 3.25 (1H,d J = 17 Hz), 3.70 (1H,d J = 17 Hz), 5.45 (1H,s), 6.9-7.4 (5H, m); ir ($CHCl_3$) 1690 (vs), 1050 cm^{-1}(s); mass spectrum (70 eV) m/e (rel. intensity) 209 (66), 193 (13), 120 (100), 118 (100), 91 (21).

Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.40; H, 5.30; N, 6.69. Found: C, 57.10; H, 5.14; N, 6.64.

Preparation of 3,t-5-dimethyl-t-2-phenyl-r-1-oxo-4-thiazolidinone, (21). Solutions of 0.64 g (3.09 mmol) of cis 3,5-dimethyl-2-phenyl-4-thiazolidinone in 10 mL of methanol and 0.66 g (3.09 mmol) of sodium periodate in 10 mL of water were mixed at 0°C and maintained at that temperature for 8 h. The solution was stirred for another 16 h at room temperature, and the resulting orange solution poured into methylene chloride and water. The aqueous layer was removed and the now pink organic layer washed once with sodium bisulfite solution (which removed the color) once with water, and dried. Filtration and solvent removal under reduced pressure gave a yellow solid which was recrystallized from chloroform/hexane to yield 0.150 g, 22%, of 21 (mp 137-139°C) which had the following spectral properties: NMR ($CDCl_3$) δ 1.5 (3H,d,J = 7Hz), 2.95 (3H,s), 3.50 (1H,q, J = 7Hz), 5.20 (1H,s), 7.1-7.5 (5H,m); ir (CCl_4) 1705 (vs), 1080 cm^{-1}(s); mass spectrum (70 eV) m/e (rel. intensity) 223 (63), 175 (71), 146 (40), 120 (100), 118 (100).

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 58.84; H, 5.79; N, 6.25.

Preparation of 3,t-5-dimethyl-c-2-phenyl-r-1-oxo-4-thiazolidinone or S(1) epimer (22). Solutions of 0.45 g (2.17 mmol) of trans 3,5-dimethyl-2-phenyl-4-thiazolidinone in 15 mL of methanol and 0.465 g (2.17 mmol) of

sodium periodate in 15 mL of water were mixed at 0°C and stirred for another 8 h at 0°C, and 12 h at room temperature. The orange mixture was poured into methylene chloride and water, the aqueous layer removed, the now pink organic layer washed once with sodium bisulfite solution, which decolorized the organic layer, and finally once more with water. The organic layer was dried, filtered, and solvent removed under reduced pressure to yield an oil. Crystallization from chloroform/hexane afforded 71 mg, 15%, of 3,5-dimethyl-1-oxo-2-phenyl-4-thiazolidinone (mp 137-139°C). While the yield of pure material was low, examination of the NMR of the crude reaction mixture showed this to be by far the major product. The spectral data were: NMR ($CDCl_3$) δ 1.5 (3H,d, J = 7.5Hz), 3.0 (3H,s), 3.4 (1H,q, J = 7.5Hz), 5.25 (1H,s), 7.1-7.5 (5H,m); ir (CCl_4) 1705 (vs), 1070 cm^{-1}(m); mass spectrum (70 eV) m/e (rel. intensity) 223 (32), 207 (11), 175 (21), 120 (100), 118 (74), 77 (21).

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.15; H, 5.85; N, 6.24.

Preparation of 3-methyl-1,1-dioxo-2-phenyl-4-thiazolidinone (23).[35] A solution of 5.0 g (25 mmol) of 3-methyl-2-phenyl-4-thiazolidinone in 150 mL of acetic acid was chilled in an ice bath, and a solution of 5.46 g (34.6 mmol) of potassium permanganate in 150 mL of water was added dropwise over a period of 2 h. The solution was decolorized by addition of solid sodium bisulfite, and poured into a mixture of methylene chloride and water. The organic layer was removed, the aqueous layer extracted twice more with methylene chloride, the combined organic extracts dried, filtered, and concentrated under reduced pressure to yield a white solid. Recrystallization from methylene chloride/hexane

yielded 3.9 g, 67%, of 3-methyl-1,1-dioxo-2-phenyl-4-thiazolidinone, (mp 122-123°C) lit. 123-124°C with the following spectral properties: NMR ($CDCl_3$) δ 2.90 (3H,s), 3.75 (2H,s), 5.45 (1H,s), 7.0-7.5 (5H,m); ir ($CHCl_3$) 1700 (vs), 1340 (s), 1130 cm^{-1}(s); mass spectrum (70 eV) m/e (rel. intensity) 161 (35), 160 (23), 132 (17), 118 (100), 77 (14).

Anal. Calcd for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22. Found: C, 53.30; H, 4.93; N, 6.29.

Preparation of cis 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone (25).

A solution of 3.0 g (14 mmol) of cis 3,5-dimethyl-2-phenyl-4-thiazolidinone in 100 mL of acetic acid was chilled in an ice bath and a solution of 3.05 g (19.3 mmol) of potassium permanganate in 150 mL of water added dropwise over 1 h. After the addition was complete, the solution was treated with solid sodium bisulfite until clear, and poured into methylene chloride and water. The organic layer was removed and the aqueous layer extracted once more with methylene chloride. The combined organic extracts were dried, filtered, and concentrated under reduced pressure to yield a white solid which was recrystallized from chloroform/hexane to yield 2.05 g, 60%, of cis 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone (mp 139-140°C), which had the following spectral data: NMR ($CDCl_3$) δ 1.57 (3H,d, J = 7Hz), 2.82 (3H,s), 3.68 (1H,q, J = 7Hz), 5.48 (1H,s), 7.1-7.5 (5H,m); ir (CCl_4) 1700 (vs), 1340 (s), 1140 cm^{-1}(s); mass spectrum (70 eV) m/e (rel. intensity) 175 (31), 146 (22), 120 (36), 118 (100), 91 (24), 77 (24).

Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.20; H, 5.35; N, 5.84.

Preparation of trans 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone (24). A solution of 300 mg (1.45 mmol) of trans 3,5-dimethyl-2-phenyl-4-thiazolidinone in 25 mL of acetic acid was chilled in an ice bath and a solution of 306 mg (1.93 mmol) of potassium permanganate in 30 mL of water added dropwise over 10 minutes. After the addition was complete, the solution was treated with solid sodium bisulfite until clear, and poured into methylene chloride and water. The organic layer was removed and the aqueous layer extracted once more with methylene chloride. The combined organic extracts were washed with saturated sodium bicarbonate, dried, filtered, and solvent removed under reduced pressure to yield 198.2 mg, 58%, of trans 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone as an oil, with the following spectral data: NMR ($CDCl_3$) δ 1.57 (3H,d, J = 7Hz), 2.95 (3H,s), 3.55 (1H,q, J = 7Hz), 5.35 (1H,s), 7.0-7.5 (5H,m); ir ($CHCl_3$) 1700 (vs), 1330 (s), 1130 cm^{-1} (s); mass spectrum (70 eV) m/e (rel. intensity) 175 (100), 146 (37), 120 (83), 118 (60), 77 (32).

Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48. Found: C, 55.03; H, 5.42.

Preparation of 3,5,5-trimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone.(26) A solution of 0.50 g (2.09 mmol) of 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone and 0.25 g (2.23 mmol) of potassium t-butoxide in 150 mL of dry t-butyl alcohol was stirred until everything had dissolved, and then 1.50 g (10.6 mmol) of methyl iodide was added all at once. The solution was stirred for 24 h, and then poured into methylene chloride and water. The organic layer was removed, the aqueous layer extracted three times with methylene chloride, and the combined extracts were dried, filtered, and concentrated under reduced pressure to give a

white solid. Recrystallization from methylene chloride/hexane afforded 0.35 g, 66%, of 3,5,5-trimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone (mp 107-108°C), which had the following spectral data: NMR ($CDCl_3$) δ 1.50 (3H,s), 1.60 (3H,s), 2.85 (3H,s), 5.40 (1H,s), 7.0-7.5 (5H,m); ir (CCl_4) 1700 (vs), 1325 (s), 1120 cm^{-1} (s); mass spectrum (70 eV) m/e (rel. intensity) 189 (45), 132 (20), 120 (100), 118 (49), 77 (12).

Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 57.16; H, 6.13; N, 5.64.

Photolysis of 3-methyl-1,1-dioxo-2-phenyl-4-thiazolidinone (23). Solutions of 3-methyl-1,1-dioxo-2-phenyl-4-thiazolidinone in methanol and acetonitrile were irradiated through both vycor and corex filters for periods of time between 35 minutes and 2.5 h. Solvent removal under reduced pressure in each case afforded only starting material and/or polymeric material, as judged by NMR and column chromatography on florisil.

Photolysis of trans 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone, (24) in t-butyl alcohol/acetonitrile. A solution of 90 mg (0.377 mmol) of trans 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone in 150 mL of a 6/1 mixture of t-butyl alcohol/acetonitrile was irradiated through a vycor filter for 35 minutes. Solvent removal under reduced pressure gave an oil which was chromatographed on a short florisil column, eluting with 5% methanol in methylene chloride. One band was obtained which contained, by NMR analysis using methylene chloride as standard, 9.2 mg, 14%, and 4.6 mg, 7%, of trans and cis 1,3-dimethyl-4-phenyl-2-azetidinone, respectively, and 15.7 mg (17%) of recovered sulfone. The recovered sulfone was, before chromatography, exclusively the cis isomer,

as shown by NMR.

Photolysis of trans 3,5-dimethyl-1,1-dioxo-5-phenyl-4-thiazolidinone in isopropanol (24). A solution of 245 mg (1.025 mmol) of trans 3,5-dimethyl-1,1-dioxo-5-phenyl-4-thiazolidinone in 175 mL of isopropanol was irradiated through a vycor filter for 2 h. Solvent removal under reduced pressure gave an oil which was chromatographed on florisil, eluting with 2% methanol in methylene chloride. One band was obtained which contained 13 mg, 7.2%, of trans 1,3-dimethyl-4-phenyl-2-azetidinone, 6.5 mg, 4%, of cis 1,3-dimethyl-4-phenyl-2-azetidinone, and 30 mg, 16.5%, of N-benzyl-N-methylpropionamide which had the following NMR spectrum: NMR ($CDCl_3$) δ 4.50 and 4.45 (combined 2H,s), 2.90 (3H,br s), 2.40 (2H,q, J = 7Hz), 1.30 (3H,t, J = 7Hz).

Photolysis of cis 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone (25). A solution of 211 mg (0.883 mmol) of cis 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone in 175 mL of a 6/1 mixture of t-butyl alcohol/acetonitrile was irradiated through a vycor filter for 40 minutes. Solvent was removed under reduced pressure to give an oil, which was taken up in methylene chloride, washed with water, dried, and solvent again removed under reduced pressure. The residue contained a mixture of cis and trans 1,3-dimethyl-4-phenyl-2-azetidinone and starting material. NMR analysis of the mixture using methylene chloride as a standard indicated yields of 54 mg, 31%, of the cis β-lactam, 28, 14 mg, 8%, of the trans β-lactam, 29, and 59 mg, 28%, of starting material.

Photolysis of identical amounts of the sulfone under identical conditions in several other solvent systems, with the same work-up, were also performed. Results of these photolyses are described in Table 4.

Photolysis of 3,5,5-trimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone, (26). A solution of 100 mg (0.395 mmol) of 26 in a mixture of 150 mL of t-butyl alcohol and 25 mL of acetonitrile was irradiated through a vycor filter for 30 minutes. Solvent removal under reduced pressure gave an oil which was chromatographed on a preparative TLC plate (EM Labs Silica Gel), eluting once with ether and then once with 5% methanol in methylene chloride. The second elution yielded a band containing a mixture of starting material and 8 mg, 10%, 1,3,3-trimethyl-4-phenyl-2-azetidinone, with the following spectral data: NMR ($CDCl_3$) δ 0.85 (3H,s), 1.50 (3H,s), 2.90 (3H,s), 4.25 (1H,s), 6.9-7.4 (5H,m); ir ($CHCl_3$) 2950 (s), 1740 cm^{-1} (vs); mass spectrum (70 eV) m/e (rel. intensity) 189 (9), 132 (100), 120 (39), 118 (33), 117 (83), 91 (24).

Thermolysis of trans 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone, (24). A 25 mL round bottom flask containing 24 mg (0.100 mmol) of trans 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone was immersed in an oil bath maintained at 210°C for 12 minutes. The flask was allowed to cool, and the residue examined by NMR spectroscopy which indicated a 42% yield of trans 1,3-dimethyl-4-phenyl-2-azetidinone, 29, 19% of recovered trans starting material, 24, and 9% of the cis sulfone 25.

Thermolysis of cis, 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone, (25). A 5 mm NMR tube containing 60.5 mg (0.253 mmol) of cis 3,5-dimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone was heated for 5 minutes in an oil bath maintained at 200°C. The tube was allowed to cool, deuterochloroform and 10 μL of trichloroethylene added, and yields determined by NMR. No starting material remained but 0.21 mmol, 83%, of trans 1,3-dimethyl-4-phenyl-2-azetidinone was present.

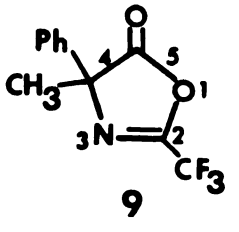
Thermolysis of 3,5,5-trimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone, (26). A 5 mm NMR tube containing 33.4 mg (0.132 mmol) of 3,5,5-trimethyl-1,1-dioxo-2-phenyl-4-thiazolidinone was heated in an oil bath maintained at 210°C for 15 minutes. The tube was allowed to cool, and the residue analyzed by NMR, which showed 18 mg, 54% of recovered starting material, and 7.6 mg, 30.5%, of 1,3,3-trimethyl-4-phenyl-2-azetidinone. The yield of β-lactam based on recovered starting material was 66%.

NMR studies of sulfoxides 20, 21 and 22. All spectra were taken on a Varian Associates T-60 NMR spectrometer at room temperatures. All solvent induced shift experiments were done using ∿ 11 mg of the sulfoxide in 0.3 mL of solvent, except for those in carbon tetrachloride, where saturated solutions were used due to limited solubility. The europium shift studies were performed using 10 mg of sulfoxide in 0.3 mL of deuterochloroform, with $Eu(fod)_3$ added in small increments up to the equivalence point.

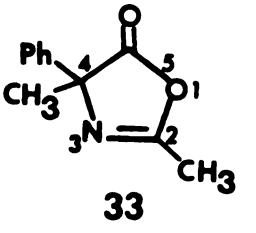
Photolysis and Thermolysis of 2,4,4-Trisubstituted Δ^2-Oxazolin-5-ones; Substituent Effect of a Trifluoromethyl Group.

Introduction

One of the intermediates in our scheme for the synthesis of 3,6-dihydropyrazinones (Part 1 of this thesis) was the heterocycle 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one, 9. Being generally interested in the photochemistry of heterocyclic compounds we wondered if 9 might have any interesting photochemistry. In particular, the possible effect of a trifluoromethyl group interested us and we wondered how the photochemistry and thermal chemistry might compare with that of the compound with methyl in place of trifluoromethyl, 33. The trifluoromethyl group has already been



9



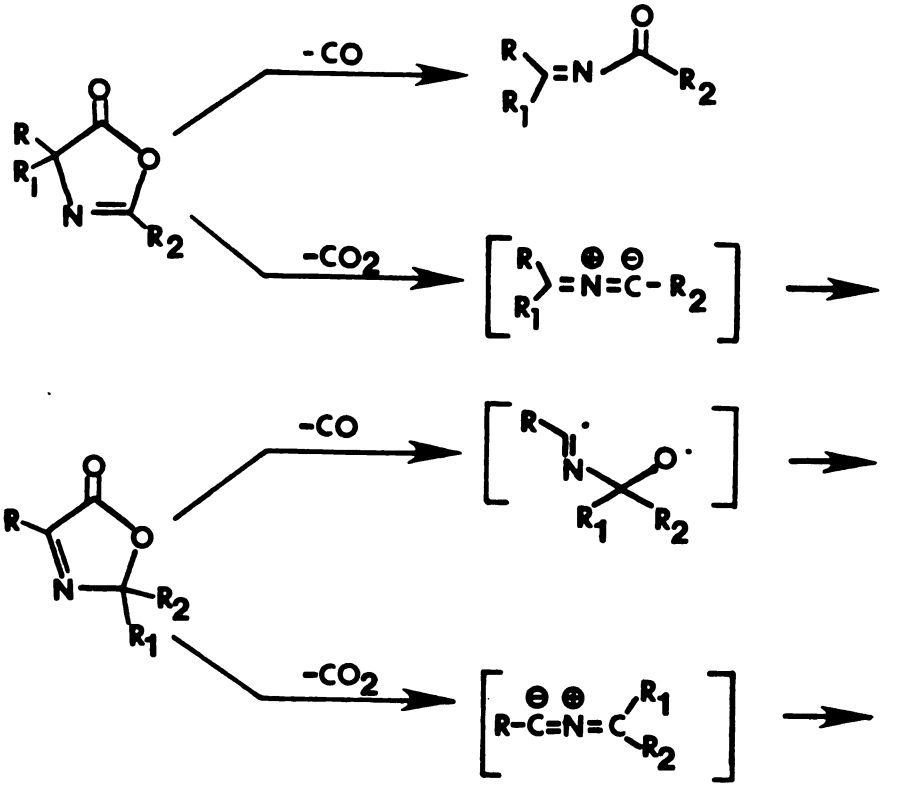
33

reported to strongly influence the regioselectivity of the photocycloaddition of isobutylene to uracils, when substituted on C(5) of the uracil.[54]

The discovery of photodirecting groups which would allow the prediction or control of photochemical reactions would considerably enhance the utility of photochemistry in organic synthesis. Currently, the principal obstacle to the use of photochemistry is the apparent capriciousness of photochemical reactions, a problem whose solution may lie in the development of photodirecting,

photoactivating or photoprotecting groups. While the trifluoromethyl group itself may not be very useful synthetically due to its relative unreactivity, its behavior may suggest other groups which may be manipulable and thus be of some practical value in organic synthesis.

