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The Synthesis and Reactions of Sterically Hindered Secondary Amines and Their Corresponding Lithium Amides

presented by

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Major professor

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THE SYNTHESIS AND REACTIONS OF A SERIES OF STERICALLY HINDERED SECONDARY AMINES AND THEIR CORRESPONDING LITHIUM AMIDES

By

Ihor Elias Kopka

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ABSTRACT

THE SYNTHESIS AND REACTIONS OF A SERIES OF STERICALLY HINDERED SECONDARY AMINES AND THEIR CORRESPONDING LITHIUM AMIDES

By

Ihor Elias Kopka

A series of highly branched secondary amines, including bis-(1,1-diethyl-2-propyl)amine was prepared by coupling propargylamines with propargyl chlorides. Hydrogenation of the resultant dipropargylamines was accomplished with W2 Raney nickel in the presence of potassium hydroxide in ethanol. The resultant amines are among the most hindered secondary amines reported to date. The pK_a values of the conjugate acids of the series of secondary amines exhibit a regular decrease with increasing size of the alkyl groups. The more hindered members of the series are inert to methyl iodide. Bis(1,1-diethyl-2-propyl)amine reacts with boron trifluoride etherate to give a primary amine adduct and 3-ethyl-2-pentene.

N-Metallation of the amines with phenylsodium, n-butyl or phenyllithium was unsuccessful. Successful N-metallation was achieved with n-butyllithium in the presence of N',N',N,N-tetramethylethylenediamine. The rate of metallation was determined in the presence of 50 and 100 mole percent of tetramethylethylenediamine. The stability of the series of lithium amides was determined in tetrahydrofuran and diethyl ether solution at 24°C. The stability of the amides first decreased, then increased with increasing amide bulk in both solvents.

The series of lithium amides was reacted with 2-bromobutane, 2-iodobutane and 2-bromo-6-heptene in tetrahydrofuran to give a mixture

of olefins. There is an increase, then a decrease, in the 1-alkene/-2-alkene ratio with increasing amide bulk. Concomitantly, the trans/cis-2-alkene ratio decreased, then increased, with increasing amide bulk. Threo and erythro-3-d-2-bromobutane were synthesized and reacted with the series of lithium amides. Product butene analysis indicated that all the amide dehydrohalogenation reactions occur by an anti-elimination mechanism.

To Molly, Puff and Rudy

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DMF	N, N-dimethylformamide
12-Crown-4	1, 4, 7, 10-tetraoxacyclododecane
LDA	lithium diisopropylamide
LiTMP	lithium 2, 2, 6, 6-tetramethylpiperidine
NCS	N-chlorosuccinamide
NBS	N-bromosuccinamide
THF	tetrahydrofuran
TMP	2, 2, 6, 6-tetramethylpiperidine
TMEDA	N, N, N', N'-tetramethylethylenediamine

CHAPTER I

THE SYNTHESIS OF A SERIES OF STERICALLY HINDERED SECONDARY AMINES

INTRODUCTION

Secondary amines with branched alkyl groups are useful chemical reagents in organic chemistry. Applications of hindered amines depend on their increased substrate selectivity resulting from steric factors. 2,2,6,6-Tetramethylpiperidine (TMP) is probably the most hindered commercially available secondary amine routinely used in organic chemistry. This amine is used commercially as a photostablizer in polyethylene and polyacrylamide polymers. The amine inhibits degradation of polymers by quenching singlet oxygen which is produced by ultraviolet irradiation of atmospheric oxygen.[1] Alkali metal amides derived from hindered secondary amines are proton selective and largely non-nucleophilic bases. Although bases of moderate steric requirements such as lithium diethyl- or diisopropylamide do not give a metallated derivative with alkylboranes 1 or vinylboranes 2, lithium tetramethylpiperidine[2] (LiTMP) produces boron stablized carbanions in both cases (eqs 1 and 2).

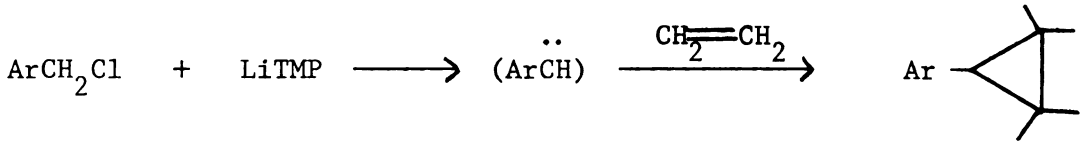
$$R_2BCH_3 + LiTMP \xrightarrow[25^oC]{\text{benzene}} R_2BCH_2Li + TMP \qquad (1)$$

$$RCH_2CH{=}CHBR'_2 + LiTMP \xrightarrow[25^oC]{THF} RCHLiCH{=}CHBR'_2 + TMP \qquad (2)$$

The failure of the smaller lithium amides to give proton abstraction is probably due to their coordination to the boron atom (eq 3). A variety

$$R_2BCH_3 + {}^{(-)}NR'_2 \xrightarrow[24^oC]{\text{benzene}} R_2B(CH_3)NR'_2 \qquad (3)$$

of related applications of LiTMP have been reported. Olofson[3] has described the use of LiTMP for a practical synthesis of arylcyclopropanes 3 from benzylhalides (eq 4). Lithium diisopropylamide was less effective (39% yield), presumably because substitution reactions of the starting benzyl halide are more likely with this less hindered amide.

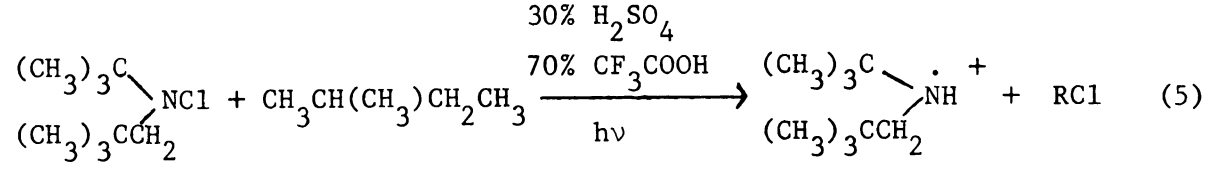


(4)

3

56% yield

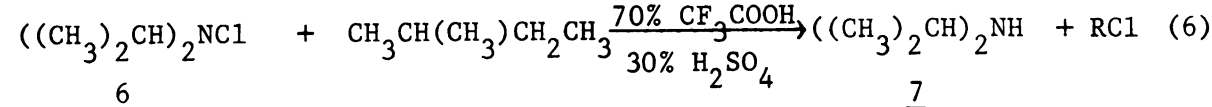
Other useful applications of hindered secondary amine derivatives have been demonstrated. The N-chloro derivatives of tetramethylpiperidine and tert-butyl neopentylamine[4] in sulfuric-trifluoroacetic acid solution were shown by Deno[5] and others[6] to produce a radical cation which initiates the regioselective chlorination of hydrocarbons at the sterically less hindered penultimate carbon atom (eqs 5 and 6).



(5)

4 5

	Ratio of 1° Cl	2° Cl	3° Cl
From 4	1.72	5.98	1
From 6	0.25	0.70	1



(6)

6 7

The reaction is catalyzed by either photochemical or chemical (Fe^{+3} salts) means. Radical cation 5, when compared to the less hindered radical cation 7, exhibits increased selectivity for primary and secondary hydrogen abstraction. This is presumably due to the greater steric hindrance of radical 5 over radical 7.

It would be useful to know if secondary amines with more hindered alkyl groups would show even greater substrate selectivity. An α,α'-enolizable non-symmetrical ketone may be deprotonated to form two regioisomeric enolates 8 and 9 (eq 7). The lack of regiocontrol in kinetic ketone deprotonation to give 8 and 9 is a significant problem which limits the use of such ketone enolates in organic synthesis.

$$RCH_2\overset{O}{\overset{\|}{C}}-CHR^1R^2 \xrightarrow{\text{Base}} \underset{8}{RCH=\overset{O^{(-)}}{\overset{|}{C}}-CHR^1R^2} + \underset{9}{RCH_2\overset{O^{(-)}}{\overset{|}{C}}=CR^1R^2} \qquad (7)$$

It is possible that hindered amide bases might favor proton abstraction from the less hindered side of the ketone to a greater extent.

A second reason for preparing highly hindered secondary amines is that their lithium amides might be stronger bases than the less hindered secondary lithium amides. C. A. Brown[7] investigated the effect of increased alkyl group size upon alkoxide basicity. He found that the base strength of alkoxides increase with alkyl group size. Potassium tricyclohexylmethoxide is a stronger base, by about 1.2 pK_a units, than potassium tert-butoxide. Brown attributed this to a decrease in solvation or ion-pair formation in the more hindered base. It seems likely that such an effect might also occur with metal amide bases in ethereal solvents.

A major goal of this study was the development of a simple, inexpensive route to a series of secondary amines of increasing steric bulk which are more hindered than commercially available secondary amines. We then planned to investigate synthetic applications of this series of amines in reactions where steric factors might lead to greater regioselectivity in product formation.

The best procedure for the preparation of hindered secondary amines is probably that reported by Hennion.[8] Hindered primary amine 10 reacts with 3-chloro-3-methyl-1-butyne 11 to give the coupled secondary bis(propargylamine) 12 (eq 8).

$$\underset{\underline{11}}{HC{\equiv}CC(CH_3)_2Cl} + \underset{\underline{10}}{HC{\equiv}CC(CH_3)_2NH} \xrightarrow[\text{8 days, } 30^{\circ}C]{\text{40\% KOH, } H_2O,\ \text{Copper Bronze, } Cu_2Cl_2} \underset{\underline{12}}{(HC{\equiv}CC(CH_3)_2)_2NH} \quad 47\%\ \text{yield} \tag{8}$$

Compound 12 was semihydrogenated to 13 using 12% palladium on charcoal as a catalyst, then hydrogenated to the saturated amine 14, using W2 Raney nickel in absolute ethanol (eq 10).

$$\underline{12} \xrightarrow[\text{petroleum ether}]{\text{palladium on charcoal}} \underset{\underline{13}}{(CH_2{=}CHC(CH_3)_2)_2NH} \xrightarrow[\text{ethanol}]{\text{Raney nickel}} \underset{\underline{14}}{(CH_3CH_2C(CH_3)_2)_2NH} \quad 41\%\ \text{yield} \tag{9}$$

Recently, we modified Hennion's procedure and prepared the highly hindered secondary amine bis(triethylcarbinyl)amine 21. We determined that

this was the most hindered secondary amine that could be synthesized in reasonable yield using Hennion's modified procedure. The sequence used to prepare this series of secondary amines is summarized in eqs 11 through 15. We found that the coupling procedure shown in eq 9 does not give significant yields of secondary propargyl amines when more hindered starting materials are used.[9]

$$R_2CO + NaC{\equiv}CH \xrightarrow{NH_3(liq)} HC{\equiv}CR_2COH \quad (11)$$

$$HC{\equiv}CR_2OH + HCl \longrightarrow HC{\equiv}CR_2CCl \quad (12)$$

$$HC{\equiv}CR_2CCl + NH_2^- \xrightarrow{NH_3(liq)} HC{\equiv}CR_2CNH_2 \quad (13)$$

$$HC{\equiv}CR_2CCl + HC{\equiv}CR_2CNH_2 \xrightarrow{DMF} (HC{\equiv}CR_2C)_2NH \quad (14)$$

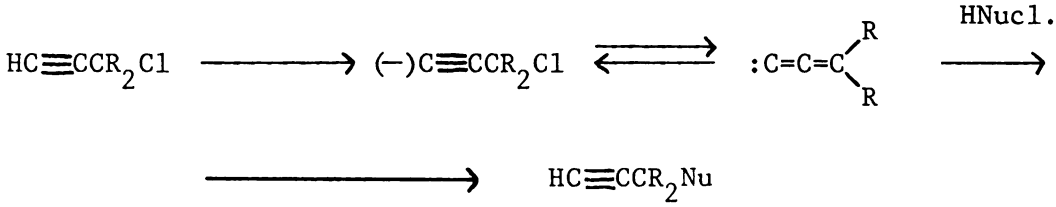
$$(HC{\equiv}CR_2C)_2NH \xrightarrow[EtOH]{Ni/H_2} (CH_3CH_2R_2C)_2NH \quad (15)$$

The best yield (52%) of 21 was obtained with an extra equivalent of the propargyl amine as an HCl acceptor in place of KOH in eq 14 with dimethylformamide (DMF) as the reaction solvent. We also found that W2 Raney nickel in ethanolic KOH solution was the most effective hydrogenation catalyst (eq 15).

RESULTS

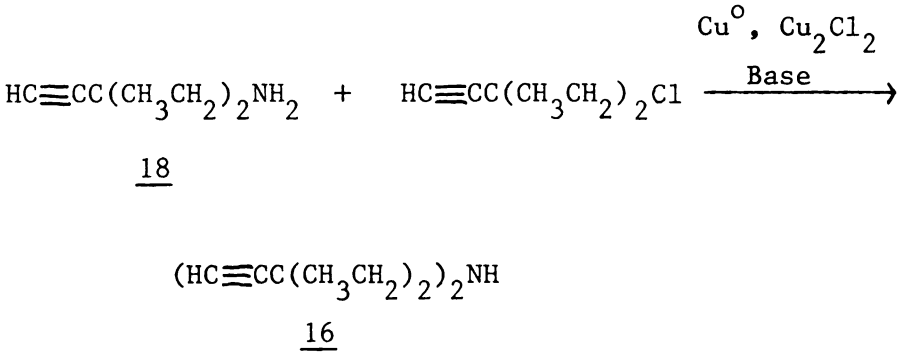
The sequence used to prepare the series of secondary amines is summarized in eqs 11-15. Most propargyl alcohols like 3-methyl-1-butyne-3-ol, 3-methyl-1-pentyne-3-ol and 1-ethynyl-1-cyclohexanol were commercially available. Both 3-ethyl-1-pentyne-3-ol and 4-methyl-3-isopropyl-1-pentyne-3-ol were synthesized from the corresponding diethyl

and diisopropyl ketones by previously reported methods.[10,11] The key steps in the synthesis (eqs 13 and 14) are based on the observations by Hennion that tertiary propargyl chlorides react with nucleophiles (eq 16) in the presence of strong base (hydroxide or amide anion) to give clean substitution at the tertiary carbon by a vinylidene carbene mechanism, as illustrated in eq 16.



(16)

The coupling procedure shown in eq 9 did not give any coupled secondary amine product when applied to more hindered reactants. The coupling of 3-amino-3-ethyl-1-pentyne with the corresponding propargyl chloride was attempted with a variety of bases (eq 17). None of the coupled product 16 was obtained with 40% KOH in H_2O or with NaH, KH or potassium tert-butoxide in tetrahydrofuran (THF).[12] However, using an extra equivalent of 18 gave, after 3 days reaction at 4°C in DMF, a 60% GLC yield of 16.[9] The coupling reaction fails when the copper bronze, cuprous chloride catalyst is omitted or when a saturated secondary amine is used. The coupling reaction works, but in low yield, when the olefinic amine is used (eq 18).[12]



(17)

$$R(CH_3CH_2)_2CNH_2 \quad + \quad HC{\equiv}CC(CH_3CH_2)Cl \longrightarrow$$

$$\longrightarrow \quad R(CH_3CH_2)_2CNHC(CH_3CH_2)_2C{\equiv}CH \qquad (18)$$

R	Yield
$-CH_2CH_3$	0%
$-CH{=}CH_2$	17%

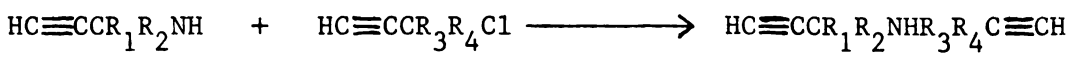
Results obtained for the coupling reactions of various propargyl chlorides with propargyl amines are presented in Table I. As expected, the lowest yields were obtained with the more highly substituted secondary amines. Results obtained with even more hindered reagents defined the ultimate steric limitations of the reaction [9] (eq 19).

$$HC{\equiv}C(CH(CH_3)_2)_2CNH_2 \quad + \quad HC{\equiv}C(CH_3CH_2)_2CCl \longrightarrow$$

$$\xrightarrow[\text{DMF, 2 weeks}]{Cu_2Cl_2,\ \text{Copper Bronze}} HC{\equiv}C{-}C(CH(CH_3)_2)(CH_2CH_3){-}NH{-}C(CH(CH_3)_2)(CH_2CH_3){-}C{\equiv}CH \qquad (19)$$

5% yield

Table I. Coupling of Propargylamines With Propargyl Chlorides



R_1	R_2	R_3	R_4	Yield	Compound
CH_3	CH_3	CH_3	CH_3	70%	12
CH_3	CH_3CH_2	CH_3	CH_3	60%	13
CH_3	CH_3CH_2	CH_3	CH_3CH_2	55%	14
CH_3CH_2	CH_3CH_2	CH_3	CH_3CH_2	55%	15
CH_3CH_2	CH_3CH_2	CH_3CH_2	CH_3CH_2	48%	16
$-CH_2(CH_2)_3CH_2-$		$-CH_2(CH_2)_3CH_2-$		66%	17

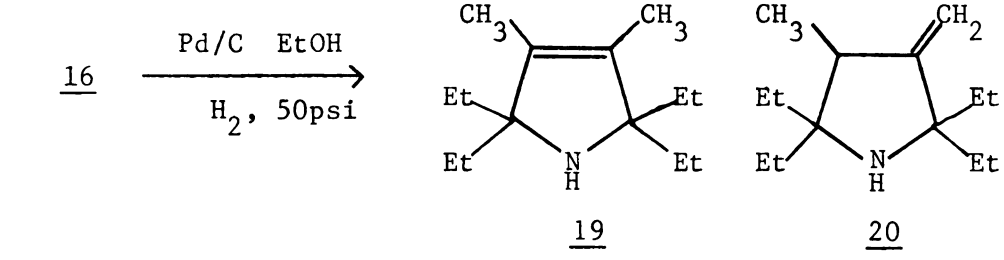
All yields are isolated yields.

Hydrogenation of Propargylamines

Hydrogenation of the series of propargylamines in Table I posed a number of problems. Hydrogenation of propargylamines or the respective amine hydrochlorides in Table I with a platinum catalyst in a variety of solvents gave almost exclusively the corresponding primary amines (eq 20).

$$HC{\equiv}CCR_1R_2NHR_3R_4CC{\equiv}CH \xrightarrow[H_2,\ 60\ psi]{PtO_2/EtOH} CH_3CH_2CR_1R_2NH_2 + CH_3CH_2CR_3R_4NH_2 \quad (20)$$

Pd on carbon gave similar results in ethereal solvents; however, hydrogenation of 16 in absolute ethanol with palladium on charcoal gave the heterocycles 19 and 20 (eq 21).[13] Hydrogenation of the other propargylamines in Table I with Pd/C was not attempted.



19 20 (21)

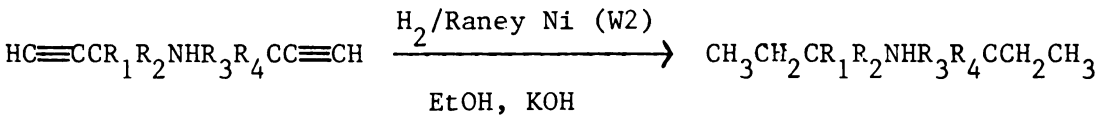
A successful preparation of bis(triethylcarbinyl)amine 21 was achieved in 20% yield by low pressure hydrogenation with W2 Raney nickel. The major side reaction of the hydrogenation was hydrogenolysis of 16 to 22 (eq 22).

$$16 \xrightarrow[\text{anhydrous EtOH}]{\text{Raney Ni/ } H_2} ((CH_3CH_2)_3C)_2NH + (CH_3CH_2)_3CNH_2 \quad (22)$$

21 22

More reactive grades of Raney nickel (W4 and W6) gave mainly incompletely hydrogenated secondary amines along with hydrogenolysis product 22. Finally, a 72% yield of 21 was obtained by adding a 1 mol excess of potassium hydroxide to the W2 catalyst to suppress hydrogenolysis. Results obtained with a series of propargylamines by this last procedure are given in Table II.

Table II. Hydrogenation of Bis-Propargylamines in Ethanol with KOH and Raney Nickel.



R_1	R_2	R_3	R_4	Compound	Yield (%)[a]
CH_3	CH_3	CH_3	CH_3	24	80
CH_3	CH_3CH_2	CH_3	CH_3	25	78
CH_3	CH_3CH_2	CH_3	CH_3CH_2	26	75
CH_3CH_2	CH_3CH_2	CH_3	CH_3CH_2	27	75
CH_3CH_2	CH_3CH_2	CH_3CH_2	CH_3CH_2	21	72
$-CH_2(CH_2)_3CH_2-$		$-CH_2(CH_2)_3CH_2-$		28	80[b]

[a] Isolated yield.

[b] No KOH used in the hydrogenation.

Acidity Constants of Amine Hydrochlorides

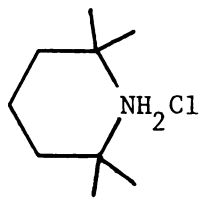
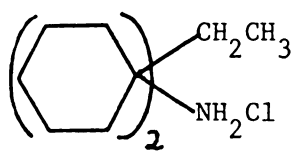
The acidity constants of the amine hydrochlorides obtained from the secondary amines of Table II were determined by potentiometric titration with standard alcoholic potassium hydroxide (carbonate free). All titrations and solution transfers were done under argon to avoid carbonate formation with with atmospheric CO_2. Titrations were attempted in dioxane and dioxane-water solutions of varying concentrations.[14] The hindered amines and their hydrochlorides were not soluble even at very low concentrations (0.005 M) in 95:5 (v/v) of dioxane: water. Ethanol (90%) was chosen as the solvent since the amines and amine hydrochlorides are both completely soluble in this solvent at the concentrations employed. The procedure for these titrations was taken from a previous report.[15]

A carbonate free solution of KOH was prepared by dissolving potassium metal in absolute ethanol under argon and diluting with degassed distilled water to the desired concentration (0.1075 M), determined by titration with standard HCl solution. The pK_a of the amine hydrochloride was calculated as the pH of the solution at half the equivalence point volume (eq 23). The titration was monitored using a combination calomel-glass electrode at 25°C attached to a digital readout

$$pK_a = pH_{\frac{1}{2}} \text{ equivalence volume} \qquad (23)$$

pH meter. Results of the titration study are reported in Table III, with the hydrochlorides of diisopropylamine and 2,2,6,6-tetramethylpiperidine being included for reference. A regular increase in acidity (apparent decrease in pK_a) is observed with increasing steric bulk

Table III. Acidity Constants of R_2NH_2Cl in 90% Ethanol

R_2NH_2Cl	pK_a
$[(CH_3)_2CH]_2NH_2Cl$	9.8[a]
	10.1[b]
$[CH_3CH_2C(CH_3)_2]_2NH_2Cl$	9.9
$[CH_3CH_2C(CH_3)_2NH_2C(CH_3)(CH_2CH_3)_2]Cl$	9.4
$[(CH_3CH_2)_2C(CH_3)]_2NH_2Cl$	8.7
$[(CH_3CH_2)_3CNH_2C(CH_3)(CH_3CH_2)_2]Cl$	8.0
$[(CH_3CH_2)_3C]_2NH_2Cl$	7.1
	9.0

[a] Lit.[16a] pK_a = 11.07 (water solvent). [b] Lit.[16b] pK_a = 11.24 (water solvent).