There are several reports in the literature relating to the photolysis and thermolysis of both Δ^2 and Δ^3-oxazolin-5-ones. In each case one of two reactions is observed, either carbon dioxide loss to give a nitrile ylide, which may be trapped, or carbon monoxide loss to give an N-acyl imine.



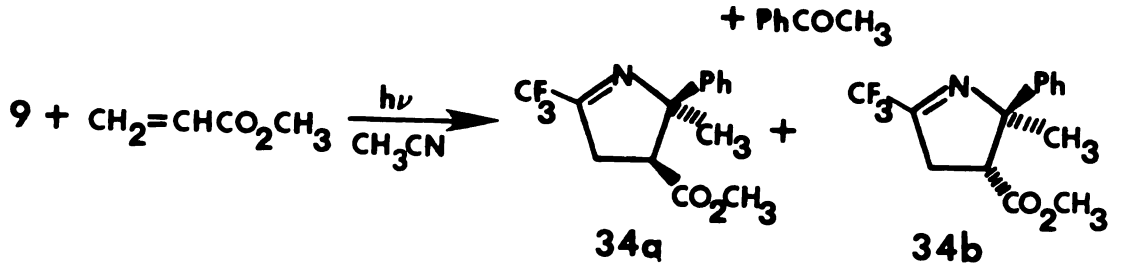
There are two reports of Δ^2-oxazolin-5-one photolysis. Slates et al report that photolysis of a 2,4,4-trialkyl-Δ^2-oxazolin-5-one, followed by acidic work-up, yields a ketone derived from C(4) and its substituents.[55] Loss of carbon dioxide to give an N-acyl imine followed by hydrolysis was postulated, but not demonstrated. Padwa and Wetmore report that photolysis of an Δ^2-oxazolin-5-one in the presence of an electron-deficient olefin dipolarophile trap gave no Δ^1-pyrroline product.[56] However the oxazolinone was not specified, nor were the identity of any products reported. This behavior contrasts with that of Δ^3-oxazolin-5-ones, which usually lose carbon dioxide photochemically to give nitrile ylide intermediates, which may be trapped with electron-deficient dipolarophiles to give Δ^1-pyrrolines in good yield.[56] [57] An exception to this behavior is the loss of carbon monoxide upon photolysis of a 2-trifluoromethyl substituted Δ^3-oxazolin-5-one.[58]

Attempted thermolysis of 2,4,4-trisubstituted Δ^2-oxazolin-5-ones in refluxing xylene is reported to give no reaction,[59] but higher temperatures do cause reaction. In these cases, loss of carbon dioxide occurs to give products expected from nitrile ylide intermediates.[60] Carbon monoxide loss is reported to occur only when a 2-trifluoromethyl and 4-thiophenoxy group are present.[61] Contrary to our results (see below) compound 9 was reported to be stable to 200° C.[62] Thermolysis of 2,4-disubstituted Δ^2-oxazolin-5-ones with dipolarophiles present, gives Δ^1-pyrrolines also,[59] but this reaction involves oxazolium ion intermediates, which are trapped by the dipolarophile and then lose carbon dioxide. Thermolysis of Δ^3-oxazolin-5-ones also gives loss of carbon

dioxide and formation of products expected from nitrile ylides.[60]

Results: Photolysis of Δ^2-Oxazolin-5-ones 9 and 33.[63]

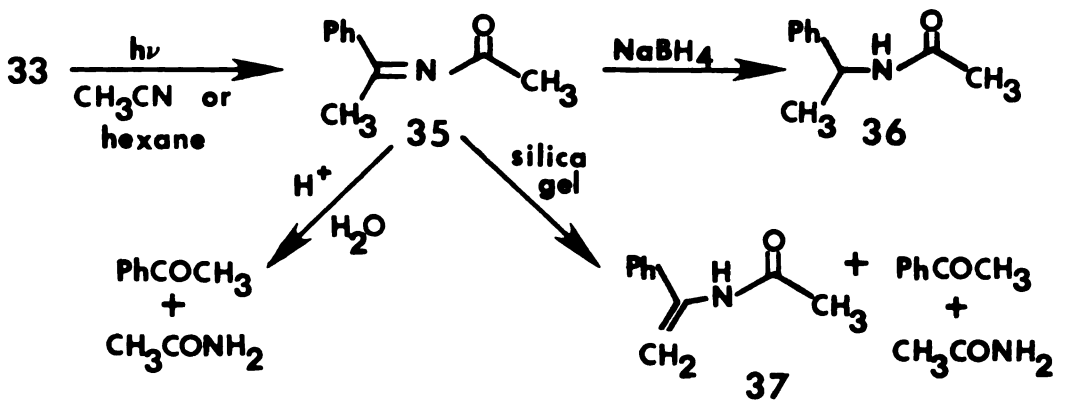
Photolysis of 9 and methyl acrylate in acetonitrile gives modest yields (26% and 17%) of cis and trans-2-trifluoromethyl-4-carbomethoxy-5-methyl-5-phenyl-Δ^1-pyrrolines, 34a and 34b respectively, along with 7% acetophenone. Spectral and elemental analysis



support the structures proposed. The stereochemical assignments are based on ^{1}H NMR spectra. Pyrroline 34a is assigned the structure with phenyl and carboxymethyl groups cis since the ester methyl group is more shielded in 34a than in 34b.[64] Apparently none of the 3-carboxymethyl substituted pyrroline is formed as there is no higher field multiplet present as would be expected from a C(4) unsubstituted Δ^1-pyrroline. Starting material was recovered unchanged from a dark control sample worked up by the same procedure, indicating that all products have a photochemical origin.

Irradiation of 33 in either hexane or acetonitrile gave a good yield of N-(1-methylbenzylidene)acetamide, 35. The structure assignment was based on the ^{1}H NMR spectrum (singlets at δ 2.1 and 2.3 and the aromatic region signals expected of a C-phenyl imine) and chemical transformations. Acid catalyzed hydrolysis immediately gave acetamide and acetophenone, while reduction with sodium borohydride gave N-(1-phenylethyl)acetamide, 36. Silica gel

chromatography gave a mixture of acetophenone, acetamide, and N-(1-phenylvinyl)acetamide, 37. Compound 37 was identified by its ^{1}H NMR spectrum and by comparison to an authentic sample, synthesized by literature methods.[65] Since enamide 37 is easily

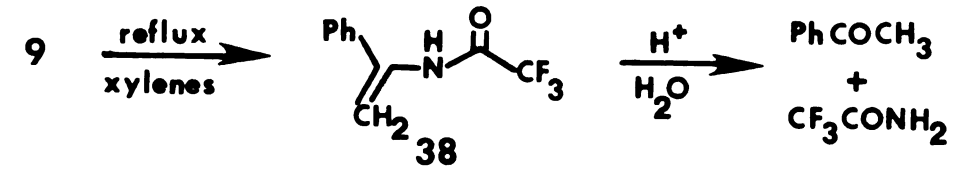


hydrolyzed to acetophenone and acetamide it is possible, but not necessary that they are formed from 37 via 35. Irradiation of 33 in acetonitrile with methyl acrylate gave, as the only additional product, polymethyl acrylate. The photoreactions of 9 and 33 were not quenched by added piperylene in concentration sufficient that excited states living for 10^{-7} seconds would have been 90% trapped.

Results: Thermolysis of Δ^2-Oxazolin-5-ones 9 and 33.

When 9 is refluxed in dry xylenes a good yield (66%) of N-(1-phenylvinyl)trifluoroacetamide, 38, is obtained, along with a small amount of acetophenone. The identification of 38 is based on its spectral properties. The ^{1}H NMR spectrum showed an exo methylene, an amide hydrogen and a phenyl group. The mass spectrum, in addition to the correct parent and parent plus one peaks, showed fragments from the loss of trifluoromethyl and trifluoroacetamide fragments. Hydrolysis of 38 gave acetophenone and presumably trifluoroacetamide. Though 38 may have formed from

N-(1-methylbenzylidene)trifluoroacetamide, no evidence for it was found in the reaction mixture. When 33 was refluxed in xylenes for periods up to 15 hours, with or without methyl acrylate, it was recovered unchanged.



Discussion: Thermolysis of Δ^2-Oxazolin-5-ones 9 and 33.

The most important feature of both the thermal and photochemical reactions is the profound effect of the trifluoromethyl group. In the thermal reaction, the trifluoromethyl group both activates the ring and diverts the normal course of the reaction from loss of carbon dioxide to loss of carbon monoxide. This means that the trifluoromethyl group has drastically lowered the activation energy for loss of carbon monoxide, with unknown effects on the alternate reaction pathway. It is important to note that this effect is different from that of a phenyl group at C(2), which accelerates thermal carbon dioxide expulsion.[60] [61] A consideration of the stability of diradicals which might be generated as intermediates or which may resemble species on a concerted reaction pathway, helps rationalize the thermal results.

The fact that the reaction of 9 is faster requires that the trifluoromethyl group enhance either 4,5 bond cleavage or 1,5 bond cleavage, or both. Cleavage of the 4,5 bond would produce a

π-type allyl radical, which would be stabilized by a 2-trifluoromethyl group, relative to a methyl group. How the trifluoromethyl group would effect the diradical from 1,5 bond cleavage is not apparent. The results require that 1,5 bond cleavage be enhanced relative to 1,2 bond cleavage by the trifluoromethyl group. Cleavage of the 1,2 bond would produce an iminoyl σ-type radical at carbon 2.[66] Trifluoromethyl groups are known to destabilize acyl radicals relative to methyl and phenyl.[67] One particularly attractive rationale which is consistent with the preceding discussion is enhanced 4,5 bond cleavage in a rate-determining step, followed by 1,5 bond cleavage rather than 1,2 cleavage in the product determining step. It is not possible to comment on the reported thermal stability of 9 as the conditions were not described.

Discussion: Photolysis of Δ^2-Oxazolin-5-ones 9 and 33.

The very different photochemical behavior of 9 and 33 shows that the trifluoromethyl group can also strongly affect excited state behavior. The photochemical expulsion of carbon monoxide in 33 evidently has precedent in the work of Slates et al.[55] However this is the first instance in which the postulated N-(methylidene)acetamide or the tautomeric enamide have been observed before hydrolysis. Substitution of the trifluoromethyl group leads to loss of carbon dioxide to evidently give a nitrile ylide which is trapped by a dipolarophile. This is in contrast to previous reports where carbon dioxide loss was not observed from Δ^2-oxazolin-5-ones. As is usually observed, the nitrile ylide shows high regioselectivity in its reaction with methyl acrylate.

The direction of this cycloaddition may be rationalized by the work of Caramella and Houk, who have shown that the direction of dipolar cycloadditions may be predicted on the basis of orbital coefficients for the HOMO and LUMO.[68]

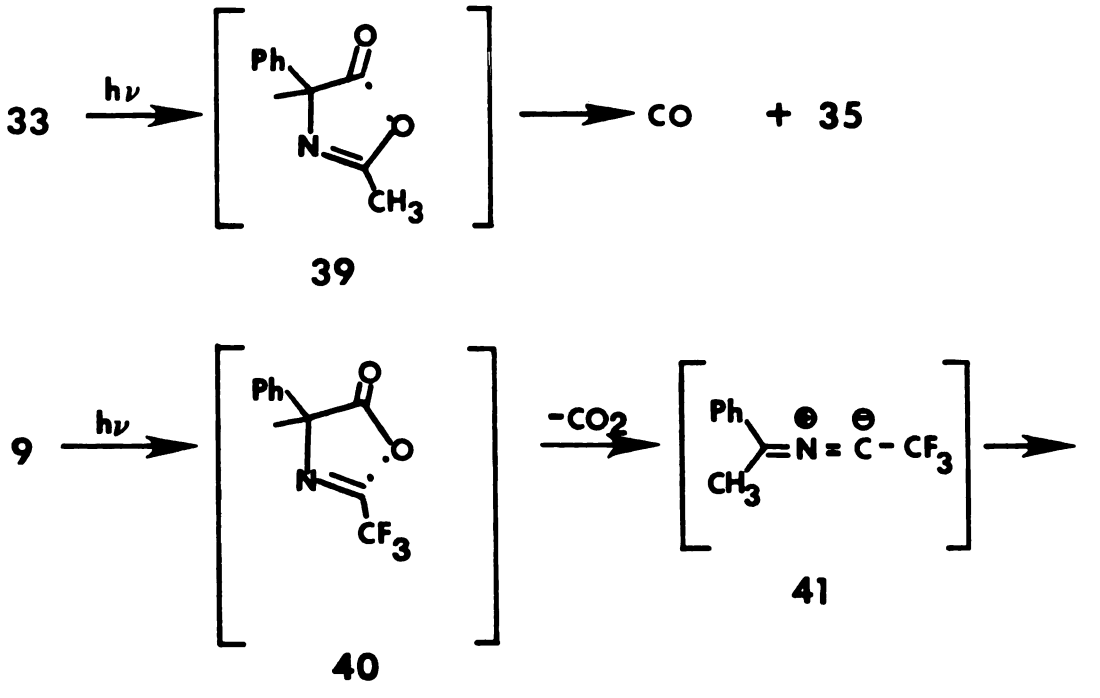
The reaction pathways of 9 and 33 may not be completely exclusive, since the acetophenone formed in the photolysis of 9 could have arisen from carbon monoxide expulsion. However, it could also arise via rearrangement of the nitrile ylide to an enamine, followed by hydrolysis. Reaction of both 9 and 33 probably involve singlet or very short-lived triplet states, since the reactions were not quenched by piperylene.

The Effect of the Trifluoromethyl Group.

The means by which the trifluoromethyl group influences the photoreaction of 9 is not clear. The fact that a number of points at which the trifluoromethyl group could control the reaction exist, and that we cannot say which is correct is perhaps indicative of our still rudimentary knowledge of photochemical reactions. However, it is certainly useful to consider these potential points of control.

The first potential point of control is, in a gross sense, the localization of the excited state energy. One might consider 9 and 33 to have one, two or three excited states, depending on the interaction of the phenyl, carbonyl, and imino groups. This localization could be determined by the state formed first on absorption of light, or by subsequent energy transfer from one "chromophore" to another. Examination of the UV spectra of 9 and 33 shows the same maxima in each, with no shifts in those maxima as solvent polarity is changed. The spectra are like that of

toluene, although extinction coefficients in the 225-250 nm region are bigger. The extinction coefficient of 9 between 250 and 280 nm is approximately twice that of 33. These small changes suggest that control of the photochemical reaction is determined at another point. Intramolecular energy transfer from the phenyl group is perhaps a more likely point of control in the reaction. α-Phenyl to ester carbonyl energy transfer has been reported in studies of ester photochemistry by Morrison et al.[69] With methyl present as in 33, energy transfer to the carbonyl may dominate, followed by α-cleavage to give diradical 39, like that postulated for the photo-Fries reaction, which may lose carbon monoxide to give the observed product 35.[70] The substitution of trifluoromethyl for methyl would lower the energy of the π-π and n-π* levels of the imine,[71] and energy transfer to the imine followed by α-cleavage, as postulated for azirines, could lead to diradical 40. Loss of carbon dioxide would give nitrile ylide 41 which when trapped by a dipolarophile would give the observed Δ^1-pyrrolines. If the



carbonyl and imine form a single excited state, the trifluoromethyl group could increase the importance of the "imine" description (by changing orbital weighting coefficients) and thus aid carbon dioxide expulsion.

Another potential point of control closely related to this involves electron transfer rather then energy transfer. Electron transfer from phenyl to carbonyl might be postulated for 33, and transfer from phenyl to imine for 9. These species may then lose carbon monoxide and carbon dioxide, respectively. The importance of electron transfer in systems like 9 and 33 is not known, and it is possible that electron transfer and energy transfer compete. Electron transfer, may, for example, be important only for 9.

The means by which the trifluoromethyl group affects the photochemistry may be more subtle. In the points of control discussed so far, trifluoromethyl and methyl cause major perturbations of the excited state. The different behavior of 9 and 33 may be due to small changes in appropriate regions of the excited state surface.[4] For example, trifluoromethyl perturbation of the "imine" region of the surface might lower activation barriers[72] and minima to favor 1,2 bond lengthening and eventually cleavage, by making the excited state more zwitterionic.

Finally, a different potential point of control involves decay to the ground state surface, in a region near the geometry of the product. This decay process is aided by a close approach of the ground and excited state surfaces.[4] This can be accomplished by increasing the energy of the ground state or decreasing the energy of the excited state. The trifluoromethyl destabilization

of the iminoyl σ-type radical, may make 1,2 bond cleavage photochemically accessible by raising the energy of the ground state. The methyl group, which would stabilize a σ-type iminoyl radical, would not force the ground state surface high enough for carbon dioxide loss to occur, resulting in decay to the ground state at a geometry corresponding to carbon monoxide loss.

The large number of possible points of control make it difficult to determine which is most important. The concurrence of several of these points of control may rationalize the sharp difference in reactivity of 9 and 33. Whatever the mechanism by which the trifluoromethyl troup perturbs the reactions of the Δ^2 and Δ^3-oxazolinones, the effect is striking. In every case studied thus far, both thermal and photochemical, the trifluoromethyl group has induced the molecule to choose an alternate reaction pathway, despite the fact that this group survives all of these reactions intact.