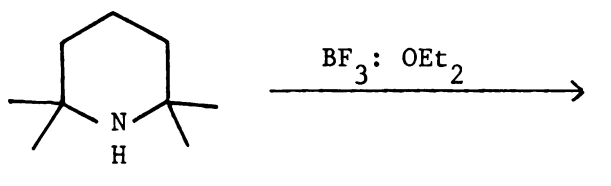
of the alkyl groups. The most highly substituted amine in the series, 21, appears to be the weakest base (pK_a of conjugate acid=7.1) of any saturated aliphatic amine yet reported. Treatment of amine 21 with an excess of either aqueous hydrochloric acid or hydrogen chloride in ether gave a dihydrochloride. This was confirmed by titrating the acid salt of 21 with standard KOH and observing two distinct inflection points in the titration curve at titrant volumes corresponding to the calculated values for the di and monohydrochloride of 21. The second molecule of hydrogen chloride was not removed even under prolonged heating under vacuum (2 weeks, 100°C). The monohydrochloride of 21 was readily obtained by treating the amine in hexane solution with slightly less than one equivalent of aqueous HCl, shaking vigorously for 5 minutes and decanting the hexane layer. The aqueous layer was dried under vacuum and the amine monohydrochloride was used without further purification.

Reacting Hindered Amines with Methyl Iodide

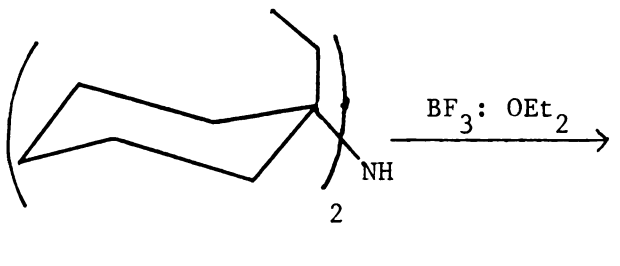
Amines 24 and 21, the least and most hindered members of the series in Table II, respectively, were reacted with methyl iodide in methylene chloride in sealed vials for 1 week at 70°C. No precipitates, indicating formation of the quaternary iodonium salts, were formed. NMR analysis of the reaction mixtures showed only unreacted methyl iodide and free amine. When 2,2,6,6-tetramethylpiperidine (TMP) was mixed with an equivalent amount of methyl iodide in chloroform under similar conditions, a white precipitate corresponding to the methyl iodonium salt of TMP was formed within a few minutes.[17]

Reaction of Amines with Boron Trifluoride

Addition of boron trifluoride etherate to either TMP or 28 in hexane solution gave within a few minutes a white precipitate of the corresponding adduct of boron trifluoride (eq 24 and 25).



(24)



(25)

28

Under the same conditions amine 21 formed only the adduct of a primary amine 29 and the olefin 3-ethyl-2-pentene (eq 26). Compound 29 was

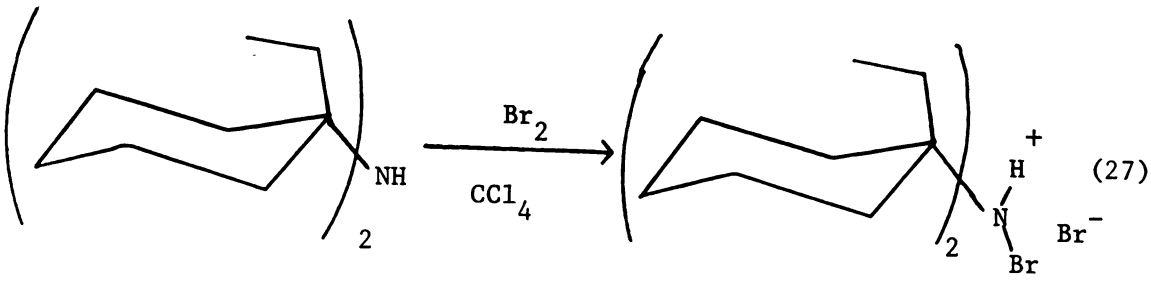
$$21 + BF_3{:}OEt_2 \xrightarrow[25^{o}]{5\ min.} CH_3CH{=}C(CH_2CH_3)_2 + (CH_3CH_2)_3CNH_2BF_3 \qquad (26)$$

29

also formed when pure BF_3 gas was added to a neat solution of 21.

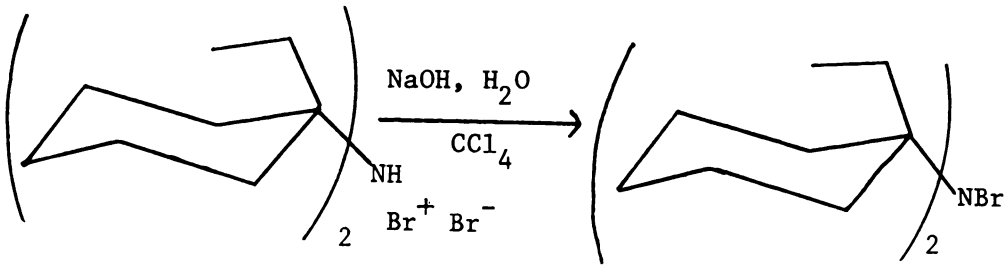
Reaction of Secondary Amines with Chlorine

Fataftah[18] showed that 28 will react with bromine in carbon tetrachloride to give the bromonium salt 30 (eq 27). Treatment of 30 with one equivalent of standard sodium hydroxide gave a 66% yield of the bromamine 31 within 30 minutes (eq 28). Repeating this reaction by



(27)

28 30

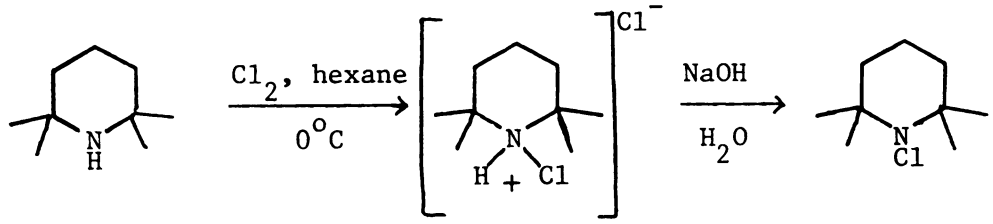


(28)

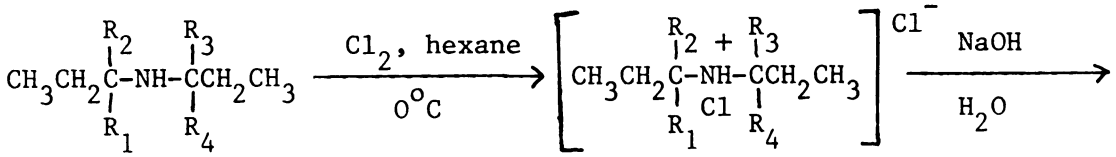
30 31

dropwise addition of bromine to a two phase reaction mixture of standard aqueous sodium hydroxide and a hexane solution of the amine gave quantitative yield of 31. This procedure is much simpler than other methods for forming haloamines. For example, N-bromosuccinamide in ether requires 1 week to convert 28 to 31. Neither N-chlorosuccinamide nor sodium hypochlorite converts 28 to the corresponding chloramine. Therefore Fataftah's procedure was adapted to forming chloramines. The only modification in technique was addition of chlorine gas from a syringe to a slowly stirring solution of hydroxide and hexane-amine solution at 0^0C. Care must be taken to insure that the chlorine does not react with the aqueous hydroxide solution to form hypochlorite ion. Stirring slowly insures that chlorine reacts first with the hexane-amine solution top layer, forming the chloronium salt. The chloronium salt subsequently reacts with hydroxide, forming the chloramine. This reaction was applied

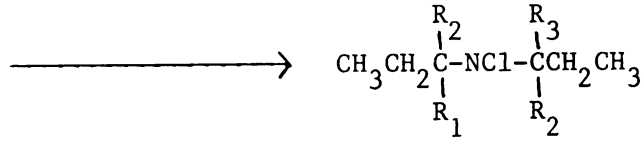
to four different hindered amines and the results are shown below in eqs 29 and 30.



(29)



(30)



$R_1=R_2=CH_3$	95% yield
$R_1=CH_3$, $R_2=CH_2CH_3$	93% "
$R_1=CH_2CH_3$, $R_2=CH_2CH_3$	94% "

All of these hindered chloramines were isolated by rough drying of the hexane layer with anhydrous sodium sulfate and removing the hexane under reduced pressure. The NMR spectrum of each chloramine could be clearly distinguished from starting amine. As the reaction proceeds, the N-H proton signal disappears and the methyl (methylene) proton signal shifts downfield for the chloramine. Benzene was used as an internal standard for determining the yields.

The chloramines were stable for at least one day at 0° except for the chloramine derived from 21, which began to decompose within 30 min

at ambient temperature (as determined by NMR). We attempted to chlorinate pentane using these hindered chloramines according to several published procedures. The first was a standard photochemical initiated procedure for forming radical cations from chloramines.[19,20] The sequence of steps involved in the chlorination of a hydrocarbon substrate is outlined in eqs 31-35.[6]

$$R_2NCl + H^+ \xrightarrow{H_2SO_4 \text{ and/or } CF_3COOH} R_2\overset{H}{\underset{Cl}{N}}{}^+ \quad (31)$$

$$R_2\overset{+H}{\underset{Cl}{N}} \xrightarrow{h\nu \text{ or } Fe^{III}} R_2NH^{+\cdot} + Cl\cdot \quad (32)$$

$$SH + R_2NH^{+\cdot} \longrightarrow R_2NH_2^+ + S\cdot \quad (33)$$

$$SH + Cl\cdot \longrightarrow S\cdot + HCl \quad (34)$$

$$S\cdot + R_2NHCl^+ \text{ (or } Cl_2) \longrightarrow SCl + R_2NH^{+\cdot} \text{ (or } Cl\cdot) \quad (35)$$

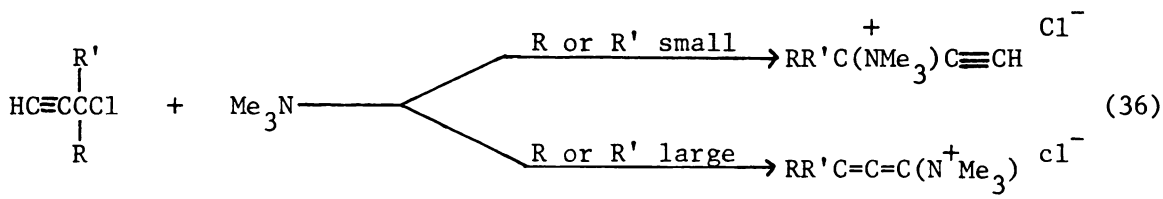
The ultimate goal of this effort was to use these sterically hindered chloramines to selectively chlorinate the terminal methyl group of a long chain hydrocarbon. Studies have demonstrated that sterically hindered amine cation radicals show greater selectivity in hydrogen radical abstraction from primary and secondary carbons over that of tertiary carbon atoms.[20]

Unfortunately, we were unable to observe any chlorination of pentane using the chloramines listed in eq 30. Both photochemical and transition metal initiated halogenation conditions were used. Neither

pentane nor chloramine was recovered; only a thick tar was obtained. Subsequent GLC analysis showed no low boiling organic products. Control reactions with chloramines of dimethyl as well as diisopropylamine synthesized using Fataftah's procedure gave halocarbons in yields and proportions corresponding to literature values.[6]

DISCUSSION

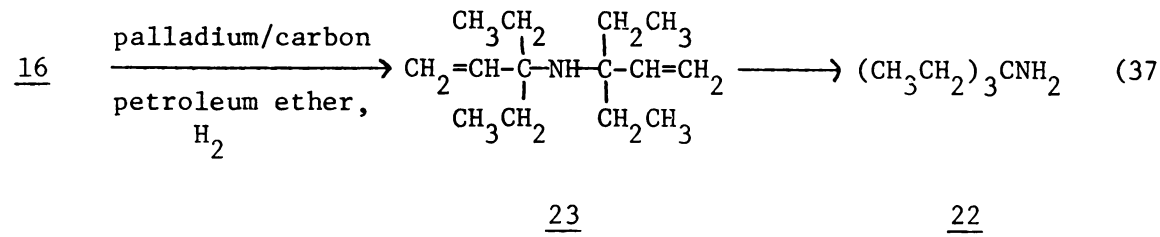
Hennion studied the reaction of trimethylamine and tertiary propargyl chlorides (eq 36).[21] Reaction products are propargyl ammonium chlorides when R and R' are methyl. If R and R' are larger than methyl, the products were allenyl ammonium chlorides.



(36)

The reaction fails if Cu_2Cl_2 and/or copper bronze are not included in the coupling reaction mixture. Thus, copper is a necessary catalyst, which may help to stabilize the vinylidine carbene and hold it close to the unsaturated amine so that the coupling reaction can occur.[9] This explanation seems to be supported by the observation that coupled product yields fall as the primary amine varies from propargyl to the saturated alkyl amine 22. The saturated amines in Table II were obtained by hydrogenation of bis(propargyl)amines with W2 Raney nickel in ethanol. More reactive Raney nickel (W4 or W6 grade) gave increased amounts of cleaved primary and unsaturated secondary amines. Hydrogenolysis occurs at the diallylamine stage, since bis(diethylallylcarbinyl)amine 23 was isolated by hydrogenation 16 in ligroin. Proton sources like water or

ethanol when added to the palladium on carbon catalyst mixture in ligroin rapidly cleaved 23 to the saturated primary amine 22 (eq 37).



(37)

23 22

The highest yields of saturated secondary amines were obtained when potassium hydroxide was added to the Raney nickel-ethanol solution. The base apparently suppressed hydrogenolysis of the amine in the protic solvent. Some incompletely hydrogenated olefinic secondary amine remained in all the hydrogenation reactions. These impurities ranged from 7% for the most hindered amine to about 3% for the least hindered amine 24 in the series. Distillation using a spinning band column gave the saturated secondary amines in 98% or better purity.

The acidity constants of the saturated secondary amines were determined and are reported in Table III. Ethanol (90%) was chosen as the solvent for the titration reactions because it dissolves all the reactants, and because pK_a's have been reported for amine hydrochlorides in different ethanol-water solution mixtures.[15,16] The effect of increasing ethanol concentration on apparent pK_a values of typical aliphatic amines is to lower the observed pK_a by approximately 1-2 units (relative to water) and to compress the range of pK_a values for a given series of amines.[16] Thus the differences in pK_a values in Table III

are expected to be even greater in water solution. Presumably, solvation of the highly hindered ammonium salt accounts for this effect.[22,23] Similar observations, of a smaller magnitude, were reported by Brown for highly branched bases.[22] Hall[24] has also argued that solvation occurs by hydrogen bonding between N^{+}—H groups in the ammonium ions and water molecules. He found that primary and secondary amines are correlated by single lines in the Taft equation (eq 38) only in cases where the amine groups have low steric hindrance.

$$pK_a = \rho^* \sigma^* \tag{38}$$

Primary and secondary amines with more sterically hindered groups do not fall on the slope ρ^* of the Taft equation. The deviation for the larger groups must be a steric effect because electronic effects are accounted for in the σ^* values. As the degree of steric hindrance increases, the base strengths become lower relative to their predicted values. This steric weakening of base strength cannot be ascribed to B-strain because the tertiary amines should show this same decrease in basicity but to a greater extent. On the contrary, tertiary amines are correlated by a single line in the Taft equation, irrespective of the steric hindrance. Furthermore, primary amines simply are incapable by definition of exhibiting B-strain. Steric hindrance of solvation can, however, explain the result.

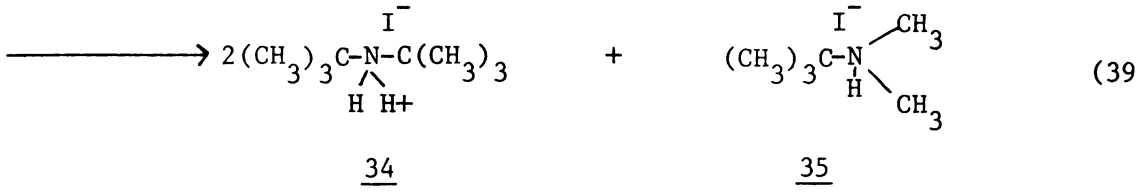
Brown[22] also reports that 2,6-di-tert-butylpyridine does not form a simple hydrochloride, giving instead a dihydrochloride. He attributes this effect to the inability of chloride ion to form a hydrogen bond to the nitrogen bound hydrogen. A second molecule of hydrogen

chloride is then required to form a hydrogen bond to the chloride ion. We observed that treatment of 21 with excess hydrochloric acid or hydrogen chloride in ether gave a dihydrochloride. The second molecule of hydrogen chloride was not removed even after prolonged heating under vacuum. The monohydrochloride was easily obtained by adding excess amine to a standard aqueous solution of hydrochloric acid. The unreacted free amine was removed by ether extraction of the aqueous phase.

Corrections normally applied in determining the acidity constant of an amine hydrochloride, such as ion activity and auto-hydrolysis of solvents, were not employed since we were unable to extrapolate the apparent pK_a's in 90% ethanol to 100% water. The hindered amines employed in the study were insoluble in concentrations as low as 0.001 M in 80% ethanol solution. Additionally, if the factors mentioned above were applied in determining the actual pK_a's of the amines, the apparent pK_a's would fall within 0.1 or 0.2 pH units of the actual pK_a values.[16] This is close to the limits of accuracy for experimental measurments.

Little is known about the reactions of sterically hindered secondary amines. Work by Klages[25] in 1963 provides an example of how steric effects reduce the nucleophilicity of di-tert-butylamine 32. Klages reacted 32 with methyl iodide for 5.5 months and obtained 34 and 35, presumably by initially forming 33 (eq 39).

$$\underset{\underline{32}}{(CH_3)_3CNC(CH_3)_3}\ \underset{H}{} \xrightarrow{MeI} \underset{\underline{33}}{[[(CH_3)_3C]_2NH_2^{+}CH_3]\ I^{-}} \xrightarrow[2\ CH_3I]{2[(CH_3)_3C]_2NH}$$

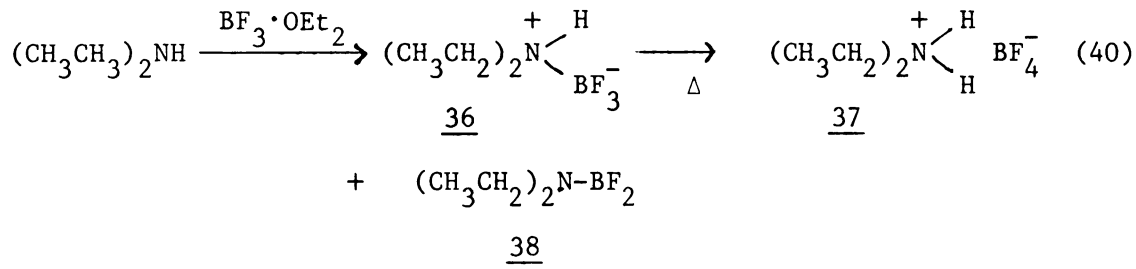


$$\longrightarrow 2(CH_3)_3C\text{-}\overset{H}{\underset{H}{N}}\text{-}C(CH_3)_3\ I^- \quad + \quad (CH_3)_3C\text{-}\overset{H}{N}(CH_3)_2\ I^- \qquad (39)$$

34 35

Niether amine 21 nor 24 reacted with methyl iodide within a two week period. This observation is not unexpected, in view of the results observed with di-tert-butylamine.

Boron trifluoride etherate and boron trifluoride gas react with diethylamine to give the addition product 36 which disproportionates when heated above 250°C giving 37 and 38 (eq 40).[26]



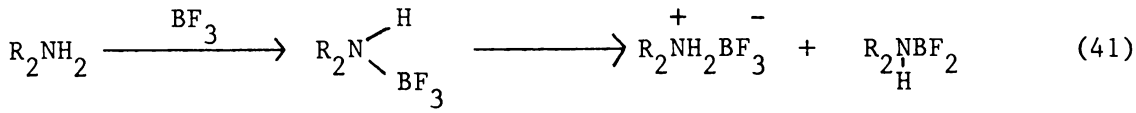
$$(CH_3CH_3)_2NH \xrightarrow{BF_3\cdot OEt_2} (CH_3CH_2)_2\overset{+}{N}H\ BF_3^- \xrightarrow[\Delta]{} (CH_3CH_2)_2\overset{+}{N}H_2\ BF_4^- \qquad (40)$$

36 37

$$+ \quad (CH_3CH_2)_2N\text{-}BF_2$$

38

Klages[25] found that di-tert-butylamine reacts with boron trifluoride to give 40 and 41, probably by the initial formation of the simple adduct 39 (eq 41).

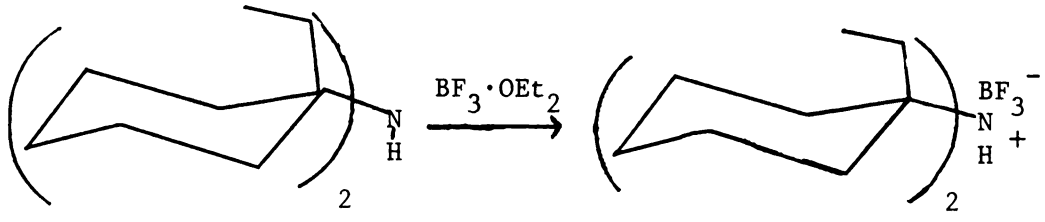


$$R_2NH_2 \xrightarrow{BF_3} R_2\overset{H}{N}BF_3 \longrightarrow R_2\overset{+}{N}H_2\ BF_3^- + R_2\overset{H}{N}BF_2 \qquad (41)$$

R= t-butyl

39 40 41

Fataftah[18] demonstrated that 28 will react with boron trifluoride etherate to give a crystalline white solid with a sharp melting point (154.5-155°C). Elemental analysis agreed with values calculated for structure 42. The formation of 42 and not disproportionation products analogous to 40 and 41 might simply be due to a difference in reaction conditions (eq 42).

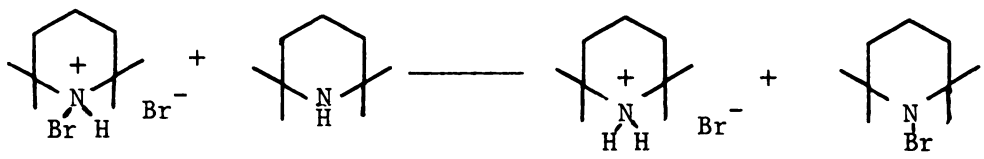


(42)

Under the same conditions as Fataftah applied in eq 42, we reacted 21 with either boron trifluoride etherate or the corresponding gas at 0°C. We obtained the primary amine BF_3 adduct and the elimination product 3-ethyl-2-pentene. We were unable to isolate the boron trifluoride adduct of the hindered secondary amine under any conditions.

Fataftah[18] demonstrated that the bromamine of 28 could be formed within 1 week using N-bromosuccinamide in ether. He developed a new procedure in which bromine was added to the hindered amine and then the bromonium salt was deprotonated to form the bromamine. This reaction was completed quickly and in high yield in either hexane or carbon tetrachloride using standard aqueous base as the deprotonating agent. This reaction was discovered when bromine was added to TMP. An orange compound, presumably the bromonium salt, was formed, but the yield was only 66%. The mother liquor was examined by NMR and showed the presence of TMP·HBr. The hydrobromide may have been formed by the reaction

of TMP with the corresponding bromonium salt as shown in eq 41.



(41)

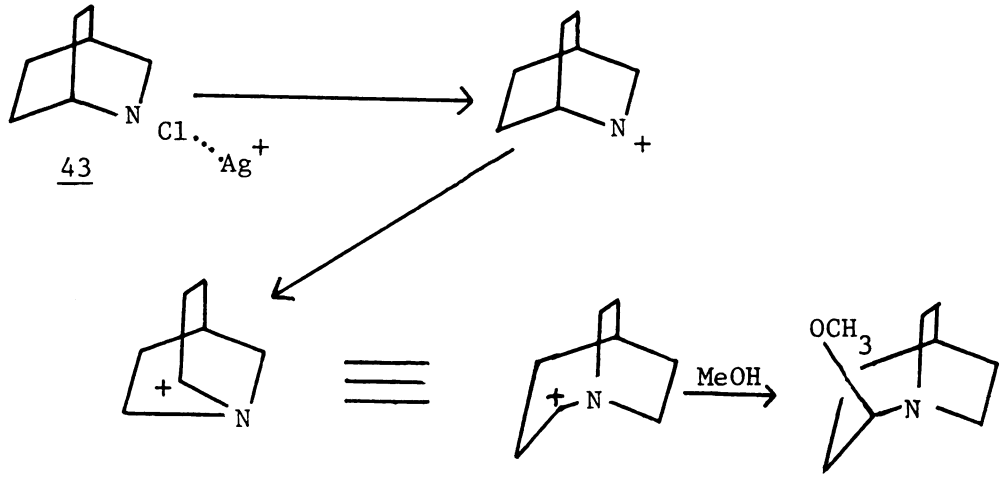
Based on reports in the literature,[6] more hindered haloamines might exhibit increased selectivity for the less substituted hydrogen atoms on a long hydrocarbon chain. Attempts at both chemically and photochemically induced chlorination of pentane with 21-Cl, 24-Cl and 26-Cl failed. Control reactions using chloramines listed in eq 42, prepared by Fataftah's procedure, gave chlorpentanes in proportions described in the literature.[6,20]

$$R_1R_2NCl \xrightarrow[0^{\circ}C]{H_2SO_4\ /\ h\nu,\ \text{pentane}} \text{1-Cl} + \text{2-Cl} + \text{3-Cl pentane} \qquad (42)$$

$R_1 = R_2 = CH_2CH_3$	2	76	22
$R_1 = R_2 = CHC_2H_6$	4	76	20
$R_1 = R_2 = -(CH_3)_2C(CH_2)_3C(CH_3)_2-$	10	70	20

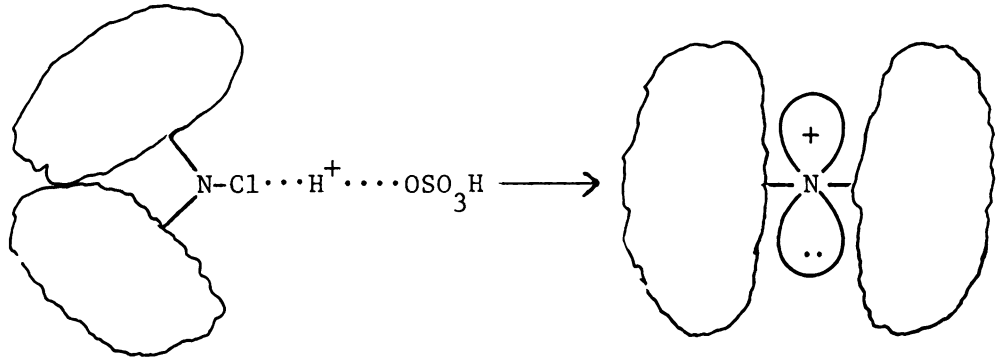
An explaination for the lack of chloropentane is that the reaction is not going through a radical cation process, but is instead forming nitrenium ions.[26] Gassman has shown that silver catalysed solvolysis of a number of secondary bicyclic chloramines proceeds through a nitrenium cation intermediate. Gassman concluded that the corresponding azabicyclic compounds would be ideal systems for establishing the existence of alkyl migration to divalent electron-deficient nitrogen. N-Chloriso-quinuclidine's solvolytic behavior was studied (eq 43) and it was

concluded that 43 goes through a nitrenium cation intermediate.



(43)

It may be that in acidic solution, our hindered chloramines are able to eject a negative chloride ion to relieve the steric strain of the sp^3 hybridized nitrogen and proceed to a less sterically crowded sp^2 nitrogen cation (eq 44). Whether this actually occurs is speculation, but



(44)

this does provide an explaination for why we do not observe chlorination of pentane nor any other identifiable hydrocarbon products in the workup of the reaction solution. The fate of the nitrenium cation is uncertain, but it is reasonable to assume that the cation might undergo an intra

molecular nitrenium ion rearrangement reaction like the one observed in eq 43. Ultimately, the amine cation would probably react in a random fashion with any hydrocarbon or amine in the highly acidic solution to form a polymeric tar. This explanation is reasonable in view of the fact that neither amine nor pentane was recovered.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Labs, Inc. IR spectra were obtained as neat films on NaCl plates with a Perkin-Elmer 237-B spectrophotometer, and ^{1}H NMR spectra were taken on a Varian T-60 spectrometer with Me_4Si internal standard. ^{13}C NMR spectra were taken with a Varian CFT-20 spectrometer and are calibrated in parts per million downfield from Me_4Si; the J values are given in Hertz. Mass spectra were taken with a Hitachi RMU-6 mass spectrometer. Gas-liquid chromatograph (GLC) was performed with a Varian 920 gas chromatograph. All reagents and solvents were dried and purified before use. Absolute ethanol (Gold Shield) was used for all hydrogenations. Dimethylformamide (DMF) was dried over calcium hydride and distilled before use under vacuum. Anhydrous cuprous chloride (Cu_2Cl_2), used for converting the propargyl alchohols to the propargyl chlorides, was obtained as a 95% pure powder from Ventron. Cuprous chloride was prepared immediately before use in an amine coupling reaction by a published procedure.[27] Copper bronze powder was obtained from the Illinois Bronze Powder Co. Raney nickel alloy was obtained from Ventron, Inc.

Propargyl Alcohols. 3-Methyl-1-butyn-3-ol, 3-methyl-1-pentyne-3-ol, and 1-ethynyl-1-cyclohexanol were commercially available (Aldrich). All other propargyl alcohols were synthesized from the corresponding ketones by previously reported methods.[10,11]

Propargyl Chlorides. All propargyl chlorides were prepared from the corresponding propargyl alcohols and used without further purification.[29] All were dried and stored over anhydrous potassium carbonate. The purity of the propargyl chlorides was determined by GLC (10% Carbowax 20M on Chromasorb W, AW-DMCS).

Propargylamines. 1-Ethynylcyclohexylamine and 3-amino-3-ethyl-1-pentyne were commercially available (Aldrich). All other propargylamines were made by a previously reported method.[28]

Preparation of 3-Ethyl-1-pentyn-3-ol. This compound was prepared according to the procedure of Vaughn and co-workers,[10] and its preparation is representative of the preparation of tertiary propargyl alcohols. A 5-L, three-necked, round bottomed flask was fitted with an efficient mechanical stirrer mounted through a glass bushing along with two gas inlet tubes for acetylene and ammonia, both of which were immersed in liquid ammonia. The third neck of the flask was fitted with a dry ice condenser which was connected to a KOH drying tower by rubber tubing. The flask was flame-dried, purged with NH_3 gas, and insulated with a 5-L heating mantle. The flask was charged with 3500 mL of liquid ammonia, the stirrer was started and a rapid stream of acetylene was passed into the solution for about 30 min to saturate the solution. Additional ammonia gas was condensed in from time to time to keep the solution volume at about 4 L. Sodium (115 g, 5 mol) was cut into strips and added at such a rate that the entire solution

did not turn blue. The addition required about 1.5 h, depending on the rate of passage of acetylene. Stirring and addition of acetylene was continued for 1 h.

3-Pentanone (430.6g, 4.95 mol, 98%) was added dropwise over 1 h to the ammonia solution. The solution was stirred overnight. Then the heating mantle was removed, and the reaction mixture was allowed to stand until all the ammonia had evaporated. The solid residue was decomposed by adding about 1500 mL of ice and water. The mixture was carefully acidified with 50% H_2SO_4 (300-500 mL). The organic layer was dissolved in 400 mL of ether and washed with 200 mL of brine. The original aqueous phase and the brine wash were then extracted with two 200-mL portions of ether. The combined ethereal solutions were dried over anhydrous $MgSO_4$ and filtered, and the ether was removed under reduced pressure. The product was distilled under reduced pressure through a 15-cm Vigreux column. The yield of 3-ethyl-1-pentyn-3-ol was 520 g (93% yield): bp 135-136°C; ν_{max} 3413, 3300, 2970,1470, 1375, 910 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (6 H, t, J=7), 1.65 (4 H, q, J=7), 2.3 ((1 H, s), 2.38 (1 H, s); n^{25}_D 1.4207.

Preparation of 4-Methyl-3-isopropyl-1-pentyn-3-ol. Application of the above procedure to 2,4-dimethyl-3-pentanone gave 133 g of 4-methyl-3-isopropyl-1-pentyn-3-ol: 89% yield; bp 69°C (16 mm); ν_{max} 3490, 3315, 2970, 1475, 985 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (12 H, d, J=7), 1.92 (3 H, m, J=7), 2.35 (1 H, s); n^{25}_D 1.4435.

Preparation of 3-Chloro-3-ethyl-1-pentyne. The following procedure for the conversion of 3-ethyl-1-pentyne-3-ol to 3-chloro-3-ethyl-1-pentyne is representative for preparing the chlorides.[29] A 1-L, three-necked flask provided with a magnetic stirrer, thermometer,

and dropping funnel was charged with 56 g (0.5 mol) of calcium chloride, 40 g (0.4 mol) of Cu_2Cl_2 (95% brown powder), 400 mg of copper bronze powder, and 430 mL (5 mol) of cold concentrated hydrochloric acid. The mixture was flushed with argon and cooled (ice bath) with stirring. One mole of 3-ethyl-1-pentyn-3-ol (113.3 h) was added dropwise over 30 min. Stirring was continued for 1 h (0-5°C). The upper organic layer was separated and washed immediately with three 100-mL portions of cold concentrated hydrochloric acid, with two 100-mL portions of water, and once with 100-mL portion of saturated aqueous sodium carbonate. The colorless product was thoroughly dried with two portions of anhydrous K_2CO_3. Analysis of the sample by GLC (10% Carbowax 20M on Chromosorb W) showed the sample to be 96% pure. The chloride was used without further purification. The total isolated yield of the chloride was 73%: ν_{max} 3290, 2970, 1950, 1460, 1380, 1315, 835 cm^{-1}; NMR ($CDCl_3$) δ 1.47 (6 H, t, J= 7), 1.92 (4 H, q, J= 7), 2.58 (1 H, s), n^{25}_D 1.4387.

Preparation of 3-Chloro-3-methyl-1-pentyne. Application of the above procedure to 3-methyl-1-pentyn-3-ol (196 g, 2 mol) gave 176 g of 94% pure product (76% yield). This solution was used without further purification: ν_{max} 3290, 2975, 1950, 1460, 1380, 1210, 815, 750 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (3 H, t, H= 7), 1.73 (3 H, s), 1.93 (2 H, q, J= 7), 2.53 (1 H, s), n^{25}_D 1.3749.

Preparation of 3-Chloro-3-methyl-1-butyne. Application of the above procedure to 2-methyl-3-butyn-2-ol (168 g, 2 mol) followed by distillation at atmospheric pressure through a 20-cm Vigreux column gave 62 g of 97% pure product: 30% yield; bp 74-76°C; ν_{max} 3290, 2110cm^{-1}; NMR ($CDCl_3$) δ 1.82 (6 H, s), 2.57 (1H, s); n^{25}_D 1. 4156.

Preparation of 3-Chloro-5-methyl-3-isopropyl-1-pentyne. Application of the above procedure to 4-methyl-3-isopropyl-1-pentyn-3-ol (137 g) gave 115 g of the corresponding propargyl chloride (70%), 94% pure by GLC. The chloride was used without further purification: bp 57-60°C (15 mm); ν_{max} 3290, 2960, 1475, 1390, 810 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (12 H, d, J=6), 2.13 (2 H, m, J=6), 2.55 (1 H, s); n^{25}_D 1.4559.

Preparation of 3-Amino-3-ethyl-1-pentyne. The following procedure for converting 3-chloro-3-ethyl-1-pentyne into 3-amino-3-ethyl-1-pentyne is adapted from a published procedure [28] and is representative for preparing all other primary propargylamines from the corresponding propargyl chlorides. Sodium (24 g, 1.04 mol) was converted to the amide (catalyzed by 0.3 g of $FeCl_3$) in 1 L of liquid ammonia (anhydrous) in a 3-L, three-necked, round-bottomed flask provided with a mechanical stirrer, dry ice condenser, and a long stem gas inlet tube for introducing ammonia. Then 130.6 g of 96% pure 3-chloro-3-ethyl-1-pentyne (0.96 mol) diluted with 4 volumes of anhydrous ether was added dropwise over a 1.5 h period with continuous stirring. The flask was insulated with a 3-L heating mantle and allowed to stir overnight. The ammonia was allowed to evaporate, and chopped ice (500 g) and ether (150 mL) were then added. The ether layer was separated and the aqueous layer extracted once with 100 mL of ether. The combined ethereal extract was washed with cold water and filtered. The extract was acidified with concentrated HCl (60 mL). The ether layer was discarded and the mixture was extracted once with 50 mL of ether. The aqueous solution was then treated with 29 g of NaOH in 30 ml of water to release the amine which was recovered by extraction with ether. Distillation gave 81.2 g (73% yield) of pure 3-amino-3-ethyl

1-pentyne: bp 36-38°C (2 mm); ν_{max} 3360, 3290, 3280, 2080cm^{-1}; NMR ($CDCl_3$) δ 1.0 (6 H, t, J= 7), 1.53 (6 H, m), 2.27 (1 H, s); n^{25}_D 1.4392.

Prepararation of 3-Amino-3-methyl-1-butyne. About 105 g of 97% pure 3-chloro-3-methyl-1-butyne (1.0 mol) was added to sodamide (1.1 mol) in liquid ammonia. After workup, 35 g (42% yield) of 3-amino-3-methyl-1-butyne was obtained: bp 79-80°C (760 mm); ν_{max} 3370, 3290, 3210, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.4 (6 H, s), 1.67 (2 H, br s), 2.25 (1 H, s); n^{25}_D 1.4180.

Preparation of 3-Amino-3-methyl-1-pentyne. 3-Chloro-3-methyl-1-pentyne (120 g, 97%, 1.0 mol) was added to sodamide (1.1 mol) in liquid ammonia. After workup and distillation, 59 g (61% yield) of 3-amino-3-methyl-1-pentyne was obtained: bp 53-54°C (100 mm); ν_{max} 3360, 3300, 3290, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (3 H, t, J= 7), 1.53 (4 H, m), 2.25 (1 H, s); n^{25}_D 1.4302.

Preparation of 3-Amino-4-methyl-3-isopropyl-1-pentyne. 3-Chloro-4-methyl-1-pentyne (51 g, 0.32 mol) was added to sodamide(0.35 mol) in iiquid ammonia. After workup and distillation, 14.5 g (41% yield) of 3-amino-4-methyl-3-isopropyl-1-pentyne was obtained: bp 56-57°C (3 mm); ν_{max} 3370, 3290, 3250 cm^{-1}; NMR ($CDCl_3$) δ 0. 98 (12 H, d, J=6), 1.27 (2 H, br s), 1.85 (2 H, m, J= 6), 2.2 (1 H, s); n^{25}_D 1.4501.

Preparation of 3-Amino-3-ethyl-1-pentene from 3-Amino-3-ethyl-1-pentyne. This experiment was adapted from a previously published procedure.[8] Sodium metal (2.3 g, 0.1 mol) was added in small pieces with stirring to a solution of 22.2 g (0.2 mol) of 3-amino-3-ethyl-1-pentyne in a 500 mL, three-necked, round-bottoned flask containing 200 mL of anhydrous liquid ammonia. Ammonium chloride (0.1 mol, 5.4 g) was then added slowly. Alternate additions of sodium and ammonium

chloride were repeated until a total of 11.3 g (0.47 mol) of sodium and 27 g (0.5 mol) of ammonium chloride had been added. A constant total volume was maintained by periodic addition of ammonia. Ether (50 mL) was added, and the liquid ammonia was allowed to evaporate overnight. The mixture was filtered, and the solid was washed with two 50 mL portions of ether. The combined ether solutions were dried over anhydrous K_2CO_3. Distillation gave 9.44 g (42% yield) of 3-amino-3-ethyl-1-pentene; bp 128-129°C (760 mm); ν_{max} 3350, 3290, 3075, 1685 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (8 H, q, J=7), 1.42 (4 H, q, J= 7), 4.8-5.9 (3 H, m).

Attempted Coupling of 3-Amino-3-ethyl-1-pentyne with 3-Chloro-3-ethyl-1-pentyne in Aqueous KOH Solution. This experiment was adapted from a previously published procedure.[8] 3-Amino-3-ethyl-1-pentyne (4.5 g, 40 mmol), 2 mL of 40% KOH solution, 10 mg of copper bronze powder, and 8.6 g of 3-chloro-3-ethyl-1-pentyne were mixed together with 10 mg of Cu_2Cl_2 and maintained at 25-30°C. After 24 h, an additional 30 mL portion of KOH solution and 10 mg of copper bronze powder were added. Five additional 30 mL portions of KOH were added, one after each 24 h period. After the eighth day, an aliquot of the sample's organic layer was analyzed by GLC (10% Carbowax 20M Chromosorb W, AW-DMCS treated, 6 ft column). Analysis of the separated components indicated that the propargyl chloride had hydrolyzed to the propargyl alcohol, and the primary amine was recovered quantitatively. No high-boiling coupled products were seen.

Attempted Coupling of 3-Amino-3-ethyl-1-pentyne with 3-Chloro-3-ethyl-1-pentyne with Equimolar Quantities of either KH or $KOC(CH_3)_3$. Potassium hydride suspension (2 mmol, 0.5 mL of 5.4 M KH) was injected into a flame-dried, 10-mL, round-bottomed flask fitted with septum

inlet, a flow control valve and a Teflon-coated stirring bar. The flask was flushed with argon. The mineral oil was removed via syringe by washing with three 2 mL aliquots of dry pentane. Copper bronze powder (15 mg) was suspended in 2 mL of dry THF and injected into the flask. Then 1 mmol of 3-amino-3-ethyl-1-pentyne was injected. The flask was thermostated at 22°C, and a gas manometer was attached. Then 0.16 g (1 mmol) of 3-chloro-3-ethyl-1-pentyne was injected dropwise. About 0.8 mmol of H_2 was evolved over a 5 h period. After the reaction was quenched with H_2O (0.5 mL), no coupled secondary amine was detected by GLC. Identical results were obtained with NaH and $KOC(CH_3)_3$. In each case, there was partial H_2 evolution, but no coupled amine was formed.

Preparation of Bis(1,1-diethyl-2-propynyl)amine (16). The following procedure for the coupling of 3-amino-3-ethyl-1-pentyne with 3-chloro-3-ethyl-1-pentyne is representative for the formation of dipropargylamines. A 500 mL, round-bottomed flask equipped with a magnetic stirring bar, septum inlet, and gas inlet valve was flame-dried under argon. Copper bronze powder (220 mg) and freshly prepared Cu_2Cl_2 (220 mg) were added followed by 109 mL of DMF (dried over CaH_2 and distilled) and 3-amino-3-ethyl-1-pentyne (29.8 g, 260 mmol). The flask was flushed with argon for 10 min and cooled to 4°C in a cold room. Then 18.3 g (133 mmol) of 95% 3-chloro-3-ethyl-1-pentyne was injected. After 72 h, the solution was quenched with 30 mL of 20% aqueous NaOH (150 mmol). Water (100 mL) was added and the solution was steam distilled. The organic layer was separated from the distillate, and the aqueous layer was extracted with three 50 mL aliquots of ether. The combined ether extracts were dried over $MgSO_4$. The ether was removed under reduced pressure and the residue distilled through a short Vigreux

column. The primary propargylamine was recovered(12.7 g, 111 mmole, 87% of extra equivalent), and the coupled amine was distilled under vacuum; bp 61-64°C (0.5 mm). There was obtained 12.9 g (48% yield) of bis(1,1-diethyl-2-propynyl)amine: ν_{max} 3290, 2965, 2925, 2870, 1460, 1375, 1170 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (13 H, t, J= 7), 1.73 (8 H, q, J= 7), 2.25 (2 H, s); mass spectrum, m/e (relative intensity) 206 (M^+ + 1), 176 (17), 82 (100), 67 (16), 55 (15), 41 (15).

Preparation of Bis(1,1-dimethyl-2-propynyl)amine (12). 3-Chloro-3-methyl-1-butyne (0.5 mol, 51 g) was reacted with 3-amino-3-methyl-1-butyne (1.1 mol, 92.5 g) for 24 h and was worked up as previously described. After distillation, 52.5 g (70% yield) of bis(1,1-dimethyl-2-propynyl)amine was isolated: bp 60-65°C (20 mm); ν_{max} 3290, 2300, 1465, 1375, 1360, 1210, 1065 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (12H, s), 2.23 (2 H, s); mass spectrum, m/e (relative intensity) 149 (M^+), 134 (46), 118 (3), 91 (3), 68 (100), 67 (16), 41 (30).

Preparation of (1'-Ethyl-1'-methyl-2-propynyl)(1,1-dimethyl-2-propynyl)amine (13). 3-Chloro-3-methyl-1-pentyne (0.78 mol, 113 g) was reacted with 3-amino-3-methyl-1-butyne (2 mol, 168 g) for 72 h, and the mixture was worked up as previously described. After distillation, 79 g (62% yield) of the product was obtained; bp 60-62°C (5 mm); ν_{max} 3290, 2290, 1380, 1065 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (3 H, t, J= 7), 1.35 (1 H, s), 1.55 (9 H, s), 1.58 (2 H, m), 2.3 (2 H, s); mass spectrum m/e (relative intensity) 163(M^+), 68 (100).

Preparation of Bis(1-ethyl-1-methyl-2-propynyl)amine (14). 3-Chloro-3-methyl-1-pentyne (0.91 mol, 123 g) was reacted with 3-amino-3-methyl-1-pentyne (1.95 mol, 187 g) for 72 h and was was worked up as previously described. After distillation, 89g (55% yield) of product was isolated: bp 50-52°C (5mm); ν_{max} 3290, 2960, 2920, 2860, 1510,

1375, 1180 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (4 H, m), 1.41 (7 H, s), 1.60 (4 H, m), 2.25 (2 H, s); mass spectrum, m/e (relative intensity) 178 (M^++ 1), 148 (42), 82 (48), 68 (100), 53 (39), 41 (35).

Preparation of (1-Ethyl-1-methyl-2-propynyl)(1',1'-diethyl-2-propynyl)amine (15). 3-Chloro-3-ethyl-1-pentyne (0.75 mol, 98g) was reacted with 3-amino-3-methyl-1-pentyne (1.5 mol, 149 g) for 72 h and was worked up as previously described. After distillation, 79 g (55% yield) of product was isolated: bp 67-68°C (5 mm); ν_{max} 3310, 2970, 2880, 1470, 1380, 1170 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (10 H, t, J=6), 1.5 (3 H, s), 1.65 (6 H, q, J= 6), 2.2 (2 H, s); mass spectrum, m/e (relative intensity) 192 (M^++ 1), 162 (36), 82 (100), 68 (67), 53 (25), 41 (29).