EXPERIMENTAL

General. Compound 9 was prepared as described in the first section of this thesis. Ultraviolet spectra were recorded on a Cary 17 spectrophotometer. All other instrumentation and procedure were as described in earlier portions of this thesis.

Preparation of 2,4,-dimethyl-4-phenyl-Δ^2-oxazolin-5-one (33).[73] A solution of 2.00 g (12.1 mmol) of α-phenylalanine in 15 mL of acetic anhydride was heated at reflux under a nitrogen atmosphere for 1 h. The solution was allowed to cool and excess acetic anhydride removed under reduced pressure. The residue was distilled under reduced pressure to yield 1.62 g (71%) of 2,4,-dimethyl-4-phenyl-Δ^2-oxazolin-5-one (33); bp 62°C (0.12 mm); NMR ($CDCl_3$) δ 1.7 (3H,s), 2.2 (3H,s), 7.1-7.6 (5H,m).

Absorption Spectra of (9) and (33). UV absorption spectra of 9 and 33 were recorded in both hexane and acetonitrile, and are summarized here: λ (ε) (an asterisk indicates maximum, λ in nm) , 9 (hexane), 268* (243), 263* (429), 261* (484), 257* (629), 251* (828), 245 (1036), 240 (1172), 230 (1930), 220 (3502), 210 (8138); 9 (acetonitrile), 268* (209), 263 (359), 261 (443), 257* (585), 251*, (802), 245 (969), 240 (1130), 230 (1595), 220 (3174), 210 (7643); 33 (hexane), 268* (137), 263* (269), 261 (288), 257* (428), 251* (607), 245 (786), 240 (866), 230 (995), 220 (3731), 210 (8407); 33 (acetonitrile), 268* (98), 263* (197), 261 (208), 257* (384), 251 (519), 245 (711), 240 (909), 230 (1081), 220 (3091), 210 (8547).

Photolysis of 2,4-dimethyl-4-phenyl-Δ^2-oxazolin-5-one (33). A solution of 205 mg (1.08 mmol) of 2,4-dimethyl-4-phenyl-Δ^2-oxazolin-5-one, 33, in 330 mL of dry hexane was irradiated through a vycor filter for a period of 2.5 h. Solvent removal under reduced pressure gave a yellow liquid (presumably N-(1-methylbenzylidene)acetamide), which had an NMR spectrum containing singlets at δ 2.1 (3H), and multiplets at δ 7.0-7.4 (4.5H) and 7.6-7.8 (2H, in addition to broad high-field signals attributed to polymeric material. No acetophenone or N-(1-phenylvinyl)acetamide were observed. Treatment of an NMR sample of this material with slightly wet trifluoroacetic acid resulted in immediate formation of acetophenone and acetamide, identified by addition of authentic samples. Chromatography of 182 mg of the initial photolysis product on silica gel (Mallinckrodt CC-7), with methylene chloride elution, yielded a mixture containing 63 mg (54%) of acetophenone and 23 mg (15%) of N-(1-phenylvinyl)acetamide which had the following spectral data: NMR ($CDCl_3$) δ 2.1 (3H,s), 5.1 (1H,br s), 5.8 (1H,br s), 6.8-7.2 (1H,br s), 7.0-7.2 (5H,m). Irradiation of 2,4-dimethyl-4-phenyl-Δ^2-oxazolin-5-one in the presence of methyl acrylate gives, as the only additional product, polymethyl acrylate.

Similar irradiation of 167 mg of 33 in the presence of 86.6 mg (1.28 mmol) of trans-piperylene for 2.5 h followed by the same workup showed no starting material to be present. The combined yield of acetophenone and 37 was 53%. The concentration of piperylene was sufficient to reduce the quantum yield to 10% of its original value for a reactive lifetime of 10^{-7} s, assuming $k_{diff} = 2.7 \times 10^{10}$ for hexane.

Photolysis of 2,4-dimethyl-4-phenyl-Δ^2-oxazolin-5-one and reduction of products. A solution of 192 mg (1.015 mmol) of 2,4-dimethyl-4-phenyl-Δ^2-oxazoline-5-one, 33, in 320 mL of dry hexane was irradiated through a vycor filter for a period of 2 h. Solvent removal under reduced pressure gave 196 mg of a yellow oil. The oil was dissolved in 50 mL of dry tetrahydrofuran, 110 mg (2.9 mmol) of sodium borohydride was added, and the solution was heated at reflux temperature for 18 h. The solution was allowed to cool and quenched with water, and then methylene chloride and more water were added. The organic layer was removed, washed once with 0.1 M HCl, dried over sodium sulfate, and filtered, and the solvent was removed to yield 165 mg of a yellow oil. The oil was chromatographed on a silica gel column (Mallinckrodt CC-7) using 2% methanol/methylene chloride elution. One band came off, which consisted of a mixture of N-(1-phenylethyl)acetamide (identified by its NMR spectrum) and polymeric material. NMR analysis of the mixture using dioxane as an internal standard indicated a yield of 41% of N-(1-phenylethyl)acetamide, which had the following NMR spectrum; ($CDCl_3$) δ 1.5 (3H,d), 1.9 (3H,s), 4.95 (1H,quintet), 6.5-7.0 (1H,br s), 7.1 (5H,m).

Photolysis of 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (9). A solution of 205 mg (0.843 mmol) of 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazoline-5-one, 9, and 2 mL of methyl acrylate in 230 mL of dry acetonitrile was irradiated for 8 h through a vycor filter. Solvent removal at reduced pressure followed by silica gel chromatography (Mallinckrodt CC-7) with methylene chloride elution gave 105 mg of a mixture containing, by NMR analysis, 52% and 34% of the cis and trans-2-

fluoromethyl-4-carbomethoxy-5-methyl-5-phenyl-Δ^1-pyrrolines, respectively. The remainder of the material, 14% was acetophenone. By repeated silica gel chromatography, eluting with methylene chloride, a pure sample of the cis pyrroline was obtained, having the following spectral data: NMR ($CDCl_3$) δ 1.85 (3H,s), 3.1 (3H,s), 2.9-3.7 (3H,m), 7.0-7.2 (5H,m); ir (neat) 1740 (vs), 1440 (m), 1200 (vs), 1150 cm^{-1} (vs); mass spectrum (70 eV) m/e (rel. intensity) 285 (28), 270 (11), 266 (6), 254 (6), 226 (42), 199 (57), 198 (25), 104 (100), 103 (88), 91 (15), 77 (57).

Anal. Calcd for $C_{14}H_{14}F_3NO_2$: C, 58.95; H, 4.95; N, 4.91. Found: C, 58.92; H, 5.07; N, 4.98.

By the same method a small portion of the pure trans isomer was also obtained, having the following spectral data: NMR ($CDCl_3$) δ 1.48 (3H,s), 2.8-3.6 (3H,m), 3.7 (3H,s), 7.0-7.2 (5H,m); mass spectrum (70 eV) m/e (rel. intensity) 285 (50), 270 (18), 266 (11) 254 (16), 226 (76), 199 (100), 198 (46), 179 (21), 104 (92), 103 (82), 91 (17), 77 (58).

Photolysis of 177.5 mg of 9 in the presence of 152.5 mg (2.24 mmol) of trans-piperylene in 230 mL of acetonitrile for 6.25 h followed by the same workup gave the same products in essentially identical yields. The concentration of quencher was sufficient to reduce the quantum yield to 10% of its original value if the reactive lifetime were 10^{-7}s, assuming $k_{diff} = 1 \times 10^{10}$ for acetonitrile.

Thermolysis of 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one (9). A solution of 143 mg (0.588 mmol) of 4-methyl-4-phenyl-2-trifluoromethyl-Δ^2-oxazolin-5-one, 9, in 5 mL of dry xylenes was heated at reflux temperature for a period of 20 h under a nitrogen atmosphere. Solvent removal under reduced pressure yielded a mixture containing, by NMR

analysis, 6.7 mg (9.6%) of acetophenone, 21 mg (15%) of starting material, and 83 mg (66%) of N-(1-phenylvinyl)trifluoroacetamide, which had the following spectral data: NMR ($CDCl_3$) δ 5.3 (1H,br s), 5.8 (1H,br s), 6.8-7.6 (1H,br s), 7.2 (5H,s) (signals assigned to acetophenone and starting material were also present); mass spectrum (70 eV) m/e (rel intensity)[74] 216 (11.5), 215 (100), 146 (75), 120, 118 (13), 105, 104 (38), 103 (96), 91 (58), 77, 69 (52), 51; ir (neat) 3300 (s), 3050 (m), 1720 (vs), 1310 (vs), 1160 cm^{-1} (vs). On standing for several weeks, the enamide hydrolyzed completely to acetophenone.

PART 2

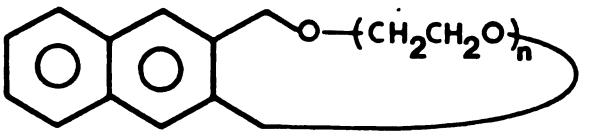
THE ^{13}C NMR SPECTRA OF NAPHTHALENE CROWN ETHER COMPLEXES: FIELD INDUCED π POLARIZATION AND CROWN ETHER CONFORMATIONAL CHANGES

Introduction

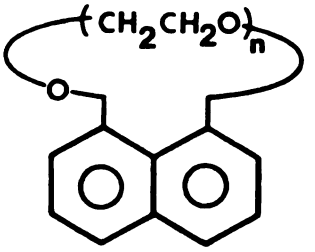
In recent years crown ethers have found a wide variety of uses, ranging from catalysis in organic reactions to models for ion transport in biological systems.[75] Information about the properties of crown ethers, such as conformation and complexation constants has therefore become important. Recently a series of naphthalene crown ethers has been used to study photo-excited state behavior, with specific emphasis on the perturbation of excited states by complexed cations.[76] With the hope of obtaining information which might assist in interpretation of photophysical behavior I undertook a study of the ^{13}C NMR spectra of these crowns and their complexes.

The crown ethers studied are shown in Figure 1. An important structural feature of these crown ethers is the one-carbon bridge between the naphthalene ring and first ether oxygen. This bridge minimizes direct resonance interaction of the naphthalene π system and the crown ether and any complexed ions.

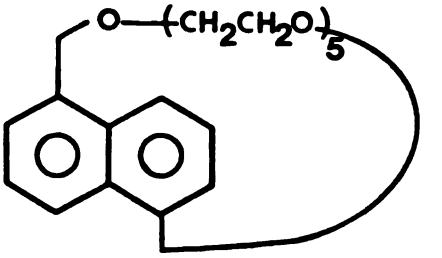
The kinds of information which might be obtained from this study fall into two classes. The first relates to the perturbation of the aromatic ring (mainly the π system) by a complexed ion. Changes in chemical shifts of aromatic systems have been extensively studied, and these changes are frequently related to charge density changes.[78] Crown ethers 42 through 48 should offer a unique opportunity to study these perturbations due to the known location of the perturbing cation, and its insulation from the aromatic ring by the sp^3 carbon atom. The second kind of information is the conformational changes in the crown ether ring of both the complexed and uncomplexed crown ether. Since



42 n=3, 2,3-Cr-4
43 n=4, 2,3-Cr-5
44 n=5, 2,3-Cr-6



46 n= 5,1,8-Cr-6
47 n= 4,1,8-Cr-5
48 n= 3,1,8-Cr-4



45, 1,5-Cr-6

Figure 1. Crown Ethers Studied by ^{13}C NMR Spectroscopy.

saturated carbon chemical shifts are sensitive to conformational changes, there is hope that some questions relating to conformation might be answered.

Methods and Results

The ^{13}C NMR spectra of crown ethers 42 through 46 were measured with increasing concentrations of alkali and alkaline earth metal salts in deuteromethanol. Chemical shifts initially were measured relative to the deuteromethanol signal at δ 47.00 ppm. It was discovered, however, that this chemical shift depended on salt concentration at high concentrations of some salts. An external aqueous acetic acid reference line was then used. For the alkali metals, the acetate salts were used as they were quite soluble in methanol and did not shift the methanol reference. For calcium and barium, the chloride and bromide salts were used, respectively, for solubility reasons, although they did shift the internal reference signal.

Titrations of the crown ethers with most salts show a clear bend near the equivalence point, and in most cases complexation is complete when the salt/crown ratio is > 2-3. Titration curves for crown ethers 42 through 46, are shown in Figures 2 through 9. Spectra of the crown ethers with less than an equivalent of salt show only one signal per carbon, indicating the rate of complexation is fast on the NMR time scale.[79] As expected, the crown 6's, 44 and 46, complex well with all the alkali metal and calcium and barium salts (Figures 2,3,6, and 7).[80] One spectrum of 2,3-Cr-6 with a 5-fold excess of lithium chloride indicated no complexation. The smaller crown, 2,3-Cr-5, 43, also complexed well with the same ions except for calcium

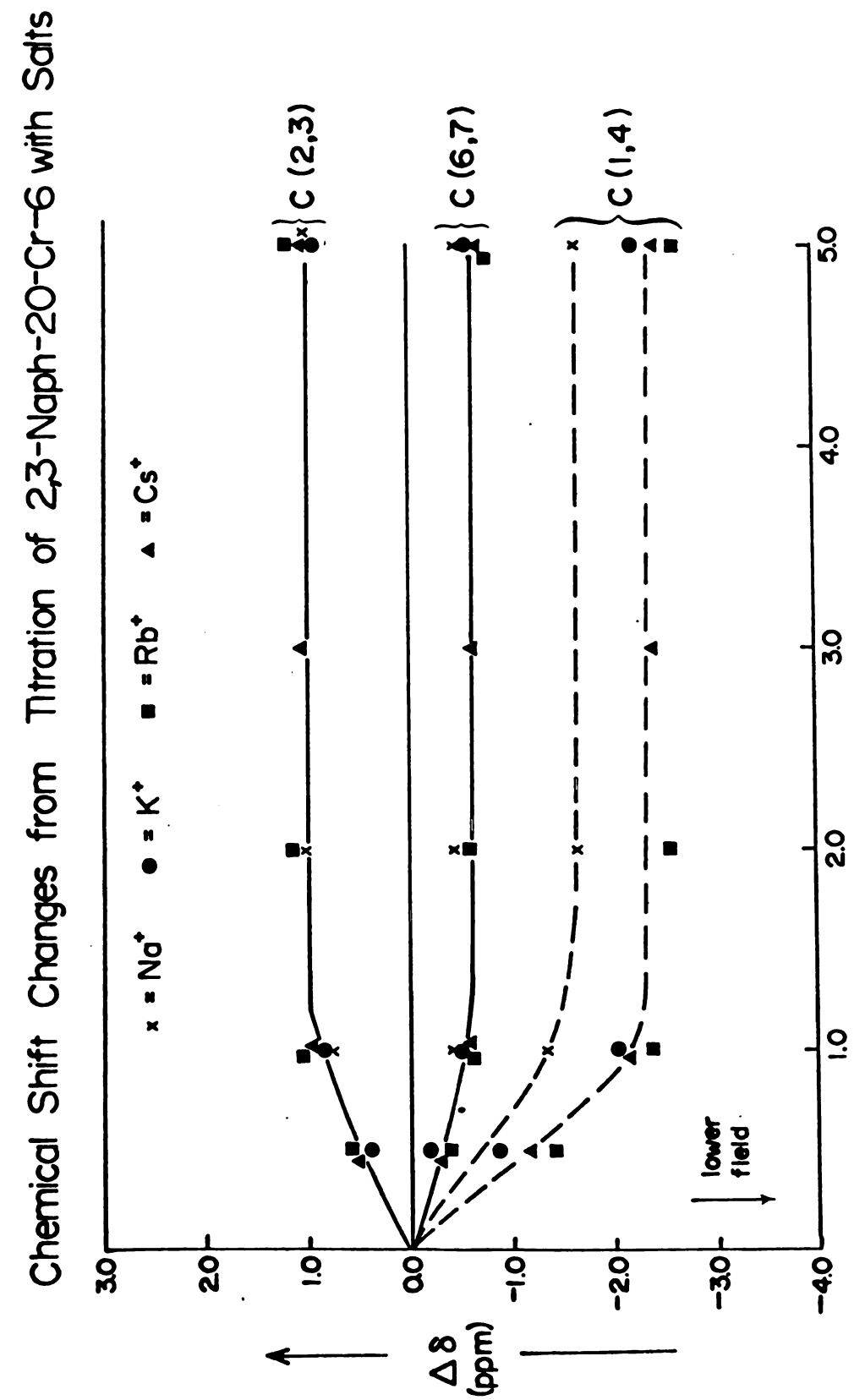


Figure 2. Chemical Shift Changes from Titration of 2,3-Naph-20-Cr-6 with Alkali Metal Salts in Deuteromethanol at Room Temperature. Crown Ether Concentration is ~0.2 M.