Preparation of Bis(cyclohexylethynyl)amine. 1-Chloro-1-ethynyl-cyclohexane (1.08 mol, 154 g) was reacted with (1- ethynylcyclohexyl)-amine (2.16 mol, 265 g) for 48 h, and the mixture was worked up as previously described. After distillation, 155 g (65% yield) of product was obtained: bp 105-106°C (2 mm); ν_{max} 3290, 2300, 1070 cm^{-1}; mp 71-72°C; NMR ($CDCl_3$) δ 1.55 (13 H, m), 2.0 (8 H, m), 2.35 (2 H, s); mass spectrum, m/e (relative intensity) 230 (M^++ 1), (M^+), 229 (17), 200 (21), 186 (52), 172 (73), 118 (50), 80 (100), 67 (49), 41 (58).

Preparation of Bis(1,1-diethylallyl-1,1-diethyl-2-propynyl)amine (23). The procedure for preparing this compound was identical with the procedure for preparing the other secondary dipropargylic amines, except that a 2:1 molar ratio of 3-amino-3-ethyl-1-pentene to 3-chloro-3-ethyl-1-pentyne was used. Characterization and yield determination was accomplished by GLC: ν_{max} 3290, 3045 cm^{-1}; mass spectrum, m/e (relative intensity) 208 (M^++ 1), 188 (5), 178 (50), 84 (100), 82 (85), 67 (13), 55 (44): NMR ($CDCl_3$) δ 0.88 (13 H, q, J= 7), 1.4 (8 H, q, J= 7)

2.18 (1 H, S), 4.73-6.18 (3 H, m); yield (GLC) 17%.

Preparation of (1,1-Diisopropyl-2-propynyl)(1,1-diethyl-2-propynyl)amine. 3-Chloro-3-ethyl-1-pentyne (0.12 mol, 14.6 g) was added to 80 mL of DMF containing 0.16 g of Cu_2Cl_2, 0.16 g of copper bronze, and 3-amino-4-methyl-3-isopropyl-1-pentyne (0.24 mol, 30.2 g) at 0°C. The reaction mixture was allowed to react for 1 week at 4°C and then warmed to 23°C for 24 h. After workup, the mixture was distilled under vacuum to collect the high-boiling organic components. GLC analysis (10% Carbowax 20M) and collection of the highest boiling peak showed it to be the title compound: ν_{max} 3290, 2950, 2920, 2860, 1455, 1375, 1150, 1060 cm^{-1}; NMR δ 1.0 (19 H, m), 1.8 (6 H, br m), 2.05 (1 H, s), 2.15 (1 H,s); mass spectrum, m/e (relative intensity) 223 (M^+), 190 (60), 96 (100); yield (GLC) 5%.

Hydrogentation of Bis(1,1-diethyl-2-propynyl)amine (16) in Absolute Ethanol with 10% Palladium on Charcoal. A 50 mL, round-bottomed flask equipped with a magnetic stirring bar, septum inlet, and gas inlet valve was attached with rubber tubing to a mineral oil gas buret. A 10 mg sample of 10% palladium on charcoal (Engelhard Industries Inc.) and 4 mL of absolute ethanol (Gold Shield U.S.P.) were added. Hydrogen gas (Matheson 99.9%) was flushed through the system and the buret was charged with the same. The solution was cooled to 0°C with an ice bath. Them 1 mmol (0.23 mL) of 16 was added to the rapidly stirring solution. Hydrogen uptake was monitored with a gas buret and product formation via GLC (10% Carbowax 20M on Chromosorb W) at 160°C. Hydrogen uptake (74 mL, 2.9 mmol) ceased within 1 h. The GLC trace showed two distinct high-boiling products and a low-boiling product eluting with the solvent. Preparative GLC and subsequent

spectral analysis identified the high-boiling components as 3,4-dimethyl-2,2,5,5-tetraethyl-3-pyrroline 19 and 3-methylene-4-methyl-2,2-5,5-tetraethyl-3-pyrrolidine 20. Repeating the experiment with tridecane as an internal standard established the yields of 19 and 20 as 48% and 15%, repectively. Spectral data for 19; ν_{max} 2970, 2925, 2875, 2340, 1465, 1420, 1385, 990 cm^{-1}; ^{13}C NMR ($CDCl_3$, $SiMe_4$) δ 134.2, 70.69, 29.79, 8.69, 7.15; ^{1}H NMR ($CDCl_3$) δ 0.80 (13 H, t, J= 6), 1.43 (14 H, s, superimposed on m); mass spectrum, m/e (relative intensity) 209 (M^+), 180 (100), 152 (22), 136 (27). Spectral data for 20; ν_{max} 3055, 2069, 2035, 2860, 1650, 1460, 885cm^{-1}; NMR ($CDCl_3$) δ 0.83 (13 H, t, J= 6), 2.3 (8 H, m), 2.4 (1 H, m), 4.63 (2 H, t, J= 3); mass spectrum, m/e (relative intensity) 209 (M^+), 180 (100).

Hydrogenation of Bis(1,1-diethyl-2-propynyl)amine (16) in Absolute Ethanol with Platinum Oxide. The same experimental conditions were used as in the palladium-catalyzed procedure, except that 5 mg of PtO_2 was substituted for 5 mg of 10% palladium on charcoal. A total of 93 mL (3.8 mmol) of hydrogen was take up. By GLC, only trace amounts of of products (<2%) having the same retention times as 19 and 20 were seen; the rest of the starting material was hydrogenated to 1,1-diethyl-1-aminopropane.

Hydrogentation of Bis(1,1-diethyl-2-propynyl)amine (16) to Bis-(1,1-diethylallyl)amine (23) in Ligroin. A 10 mmol sample of 16 (2.05 g) was dissolved in 30 mL of ligroin in a 250 mL centrifuge bottle. Then 20 mg of 10% palladium on charcoal was added. The bottle was placed on a Parr hydrogenation apparatus and hydrogenated for 10 h; the initial H_2 pressure was 50 psi and the pressure dropped 37 psi. The GLC analysis revealed three peaks, one of which was 23. Its spectral

properties were identical with the semihydrogenation product obtained by using W4 or W6 Raney nickel in ethanol. Addition of 10 mL of absolute ethanol to the ligroin solution and continuation of the hydrogenation completely hydrogenolyzed the bis(1,1-diethylallyl)amine. Spectral data for the diallyl amine are as follows: ν_{max} 3390, 3045, 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.75 (13 H, t, J= 7), 1.43 (8 H, q, J= 7), 4.67-6.0 (6 H, m); mass spectrum, m/e (relative intensity) 209 (M^+), 180 (100).

Hydrogenation of Bis(1,1-diethyl-2-propynyl)amine in Absolute Ethanol with W2 Raney Nickel Catalyst. Raney nickel alloy was activated by a literature procedure.[30] W2 Raney nickel (2 g) was added to a solution of 40 mL of absoute ethanol and 10 mmol (2.05 g) of 16 in a 500 mL centrifuge bottle. The bottle was placed in a Parr hydrogenation apparatus and purged with hydrogen five or six times. The bottle was pressurized to 60 psi and the shaker turned on. The pressure dropped 5 psi in 18 h. The solution was filtered to remove the catalyst and the ethanol evaporated under reduced pressure. Bulb to bulb distillation [62-64°C (0.2 mm)] gave 0.54 g (20%) of the saturated amine 21. GLC analysis (5% OV-101 Chromosorb W, AW-DMCS treated) showed the sample to be 95% pure; the remaining 5% was bis(1,1-diethylallyl)-(1,1,1-triethylcarbinyl)amine.

The same experiment was performed with W4 and W6 Raney nickel under identical conditions. Tridecane was added as an internal standard in each case. Analysis of the products of each experiment by GLC showed that as the reactivity of the catalyst increased, the degree of hydrogenation of the dipropargyl secondary amine decreased. Thus W2 Raney nickel was the most satisfactory catalyst for the hydrogen

ation of 16 to the saturated secondary amine 21. The same experiment was performed under identical conditions, except that 20 mmol (1.12 g) of potassium hydroxide was dissolved in the ethanolic solution of 16 before the W2 Raney nickel catalyst was added. The catalyst was filtered and the ethanol was remove under reduced pressure. Water (20 mL) was added to the viscous residue. The solution was transferred to a separatory funnel and the aqueous layer extracted with two 20 mL portions of ether. The ether layer was pooled, dried over anhydrous potassium carbonate and then evaporated under reduced pressure. About 1.52 g (71% yield) of the saturated amine was obtained (93% pure). The remaining unsaturated secondary amine was separated by spinning-band distillation. All subsequent hydrogenations with the remaining dipropargylamines were carried out under identical conditions with the same proportions of amine, solvent, catalyst and base and were scaled up to a 50 mmol scale. In the case of bis(cyclohexylethynyl)amine, hydrogenation without KOH gave a higher yield and increased purity of the saturated amine than when KOH was present. The amount of semihydrogenated amine decreased from a maximum of 9% for the most hindered amine 21 to 3% for the least hindered amine 24.

Product Analysis of Bis(1,1-diethyl-2-propyl)amine (21): NMR ($CDCl_3$) δ 0.78 (19 H, t, H= 7), 1.4 (12 H, q, J= 6); mass spectrum, m/e (relative intensity) 214 (M^++ 1), 184 (8), 86 (100), 57 (32), 56 (10), 43 (14), 41 (23); yield 7.6 g (71%). Anal. Calcd for $C_{14}H_{31}N$: C, 78.79; H, 14.64; N, 6.56. Found: C, 78.68; H, 14.57; N, 6.60.

Product Analysis of Bis(1,1-dimethyl-2-propyl)amine (24): NMR ($CDCl_3$) δ 0.83 (7 H, t, J= 6), 1.06 (12 H, s), 1.13 (4 H, q, J= 6); mass spectrum, m/e (relative intensity) 156 (M^++ 1), 142 (7), 128 (7), 58

(100), 43 (30); yield 6.4 g (80%). Anal. Calcd for $C_{10}H_{23}N$: C, 76.35; H, 14.74; N, 8.90. Found; C, 76.16; H, 14.57; N, 8.83.

Product Analysis of (1'-Ethyl-1'-methyl-2-propyl)(1,1-dimethyl-2-propyl)amine (25): NMR ($CDCl_3$) δ 0.80 (10 H, t, J= 6), 1.1 (6 H, s), 1.4 (6 H, q, H= 6); mass spectrum, m/e (relative intensity) 172 (M^++ 1), 142 (17), 86 (11), 72 (100), 58 (64), 43 (33); yield 6.7 g (78%). Anal. Calcd for $C_{11}H_{25}N$: C, 77.12; H, 14.71; N, 18.18. Found: C, 76.84; H, 14.57; N, 8.09.

Product Analysis of Bis(1-ethyl-1-methyl-2-propyl)amine (26): NMR ($CDCl_3$) δ 0.52 (1 H), 0.8 (12 H, t, J= 6), 1.05 (6 H, s), 1.3 (8 H, q, J= 6); mass spectrum m/e (relative intensity) 186 (M^++ 1), 156 (15), 86 (16), 72 (100), 55 (17), 43 (46); yield 7.0 g (75%). Anal. Calcd for $C_{12}H_{27}N$: C, 77.76; H, 14.68; N, 7.56. Found: C, 77.70; H, 14.58; N, 7.46.

Product Analysis of (1-Ethyl-1-methyl-2-propyl)(1',1'-diethyl-2-propyl) amine (27): NMR ($CDCl_3$) δ 0.49 (1 H, s), 0.78 (15 H, t, J= 6), 1.05 (1H, s), 1.35 (10 H, q, J= 6); mass spectrum, m/e (relative intensity) 200 (M^++ 1), 170 (14), 112 (2), 86 (100), 72 (95), 57 (26), 43 (39); yield 7.5 g (75%). Anal. Calcd for $C_{13}H_{29}N$: C, 78.31; H, 14.66; N, 7.03. Found: C, 78.43; H, 14.54; N, 7.08.

Product Analysis of Bis(1-ethylcyclohexyl)amine (28): NMR ($CDCl_3$) δ 0.80 (7 H, t, H= 6), 1.40 (24 H, m); mass spectrum m/e (relative intensity) 237 (M^+), 184 (4), 128 (4), 98 (11), 86 (100), 72 (15), 57 (20) yield 9.5 g (80%). Anal. Calcd for $C_{16}H_{31}N$: C, 81.01; H, 13.08; N, 5.91. Found: C, 81.11; H, 12.94; N, 5.79.

Reaction of Bis(1,1-diethyl-2-propyl)amine (21) with Methyl Iodide. Methyl iodide (0. 75 mL, 10 mmol) was added to a 50 mL, round-bottomed flask containing a stirring bar, side arm septum, gas inlet valve and 25 mL of THF. Then 10 mmol (2.52 mL) of 21 was injected. The flask was sealed, and the solution was stirred for 2 weeks. The solvent was evaporated under reduced pressure and the product analyzed by GLC and NMR spectroscopy. Analysis showed that no ammonium salt was formed; 21 was recovered quantitatively.

Reaction of $BF_3 \cdot OEt_2$ with Bis(1-ethylcyclohexyl)amine (28). $BF_3 \cdot OEt_2$ (1 mmol; distilled and stored under argon, 0.125 mL) was added to hexane (1 mL) under argon in a round-bottomed flask equipped with a gas inlet valve, septum side arm, and stir bar. A white air-stable solid was quickly formed. Drying under vacuum overnight gave a white crystalline powder free of ether (by NMR): NMR ($CDCl_3$) δ 1.05 (6 H, t, J= 7), 1.6 (20 H, br m), 1.95 (4 H, br q, J= 7), 5.6 (1 H, br s); mass spectrum, m/e (relative intensity) 237 (M^+), remainder identical with spectrum of free amine. Anal. Calcd for $C_{16}H_{31}NBF_3$: C, 62.96; H, 10.23; N, 5.69; B, 3.54: F, 18.67. Found: C, 61.11; H, 10.34; N, 4.39; B, 4.83; F, 19.22.

Reaction of $BF_3 \cdot OEt_2$ and BF_3 Gas with Bis(1,1-diethyl-2-propyl)amine (21). $BF_3 \cdot OEt_2$ (1 mmol, 1.125 mL) and 21 (1 mmol, 0.25 mL) were injected into a pyrolysis tube, and the glass tube was flame sealed. The neat solution reacted for 1 h at 25°C. The tube was opened and the liquid removed. The remaining air-stable solid was analyzed by NMR and mass spectroscopy. It was identified as the aminolysis product $(CH_3CH_2)_3CNH_2BF_3$: NMR ($CDCl_3$) δ 0.93 (6 H, q, J= 6), 5.76 (2 H, s, D_2O exchangeable); mass spectrum, m/e 184 (M^+).

Repeating the same reaction but with BF_3 gas (24 mL) gave a liquid fraction as well as the BF_3 amine complex. The liquid was identified by NMR and mass spectrometry as 3-ethyl-2-pentene.

Titration of Amine Hydrochlorides in 90% Ethanol with 0.1075 N KOH under Argon. The procedure for the titration reactions were taken from a previously reported procedure.[15] Potassium hydroxide was prepared by dissolving potassium metal in absolute ethanol under argon and diluting with degassed H_2O to the required concentration. All solutions were stored in polypropylene containers under argon. All transferring of solutions was done via cannula, and the titrations were done under argon. The amines were converted to the hydrochlorides by stoichiometric titration with standardized aqueous HCl (0.0954 N). Water was removed from the amine hydrochlorides by drying for 1 week under high vacuum in a desiccator over phosphorus pentoxide. The titration was followed by using an Orion 1601-A Digital Ionalizer with a Markson combination pH reference electrode at 20°C. All of the titrations were carried out so that the solution was 0.01 N at the equivalence point. The pK_a was calculated as the pH of the solution at half the equivalence point volume. All titrations were carried out three times, and the theoretical equivalence point was within 0.25% of the experimental value. In each case, only a single inflection point was observed. For a discussion on the effect of ethanol on the apparent strength of organic amine bases and for a method frequently used for the extrapolation of the pK_a from solutions which are progressively less alcoholic, see the paper by Hall et al.[16a]

Melting Points of Saturated Amine Hydrochlorides. The melting points are as follows: diisopropylamine·HCl= 214-216°C, tetramethylpiperidine·HCl= >270°C, bis(1,1-dimethyl-2-propyl)amine·HCl= 196-197°C, (1'-ethyl-1'-methyl-2-propyl)(1,1-dimethyl-2-propyl)amine·HCl= 158-160°C, bis(1-ethyl-1-methyl-2-propyl)amine·HCl= 142-144°C, (1-ethyl-1-methyl-2-propyl)(1',1'-diethyl-2-propyl)amine·HCl= 144-145°C, bis(1-ethylcyclohexyl)amine·HCl= 190-192°C and bis(1,1-diethyl-2-propyl)amine·HCl = >260°C.

Preparation of Bis(1,1-dimethyl-2-propyl)chloramine. The following procedure for the synthesis of the chloramine adduct of 24 is representative of the n-chlorosuccinamide procedure. To a 25 mL round-bottomed flask were added 6 mmol of N-chlorosuccinamide (0.67 g) and 10 mL of ether. The heterogeneous mixture was stirred for 10 min at 22°C and 5 mmol of 24 (1.01 mL) was added to the mixure. Monitoring by NMR showed that the reaction was completed in 4.5 h. The succinamide was filtered from the solution and the ether layer washed 3 times with 3 mL aliquots of water. The ether was dried with anhydrous sodium sulfate and removed under reduced pressure.

Preparation of Bis(1,1-dimethyl-2-propyl)chloramine with Chlorine and Sodium Hydroxide. This procedure for forming the chloramine of 24 is representative for forming chloramines of 21 and 26. A 25 mL Bantamware round-bottomed flask was fitted with a Teflon stirring bar, septum side arm, and a gas inlet valve. The flask was charged with 4 mL of hexane, 2 mL of 1.18 N NaOH and 2 mmol of 24 (0.40 mL). The flask was cooled to 0°C and 55 mL of chlorine gas (2.2 mmol) was added by syringe. The reaction was complete within 10 min. The solvent was removed under reduced pressure and the chloramine was added to an NMR

tube with an equal molar amount of benzene. The yield of chloramine 24 was 95% by NMR. There were no signals at δ 1.07 or 1.3 (relative to TMS), corresponding to the methyl and methylene protons of the free amine 24. Spectral data; ν_{max} no N-H bend at 1500cm^{-1}; NMR (CCl_4) δ 0.89 (6 H, t, J= 6), 1.27 (12 H, s), 1.57 (4 H, q, J= 6).

Preparation of Bis(1-ethyl-1-methyl-2-propyl)chloramine Using Chlorine and Sodium Hydroxide. Hexane (10 mL), 5 mL of 1.18 N NaOH and 1.12 mL of 26 (5 mmol) were added to a round-bottomed flask as previously described. The yield by NMR was 93%. Spectral data; ν_{max} no N-H bend at 1510cm^{-1}; NMR (CCl_4) δ 0.93 (12 H, t, J=6), 1.32 (6 H, s), 1.63 (8 H, q, J= 6).

Preparation of Bis(1,1-diethyl-2-propyl)chloramine using Chlorine and Sodium Hydroxide. Carbon tetrachloride (2 mL), standard NaOH (2 mL, 1.18 N) and 2 mmol of 21 (0.51 mL) were added to a round bottomed flask as previously described. Then 55 mL of chlorine gas was added by syringe to the stirring solution at 0°C. The reaction was complete within 30 min. The NMR spectrum could not be taken in chloroform because a chemical reaction occured in which the NMR tube became hot and the reaction mixture turned red. The NMR spectrum showed that the chloramine decomposed within 1 h at room temperature. Spectral data; NMR (CCl_4) δ 0.9 (18 H, t, J= 6), 1.77 (12 H, q, J= 6); ν_{max} no N-H bend at 1510cm^{-1}.

Attempted Chlorination of Pentane in 90% Trifluoroacetic Acid: 10% Sulfuric Acid with Bis(1-ethyl-1-methyl-2-propyl)chloramine at 0°C. Chloramine 26 (1.1 g, 3.5 mmol) was added to a quartz flask under subdued light containing 25 mL of 90:10 (v/v) mixture of trifluoroacetic acid - sulfuric acid under argon. The flask's contents immediately turned red. Then a five fold molar excess of pentane (3.4 mL) was

added to the mixture by syringe. The flask was irradiated by a 300W sunlamp placed 18" from the cooling bath (5°C) immersed reaction mixture. The flask was irradiated for 2 h until a test for positive Cl became negative (formation of I_2 with aqueous KI). The contents of the flask darkened to a soot brown during the irradiation. The products were isolated by pouring the reaction flask's contents into 100 mL of chopped ice. The organic layer (0.5 mL) was washed with water and analyzed by GLC using a 50' x 1/8" 20% SE-30 Chromosorb W column. No products corresponding to either 1, 2 or 3 - chloropentane were observed. The organic layer consisted of pentane and high boiling organic components (> 270°C)

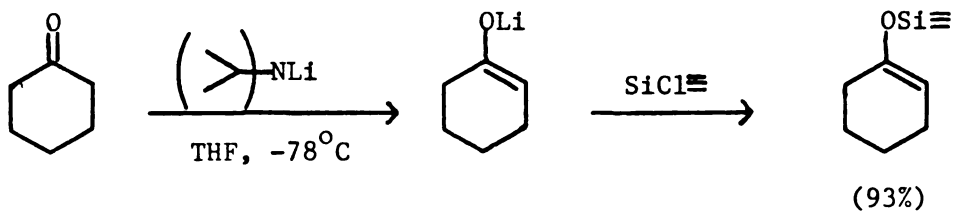
Identical results were obtained for chloramines corresponding to 21, 24, and 28. No chloropentanes were obtained when $FeCl_3$ was substituted as the free radical initiator in each of the previously described reactions.

CHAPTER II

THE SYNTHESIS AND STABILITY OF HINDERED SECONDARY LITHIUM AMIDES

INTRODUCTION

Lithium dialkylamide bases have achieved widespread applications in organic synthesis during the last decade. Since the early investigations by Levine [31] in which lithium and sodium diisopropylamide (LDA and NaDA) were used to metallate picoline, hindered lithium amides have enjoyed widespread application as powerful nonnucleophilic proton selective bases. Their most common application has been as bases for proton removal from weakly acidic compounds. Ketones[32] and esters[33] are completely and rapidly deprotonated by lithium amide bases in ethereal solvents to give the corresponding enolate anions (eqs 44 and 45).



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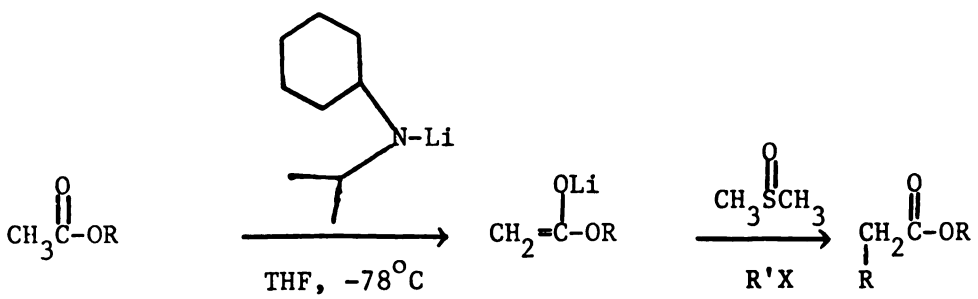
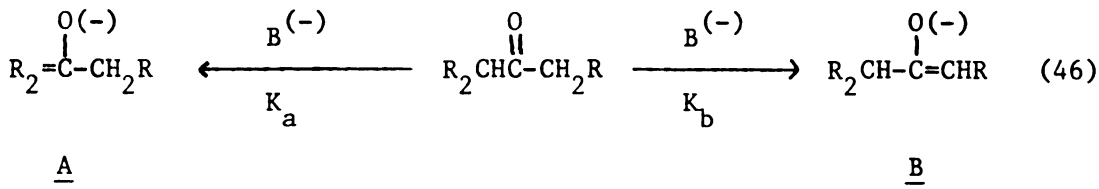


(45)

Hindered lithium amides are very useful for the regioselective generation of ketone enolates. By adjusting the conditions under which a ketone enolate mixture is formed, it is possible to establish

either kinetic or thermodynamic control. Kinetic control will be observed when the enolates, once formed, are interconverted only slowly. This situation is seen when very strong bases such as hindered lithium amides are used in an aprotic solvent in the absence of excess ketone. The small lithium cation is tightly coordinated to the oxygen atom of the enolate anion and this tends to decrease the rate of proton exchange reactions (eq 46).

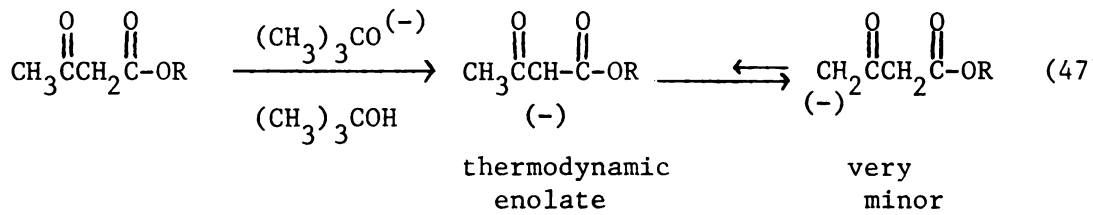


(46)

The conditions for kinetic control usually favor the less substituted enolate B, probably because removal of the less hindered hydrogen is more rapid, for steric reasons, than removal of the more hindered proton. On the other hand, at equilibrium, it is the more substituted enolate A that is usually the dominant specie. This is because the stability of the carbon-carbon double bond increases with increased substitution.

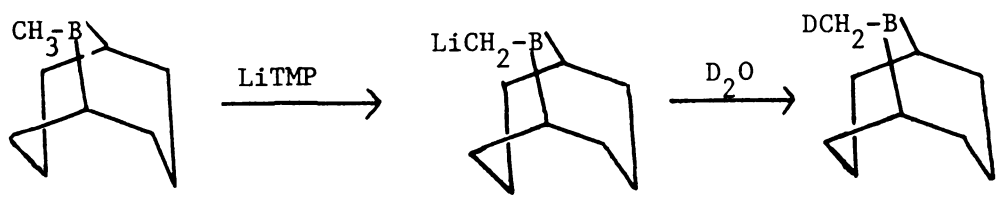
For weakly acidic compounds such as ketones, lithium amide bases are well suited to kinetic enolate formation because of two principle features. They are very strong bases ($pK_a \sim 35$-38) which completely and rapidly enolize relatively weakly acidic compounds. A consistant relationship is found in that kinetic control in enolate formation usually favors the less substituted regioisomer. For relatively acidic compounds such as diketones or β-ketoesters, secondary or tertiary alkoxide bases are sufficiently basic ($pK_a \sim 16$-19) for quantitative enolate formation. The resulting carbanion is more stable than the

isomeric anion in which only one of the carbonyl substituent can delocalize the negative charge (eq 47).



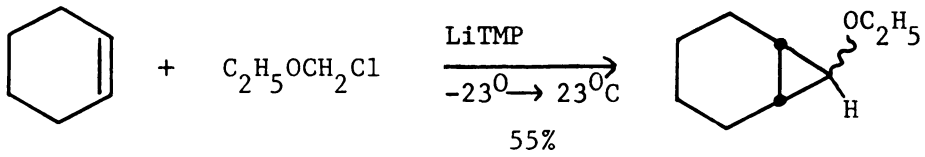
(47)

Besides showing increased regioselectivity in ketone enolate formation, hindered lithium amides apparently are thermodynamically stronger bases than less hindered amide bases. Presently, 2,2,6,6-tetramethylpiperidine is the most hindered secondary amine commercially available. The corresponding lithium amide has found applications in organic synthesis which other less powerful amide bases have been unable to fulfill. Rathke and Kow[34] report that lithium tetramethylpiperidine (LiTMP) or lithium tert-butylneopentylamine can remove the α-proton from an organoborane to generate carbanions (eq 48).



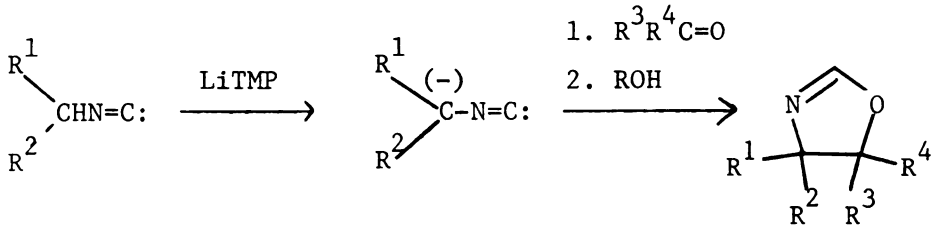
(48)

Other applications of LiTMP, where less basic secondary lithiums fail to react, include the synthesis of cyclopropyl ethers by reaction of excess alkene with chloromethyl ethers and LiTMP.[35] The base removes HCl from the ethers with formation of ROCH: (eq 49).



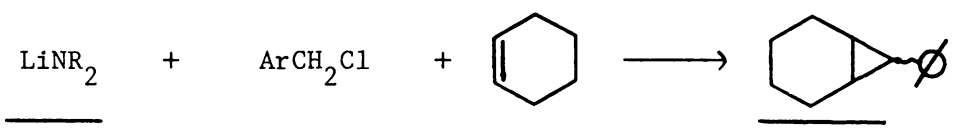
(49)

Even weakly acidic isocyanides that are not metallated by n-butyllithium can be metallated in the α-position by LiTMP.[36] The reaction has been used as the first step in a synthesis of 2-oxazolines (eq 50).



(50)

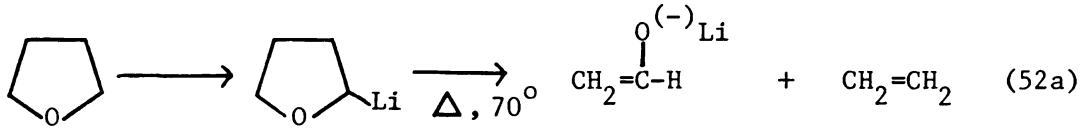
Olofson has shown that as lithium amide bases become more hindered, they become more effective bases for the synthesis of arylcyclopropanes[37] (eq 51).



R = Et	19%
R = i-propyl	39%
R = (i-pro)(cy)	41%
R = $(cy)_2$	45%
R = $[(CH_3)_2CCH_2{-}]_2CH_2$	54%

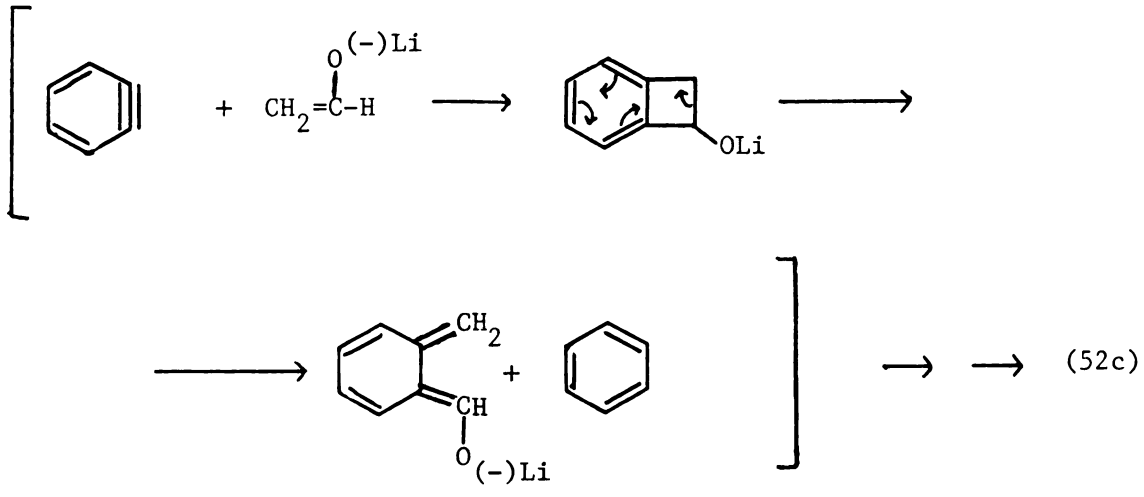
(51)

Finally, the hindered amide LiTMP is a powerful enough base to convert THF to the enolate anion of acetaldehyde as well as to convert bromobenzene to benzyne. These two components react <u>in situ</u> to form anthracene[38] (eq 52a-c).



(52a)

(52b)



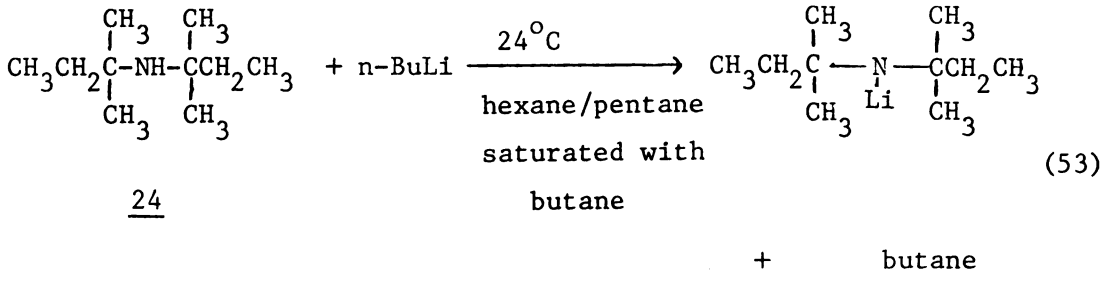
(52c)

66% overall yield

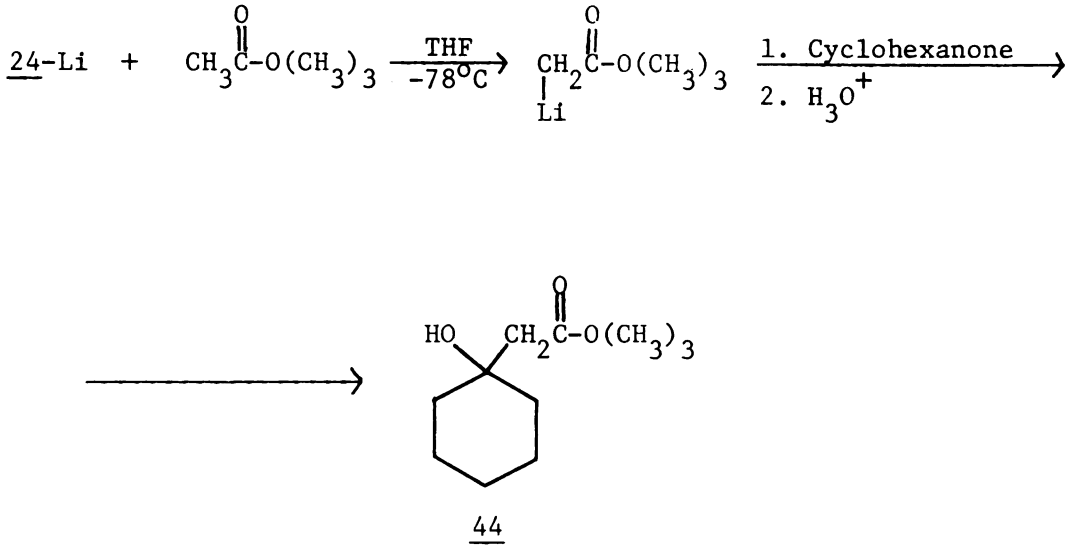
Because hindered secondary amides such as LiTMP exhibit some unique metallating properties, we undertook to synthesize the sodium and lithium amides of the very hindered amines in Chapter I. We will describe attempts at metallating the amines with various alkyl and aryl metal reagents. We will describe the successful lithiation of all the hindered amines in Table I by chelate assisted metallation with n-butyllithium. Factors will be described which effect the rate of amine metallation. Finally, the stability of hindered lithium amides in THF and diethyl ether will be investigated, along with the study of the relative stability of each amide in Table I. An explanation for the observed results will be suggested.

RESULTS

Initial attempts to metallate the series of hindered amines described in Chapter I focused on n-alkyl and aryl lithium metallation of the least hindered amine in the series, compound 24. We were completely unsuccessful in metallating 24 under a variety of conditions. Two criteria were used to verify metallation of 24. They are quantitative butane evolution as measured by manometry and quantitative β-hydroxyester formation by ester enolate condensation with cyclohexanone (eq 53,54).



24 + n-BuLi —(24°C, hexane/pentane saturated with butane)→ + butane (53)



(54)

44

Methyllithium in ether (2.1 M) was diluted with anhydrous ether to a 1.0 M solution. One equivalent of 24 was added and gas evolution was monitored over 7 h. Initially, about 40 mL of gas evolved within the first hour with a total of 60 mL evolving over 7 h. At STP one mmol of gas occupies about 25 mL, therefore the calculated gas displacement for the 3 mmole reaction is 75 mL. Apparently, the reaction was 85% complete within 7 h. By NMR, no methyllithium remained in the ether solution (δ = -1.7 using TMS as the reference standard). After removing the ether solvent under reduced pressure and treating the reaction mixture with tert-butyl acetate, cyclohexanone and aqueous acid, we observed only an 8% yield of 44. A control reaction using LiTMP made from TMP and methyllithium gave a 97% yield of 44 by GLC analysis.

The same reaction sequence was repeated with n-butyllithium and phenyllithium substituted for methyllithium. Very slow gas evolution from the butane saturated reaction mixture (20 mL butane in 8 h) was observed with n-butyllithium. Quenching the n-butyllithium-amine

mixture with t-butyl acetate and cyclohexanone gave a 10% yield of the β-hydroxy ester 44. The same reaction sequence with phenyllithium in benzene gave, after 10 h, 9% of 44.

Since alkyl and aryllithium reagents apparently metallate 24 poorly, we decided to use the more powerful metallating agent phenylsodium. Phenylsodium was synthesized from chlorobenzene and sodium metal dispersion. The reaction of 24 with phenylsodium in hexane for 12 h gave, after quenching with tert-butyl acetate and cyclohexanone, a 4% yield of 44. Thus phenylsodium is apparently as poor a metallating agent for 24 as are the previously mentioned alkyllithium reagents. Phenylsodium is insoluble in hexane, and the addition of 24 did not bring it into solution. There was no change in the appearance of the heterogeneous reaction mixture during the course of the reaction.

The next course of action was to return to the soluble alkyl lithium reagents and repeat the reactions with 24 using the amine ligand chelating agent N, N, N', N'-tetramethylethylenediamine (TMEDA) to assist in the metallation of 24. Ligands like TMEDA coordinate to the lithium ion of alkyl lithium reagents and break up the organolithium aggregates that are found in solution. The resulting monomeric alkyllithiums are generally more reactive metallating agents than the uncomplexed aggregates.

TMEDA was added to n-butyllithium (1:1 mol equivalent), and enough hexane was added to make a one molar solution, which was then saturated with butane. Upon injection of 3 mmol of 24 into the reaction mixture, (thermostated at 22.0°C) there was an immediate and quantitative evolution of butane (74 mL), as measured manometrically. The hexane solvent was removed under reduced pressure and replaced with THF. The

flask was immediately cooled to -78°C and quenched with tert-butyl acetate and cyclohexanone, as previously described, to give a 97% yield of 44. This was taken as confirmation that nearly quantitative metallation of 24 had been achieved. A control reaction with 24, TMEDA and n-butyllithium was performed to establish that neither the lithium amide nor n-butyllithium was metallating TMEDA. The reaction mixture was quenched with deuterium oxide and examined with proton NMR. Product analysis showed that the TMEDA had not been metallated.

The same reaction sequence was repeated with diisopropylamine, TMP, 21, 25, 26 and 27. The progress of the metallation reaction was followed by monitoring butane evolution with a mercury filled manometer. Metallation of the hindered amines was confirmed by the quantitative formation of 44 obtained by quenching each amide solution with tert-butyl acetate and cyclohexanone in either THF or diethyl ether. At least a 96% yield of 44 was obtained with each amide solution studied. Table IV lists the data for these metallation reactions. The reactions were run at 1 molar concentration in n-butyllithium and hindered amine, using 1.0 and 0.5 mol equivalents of TMEDA. The data is based on the volume of butane evolved with respect to time. The numbers T_{50} and T_{90} represents 50% and 90% evolution of butane, respectively.

Table IV. Amide Formation in Hexane (T_{50} and T_{90}) with n-Butyllithium

$$R_2NH \xrightarrow[\text{hexane, } 22.0^{\circ}C]{\text{n-butyllithium, TMEDA}} R_2NLi + \text{butane}$$

100% TMEDA	T_{50}	T_{90}
LDA	<1 min	<1 min
LiTMP	<1 min	<1 min
24-Li	<1 min	<1 min
25-Li	<1 min	<1 min
26-Li	1.5 min	4 min
27-Li	10 min	25 min
21-Li	3 h	20 h

50% TMEDA	T_{50}	T_{90}
LDA	<1 min	<1 min
LiTMP	<1 min	<1 min
24-Li	<1 min	<1 min
25-Li	<1 min	1 min
26-Li	10 min	35 min
27-Li	65 min	265 min
21-Li	7 h	40 h

Stability of Hindered Lithium Amides in THF and Diethyl Ether.

The stability of these hindered lithium amides in THF and diethyl ether solution was examined. The hindered lithium amides were synthesized using n-butyllithium and one equivalent of TMEDA. The hexane solvent was removed under vacuum and the remaining amide-TMEDA complex was dissolved in either THF or diethyl ether at 24°C. At least six reactions for each amide were performed in THF and diethyl ether. The ethereal solutions were quenched with tert-butyl acetate and cyclohexanone at time intervals rangeing form 15 min to 13 h. A steady, continuous decrease in the yield of 44 with time was observed, reflecting a slow decomposition of the hindered amide. The reaction products formed by attack of the lithium amides on the ether solvents are apparently incapable of enolizing the tert-butyl ester. The yield of 44 obtained in the quenching experiments provides a method for monitoring how fast each amide attacks THF and diethyl ether.

Figure 1 shows the rate of decomposition of the metallated hindered amides in THF. Figure 2 shows the decomposition rate of the same metallated amides in diethyl ether. Amine 21 was not included in the study because the amine peak appeared in the GLC trace at the same position as the β-hydroxy ester 44. All reactions were carried out using a one molar concentration of amide in ethereal solution at 24°C.

In THF, amides 24-Li and 25-Li appear to be the least stable of the six studied, whereas in diethyl ether, LiTMP is by far the least stable amide. Apparently, LiTMP attacks diethyl ether just about as fast whether or not TMEDA is present. In THF, LiTMP, LDA and 27-Li are fairly stable (T_{50} > 6 h). In diethyl ether solution, LDA and lithium

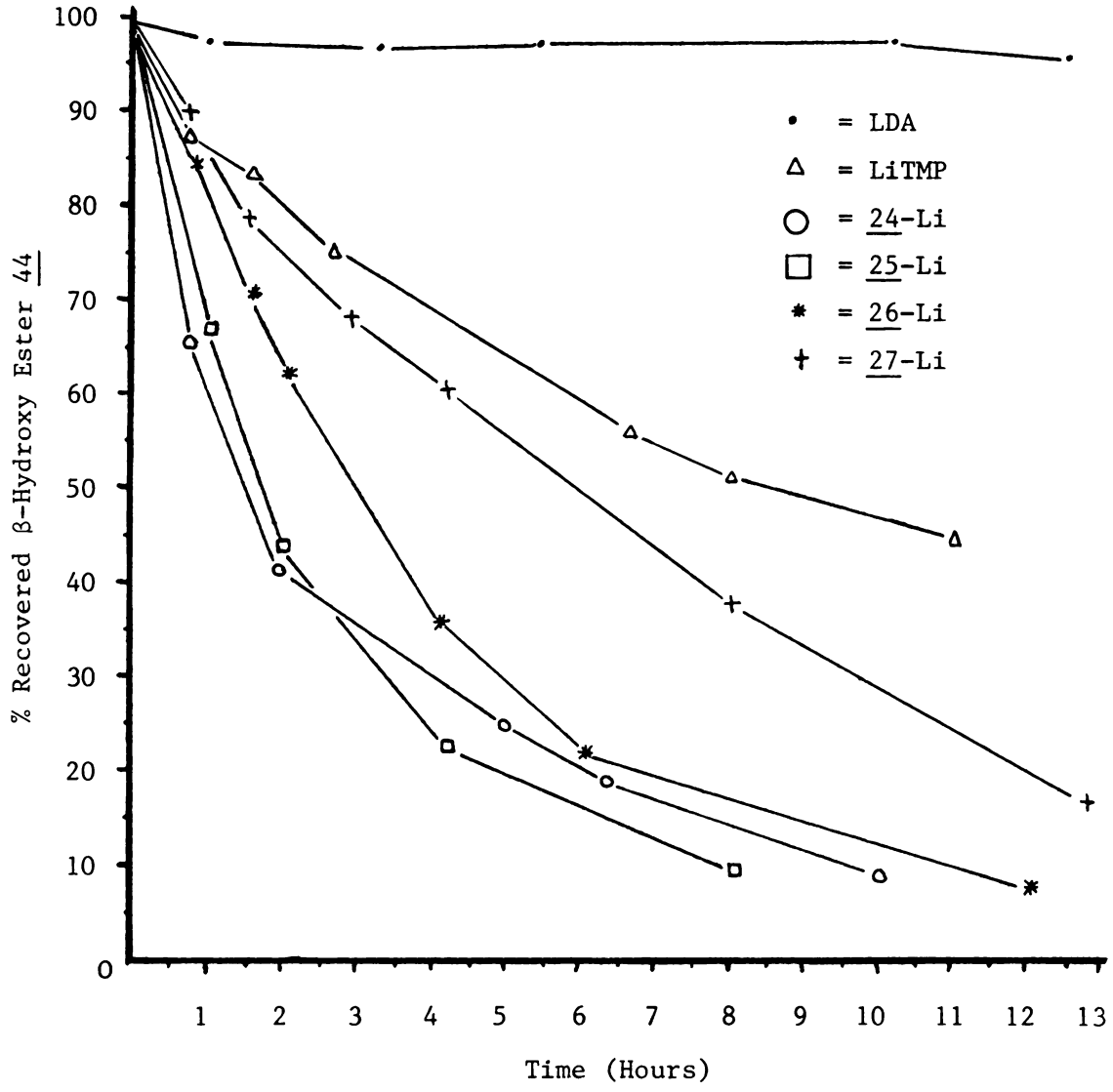


Figure 1. Lithium Amide Stability in THF at 24°C. Recovered 44 After Quenching by tert-Butyl Acetate and Cyclohexanone at -78°C. All Amides Made with TMEDA (1 equivalent).