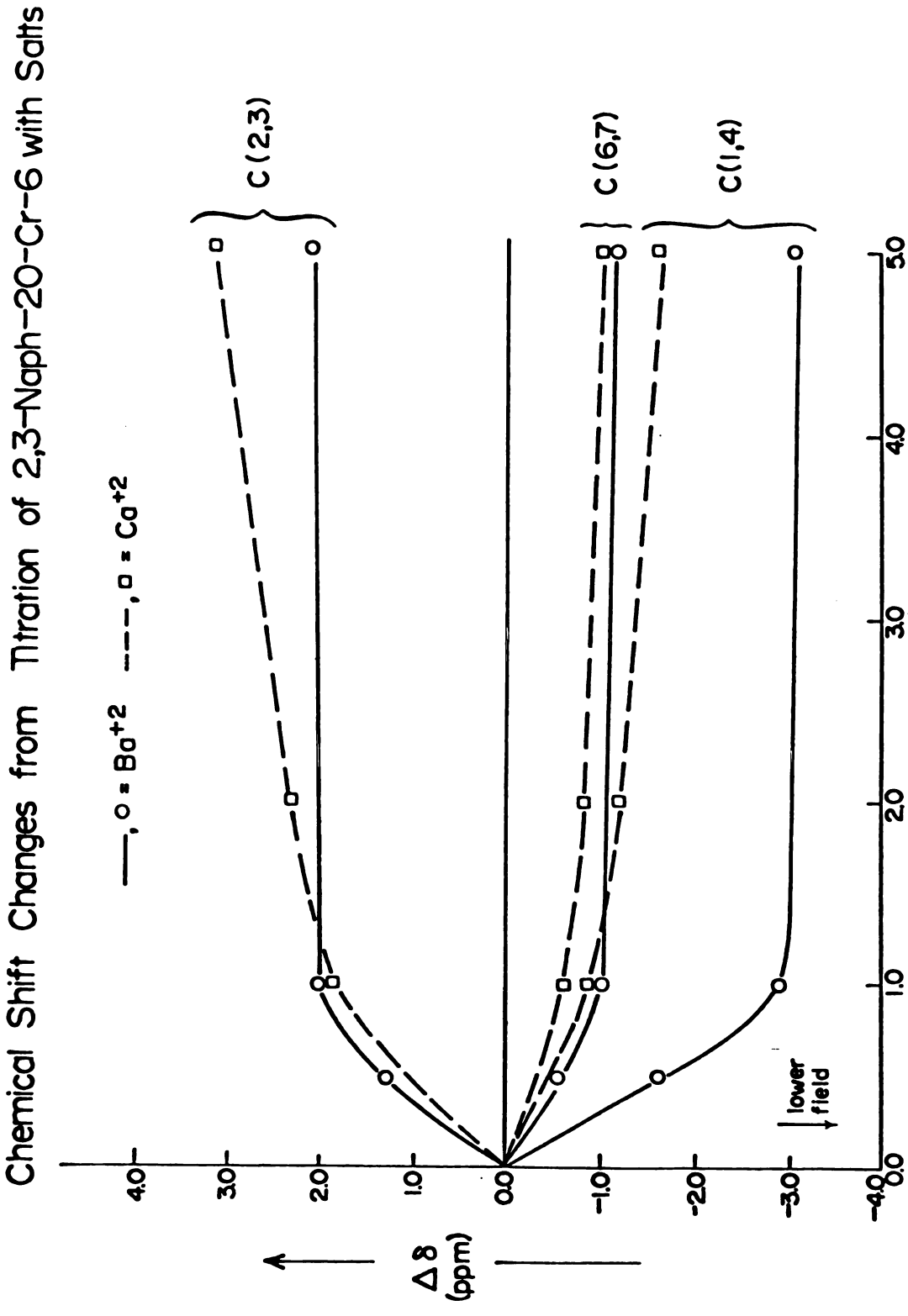


Figure 3. Chemical Shift Changes from Titration of 2,3-Naph-20-Cr-6 with Barium and Calcium Salts in Deuteromethanol at Room Temperature. Crown Concentration is ~0.2 M.

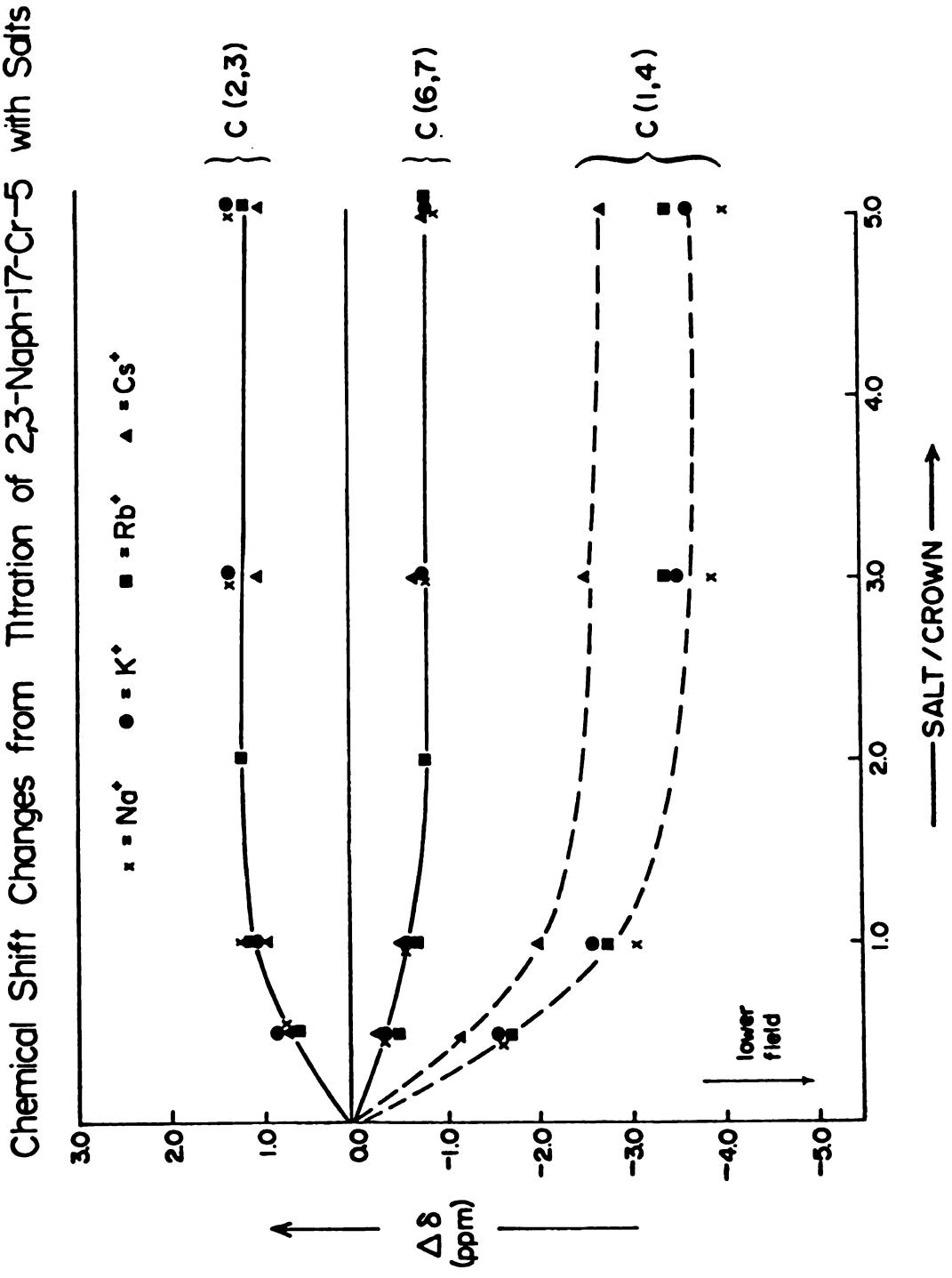


Figure 4. Chemical Shift Changes from Titration of 2,3-Naph-17-Cr-5 with Alkali Metal Salts in Deuteromethanol at Room Temperature. Crown Ether Concentration is ~0.2 M.

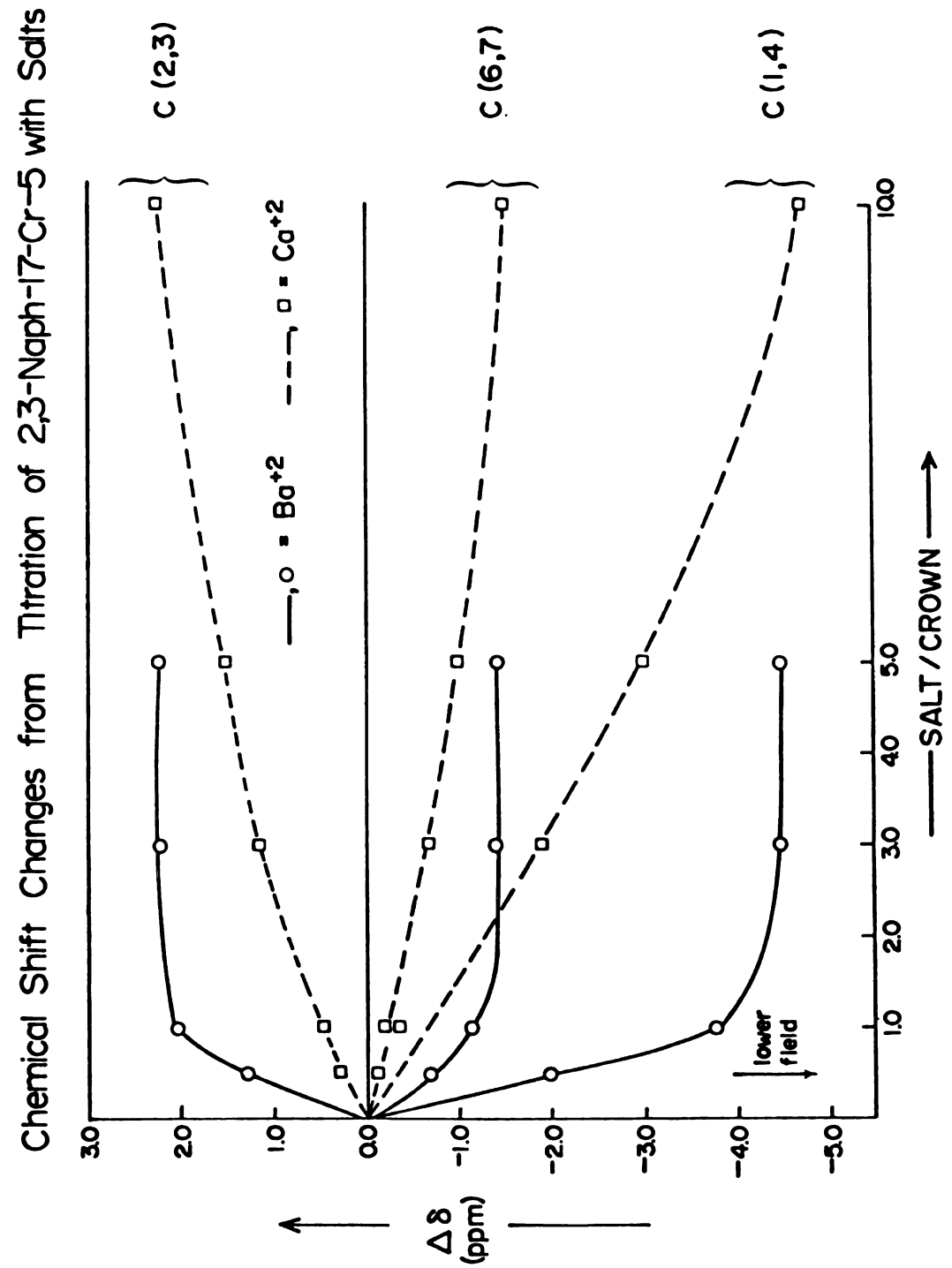


Figure 5. Chemical Shift Changes from Titration of 2,3-Naph-17-Cr-5 with Barium and Calcium Salts in Deuteromethanol at Room Temperature. Crown Ether Concentration is ~0.2 M.

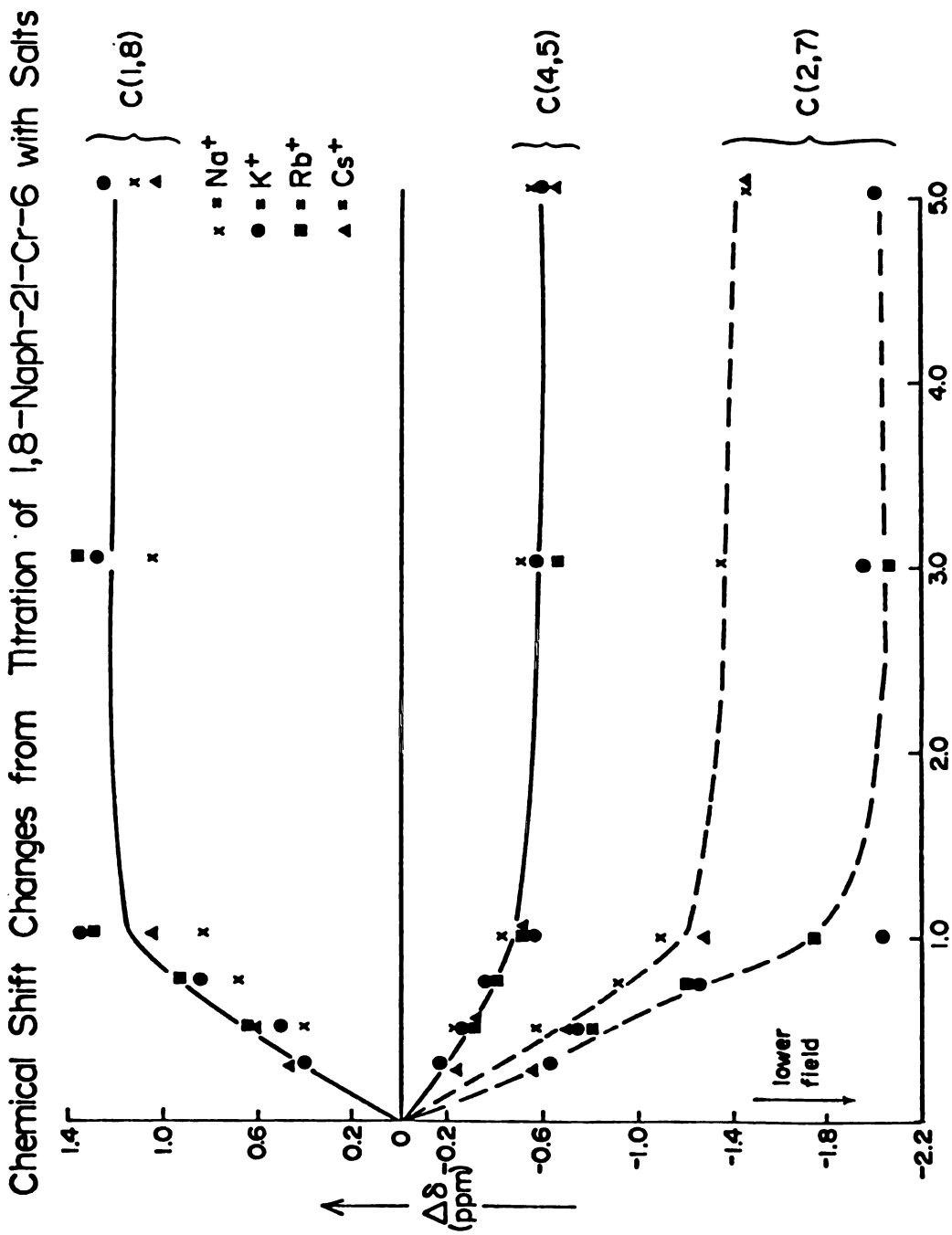


Figure 6. Chemical Shift Changes from Titration of 1,8-Naph-21-Cr-6 with Alkali Metal Salts in Deuteromethanol at Room Temperature. Crown Ether Concentration is ~0.2 M.

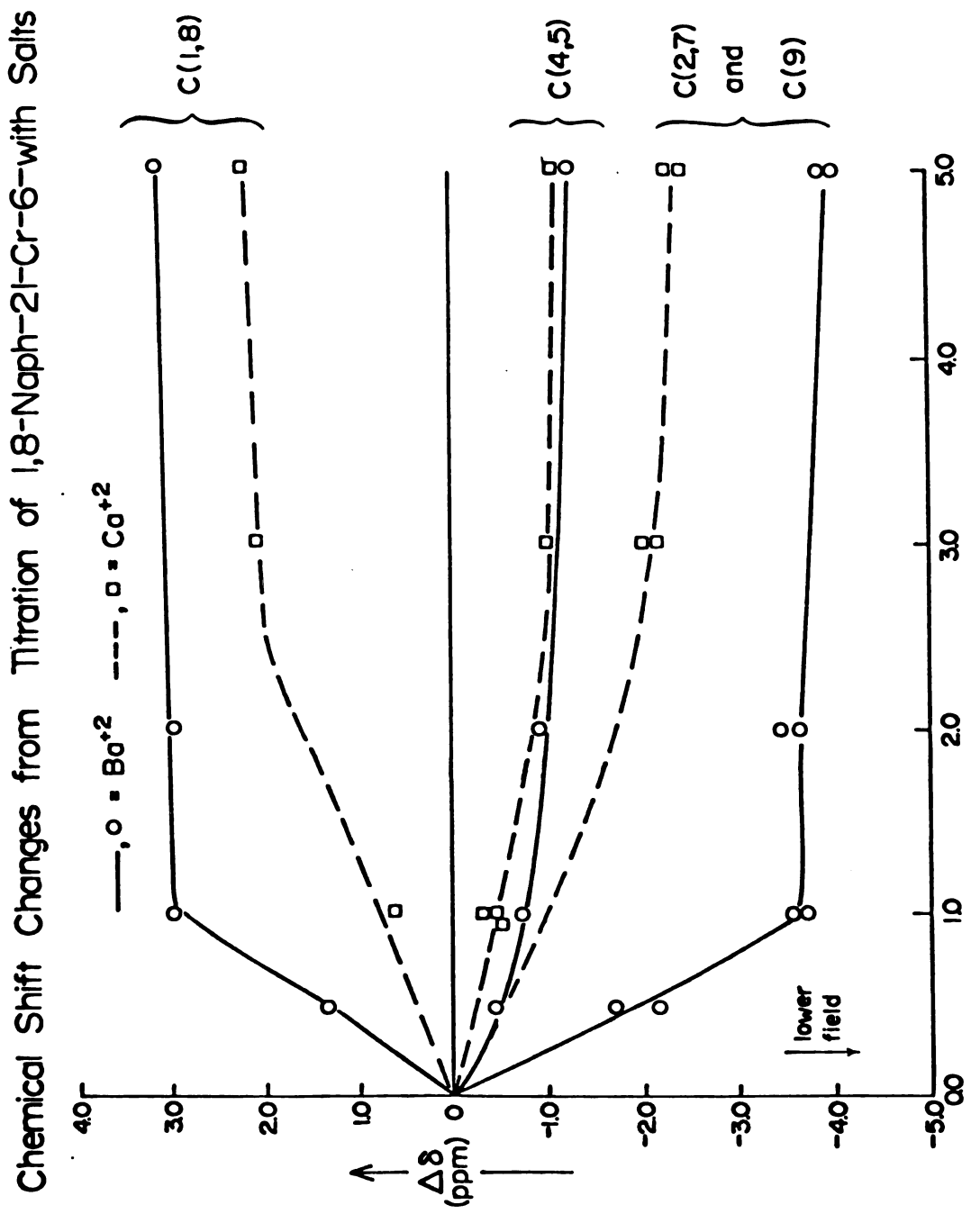


Figure 7. Chemical Shift Changes from Titration of 1,8-Naph-21-Cr-6 with Barium and Calcium Salts in Deuteromethanol at Room Temperature. Crown Ether Concentration is ~0.2 M.

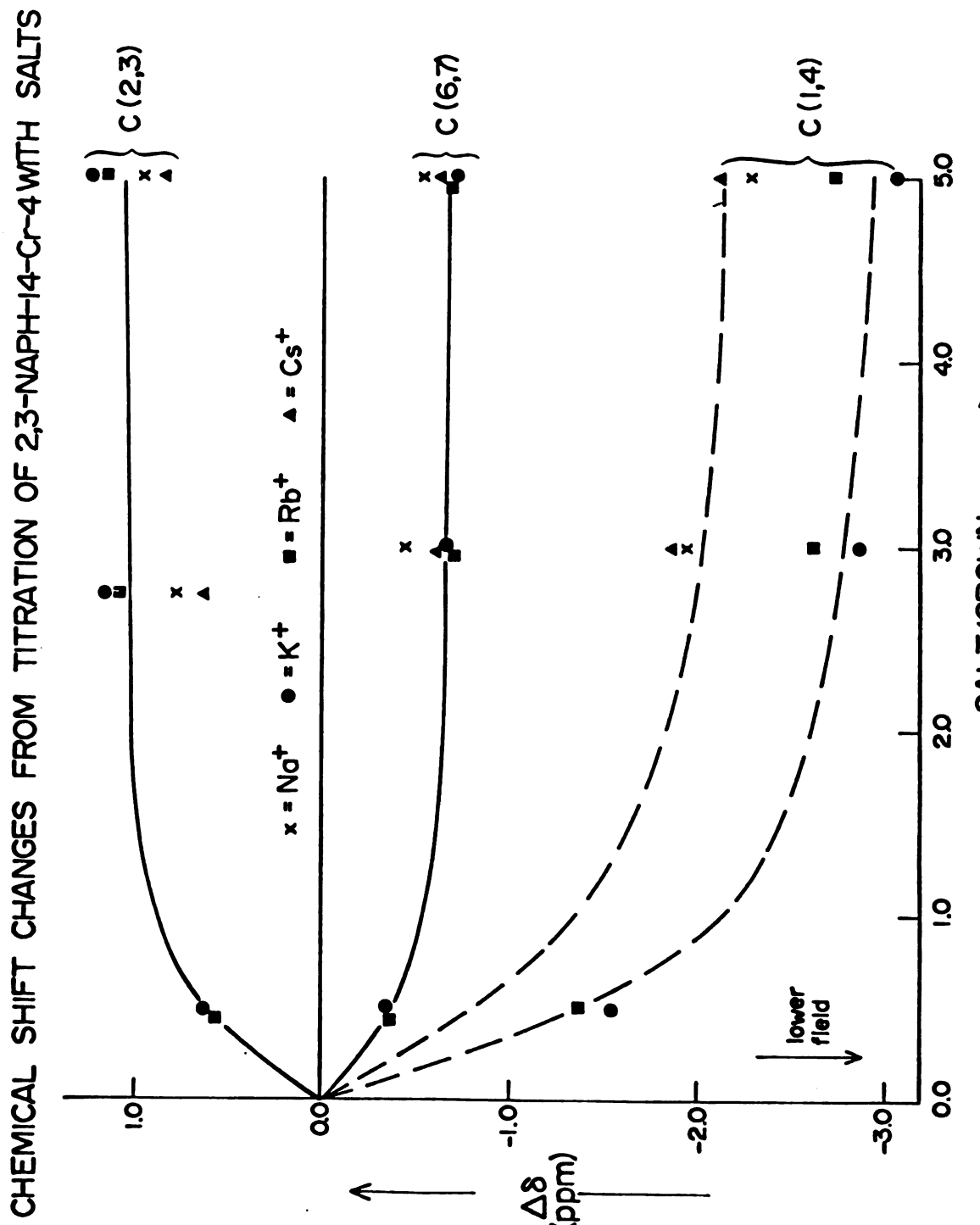


Figure 8. Chemical Shift Changes from Titration of 2,3-Naph-14-Cr-4 with Alkali Metal Salts in Deuteromethanol at Room Temperature. Crown Ether Concentration is ~0.2 M.

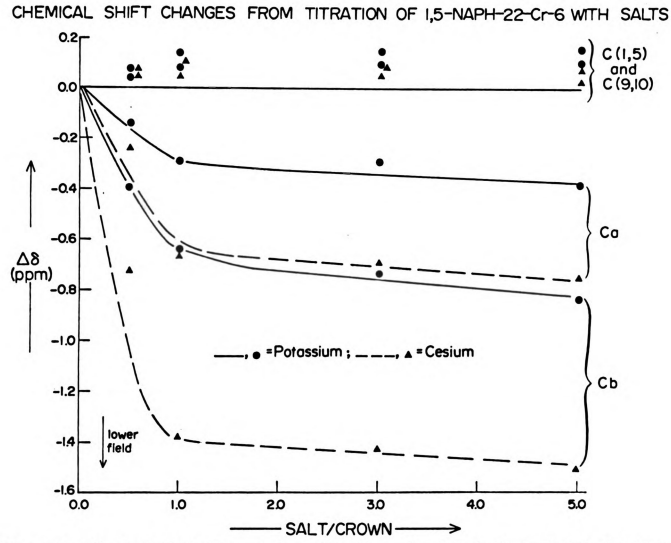


Figure 9. Chemical Shift Changes from Titration of 1,5-Naph-22-Cr-6 with Alkali Metal Salts in Deuteromethanol at Room Temperature. Crown Ether Concentration is ∿0.2 M.

(Figures 4 and 5). The shift changes with a 10-fold excess of calcium chloride may be limiting, but haven't been shown to be. This result with a crown-5 and calcium is not unexpected.[80] The smallest crown ether, 2,3-Cr-4, 42, also complexes adequately with all of the alkali metal ions tried, including cesium (Figure 8). No experiments with calcium or barium salts and 2,3-Cr-4 were performed. Limiting behavior with 1,5-Cr-6, 45, was also observed, with potassium, rubidium, and cesium salts (Figure 9). No experiments were done with sodium, calcium, or barium. The spectra of 1,8-Cr-5, 47, and 1,8-Cr-4, 48, were taken without any salts present, but no spectra have been taken yet with any ions present.

Assignments of the carbon signals were made based on three kinds of information. The naphthalene ring assignments were made initially based on the assignments reported for 2,3-dimethylnaphthalene[81] and 1,8-dimethylnaphthalene.[82] These were confirmed by ytterbium shift studies and ^{1}H-^{13}C coupling experiments. The relative shifts of sets of equivalent carbons in 2,3-Cr-6, 44, with $Yb(dpm)_3$ are; C(2,3) 1.0, C(1,4) 0.66, C(9,10) 0.33, C(5,8) 0.13, C(6,7) 0.11 These shifts should be proportional to the distance of the carbon from the paramagnetic ion, as is observed.[83] For the 1,8-Cr-6, the relative $Yb(dpm)_3$ induced shifts are C(1,8) 1.0, C(2,7) 0.82, C(4,5) 0.68, C(3,6) 0.68. For both of these crowns these spectra were taken in deuterochloroform, and the shifts are relatively small due to poor complexation of the crown by the ytterbium ion. In one case, not all carbon signals are observed. The assignments for the crown-5's and crown-4's were extrapolated from the crown-6 assignments. No assignments for the naphthalene carbons of 1,5-Cr-6, 45, were made.

The naphthylic carbons in each crown ether were also assigned. Initial assignments were based on the expectation that the naphthylic carbons would resonate at lower field than the other sp^3 carbons. In some cases, such as 2,3-Cr-5, 43, this signal was uncomfortably close (<0.1 ppm) to one of the other methylene carbons, so the assignments were confirmed by deuterium labeling. Treatment of the crown ethers with butyllithium in dimethyl sulfoxide-d_6 exchanged the naphthylic hydrogens. In each case tried, the initial assignment was correct. These experiments were performed on 2,3-Cr-6, 44, 1,8-Cr-6, 46, 2,3-Cr-5, 43, 2,3-Cr-4, 42, and all the complexes of 2,3-Cr-5.

The spectra of each of the crown ethers and their complexes, including assignments and correlations are shown in Figures 10-14. The spectra of a series of 1,8-disubstituted naphthalenes and 2,3-disubstituted naphthalenes are shown in Figures 15 and 16, respectively.

Aromatic Carbon Shifts

Chemical shift changes in substituted aromatic systems are generally thought of in terms of classical substituent effects, and, in fact, these shift changes have been used to investigate the existence and/or magnitude of some of these effects.[84] One substituent effect which has received some attention recently is field induced π polarization. This kind of perturbation is defined as a change in the distribution of π electrons, induced by a nearby monopole or dipole, which does not involve transfer of electrons or charge into or out of the π system.[84] This has been incorrectly called the π inductive effect several times in the recent literature.[85] Not long ago, it had been suggested that field induced π polarization was an

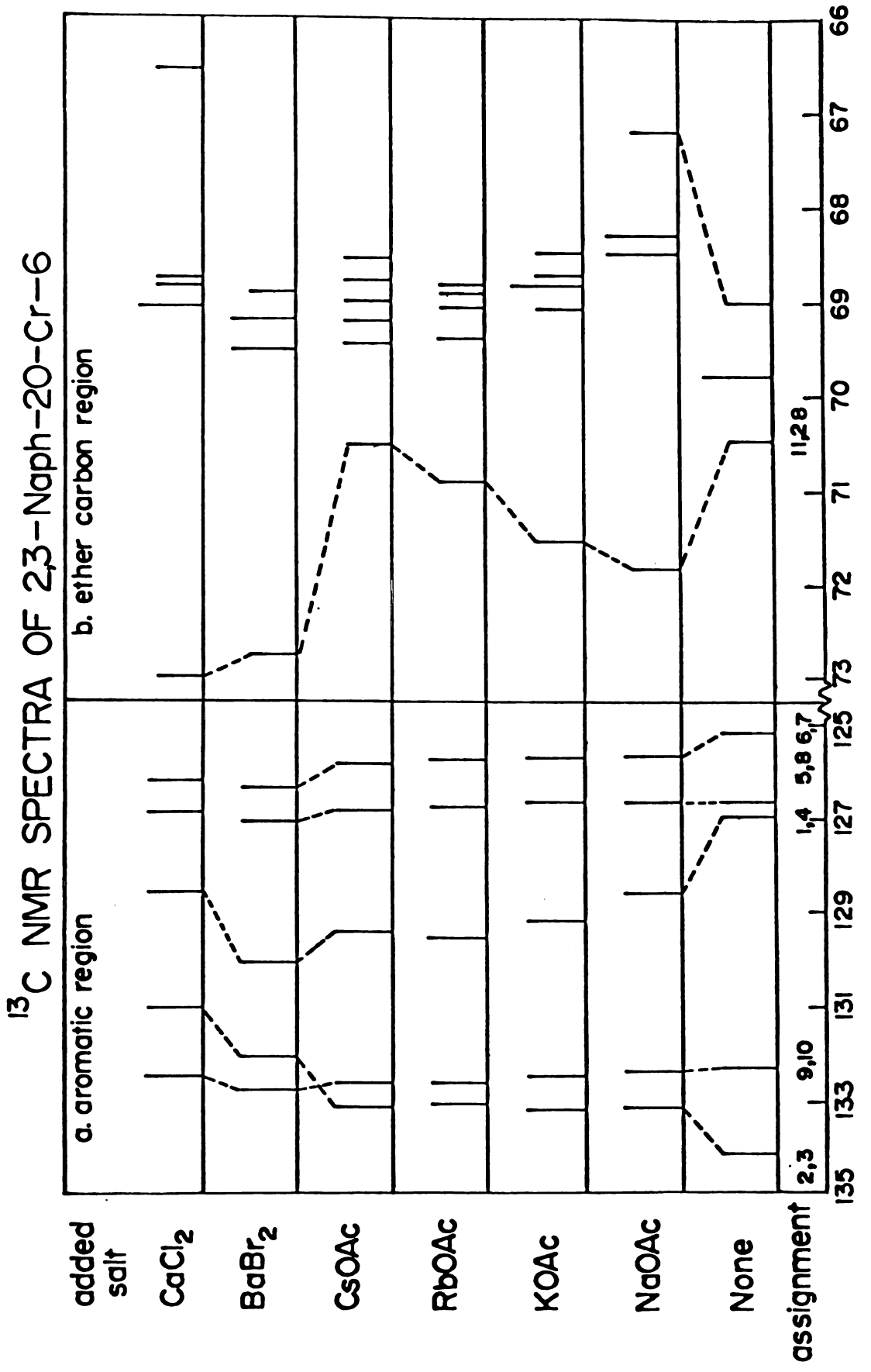


Figure 10. ^{13}C NMR Spectra of 2,3-Naph-20-Cr-6 and 1:1 Complexes in Deuteromethanol at Room Temperature. Crown Ether Concentrations are ~0.2 M.

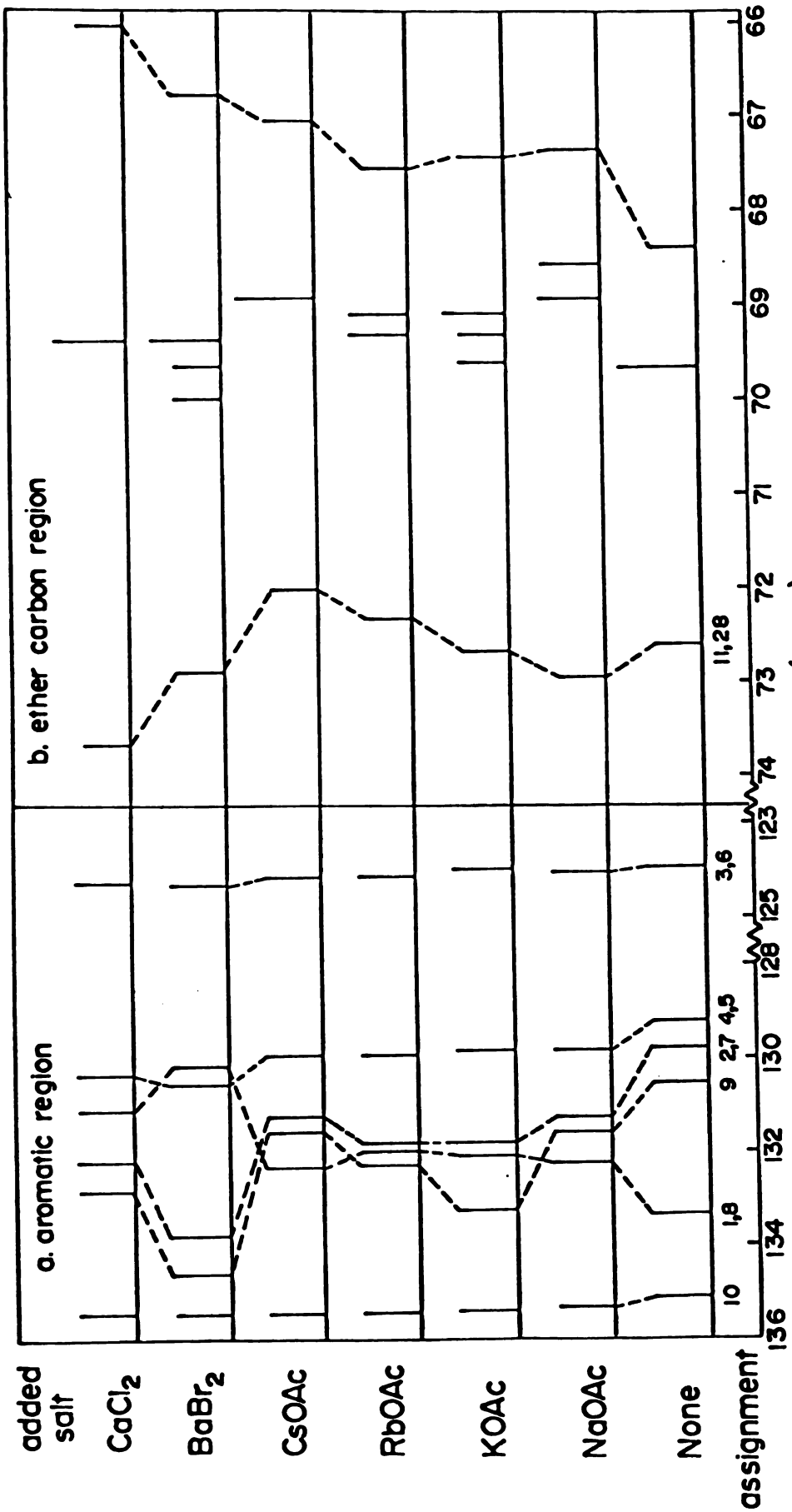


Figure 11. ^{13}C NMR Spectra of 1,8-Naph-21-Cr-6 and 1:1 Complexes in Deuteromethanol at Room Temperature. Crown Ether Concentrations are ~0.2 M.