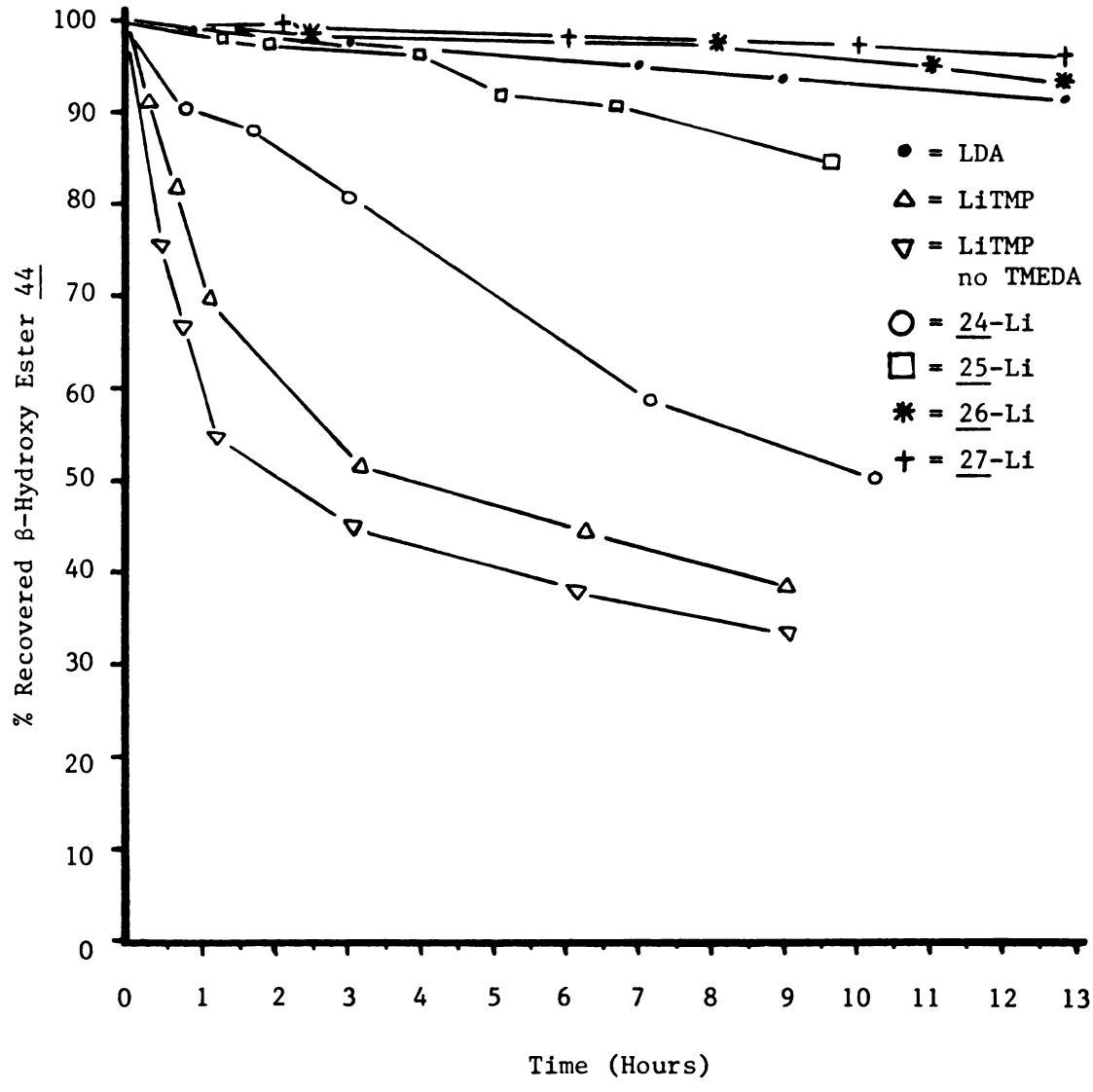


Figure 2. Lithium Amide Stability in Ether at 24°C. Recovered 44 After Quenching by tert-Butyl Acetate and Cyclohexanone at -78°C. All Amides Made with TMEDA (1 equivalent).

amides of 24, 25, 26 and 27 are all quite stable (T_{50} > 12 h).

Comparing the stability of all the amides in both THF and ether, one observes that, except for LiTMP, all of the amides studied are more stable in ether than in THF. A discussion of the amide formation reactions and the amide stabilities in ethereal solvents is presented in the next section.

DISCUSSION

Metallation of simple primary and secondary aliphatic amines is a well established experimental procedure. Lithium and sodium amide have both been made by lithium and sodium reduction of liquid ammonia.[10] Primary amines have been metallated by sodium and lithium alkyl reagents as well as by potassium hydride.[40] However, the most useful metal amides are the sterically hindered secondary lithium amides. They are easily made by reacting commercially available amines such as diisopropylamine and tetramethylpiperidine with hydrocarbon-soluble alkyl lithium reagents. These hindered amides achieved a prominent role in organic synthesis because they are very basic ($pK_a \sim$ 35-38) non-nucleophilic organic bases.

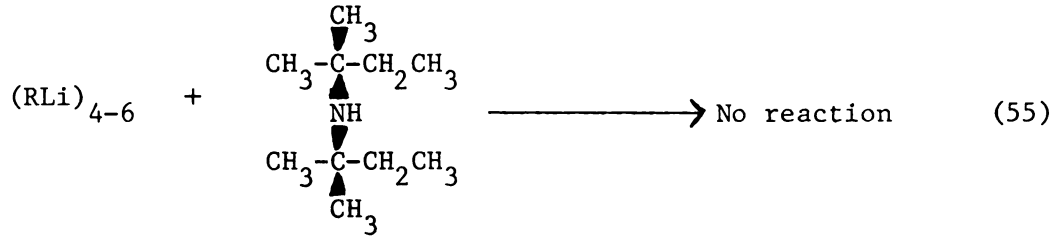
The goal of this study was to devise a procedure for the metallation of hindered secondary amines and to determine whether the corresponding amides exhibited distinctive chemical properties related to their steric bulk.

Neither phenyl or n-butyllithium metallated amine 24 within a period of time sufficient for less hindered amines. The criteria used to judge whether an amine was metallated were the enolization of tert-butyl acetate by the amide to give, after condensation with cyclohexanone, the hydroxy ester 44. None of the two lithium reagents mentioned above

gave any 44 when directly reacted with tert-butyl acetate and cyclohexanone. Alkyl lithium reagents are powerful nucleophiles which attack esters, ketones and other carbonyl compounds at the electron deficient carbon more rapidly than they abstract a proton from the relatively acidic α-carbon atom. Control reactions with LDA and LiTMP showed that an amide base was required to enolize the tert-butyl ester. The ester enolate subsequently reacted with cyclohexanone in an aldol type reaction to give, after quenching with aqueous acid, the β-hydroxy ester 44. Phenylsodium was equally ineffective in metallating 24, probably because the metallating reagent was completely insoluble in the hexane solvent. Methyllithium is apparently metallating 24, based on methane evolution and the loss of the methyllithium proton NMR signal. However, only low yields of 44 were obtained in quenching experiments. This dichotomy can be explained when one looks at the stability of 24-Li in ether. The T_{50} for 24-Li in ether is about 10 h. Apparently, the metallated amine is attacking the ether solvent. This would explain the low yields of 44 in the quenching reactions with cyclohexanone and tert-butyl acetate. Based on this observation, methyllithium in ether is not the metallating reagent of choice for forming very basic hindered alkyl lithium amides.

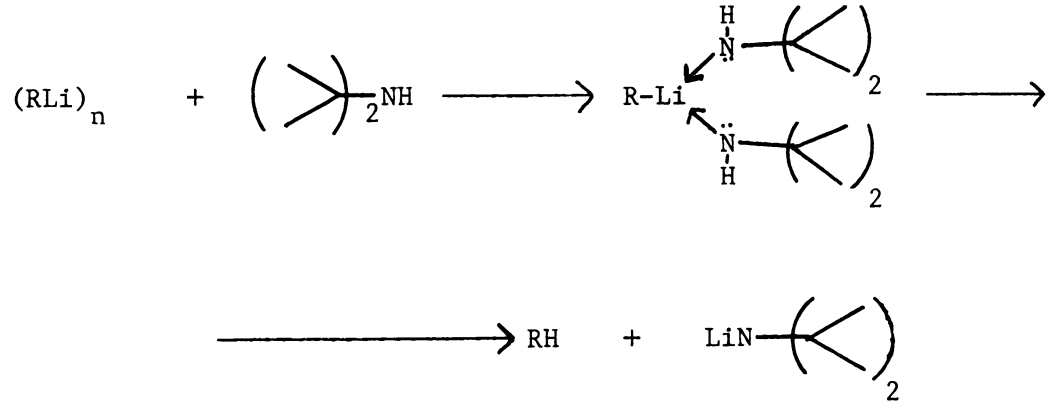
The formulae of alkyl lithiums are often written as "RLi", but this representation is not accurate. Alkyl lithium reagents are highly associated in solid and solution phase.[42] In common ether solvents, there is evidence that tetramers solvated by ether molecules are dominant. Hindered alkyl lithiums such at t-butyllithium, are often more reactive metallating agents than simple alkyl lithiums. This increased reactivity has been correlated with a less aggregated lithium species.[43]

We believe that with very hindered secondary amines, alkyl lithium aggregates are too large to deprotonate the nitrogen atom (eq 55).



(55)

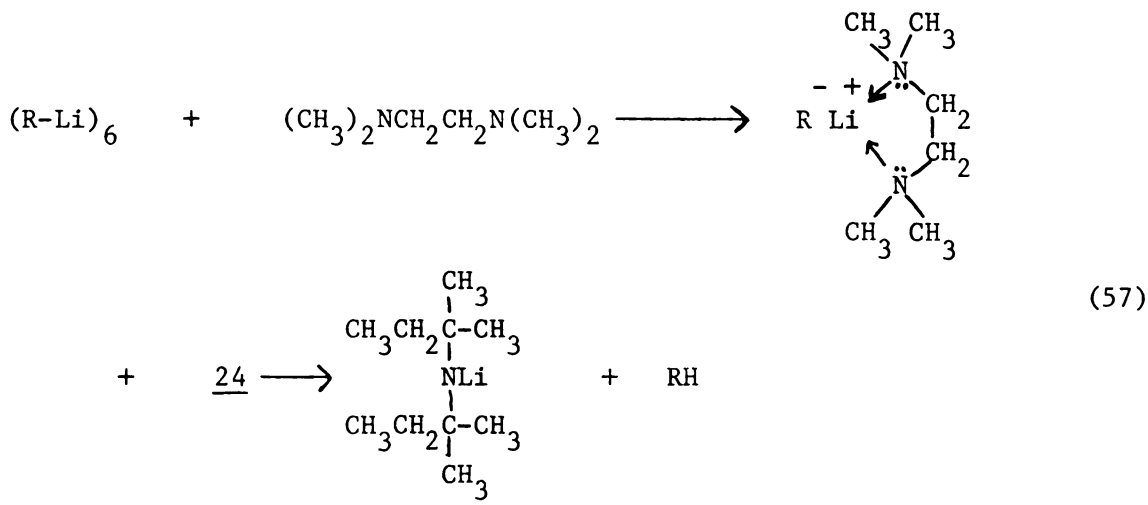
With less hindered amines, such as diisopropylamine and tetramethylpiperidine, two factors contribute to metallation by n-butyllithium. First, the less hindered amine nitrogen is not as crowded by the surrounding alkyl groups as in the case of more hindered amines. This permits a less obstructed approach to the amine proton by the n-butyllithium molecule. More important, however, the less hindered nitrogen atom can act as a Lewis base which can coordinate with lithium atoms of the alkyl lithium aggregate. This Lewis base might therefore be expected to break down the aggregate and, as a result, increase the effective carbanion character of the alkyl lithium reagent. The increased carbanion character would manifest itself by increasing the rate of amine metallation (eq 56).



(56)

Amine 24 as well as the other amines in Table I are probably too hindered to act as effective Lewis bases to de-aggregate n-butyllithium. An example of the poor Lewis base character of 24 was described in Chapter I, where CH_3I failed to form a quaternary ammonium salt with 24, while TMP readily reacted with CH_3I.[18]

In order to de-aggregate n-butyllithium, the chelating ligand TMEDA was added to the hexane- n-butyllithium solution. There was an immediate warming of the reaction mixture along with a very rapid quantitative evolution of butane gas when TMEDA was added (eq 57).



(57)

It appears that as the amide bases become more hindered, the rate of metallation decreases. A pronounced slowing in the amine metallation reaction occurs with amines 27 and 21 when 1.0 equivalent of TMEDA is used. The two most hindered amines 27 and 21 require 0.5 and 24 h for complete conversion to the corresponding amides, respectively. All of the other amines are metallated within 4 min at 24°C with 1.0 equivalent of TMEDA. There is a substantial decrease in the metallation rate for 26, 27, and 21 when 0.5 equivalents of TMEDA is used; 0.75, 5 and 40 h are needed, respectively, to completely metallate the amine.

Steric considerations in amine metallation do not seem to play an important role until the very hindered amines 27 and 21 are used. With 1.0 equivalent of TMEDA, 21 is metallated 500 times more slowly than any other amine except 27. The additional methyl group on 21 compared to 27 dramatically increased the amine's resistance to metallation by n-butyllithium. This is probably due to the increased steric congestion presented by the extra methyl group.

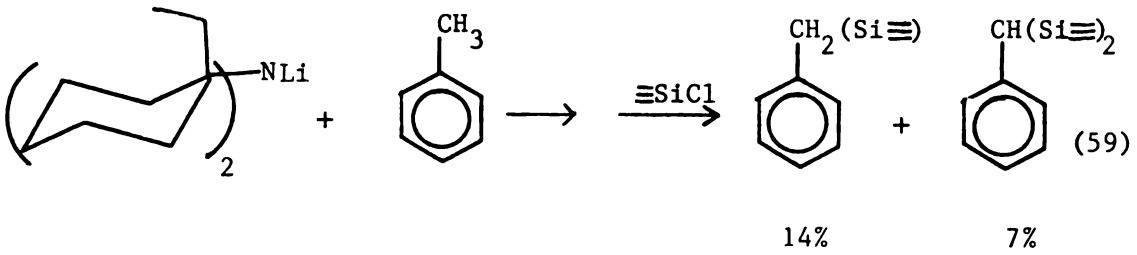
The rate of metallation of the hindered amines is reduced when 0.5 instead of 1.0 equivalent of TMEDA is used. This is expected based on the fact that 0.5 equivalent of TMEDA would not completely dissociate the alkyl lithium aggregates in solution. Thus the effective size of the alkyl lithium reagent is increased while the effective carbanion character of the anion is reduced.

Another factor which might effect the metallation rate of the very hindered amines is the thermodynamic basicity of the hindered amides. If the thermodynamic base strength of hindered amides increases with increasing steric bulk, the metallation of 27 and 21 might be equilibrium controlled (eq 58).

$$R_2NH + \text{n-BuLi} \underset{k_1}{\overset{k_2}{\rightleftharpoons}} R_2N\text{-Li} + \text{butane} \quad (58)$$

$$+ \text{TMEDA}$$

Though this proposal may seem unlikely, there is some evidence to support the proposition that very hindered amides are more basic than less hindered amides. Fataftah[18] showed that the lithium amide of 28 metallates toluene (pK_a = 41). Under the same conditions, LDA and LiTMP did not metallate toluene (eq 59).



(59)

14% 7%

The major reason for the decrease in the metallation rate of very hindered amides is probably the increased steric repulsion between the hindered amine and the alkyl lithium reagent. The next section will discuss the stability of lithium amides in THF and diethyl ether.

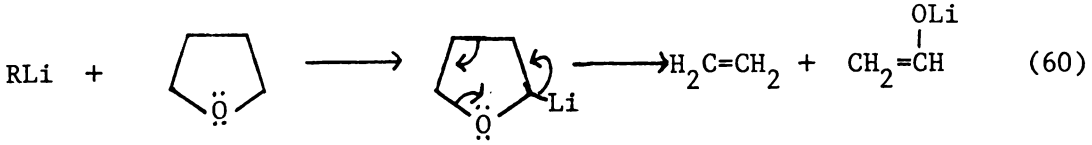
Lithium Amide Stability in THF and Diethyl Ether.

The results of the amide stability study provided interesting and unexpected results. The lithium amides show considerably different stabilities in THF and diethyl ether. All of the lithium amides in Table I are more stable in diethyl ether than they are in THF, except for LiTMP (Figure II). Except for LiTMP and 24-Li, all of the hindered amides that were studied have a T_{50} greater than 18 h at 24°C. Both LiTMP and 24-Li are relatively unstable with a T_{50} of 3.5 and 11 h, respectively. Suprisingly, amide 25-Li is much more stable than amide 24-Li in diethyl ether while in THF, amides 24-Li and 25-Li are nearly identical in stability. Amides 25-Li, 26-Li and 27-Li are all much more stable in diethyl ether (T_{50}> 18 h) than in THF. As the substitution near nitrogen increases and the amides become more hindered, a large

relative decrease in their stability in THF is seen. LiTMP's half life is 8.5 h, while the amides 24-Li and 25-Li are half destroyed within 1.5 and 1.7 h, respectively. But as the steric hindrance of the amides becomes even greater, their relative stability improves. The T_{50} of 26-Li and 27-Li in THF increase to 2.8 and 6 h, respectively. The stability of the lithium amide of 21 was not studied due to analytical problems. The observation that the stability of progressively more hindered amides increase, then decrease was unexpected. If amide base strength increases with the steric hindrance of the amide, the most hindered amides in the series would be expected to be most basic.

One could infer from the data in Tables I and II that the decomposition of the alkyl lithium amides is probably caused by the deprotonation of the ether solvents. Figure I and II also suggest that the rate of ether deprotonation is directly proportional to the kinetic basicity of the lithium amides. For the less hindered amides, kinetic base strength apparently increases with with increasing amide bulk. This is reflected by the drop in amide stability in THF for LDA through 25-Li. Amides 27-Li and 21-Li are apparently so hindered that they cannot deprotonate THF as quickly as the moderately hindered amides, reflecting a decrease in the kinetic base strength of these amides.

The generally greater stability observed for hindered amides in diethyl ether is not unexpected. Organolithium compounds are generally more stable in diethyl ether than in THF because THF is readily metallated to give ethylene and the stabilized acetaldehyde enolate anion (eq 60).



(60)

Diethyl ether is less polar than THF. The more polar the aprotic solvent, the better it is at solvating the small lithium counterion. This increased solvation of lithium generally increases the kinetic basicity of the anion base. If THF solvates lithium amides better than diethyl ether, one would expect to see an apparent increase in the kinetic basicity of hindered lithium amides in THF. Only when the amides become too bulky for THF to solvate the lithium ion would a drop in the kinetic basicity be expected. This rationalization would explain the results observed with 26-Li and 27-Li in THF.

Amide ion stability in ether solvents might also be influenced by TMEDA. Some TMEDA remains with the amides after the amine is metallated and the hexane solvent is removed. A metallation reaction of diethyl ether by LiTMP was performed without TMEDA. The amide decomposed somewhat faster without than with TMEDA. Studies with more hindered amides were impossible without TMEDA, since TMEDA was necessary to help metallate the hindered amines. No conclusions on the effect of TMEDA on the amide decomposition rate can be drawn until a reliable measure for TMEDA content in amide solution is obtained. This might be accomplished using NMR by noting the relative peak ratios for the hindered amide and TMEDA.

EXPERIMENTAL

All solvents and reagents were reagent grade quality. All alkyl lithium reagents were purchased from Aldrich and standardized before use by titrating with sec-butyl alcohol using 1,10-phenanthroline as an indicator.[39] Diethyl ether and THF were distilled from lithium aluminum hydride and stored under argon. All of the hindered amines synthesized in Chapter I were at least 98% pure and stored over molecular sieve.

Diethyl and diisopropylamine, tetramethylethylenediamine and tetramethylpiperidine were distilled from calcium hydride and stored over molecular sieve. Cyclohexanone and tert-butyl acetate were purchased from Aldrich and used without purification. Analysis of hydroxy ester 44 was performed by GLC at 120° using a 6' x 1/4" column with 5% OV-101 on Chromosorb W, AW-DMCS treated support.

Reaction of Methyllithium with Bis(1,1-dimethyl-2-propyl)amine (24).

A 10 mL flame dried round-bottomed flask was fitted with a rubber septum sidearm and Teflon stirring bar. The flask was connected to a mercury manometer by a ground glass joint and the entire system flushed with argon. The flask was immersed in a thermostated water bath at 24°C. A magnetic stirrer was placed beneath the bath and the manometer purged with methane. Then 1.8 mL (2 mmol) of 2.1 M methyllithium was injected into the reaction flask by syringe. Then 2 mmol of 24 was added by syringe (0.40 mL), the manometer readings were noted periodically and the manometer reservoir was adjusted as needed. After 14 h, the readings were off scale, indicating evolution of more than the theoretical 50 mL of methane gas. Other gaseous products had been evolved. An aliquot of sample was removed by syringe and a proton NMR was taken. Benzene (d_6) was added as a reference standard (δ= 7.25). No methyllithium was seen by NMR (δ = -1.93) (TMS = 0.0).

Quantitative Determination of Secondary Lithium Amide by Quenching with tert-Butyl Acetate and Cyclohexanone.

An example,representative of the procedure used in the quantitative

determination of lithium amide 24-Li is given below. This procedure applies for the determination of secondary lithium amides of LDA, LiTMP, 25-Li, 26-Li, 27-Li and 21-Li; the attempted formation of 24-Li and 24-Na using methyllithium, phenyllithium and phenylsodium, and the actual formation of lithium amides using n-butyllithium. The only variations in this procedure occur when; 1. diethyl ether is used as the reaction solvent for quenching with tert-butyl acetate and cyclohexanone and 2. the reaction times vary for hindred secondary lithium amides reacting with either THF or diethyl ether and 3. TMEDA is used in the amide formation reaction with n-butyllithium.

A 25 mL Bantamware round-bottomed flask was fitted with a septum sidearm, Teflon stirring bar and a gas inlet valve. The flask was flame dried and flushed with argon. After cooling, 1.8 mL of methyllithium (4 mmol, 1.80 mL) was added to the flask by syringe. Then 2.2 mL of diethyl ether was added to the reaction mixture to make the solution 1 M in concentration. Then 0.80 mL of 24 (4 mmol) was added and allowed to react for 7 h. After 7 h, the solution was cooled to -78^{o}C with a dry ice - acetone bath. Tert-butyl acetate (4 mmol, 0.53 mL) was added dropwise to the reaction mixture over a 5 min period. The solution was stirred for 15 min. Cyclohexanone (0.42 mL, 4 mmol) was added dropwise to the stirring solution over a 5 min period and allowed to stir at -78^{o}C for 15 min. Then 1 mL of 3 N HCl was added dropwise to the cold solution, the dry ice bath removed and the solution mixture allowed to warm to room temperature. One gram of anhydrous Na_2SO_4 was added to the flask along with 1.10 mL of pentadecane (4 mmol). A sample aliquot was injected into a gas chromatograph and an 8% yield of 44 was obtained. The yield of 44 was calculated from the correction factor determined

previously for 44 and pentadecane. Spectral properties for 44; IR ν_{max} 3650, (-OH) and 1740 cm^{-1} (COOR absorption).