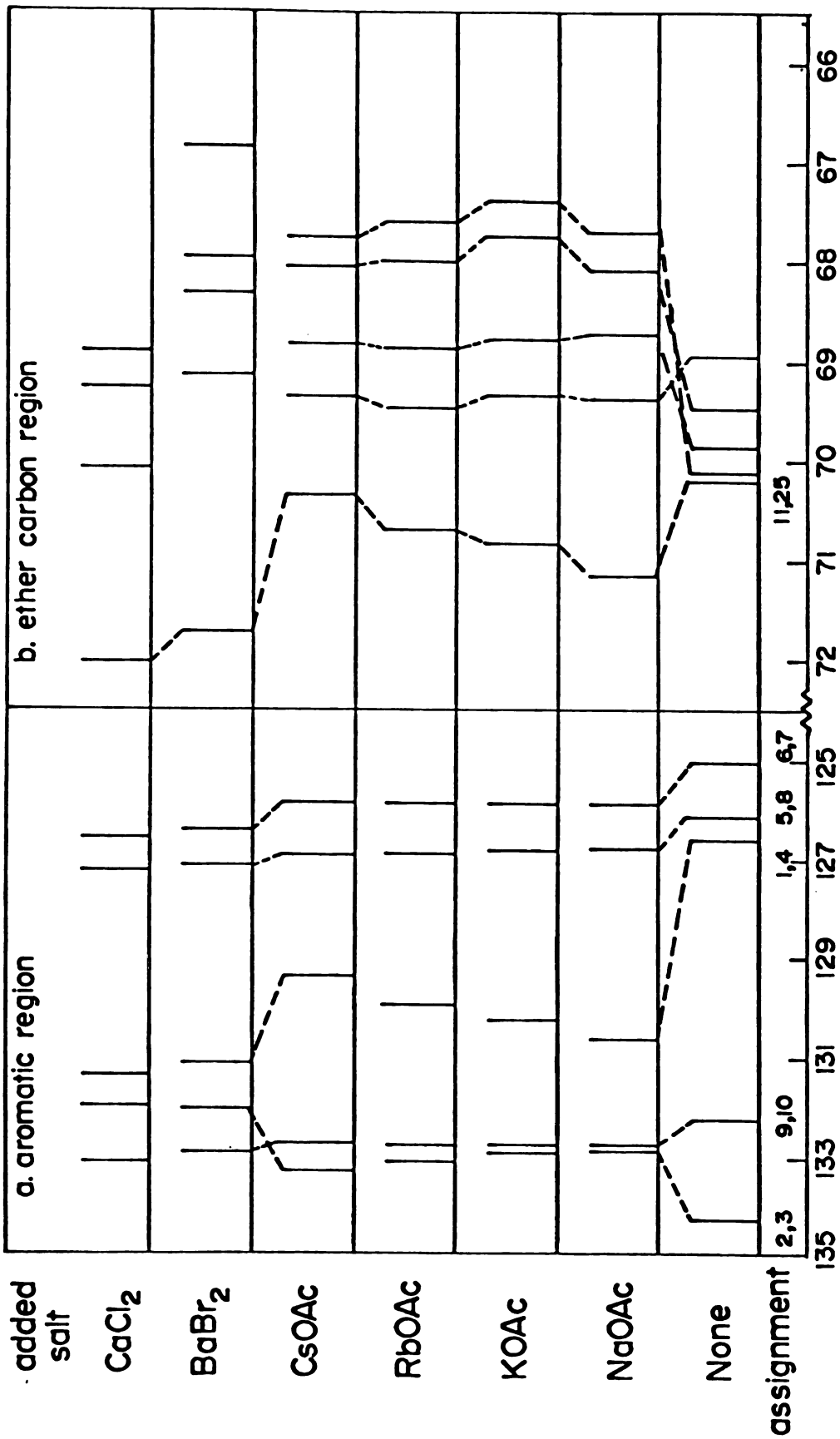


Figure 12. ^{13}C NMR Spectra of 2,3-Naph-17-Cr-5 and 1:1 Complexes in Deuteromethanol at Room Temperature. Crown Ether Concentrations are ~0.2 M.

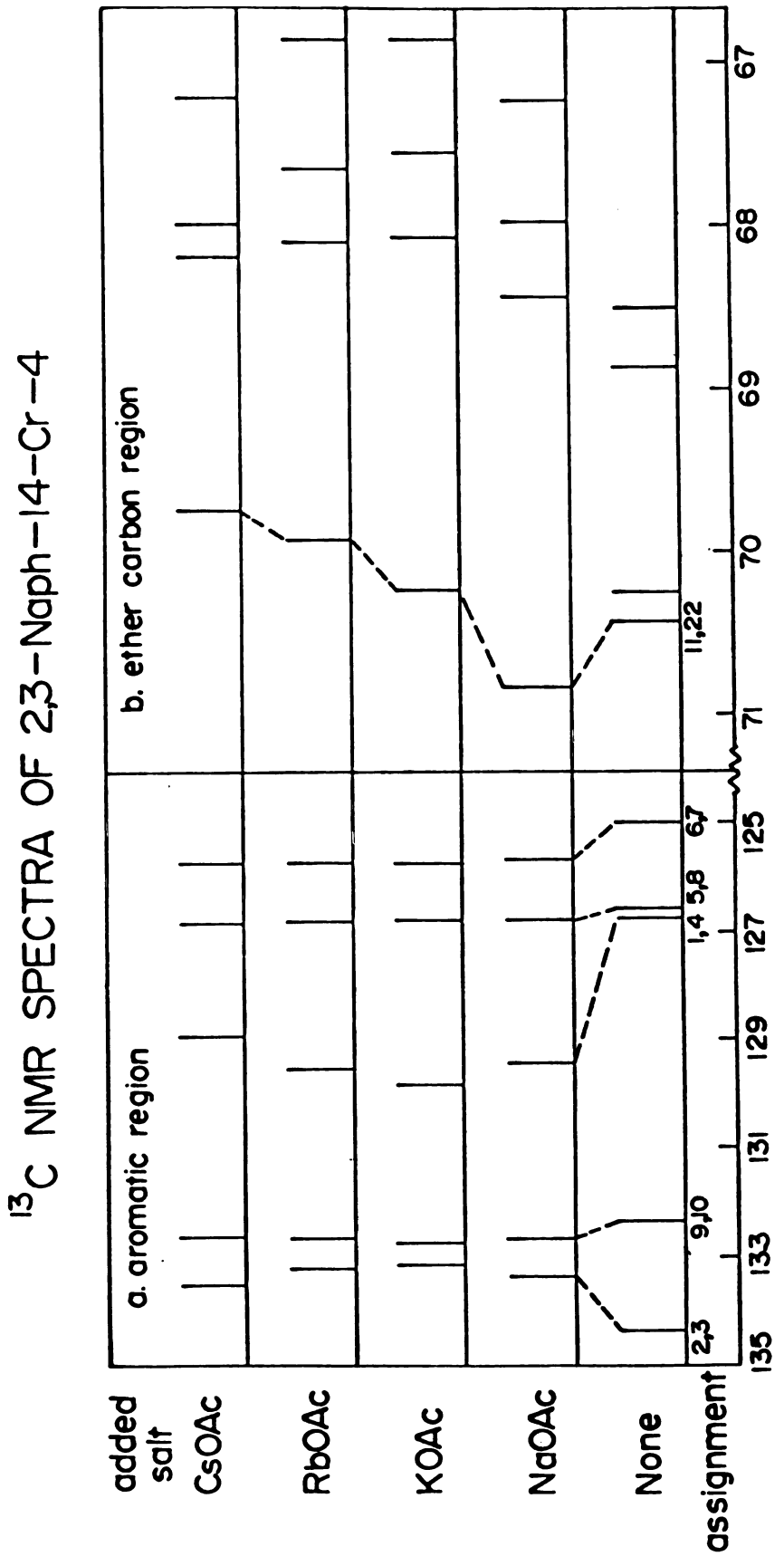


Figure 13. ^{13}C NMR Spectra of 2,3-Naph-14-Cr-4 and 1:1 Complexes in Deuteromethanol at Room Temperature. Crown Ether Concentrations are ~0.2 M.

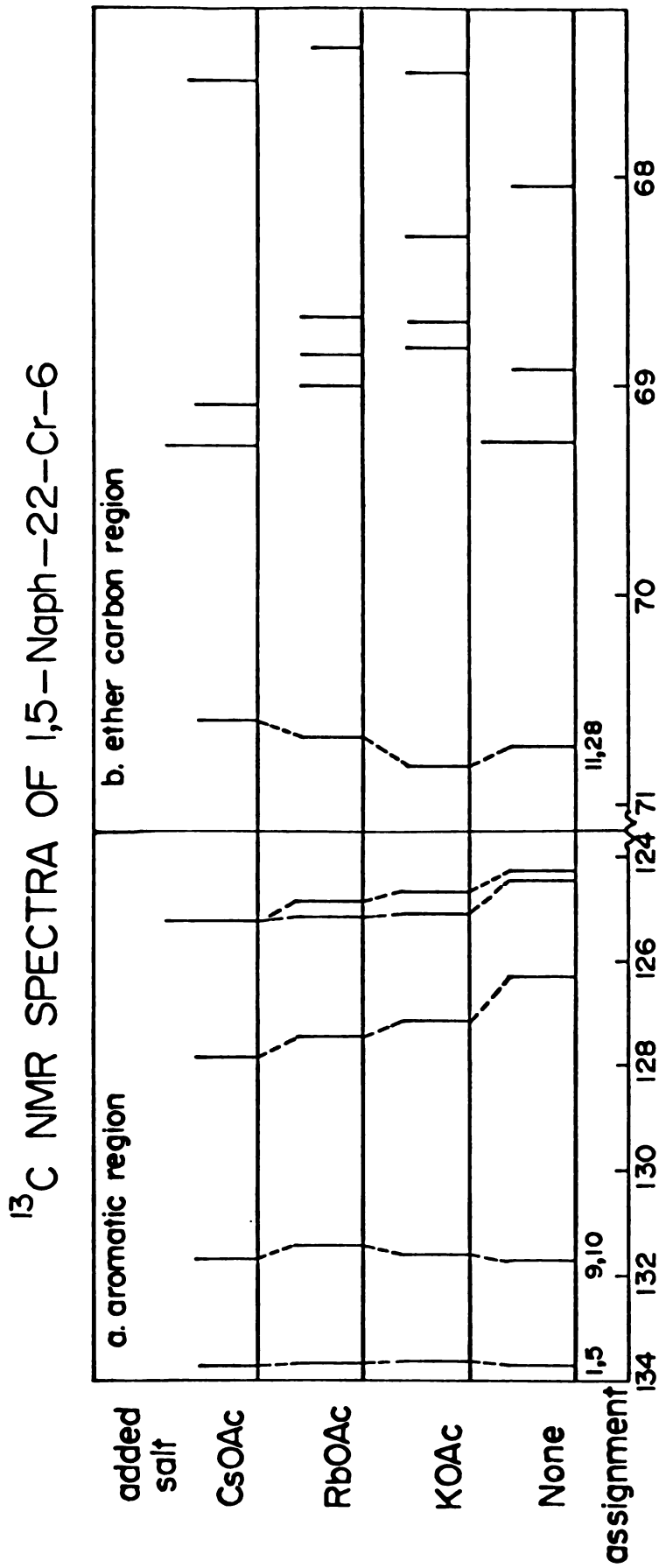


Figure 14. ^{13}C NMR Spectra of 1,5-Naph-22-Cr-6 and 1:1 Complexes in Deuteromethanol at Room Temperature. Crown Ether Concentrations are ~0.2 M.

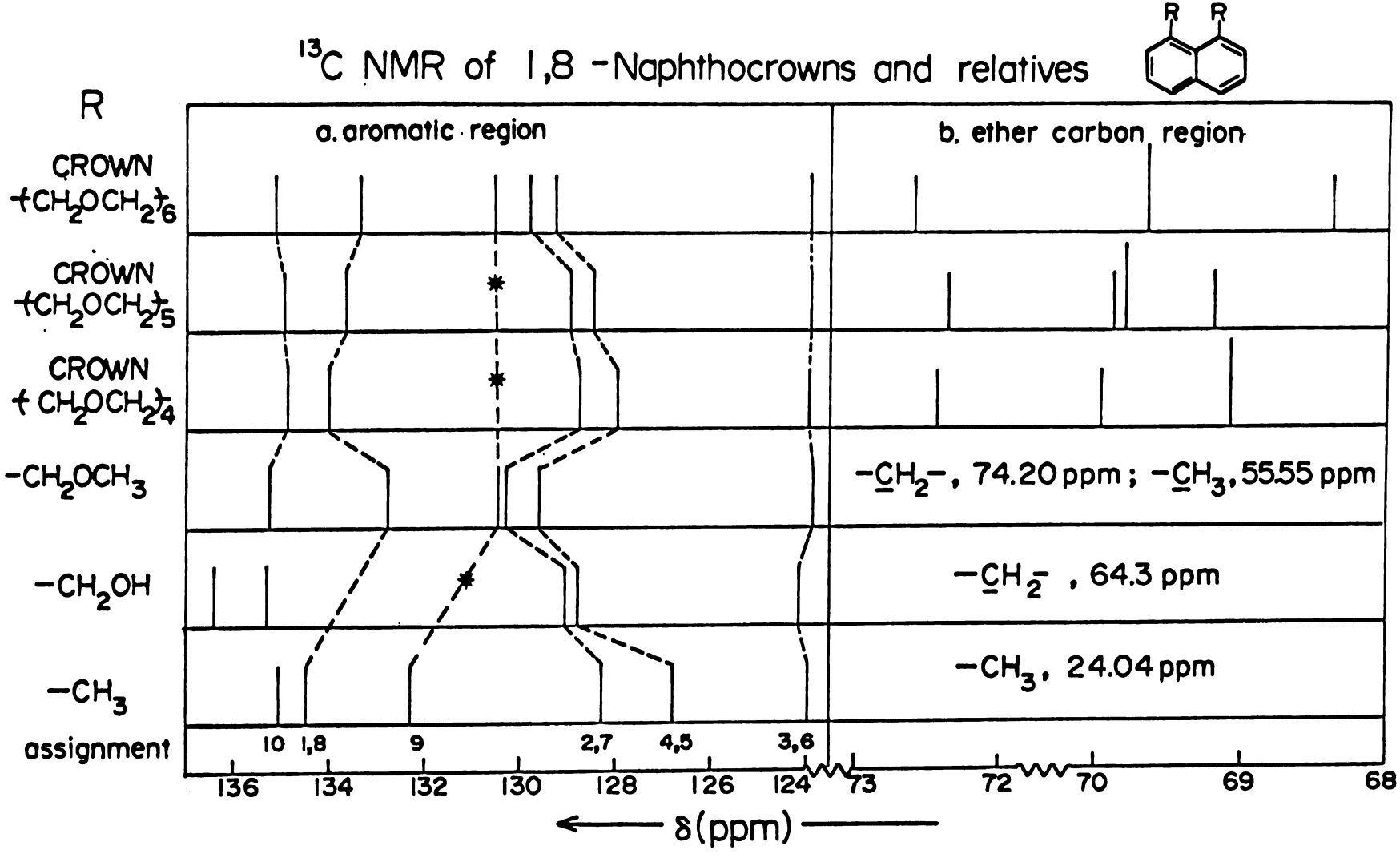


Figure 15. ^{13}C NMR Spectra of 1,8-Naphthocrowns and other 1,8-Disubstituted Naphthalenes in Deuteromethanol at Room Temperature.