The reactions of the lithium amides in Figure I and II with tert-butyl acetate and cyclohexanone were done as previously described, but with the following modifications. After the lithium amides were formed with n-butyllithium and TMEDA, the solvent hexane was removed under vacuum and replaced with either THF or diethylether to make the solution 1.0 M in amide. Then at time intervals ranging form 10 min to 13 h, the amide solutions were cooled to -78°C with a dry ice - acetone bath and treated as previously described (vide supra).

Attempted Metallation of 24 with Phenyllithium

Phenyllithium (1.6 M in benzene, 2.5 mL, 4 mmol) was added to a 10 mL round-bottomed flask which was flushed with argon and fitted with a stirring bar, septum side arm and gas flow valve. Amine 24 (0.80 mL, 4 mmol) was added by syringe to the reaction mixture and the mixture was stirred at 24°C for 6 h. The benzene was removed under vacuum and THF was added (4.0 mL). The solution was cooled to -78°C and treated with tert-butyl acetate and cyclohexanone as previously described. The yield of 44 was 15% by GLC.

Preparation of Phenylsodium[44]

To 54 g (2.35 g-atoms) of finely dispersed sodium suspended in 300 mL of toluene in a three neck round-bottomed flask was added 10 to 15 mL of a mixture of 112.6 g (1 mol) of chlorobenzene and 125 mL of toluene. The entire reaction sequence is performed under argon.

Reaction initiation occurs 1 to 5 min after adding the first 10 to 25 mL of chorobenzene-toluene mixture and is characterized by an increasingly rapid temperature rise, plus the appearance of black phenylsodium particals. The reaction mixture is vigorously stirred with a mechanical stirrer until the initial exothermic reaction has occured and been brought under control. As the temperature approaches 30 to 40°C, an ice bath should be raised around the reaction flask. The internal temperature should not be permitted to exceed 40°C.

After the reaction has started and has been brought under control, the addition of the chlorobenzene-toluene mixture is resumed. The addition requires between 30 and 40 min. After the reaction is completed, the toluene solution is filtered using a coarse glass frit (under argon!) and the solid phenylsodium transfered into a 250 mL Schlenk tube, also under argon. The air sensitive material is dried overnight under vacuum and yields 89 g (89%) of product. The material is extremely pyrophoric and transfering of phenylsodium into a reaction vessel should only be done under argon or nitrogen.

Attempted Metallation of 24 Using Phenylsodium.

About 0.5 g (5 mmol) of phenylsodium was added to a 25 mL round bottomed flask fitted with a septum side arm, Teflon coated stirring bar and gas inlet valve. The flask was flushed beforehand with argon and 5 mL of hexane was added by syringe into the reaction mixture. Then 1.0 mL of 24 was added to the reaction mixture (5 mmol) and the heterogeneous solution was stirred for 12 h. No change in the solution appearance was noted during the course of the reaction. After removing the

hexane solvent under vacuum and replacing it with THF, the solution was quenched with tert-butyl acetate and cyclohexanone as previously described. A 4% yield of 44 was obtained.

Metallation of Secondary Amines with n-Butyllithium and TMEDA

A 10 mL round-bottomed flask was fitted with a Teflon stirring bar, septum side arm and a ground glass joint which was connected to a 100 mL buret that was converted to a mercury manometer. One end of the buret was connected with Tygon tubing to a mercury reservoir and the other end to the reaction flask. The flask and manometer were purged with argon three or four times. The entire system was then filled with butane (Matheson) and 3 mmole of 1.63 N n-butyllithium (1.84 mL) was added by syringe to the reaction flask. Pentane was added to the flask to make the solution 1.0 M in n-butyllithium. The reaction flask was thermostated at 24.0 (± 0.2^{o}C) and the system was equilibrated. Butane was added periodically to the system until no more butane dissolved into the reaction solution. This generally required about 1 h. Then 3 mmol of TMEDA was injected into the reaction solution. The manometer was zeroed and the solution again permitted to equilibrate (20 min). Then 3.0 mmol of the appropriate secondary amine was added all at once to the reaction flask. Diisopropylamine (0.42 ml), tetramethylpiperidine (0.51 mL), 24 (0.60 mL) and 25 (0.60 ml) reacted immediately with n-butyllithium and evolved about 75 mL (± 2 mL) of butane within 1 min. Amines 26 (0.68 mL), 27 (0.72 mL) and 21 (0.76 mL) reacted more slowly. The reaction progress was easily followed by keeping the mercury reservoir level with the buret mercury level and noting gas displacement with time.

The same procedure was followed with 50 mol percent of TMEDA (0.22 mL).

CHAPTER III

BIMOLECULAR ELIMINATION REACTIONS OF ALKYL HALIDES WITH LITHIUM AMIDES

INTRODUCTION

Base promoted E2 or β-elimination reactions have been an intensively studied area in organic chemistry. Recent reviews [45-49] have summarized the effects of 2-alkyl groups, leaving groups, solvent and base promoted β-elimination reactions. The β-elimination reaction involves concerted, but not necessarily synchronous, making and breaking of four bonds in the transition state. Bunnett[50] formulated a "variable E2 transition state" theory from experimental evidence, which recognized the existence of a spectrum of transitions states for bimolecular elimination reactions. In a true E2 process, the C-H and C-X bonds break simultaneously, but the stretching of one bond may be further advanced than the other in the transition state. At one extreme, the transition state may resemble a carbonium ion (E1 like) while at the other extreme, the transition state resembles a carbanion ($E1_{cB}$). Between these extremes lie a range of transition states where C-H and C-X bonds break simultaneously (Figure 3).

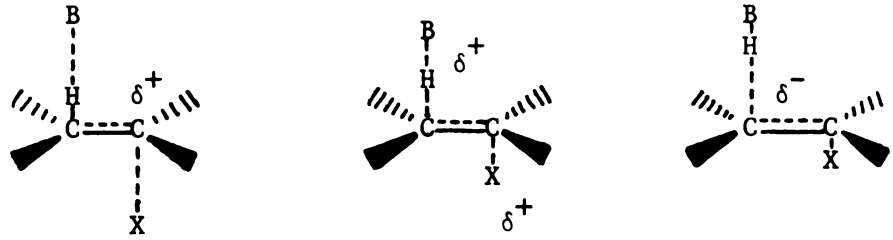


Figure 3. Variable Transition State Spectrum

The E2 mechanism operates for a wide variety of leaving groups and bases (eq 61). Provided that the substrate and base have comparable concentrations, second order kinetics should be observed for the E2 process. A third mechanism, which is also consistant with second order

$$B + R_2CHCXR_2 \longrightarrow BH^+ + R_2C{=}CR_2$$

(X= $^+NR_3$, PR_3, SO_2R, OCOR, F, Cl, Br, I
B= NR_3, ^-OH, ^-OAc, ^-OR, ^-OAr, $^-NH_2$, $^-NR_2$, ^-CN) (61)

kinetics, is the El_{cB} or carbanion mechanism[51] (eq 62). This is a two step process in which proton abstraction is followed by unimolecular loss of the leaving group from the conjugate base of the substrate.

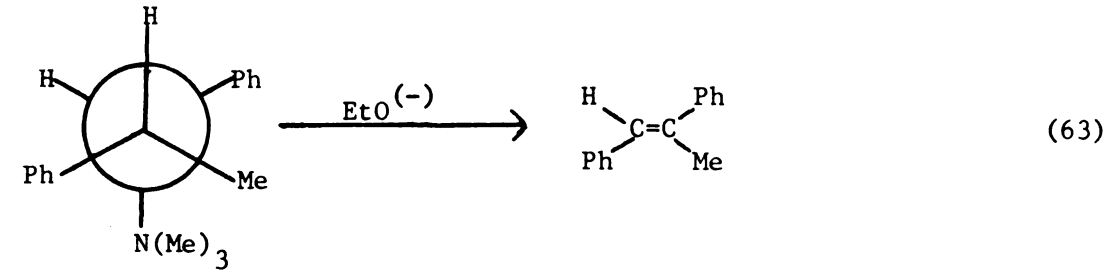
$$B + R_2CHCXR_2 \longrightarrow BH^+ + R_2\overset{(-)}{C}CXR_2$$

$$R_2\overset{(-)}{C}CXR_2 \longrightarrow R_2C{=}CR_2 + X^{(-)} \qquad (62)$$

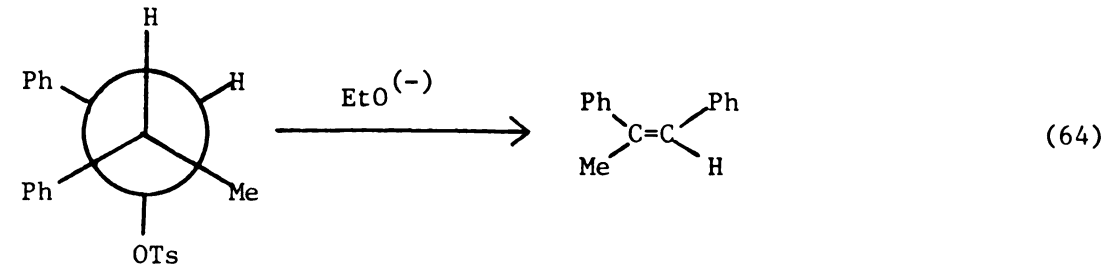
Criteria which permit differentiation among E_2 and the two E_{1cB} mechanisms [a) where the first step is rate limiting and the second is fast, b) the first step is a rapidly attained equilibrium and the second is the rate determining step] have been summarized.[5,46] Many elimination reactions have been examined and the El_{cB} mechanism has been shown to operate in only a few cases. 1,1,1-Trifluoro-2,2-dihalogenoethanes undergo alkoxide-catalyzed hydrogen - deuterium exchange much faster than dehydrofluorination. In these cases, the electron-withdrawing effect of the halogens and the poor leaving ability of fluoride are important factors favoring carbanion formation over halide elimination.[45] Strong evidence for an El_{cB} mechanism has been obtained recently for the elimination reaction of phenyl ethers like $MeSOCH_2CH_2OPh$[45] and $Me_2S^+CH_2CH_2OPhI^-$. These compounds contain a poor leaving group (^-OPh)

and a substituent capable of stabilizing a carbanion. Proof of the character of the elimination mechanism for the $E1_{cB}$ reaction is obtained by measurement of the elimination rates of substrates labelled in the β-position with deuterium. For an E2 elimination reaction which passes through a symmetrical transition-state, the theoretical maximum (about 7) for the kinetic deuterium isotope effect k_H/k_D is predicted. As the character of the transition state becomes increasingly carbanionic, the isotope effect should decrease to 1.0 in the limiting $E1_{cB}$ mechanism, since any isotope label would be exchanged rapidly with the medium. The isotope effects k_H/k_D in the dehydrofluorination of CF_3CHCl_2 and $CF_3CHBrCl$ are 1.26 and 1.41, respectively.[45]

The E2 elimination mechanism is by far the most commonly observed reaction pathway. During the past decade, considerable effort has been directed towards determination of the transition state structure for E2 reactions and the effects exerted upon this structure by the nature of the reactants and the reaction conditions. There is a close relationship between the transition state structure of an E2 reaction and the reaction products especially with regard to positional and stereochemical orientation. Generally, E2 reactions proceed most readily with the leaving groups in an antiperiplanar conformation. The anti- elimination is favored by the need to minimize the repulsion energy between the migrating electron pairs. Numerous examples are available illustrating the preference for anti-eliminations. Both acyclic and alicyclic compounds show an anti-preference in base promoted elimination reactions (eq 63-66).[52]



(63)



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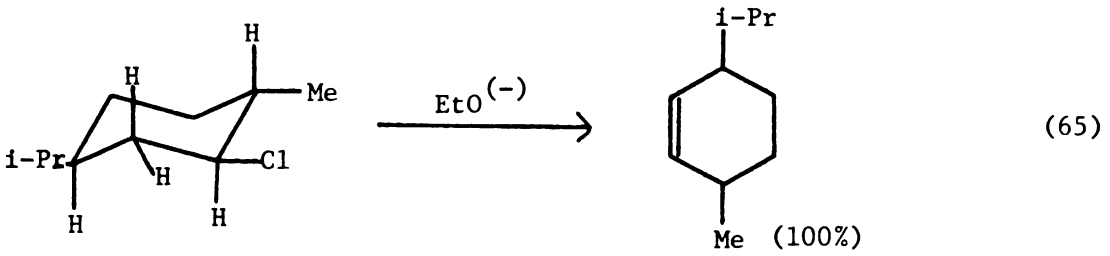

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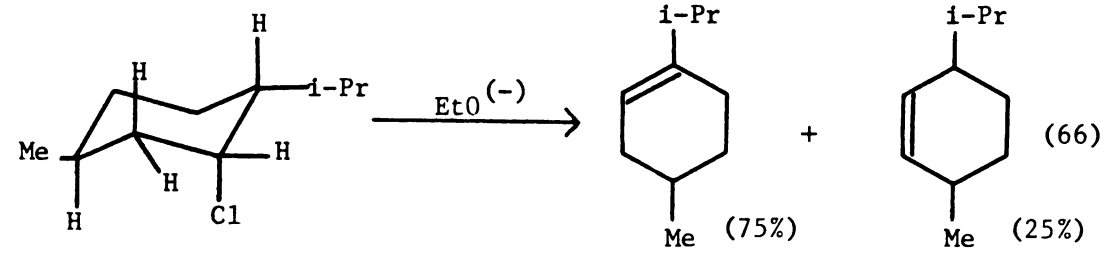
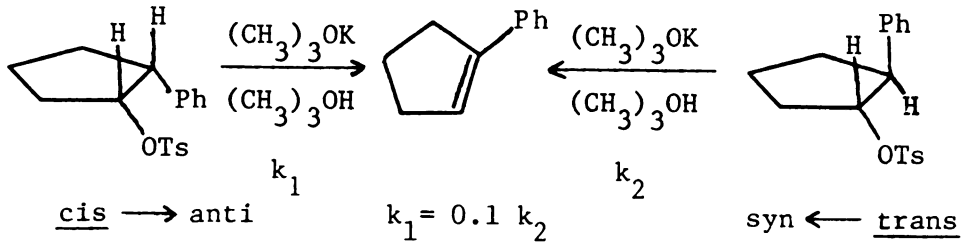


(66)

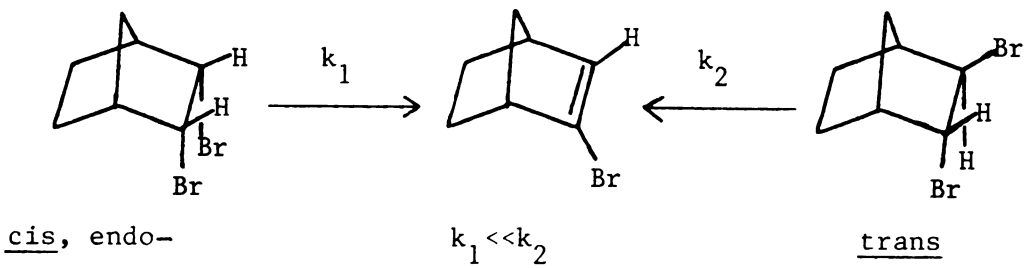
Although anti stereochemistry for elimination reactions is prefered, there are quite a few examples where the eliminated groups are syn and coplanar. For some substrates such as trans-2-phenylcyclopentyl tosylate, the elimination reaction with potassium tert-butoxide in tert

butanol is only 10 times slower than elimination of the corresponding cis isomer (eq 67).



(67)

In some cases, syn-elimination may be favored over anti-elimination. One example involves substrates in which trans leaving groups have a dihedral angle of 120° or 150° due to restricted rotation in a rigid ring system, but cis groups have a 0° angle. Thus syn- elimination from trans 2,3-dihalogenonorbornane is faster than anti-elimination from cis-endo-2,3-dihalogenonorbornane, because coplanarity can be achieved in the transition state for syn- elimination but not for the trans-elimination.[54]



(68)

The factors determining whether a syn-elimination takes preference over anti-elimination are varied and have not been clearly defined. Among the factors which can influence the transition state of an E2 reaction, changes in base structure (basicity, steric requirements and the state of association) certainly play a large role.

Most quantitative information concerning base strength effects involve β-aryl activated substrates and the determination of ρ and k_H/k_D values with different bases in the same solvent. Compounds such as 2-arylethyl bromides, 2-arylsulfonyl ethyl chlorides and tosylates show a very clear trend in base mediated E2 reactions.[48] For all the systems investigated, an increase in base strength leads to an increase in the ρ value, indicating a shift of the transition state structure towards the carbanion extreme (more $E1_{cB}$-like).

Information about the transition state structure for E2 reactions of nonactivated substrates such as alkyl halides and alkyl tosylates is furnished by the isomer composition of the product olefins. In particular, an increase in the proportion of the least substituted olefin (Hoffmann product) indicates an increase in the carbanionic character of the transition state. Bartsch has shown[55] that for alkoxide promoted eliminations of 2-iodobutane in dimethylsulfoxide (DMSO), the relative amount of 1-butene increases as the base becomes stronger. This is evidence of a corresponding increase in the carbanionic character of the transition state (an explanation for this conclusion is presented later).

Similar results have also been obtained by Bunnett[56] using 2-hexyl and 2-pentyl halides in methanol with methoxide. The 2-ene/1-ene ratio and the <u>trans</u>/<u>cis</u> ratio increase regularly with a change in leaving group F < Cl < Br < I (Table V). The elimination of 2-fluorohexane follows Hoffmann's rule almost exclusively, and E1 and $E1_{cB}$ mechanisms have been ruled out by second order kinetics and lack of H-D isotope exchange in the elimination with deuterated ethanol-ethoxide. In Table V, the same base is used, but the leaving groups have been changed. An explanation for both the positional and sterochemical orientation can be derived

Table V. E2 Reaction of 2-Hexenyl Halides with NaOH in Methanol

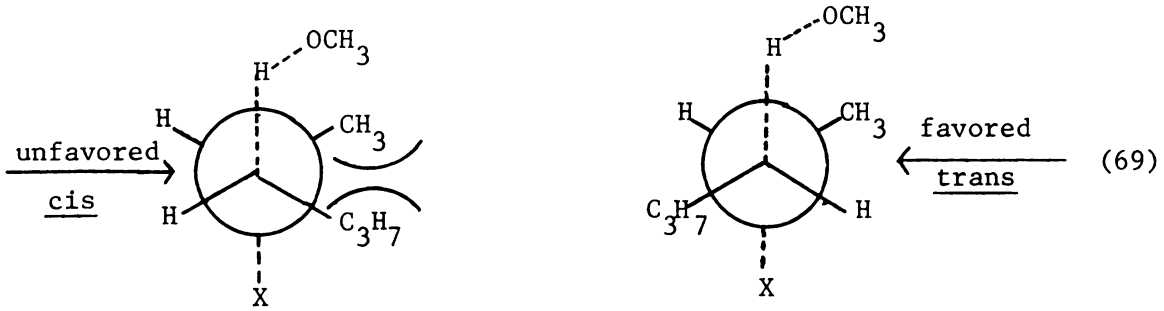
Leaving Group	% 1-Hexene	trans-2-Hexene	cis-2-Hexene	$\frac{\text{trans}}{\text{cis}}$
F	70	21	9	2.3
Cl	33	50	17	2.9
Br	24	54	18	3.0
I	19	63	18	3.6

Reaction run at 100^{0}C with NaOMe and MeOH

from the variable transition state theory. According to this theory, Hoffmann or Saytzeff (more highly substituted double bond) orientation is determined by the effect of a β-alkyl group on the activation energy. For elimination reactions with symmetrical E2 transition states, a β-alkyl group lowers the energy of the transition state by electron-release to the developing double bond so that Saytzeff elimination is favored. For carbanion like transition states, the degree of double bond character is small, and a β-alkyl group destablizes the developing negative charge on the β-carbon and Hoffmann orientation predominates. The nature of the transition state would be expected to change in reactions of 2-hexyl halides as the leaving group changes from iodine to fluoride. For the poor leaving group fluoride, the carbanion character of the transition state increases because the C-X bond becomes harder to break while C-H bond breakage is assisted. The change to a more carbanion-like transition state is favored by an increase in the electron

withdrawing effect of the halogen atoms with decreasing atomic number. The experimentally observed order of increasing Hoffmann orientation from iodide to fluoride conforms to the above analysis.

Stereomeric orientation is also determined by the character of the transition state. The degree of double bond character in the C_β-C_α bond is small at both extremes of the spectrum of E2 transition states, but relatively large at the center. For a central E2 transition state, the formation of cis olefin is unfavorable due to eclipsing effects between alkyl groups (eq 69).



(69)

A decrease in the trans/cis ratio would therefore be predicted with increasing carbanion like character of the transition state. For 2-hexyl halides, the trans/cis ratio does decrease through the series form iodide to fluoride in line with this hypothesis (Table V).

Two very active areas of research on E2 reactions have been the study of base association and steric requirements of oxyanion bases on the positional and stereochemical orientation of olefin products. While association and steric effects appear to have little effect in determining positional orientation for products from the reaction of 2-hexyl halides with sodium methoxide in methanol, the same cannot be said for

reactions with more hindered bases.

Very strong evidence for a dichotomy of active base species is provided by the influence of crown ethers upon orientation in reactions of 2-butyl bromide and tosylate with tert-BuOK / tert-BuOH.[45] Both positional (relative amounts of 1- and 2-butenes) and geometrical (cis-trans-butene ratios) orientation are affected by the degree of alkoxide base association. For both 1-butyl bromide and tosylate, addition of dicyclohexano-18-crown-6 ether 45, decreases the 1-butene/2-butene ratio and increases the trans/cis 2-butene ratio (Table VI). Since 45 is a powerful potassium ion complexing agent, the degree of alkoxide-alcohol aggregation should be greatly reduced and the equilibria represented in eq 70 should be strongly shifted towards the left in the presence of 45.

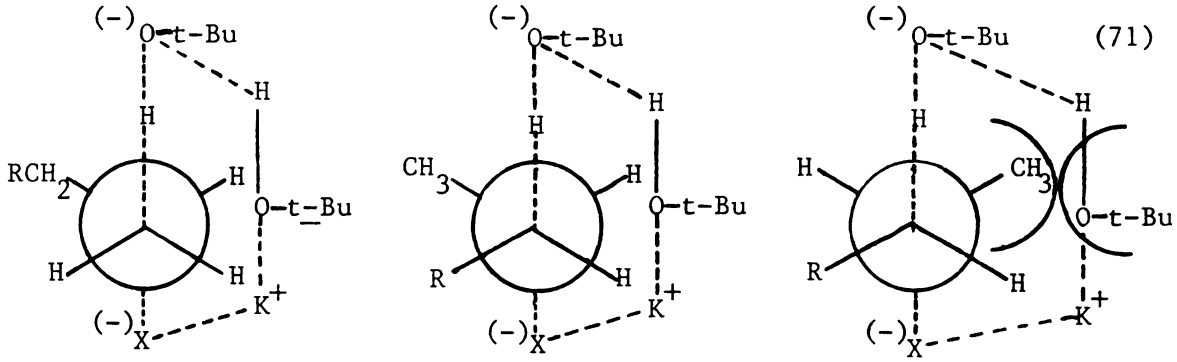
Table VI. Olefin Products from Reactions of 2-Substituted Butanes[47] with 0.05 M tert-BuOH and tert-BuOH at 50°C.

leaving group	dicyclohexano 18-crown-6	% 1-butene in total alkenes	trans / cis
Br	0 eq	44.1	1.66
Br	1.0 eq	32.5	2.92
OTs	0 eq	63.5	0.40
OTs	1.0 eq	53.6	1.88

$$RO^{(-)} + M^{(+)} \rightleftharpoons (RO^{-}M^{+}) \rightleftharpoons (RO^{-}M^{+})_2 \rightleftharpoons (RO^{-}M^{+})_n \qquad (70)$$

Bartsch proposed that the orientation observed in the presence of 45 results from free tert-butoxide base, while in the absence of 45, both free and associated base forms are the active species.