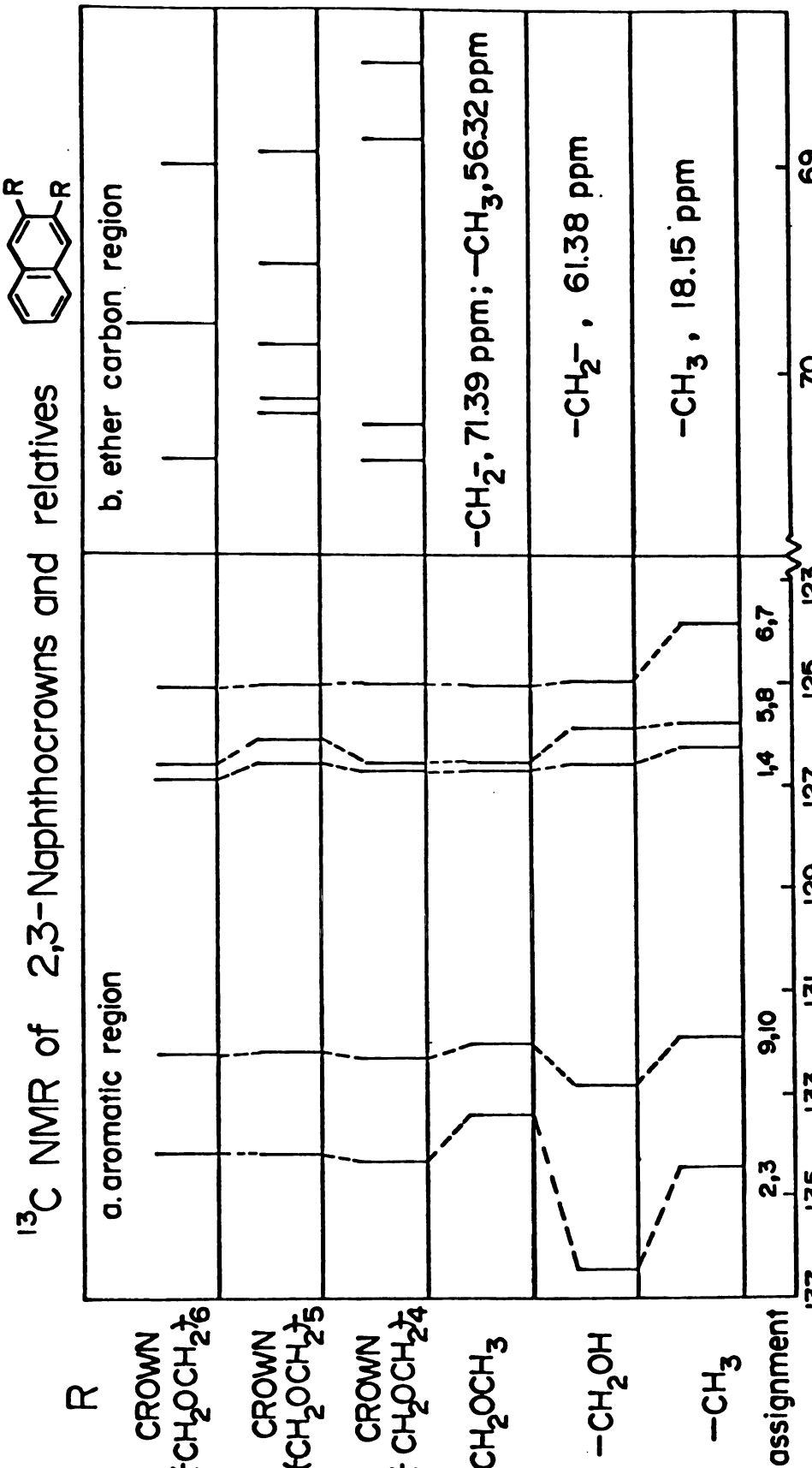


Figure 16. ^{13}C NMR Spectra of 2,3-Naphthocrowns and other 2,3-Disubstituted Naphthalenes in Deuteromethanol at Room Temperature.

unimportant mechanism for the transmission of substituent effects. However, two recent studies offer evidence to the contrary. The first of these studies involved examination of the ^{13}C NMR spectra of benzene rings substituted with alkyl groups with dipoles attached several atoms removed from the aromatic ring.[87] The second involved ^{13}C NMR spectra of phenyl substituted amino acids in which the chemical shifts of the aromatic carbons were measured at several different pH's.[88]

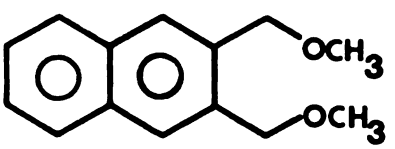
Crown ethers 42 through 48 offer several unique advantages for the study of this effect. The naphthalene crown ethers offer a more extensive and perhaps more general π system to be perturbed than substituted benzenes. The location of the monopole (the complexed ion) is known quite well, and can be varied such that polarization from either the C(2,3) side, the C(1,8) side, or the face can be effected. The distance of the ion from the aromatic system can be varied by changing the crown ring size, and the charge on the ion can also be varied.

These chemical shift changes in aromatic systems are often correlated with calculated charge density changes.[78] Frequently, good linear correlations are obtained, though not always. There is some theoretical justification for a linear charge density/chemical shift relationship.[89] However, the theoretical expressions for chemical shift changes are too complicated and not well enough understood to be useful. For this reason, most workers in this area attempt to explain chemical shifts in terms of charge density changes.

Examination of the NMR spectra of 2,3-Cr-6 and its complexes (Figure 10), reveals several interesting features. Except for C(1,4),

the aromatic shifts are the same for all of the plus one ions. These are, in turn, different from those of the plus two ion complexes. This indicates that the aromatic chemical shift changes are induced by the presence of a nearby charge, rather than some other property of the ion (C(1,4) shifts will be discussed later). The NMR spectra of 1,8-Cr-6 and its complexes (Figure 11), show the same behavior. Except for C(2,7) and C(9), the aromatic shifts are largely independent of the identity of the complexed plus one ion. Note that in each case the ipso carbon is shifted upfield, while all the other aromatic carbons are shifted downfield by complexation. This is what might be expected for field induced π polarization, which would build up electron density at the ipso carbons.

These shifts were correlated with charge density changes calculated at the INDO level. As the crown ether itself contained more atoms than the INDO program was equipped to handle, calculations were performed on the bis(methoxymethyl) compounds, 49 and 50, with and without ions present. For the 2,3-diether, 49, coordinates were



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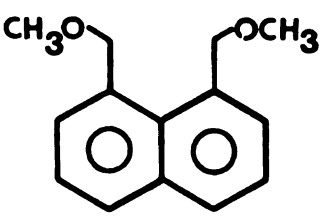

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taken from the x-ray crystal structure determination of the 2,3-Cr-6/K^+ complex.[90] For the 1,8-diether, 50, coordinates were taken from a preliminary x-ray crystal structure determination of 1,8-Cr-6.[91] Calculations were first done on 2,3-diether, 49, using standard

parameters for the plus one ion (Li^{+}). However, attempts to use a plus two ion (Be^{+2}), resulted in the SCF calculation diverging. The parameters for the ions were then adjusted to mimic a plus one or plus two monopole (see experimental section), and this allowed the calculations to work.

A plot of the calculated charge density changes on complexation versus the chemical shift changes for the 2,3-Cr-6 with a plus one ion is linear for both the conventional plus one ion and the adjusted plus one ion. Inclusion of both plus one and plus two ions for either or both the 2,3-Cr-6 and 1,8-Cr-6 results in satisfactory correlations also (Figure 17). Slopes and correlation coefficients for various plots are summarized in Table 5. Considering the quality of the calculations and the expected sensitivity of ortho carbon chemical shifts to steric effects (see below), the correlation is as good as might be expected. Note that C(9) of the 1,8-Cr-6 is way out of line, and is not included in the calculations of slope or correlation coefficient. The slopes of these plots mean very little in this case, as the use of "adjusted" ions, and the diethers rather than the entire crown ethers, should cause considerable changes in the magnitude of the charge density changes, although the relative magnitudes should stay nearly the same.

If the shifts of the aromatic carbons in the naphtho crown ethers are due to field induced π polarization, as predicted, we would expect the INDO calculations to show little π charge transfer into or out of the naphthalene ring. In fact, for 2,3-Cr-6 and 1,8-Cr-6, the π charge transfer is small. For 2,3-Cr-6 calculations the charge transfer is 15 millielectrons (me^{-}) out of the naphthalene,

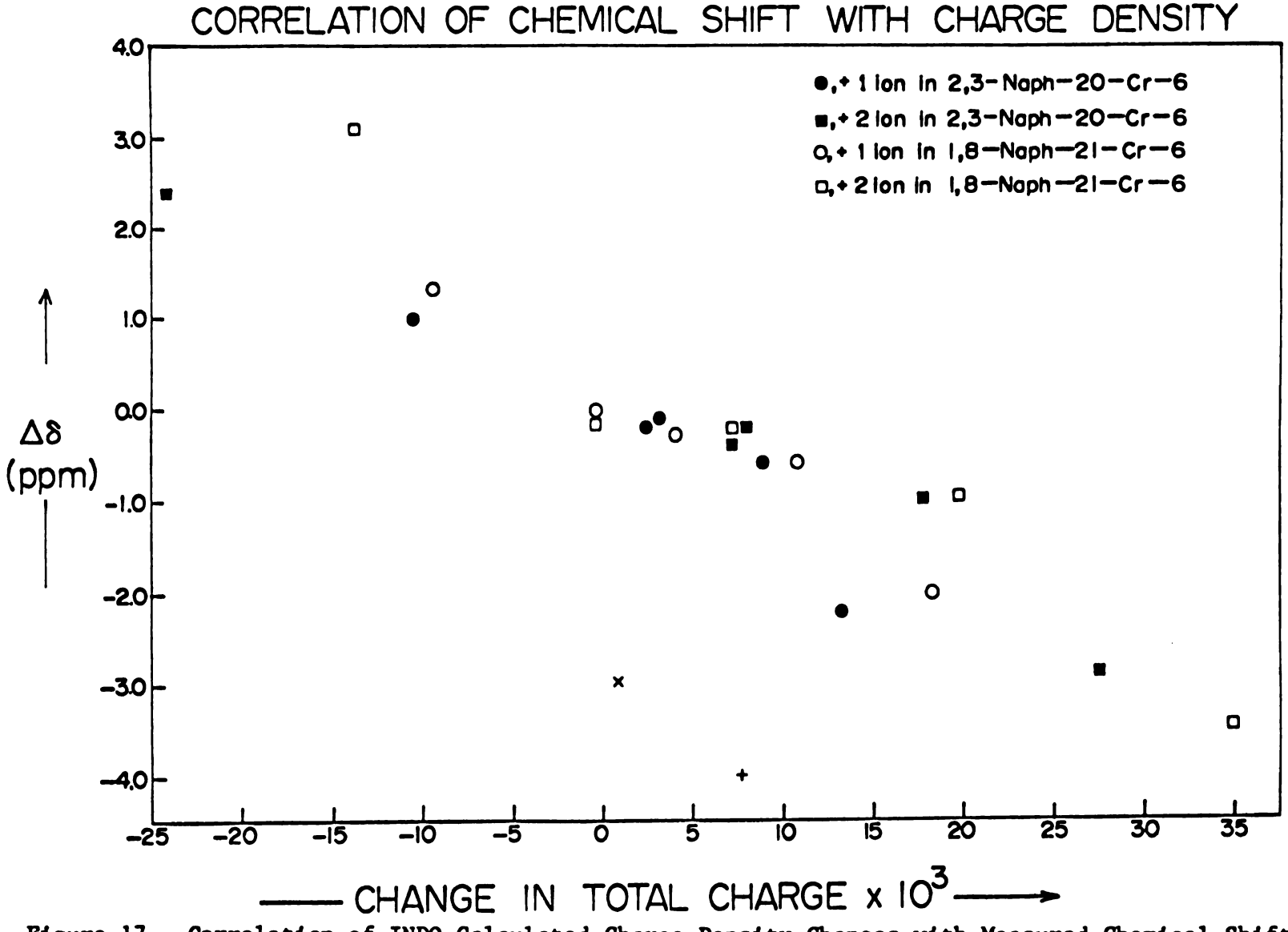


Figure 17. Correlation of INDO Calculated Charge Density Changes with Measured Chemical Shift Changes for Potassium and Barium Complexes of 2,3-Naph-20-Cr-6 and 1,8-Naph-21-Cr-6 in Deuteromethanol. x and + are C(9) of Potassium and Barium Complexes of 1,8-Naph-21-Cr-6, Respectively.

Table 5

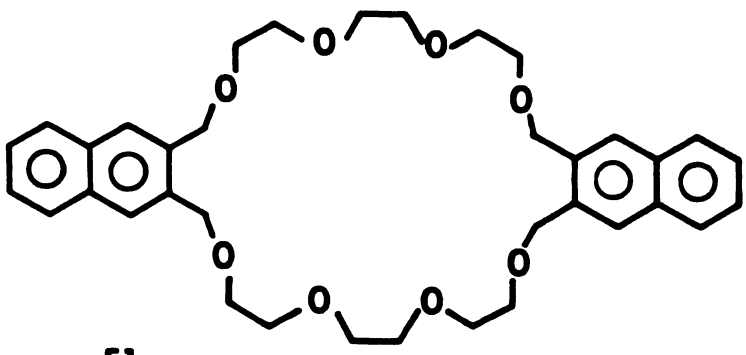
Correlations of Chemical Shift Changes with Charge Density Changes

Crown Ether(s)	Crown Ion(s) (NMR)	"INDO Ion"	Slope (ppm/e^-)	Correlation Coefficient
2,3-Cr-6	Cs^+	ordinary	95	0.927
2,3-Cr-6	Cs^+	adjusted	129	0.921
2,3-Cr-6	Cs^+, Ba^{++}	adjusted	99	0.943
1,8-Cr-6	K^+, Ba^{++}	adjusted	114	0.946
2,3-Cr-6	K^+, Ba^{++}	adjusted	97	0.949
2,3-Cr-6 and 1,8-Cr-6	K^+, Ba^{++}	adjusted	105	0.940

as compared to the total change in π charges at all carbons (absolute values) of 136 me^-. For 1,8-Cr-6, the corresponding numbers are 28 me^- and 143 me^-.[92] This is in the range expected based on previous ab initio calculations on substituted benzenes.[78] As expected from other calculations,[78] the changes in σ charge density are in the direction opposite those of the π charge changes, and are smaller than the π charge changes, indicating that σ charge changes are in response to the π charge changes (Figure 20).

As the crown ring is made smaller, the distance of the complexed ion from the naphthalene ring should decrease, and the polarization of the π system should be increased. Examination of the data for 2,3-Cr-5 (Figure 12), reveals this to be the case. All of the aromatic carbon shifts increase by a modest amount compared to 2,3-Cr-6. INDO calculations in which the ion is moved 1 Å closer to the aromatic ring are also in agreement with this, as all of the charge density changes become a little larger (Figure 18).

One would then have expected the shifts to further increase in magnitude as the crown ring was shrunk again to the crown-4 size. This, however, is not the case. The aromatic carbon shifts for 2,3-Cr-4 and its complexes are smaller than those of 2,3-Cr-5, and like those of 2,3-Cr-6 (Figures 13 and 19). One possible explanation for this was that the crown was not the crown-4, but a dicrown, such as 51.[93]



51

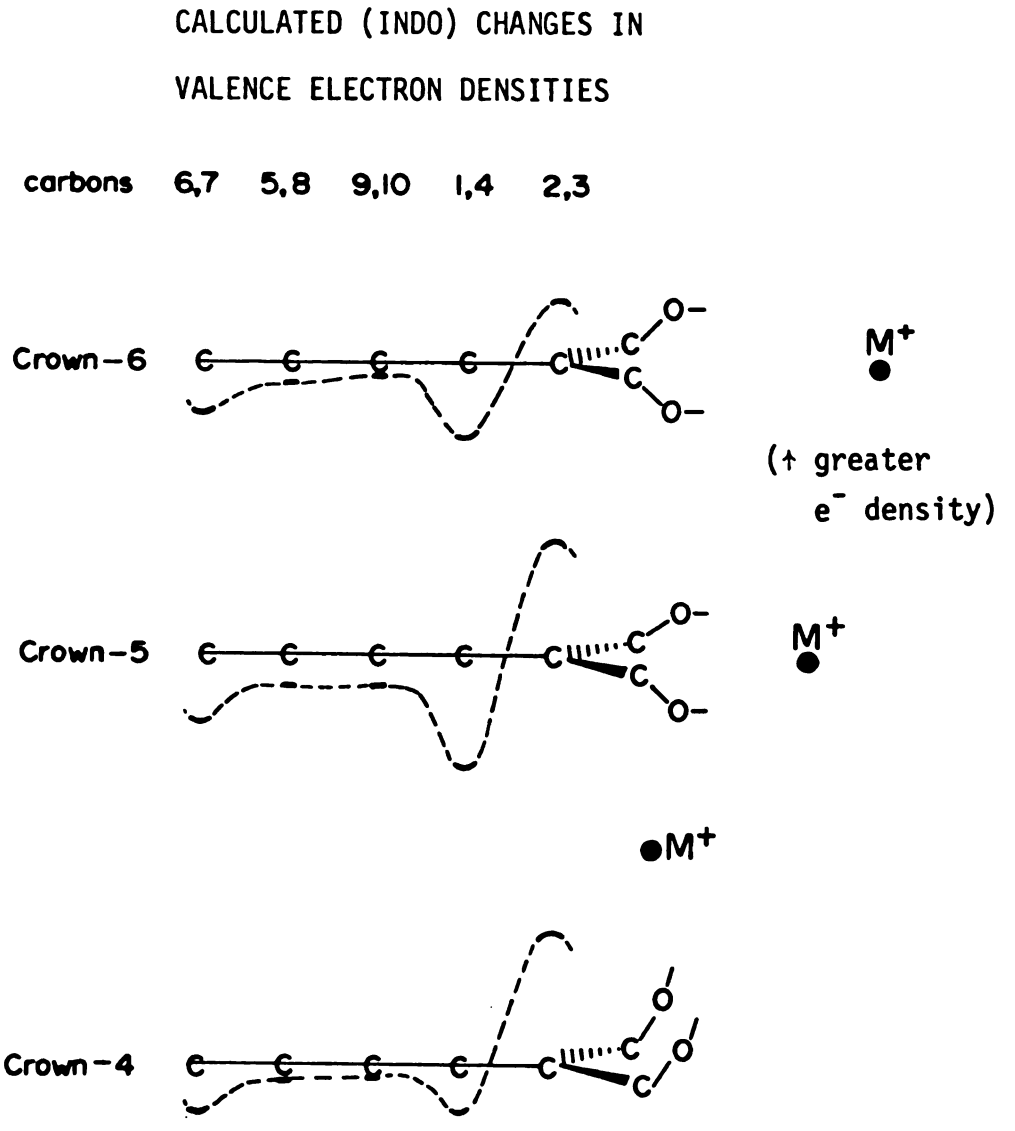


Figure 18. INDO Calculated Charge Density Changes for Aromatic Carbons of 2,3-Crowns with Plus One Monopole (M^+) in Indicated Positions. Charge Density Change is Proportional to Distance of Dashed Line from Carbon.

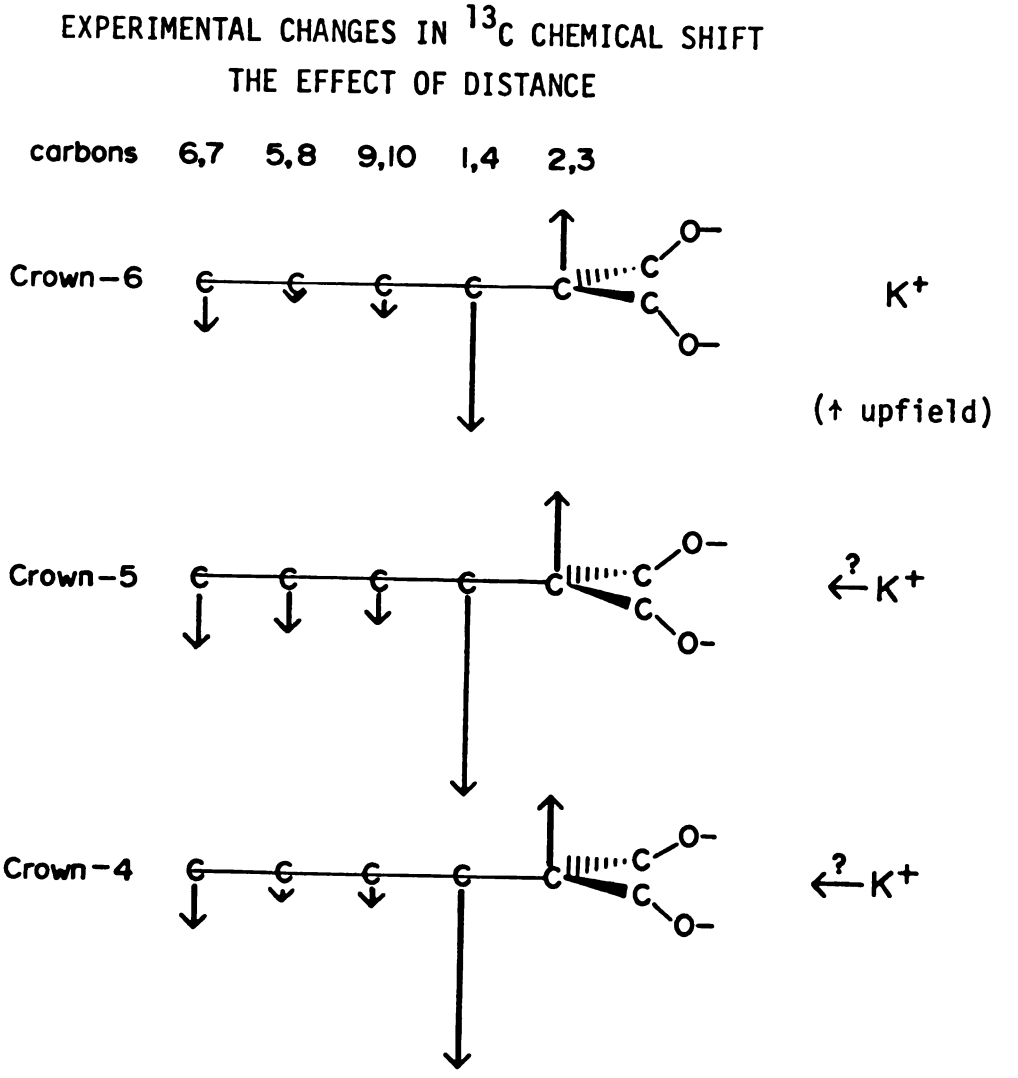


Figure 19. Chemical Shift Changes of Aromatic Carbons of 2,3-Crowns upon Complexation with Potassium. Chemical Shift Change is Proportional to Size of Arrow.

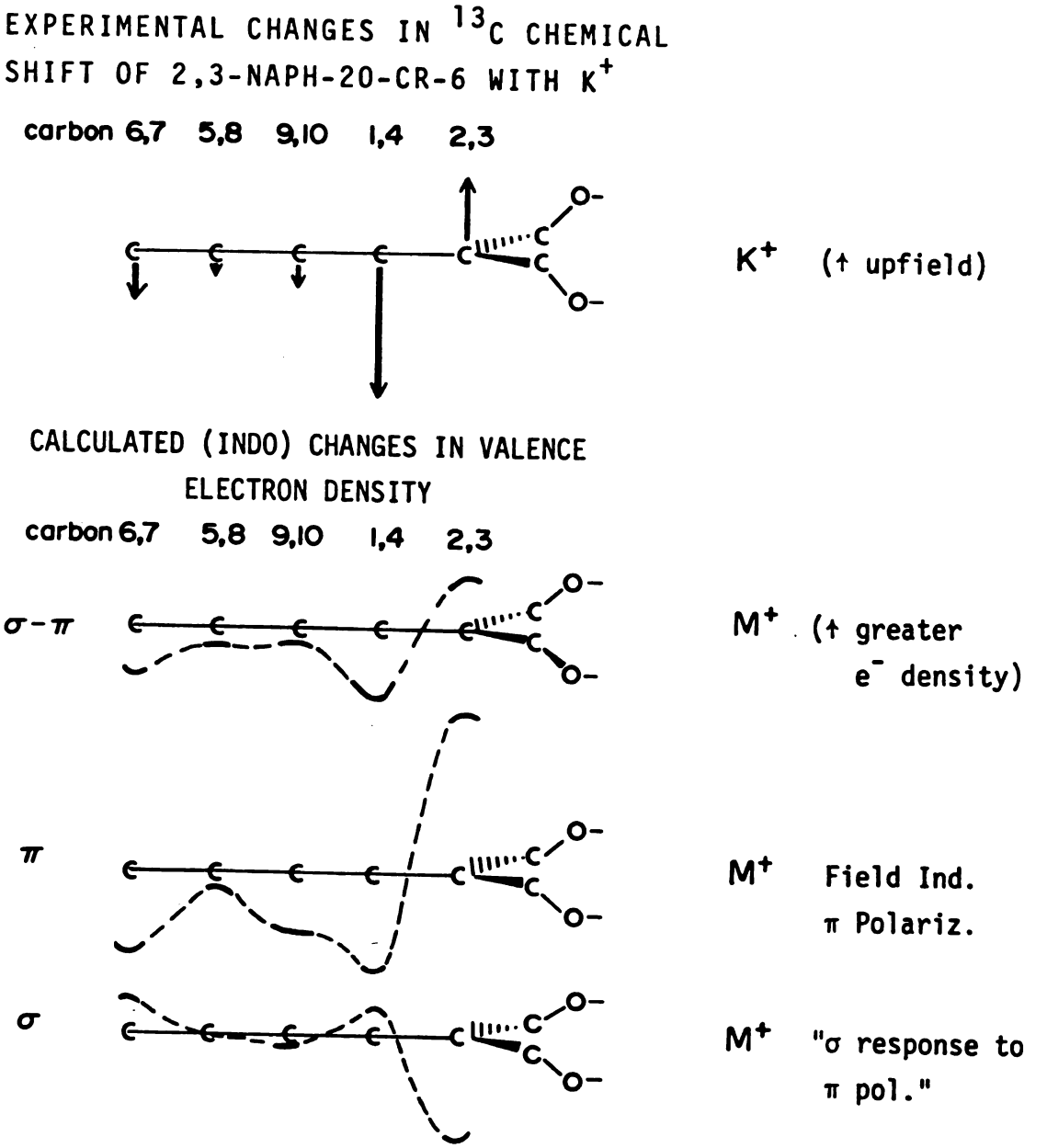


Figure 20. INDO Calculated σ, π, and Total Charge Density Changes for Complexation of 2,3-Naph-20-Cr-6 with Plus One Monopole and Measured Chemical Shift Changes for 2,3-Naph-20-Cr-6 with Potassium Salt.

This would have the ion placed further away from the naphthalene ring. This possibility was ruled out by doing a Rast molecular weight determination on the crown ether.[94] Another possible explanation is that the ion, on the average, is located out of the plane of the naphthalene. This would be expected to reduce the π polarization. INDO calculations with the ion moved out of the plane of the naphthalene agree with this prediction, as charge density changes are reduced somewhat. Agreement, of course, is not perfect, as the exact location of the ion is not known, and additional γ effects are expected as discussed below. Further evidence that the complexed ions in 2,3-Cr-4 sit out of the plane of the naphthalene ring may be obtained from examination of the spectra of 1,5-Cr-6, 45, (Figure 14). In each case all of the aromatic carbon chemical shift changes are small. This is what would be expected for field induced π polarization effects, as the ion is brought over the face of the aromatic system.[95]

The chemical shift changes of C(2,7) and C(9) of 1,8-Cr-6, and, to a lesser extent C(1,4) of the 2,3-crowns display a dependence on the identity of the cation. This dependence may be explained on the basis of γ effects of second-row heteroatoms. Ths chemical shift of a carbon with a second-row heteroatom γ to it is moved to higher field, with the effect largest for syn and anti conformations. These upfield shifts are typically in the range of 1-3 ppm. This has been shown to be the case for both saturated carbons[96] and aromatic carbons.[97] Curiously, the upfield shifts aren't observed for other non-second-row heteroatoms, such as sulfur. The aromatic carbons for which we see the cation dependence are all γ to a crown ether oxygen atom. The large chemical shift change differences for these

carbons in 1,8-Cr-6 suggests a crown ring adjustment, as the cation size is changed, by changing the dihedral angle C(2): C(1): C(11): O(12). As yet, no satisfactory explanation for such γ effects has been offered in the literature. Several INDO calculations with the 2,3-diether, 49, were performed with the appropriate dihedral angle varied. No simple charge density variations that could be correlated with chemical shift changes were observed. Of course, this is not the best model system for an investigation of such a possible correlation. It is quite possible (even likely) that these effects will not correlate at all with charge density changes.

Ether Carbon Shifts

The chemical shift behavior of the ether carbons of the crowns contains information about the conformations and conformational changes of the crown ring, as ^{13}C shifts are quite senstitve to conformational changes. Information about conformation in solution is frequently obtained from examination of ^{1}H NMR spectra. However, this technique, which is applicable to a few kinds of crown ethers, is not applicable when most of the hydrogen signals coincide, as is the case for crown ethers 42 through 48. In the absence of this tool, other sources of conformational change information must be examined. In the case of these naphtho crown ethers, no specific information about solution conformation is available from the ^{13}C NMR spectra, but more general information about flexibility and conformational changes upon complexation is available.

Examination of the ether carbon regions of the spectra of the uncomplexed crown ethers (Figures 15 and 16) reveals chemical shift

degeneracies for the larger crown ethers, which disappear as the crown ring size diminishes. We would expect that as we went down the side chain away from the naphthalene ring, the effect of the naphthalene would decrease until at some point the chemical shifts would be the same. This, of course, will be complicated by conformational changes. For ether carbons held rigidly in a particular conformation, chemical shifts are more likely to be different. The chemical shift degeneracies in 2,3-Cr-6 and 1,8-Cr-6, then, suggest a rapid averaging of conformation on the NMR time scale. On going from 2,3-Cr-6 to 2,3-Cr-5, a dramatic change occurs, there being no shift degeneracies for the smaller crown. This change may be reasonably attributed to a more rigid crown ether ring which diminishes conformational averaging on the NMR time scale, or a change in the nature of the conformational changes which results in different average conformations for the ether carbons. This behavior is also seen for the 1,8-crowns, although to a lesser extent.

Cation complexation for each of the crown ethers results in shift changes for the ether carbons. For some crowns it is possible to follow the individual carbon shift changes. In these cases (for instance 2,3-Cr-5) shifts may change by as much as 2 ppm, and may go upfield or downfield. These shifts are probably due to two kinds of effects, electron polarization by the ion, and conformational changes due to ion complexation. In each case, complexation tends to break chemical shift degeneracies (or leave them unchanged). This effect may be due to the conformational changes induced by ion complexation. It is perhaps more likely due to a slightly non-symmetrical placement of the ion in the crown ring, such that different

carbons are different distances away from the ion, with different alignments of bonds, resulting in different chemical shifts due to simple polar effects.

Comparison of the ether carbon shifts of a given crown with different plus one ions reveals a remarkable similarity in most cases. This suggest that crown conformations are similar for the different ions, and that the ion is located in nearly the same place in each complex. The most notable exception to this is the 2,3-Cr-6/Na^+ complex, where a conformational change might be expected due to the poor fit of the small Na^+ in the fairly large crown ring.

Finally, perhaps the most obvious pattern in the ether carbon shifts is that of the naphthylic carbons. For every crown ether studied, the chemical shift of the naphthylic carbon proceeds upfield as the cation is changed from sodium through cesium. The shifts of the calcium and barium complexes show the same pattern, with the shift of the carbon at the lower field in the calcium complex. While the pattern is striking and persists through changes in crown size, point of attachment, and ion charge, no obvious explanation presents itself. The center of the complexed ion would be expected to be similar for all of the ions, so polarization effects should not be responsible. A consistent conformational change that was responsible for such a change would be most surprising, since the effect is constant for a variety of changes in crown structure. Since the effect persists through a variety of crown ether changes, it might be reasonable to associate it with some property of the ions, rather than the crowns, though what property that might be is still not clear.

Conclusions

In the preceding sections a number of observations about the properties and behavior of these crown ethers have been made, along with some observations on the nature of field induced π polarization. These observations are summarized here: 1) Complexation constants can be roughly measured from titration plots of chemical shift changes vs. mole-fraction of added salt; 2) Rates of complexation of all the crowns and ions studied are fast on the NMR time scale ($>10^3$ sec^{-1}); 3) The small crown, 2,3-Cr-4, complexes even large cations such as cesium, and holds them out of the plane of the naphthalene ring; 4) The chemical shift changes of the aromatic carbons correlate reasonably well with INDO calculated charge density changes, for both plus one and plus two ions; 5) The aromatic chemical shift changes are nicely rationalized by a combination of field induced π polarization and the σ response to π polarization; 6) The aromatic carbons γ to oxygens display chemical shift changes which are frequently ion dependent, as expected for a variation in the appropriate dihedral angle; 7) In the absence of complexed cations, the larger crown rings are more flexible than the smaller ones, judging from chemical shift degeneracies; 8) Cation complexation tends to break chemical shift degeneracies and to shift the ether carbons; 9) The ether carbon shifts may be either upfield or downfield, as large as 2 ppm, and mostly unpredictable and uninterpretable; 10) A curious and still unexplained pattern of naphthylic carbon shifts is observed, which, when explained, might offer more information about the behavior of crown ethers and their complexes in solution.

The ^{13}C NMR spectra of these crown ethers have been a useful tool for the understanding of both crown ether behavior as well as substituent effects in aromatic systems (as has been often demonstrated). Application of ^{13}C NMR spectroscopy to the study of other crown ethers may offer more insight into the behavior of these important compounds.

EXPERIMENTAL

Materials. The crown ethers used in this work were available from a previous study.[98] Deuterium labeling of the napthylic hydrogens was accomplished by treatment of the crown ether in dimethyl sulfoxide-d_6 with butyl lithium. All salts used were commercially available and were used as received.

NMR Spectra. All ^{13}C NMR spectra were obtained on a Varian Associates CFT-20 operating at 20 MHz, with broad-band proton decoupling. Spectra were obtained using either an 8 mm or 10 mm probe. With the 8 mm probe, a 5 mm tube was placed in an 8 mm tube, and the sample solution placed in the inner tube and the reference solution in the outside tube. With the 10 mm probe, an 8 mm tube was placed in a 10 mm tube, with the reference solution in the inside tube and sample solution in the outside tube. Sample solutions were approximately 0.2 M in crown ether. The reference solution was 1.295 M aqueous acetic acid, with the methyl carbon signal at 406.8 Hz taken as the reference line.

INDO Calculations. Atomic coordinates for 2,3-bis(methoxymethyl)-naphthalene were taken from the x-ray crystal structure of the potassium thiocyanate complex of 2,3-Cr-6.[90] All carbon-hydrogen bond lengths were adjusted to standard values. The atomic coordinates for 1,8-bis (methoxymethyl) napthalene were taken from a preliminary crystal structure of 1,8-Cr-6,[99] with carbon-hydrogen bond lengths adjusted as appropriate. Coordinates for other conformations were determined by

application of simple trigonometry to these coordinates, without changing any bond lengths. All bond lengths were checked using a computer program which measures interatomic distances given atomic coordinates.[100]

INDO calculations were performed using a computer program written by Professor J.F. Harrison of this department.[101] Calculations were done on Michigan State University's CDC 65000 computer. Monopoles were simulated in these calculations by setting $\alpha = 10$, $\beta = 10$, $G = 0$, and $F = 0$, for both berrylium and lithium, resulting in charges of + 0.97 and + 1.97 for "lithium" and "berrylium", respectively in the calculations performed.[102] Calculation of π charges was accomplished using a computer program which squared and summed appropriate atomic orbital coefficients in each occupied molecular orbital.[100]

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