A number of models have been proposed to rationalize the generation of substanially higher proportions of 1-alkene and lower trans-cis 2-butene ratios by associated base species. The most recent explanation for positional orientation control produced by associated bases involves the transition state structures in eq 71 for 2-bromobutane.



(71)

Zavada and Pankova[57] demonstrated that the steric properties of associated and dissociated tert-BuOK are very similar for eliminations conducted in tert-BuOH. The base specie is assumed to be a homohydrogen-bonded tert-BuOH ion pair which provides substantial electrostatic interactions of the base counterion with the leaving group. For associated bases (no crown present), the attractive base interactions are stronger in transition states forming 1-alkene A, and cis-2-alkene B, than in that leading to trans-2-alkene C, because of the steric interaction with the methyl group in C. In going from dissociated to associated

base, the supression of trans-2-alkene formation results in proportional increases in the production of 1-alkene and cis-2-alkene. This leads to the observed enhancement of 1-alkene proportion and a decrease in the trans/cis ratio with associated base.

Hindered unassociated bases produce greater proportions of the thermodynamically less stable 1-alkene in eliminations from 2-alkyl halides and tosylates, than do unassociated bases of more moderate size. Since hindered unassociated alkoxide bases are more reactive than associated alkoxide bases, studies were performed to investigate the orientation control provided by the two types of bases. Reactions of 2-butyl iodide with a number of tertiary alkoxides in DMSO were examined.[58] The results are shown in Table VII.

Table VII. Olefinic Products from Reaction of 2-Iodobutane with 0.25 M Potassium tert-Alkoxides in Dimethyl Sulfoxide at 50°C.

Base	% 1-Butene	trans/cis 2-butene
tert-butoxide	20.7	2.99
triethyl methoxide	20.9	3.13
di-tert-butyl-n-octyl methoxide	24.5	3.31
tricyclohexyl methoxide	27.2	3.04
tri-2-norbornyl methoxide	29.4	3.41
tert-butoxide (0.25 M in tert butanol)	29.9	2.09

None of the sterically congested unassociated bases showed better orienation control than associated tert-BuOK in tert-BuOH.

A decrease in orientational selectivity is observed with the hindered lithium amide base 2,6-di-tert-butylpiperidine 46.[59] The results are shown in Table VIII.

Table VIII. Olefin Products from Reactions of 2-Halobutanes with Anionic Bases.

Substrate	Base	Solvent	Crown	1-butene	$\frac{\text{trans}}{\text{cis}}$ ratio
2-iodobutane	tert-BuOK	diglyme	none	17.7	3.43
"	"	"	18-crown-6	18.6	3.58
"	"	Me_2SO	none	18.5	3.39
"	46	diglyme	none	26.1	3.92
"	"	"	15-crown-5	20.6	4.13
"	"	"	12-crown-4	17.2	3.98
"	tert-BuOK	tert-BuOH	none	34.4	2.17
2-bromobutane	46	diglyme	none	40.3	3.81
"	tert-BuOK	tert-BuOH	none	50.0	1.51

Positional orientation in the reaction of 46 with 2-iodobutane in diglyme is similar to that previously observed in reactions of this substrate with tertiary alkoxides in DMSO (see Table VI). However, the importance of base ion pairing is shown by the decreased percentages of 1-butene noted in the presence of suitable macrocyclic crown ethers. Free 46 provides poorer directional orientational control than the previously examined dissociated but highly hindered tertiary alkoxides. That this unexpected result is not due to some fundamental difference between dissociated nitrogen and oxygen bases is strongly suggested by recent investigations of orientation in eliminations from 2-iodobutane involving more ordinary nitrogen and oxygen bases. Bartsch demonstrated, using linear free energy relationships, that sensitivity of positional orientation to base strength variation is the same for amide ion and oxyanion bases.[60]

RESULTS

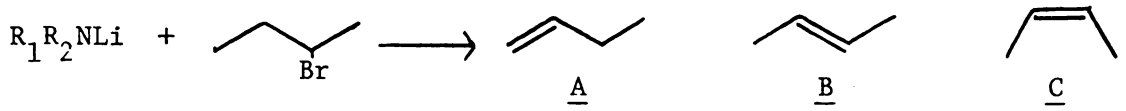
Reagent grade 2-bromobutane, distilled and stored over copper wire in an amber bottle was added (1.0 eqivalent) to a 1.0 M solution of hindered secondary amide in THF at 0°C. Elimination reaction progress was followed by GLC analysis of the product butenes using n-pentane as an internal standard. Aliquots of the reaction mixture was analyzed at 90 min intervals. Total butene yield increased with time, but the relative butene ratios remained unchanged during the course of the reaction. Butene isomer interconversion was not observed for any of the lithium amide elimination reactions studied. 1-Butene was subjected to LDA, 24-Li, 26-Li and 21-Li in THF at 0°C for 6 h. None of the 1-butene

was converted to either cis or trans-2-butene. A similar lack of isomer interconversion was observed when trans-2-butene was reacted under the same experimental conditions. Table IX lists the results of the E2 reaction of 2-bromobutane with various lithium amides. Almost complete mass balance was observed in these elimination reactions. The difference in the actual and the theoretical butane yield was accounted for (to within 3 or 4%) by unreacted 2-bromobutane. Each amide in Table IX was formed using 1 equivalent of TMEDA and n-butyllithium, except where noted. The rate of E2 reactions varied with the amide used. Table X lists the time required for the elimination reactions in Table IX to reach 50% and 90% completion.

A control reaction was performed to insure that the decomposition product(s) of lithium amide attack on THF (see Figure I) did not itself effect dehydrohalogenation of 2-bromobutane. The lithium amide of 24 was reacted with THF for 2 days to insure that the amide had decomposed completely. One equivalent of 2-bromobutane was then added to the solution mixture along with pentane as an internal standard. After addition of 2-bromobutane, no more than 2% of butene products were observed by GLC after 5 days reaction time.

The product analysis of these elimination reactions was conducted by GLC. Results obtained by quenching the amide-halide solutions with 1 equivalent of H_2O were identical with results obtained from unquenched solutions. Quenched amide-THF solutions were very viscous gels. This made sampling the solution mixture by syringe very difficult. All subsequent analyses for butenes were performed without quenching the amide solutions.

Table IX. Product Ratios for the Dehydrohalogenation of 2-Bromobutane with Secondary Lithium Amides in THF at 0°C.



R_1 R_2	A(%)	B(%)	C(%)	B/C	Yield GLC (%)
R_1= R_2= Et	55	31	13	2.4	97
" no TMEDA	56	30	14	2.2	96
R_1= R_2= i-Propyl	67	22	11	2.0	80
" no TMEDA	67	22	11	2.0	90
tetramethylpiperdine	86	7	7	1.0	81
" no TMEDA	85	8	7	1.2	80
R_1= R_2= $EtMe_2C$- 24	90	6	4	1.5	82
R_1=$EtMe_2C$-; R_2=Et_2MeC- 25	89	7	4	1.7	68
R_1= R_2= Et_2MeC- 26	71	23	6	3.8	56
R_1=Et_3C-; R_2=Et_2MeC- 27	57	34	9	3.7	58
R_1= R_2= Et_3C- 21	55	36	9	4.0	74

All the amides were prepared using 1 equivalent of TMEDA in hexane with n-butyllithium.

Table X. Reaction Times Required to Obtain 50% and 90% of Total Butenes Evolved in the E2 Reactions of 2-Bromobutane.

Amide	T_{50}	T_{90}
$Ethyl_2NLi$	<1 min	<5 min
$Isopropyl_2NLi$	∿30 min	∿1.5 h
Lithium Tetramethyl-piperidide	<5 min	∿1 h
24-Li	∿15 min	∿2 h
25-Li	∿30 min	2.5 h
26-Li	2 h	13 h
27-Li	3 h	30 h
21-Li	∿11 h	90 h

All amides were made using 1 equivalent of TMEDA in THF at 0°C.

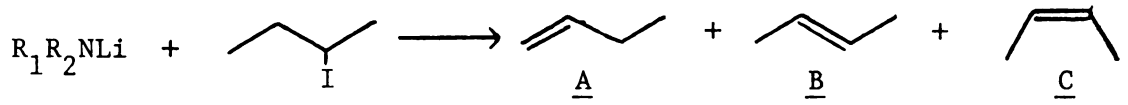
The results presented in Table IX reflect the actual butene composition obtained from amide base-induced β-elimination reactions. GLC analysis of the product butenes shows that the relative butene ratios remain unchanged from the inception to the completion of the dehydrohalogenation reaction for all of the amides studied.

Several interesting trends appear in the elimination reactions. As the amide bases increase in steric bulk, the relative proportion of 1-butene increases (Hoffmann product), while the trans/cis 2-butene ratio decreases. This trend holds for moderately hindered amides. However, as the steric hindrance of the amides becomes even greater (amides 25-Li, 26-Li, 27-Li and 21-Li), the relative proportion of 1-butene begins to decrease steadily with increased steric hindrance. There is also a concomitant drop in the trans/cis 2-butene ratio with the very hindered amides (25-Li, 26-Li, 27-Li and 21-Li).

The increase and subsequent decrease in the 1-butene ratio with increasing amide bulk was unexpected. In order to determine whether this trend was unique to 2-bromobutane, several other substituted butanes were studied. The same experimental procedure and conditions were used to study the E2 reaction of 2-tosyl-butane and the trifluoroacetic ester of 2-butanol.[61] Neither substrate gave measurable amounts of butenes with any of the amide bases in Table IX. However, 2-iodobutane readily reacted with the amides. Table XI presents the results obtained under conditions identical with those used in Table IX.

Again, the same rise and fall in the 1-butene ratio with increasing amide bulk is observed. Also observed is a decrease followed by an increase in the trans/cis 2-butene ratio. Moderately hindered amides such as LiTMP and 24-Li offer better orientational selectivity in the

Table XI. Product Ratios for the Dehydrohalogenation of 2-Iodobutane with Secondary Lithium Amides in THF at 0°C.

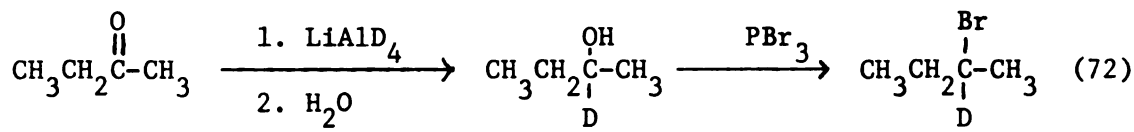


R_1R_2	A(%)	B(%)	C(%)	B/C	Yield GLC (%)
R_1=R_2= Et	37	21	41	1.9	98
R_1= R_2= i-Propyl	40	22	38	1.7	100
tetramethylpiperidine	61	19	20	1.05	97
R_1= R_2= $EtMe_2C$- 24	69	12	18	1.5	97
R_1=$EtMe_2C$-; R_2=Et_2MeC- 25	58	15	26	1.7	96
R_1= R_2= Et_2MeC- 26	38	20	42	2.1	84
R_1=Et_3C-; R_2=Et_2MeC- 27	28	22	50	2.3	94
R_1= R_2= Et_3C- 21	28	23	49	2.2	85

All of the amides were prepared using 1 equivalent of TMEDA in hexane with n-butyllithium.

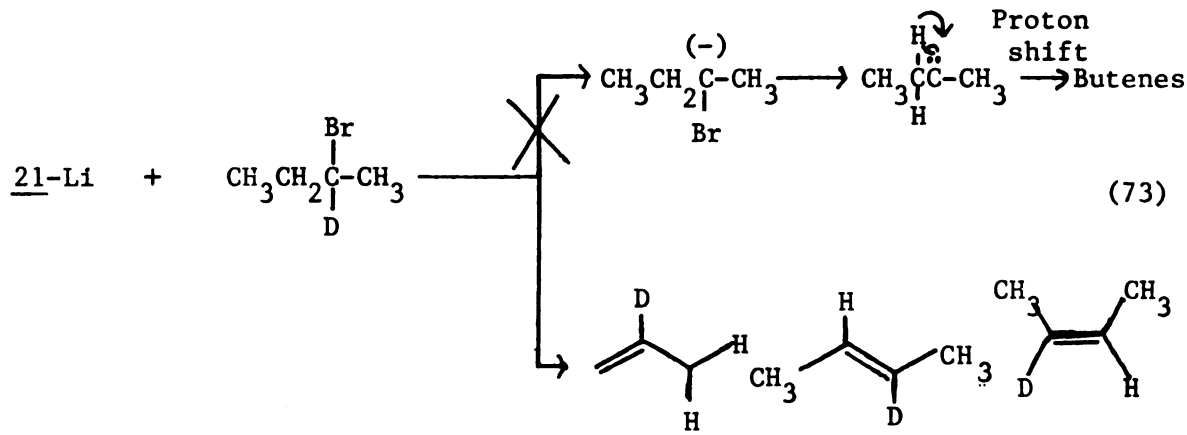
dehydrohalogenation of 2-bromobutane, compared with 2-iodobutane. Relatively unhindered as well as very hindered amides have a similar lack of orientational selectivity in dehydrohalogenation of either 2-bromo or 2-iodobutane.

A number of other experiments were performed to determine the cause behind the puzzling decrease in orientational control with increasing steric bulk for the very hindered amide bases. The possibility of an initial α-elimination was considered. Isotopically labeled 2-d-2-bromobutane (eq 72) was synthesized and dehydrohalogenated with lithium diethylamide, LiTMP and 21-Li. The product butene ratios for all three trials were, within experimental error, identical with the butene ratios obtained with undeuterated 2-bromobutane.



(72)

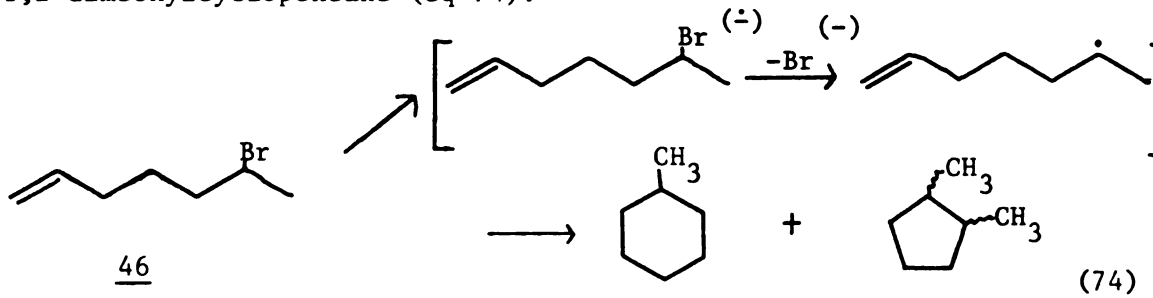
Mass spectral and proton NMR analysis of the product butenes showed no deuterium loss or scrambling due to α-deuterium abstraction by the amide bases, as depicted in eq 73.



(73)

Alternatively, the poor regioselectivity observed with hindered amide attack on 2-halobutanes might be due to an electron transfer initiated radical anion dehydrohalogenation reaction. A suitable alkyl bromide substrate, 2-bromo-6-heptene, was synthesized[62] and reacted with a number of lithium amides. This alkenyl halide is commonly used as a radical trap in photochemical and chemical induced electron transfer reactions.

According to the results in Table XII, no more than 2% of the reaction products in any of the amide dehydrohalogenation reactions are a result of an electron transfer from an amide anion to the haloalkene substrate. The free radical trapped products are methylcyclohexane and 1,2-dimethylcyclopentane (eq 74).



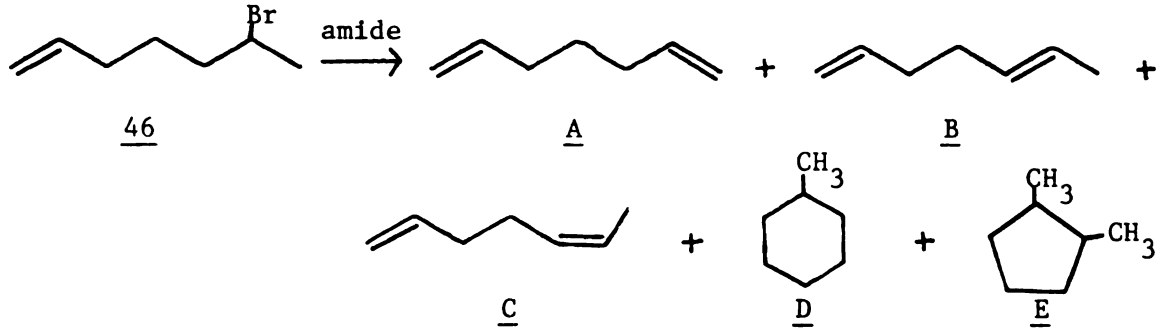
46 (74)

The same trends in 1-butene/2-butene ratios and trans/cis-2-butene ratios are observed for 46 as with 2-bromo and 2-iodobutane. Thus the 1,6-/1,5-heptadiene ratio rises, then falls and the trans/cis 1,5-heptadiene ratio falls, then rises, with increasing amide bulk.

Reaction of lithium diisopropylamide with 2-chlorobutane in THF proceeded much more slowly than with any other butyl halide. Almost 24 hours was required for complete reaction and a total butene yield of 64% (eq 75) was obtained.

$$\text{LDA} + \text{2-chlorobutane} \xrightarrow[\text{THF}]{0^{\circ}\text{C}} \underset{69\%}{\text{1-butene}} + \underset{20\%}{\underline{\text{cis}}\text{-butene}} + \underset{11\%}{\underline{\text{trans}}\text{-butene}} \qquad (75)$$

Table XII. Product Ratios for Dehydrohalogenation of 2-Bromo-6-heptene with Secondary Lithium Amides in THF at 0°C.



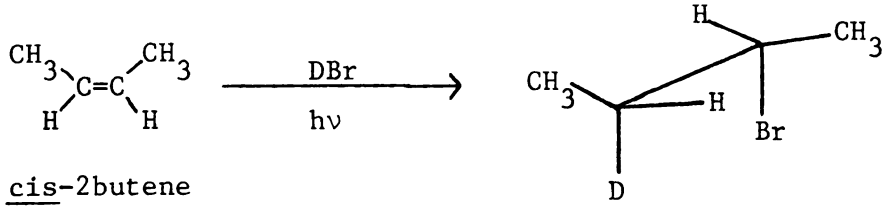
R_1R_2	A(%)	B(%)	C(%)	B/C	D + E	Yield
R_1=R_2= Et	81	4	12	3.0	1%	-
R_1=R_2= i-Propyl	87	3	9	3.0	2%	89
tetramethylpiperidine	96	1	3	3.0	1%	81
R_1= R_2= $EtMe_2C$- 24	93	2	4	2.0	1%	-
R_1=$EtMe_2C$-;R_2=Et_2MeC- 25	92	2	5	2.5	1%	-
R_1= R_2= Et_2MeC- 26	85	4	10	2.5	1%	-
R_1=Et_3C-;R_2=Et_2MeC- 27	74	6	18	3.0	2%	-
R_1= R_2= Et_3C- 21	76	6	17	2.8	1%	90

All of the amides were prepared using 1 equivalent of TMEDA in hexane with n-butyllithium. Analyses were performed by GLC.

Butene values are precise to within 2%.

Reactions of more hindered amides with 2-chlorobutane in THF failed to give better than 10% total yields of butenes. Further study of 2-chlorobutane and 2-bromobutane elimination reactions with lithium amides in diethyl ether was abandoned when LDA failed to give better than a 10% yield of butenes after 24 h.

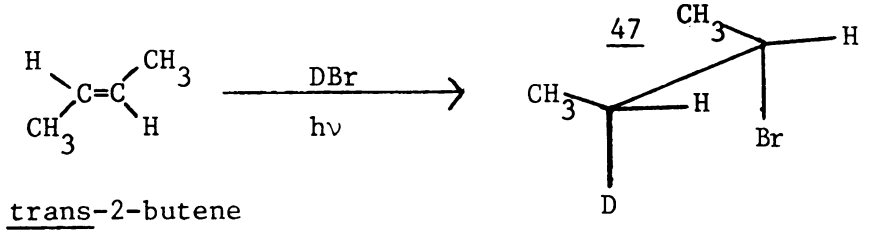
None of the previous experiments yielded information which could be unequivocally interpreted by a simple concerted elimination mechanism for all the amides and haloalkanes. As a last recourse, a study of stereoisomeric 3-deutero-2-bromobutanes was initiated to investigate whether the dehydrohalogenation reactions of haloalkanes with lithium amides is a syn or anti-elimination process. If the elimination reaction is indeed concerted, an isotope effect should be observed. Therefore, threo-3-d-2-bromobutane 47 and erythro-3-d-2-bromobutane 48 were synthesized and reacted with a number of hindered lithium amides. Equation 76 and 77 outline the synthesis of 47 and 48.[63]



cis-2butene

threo-3-d-2-bromobutane

(76)



trans-2-butene

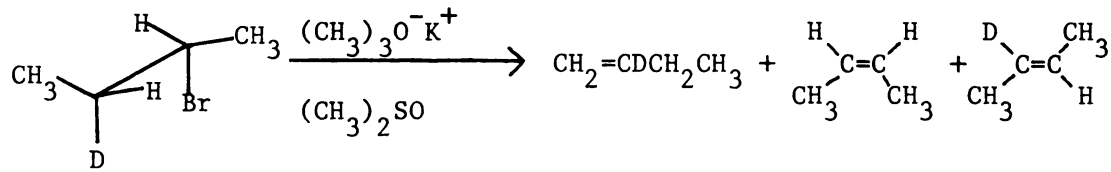
47

erythro-3-d-2-bromobutane

48

(77)

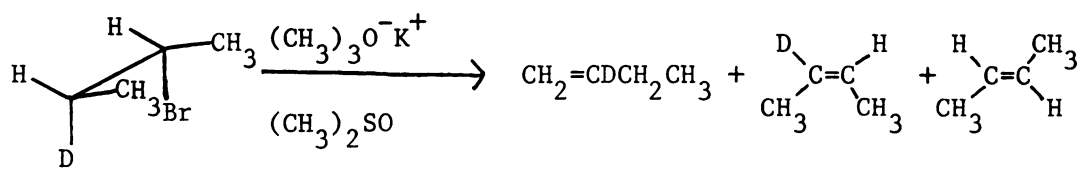
The purity of each isomer was determined by reacting 47 and 48 with 1 molar potassium tert-butoxide in dimethylsulfoxide at 30°C and collecting the butenes evolved from solution. The three butene isomers were separated by preparative GLC and the deuterium content of the cis and trans-2- butene isomers determined by mass spectral analysis. This dehydrohalogenation reaction is known to proceed with anti-stereochemistry. Isomers 47 and 48 should therefore yield the butene products predicted in eqs 78 and 79, respectively.



47- threo

d_1-1-butene cis-d_o trans-d_1

(78)

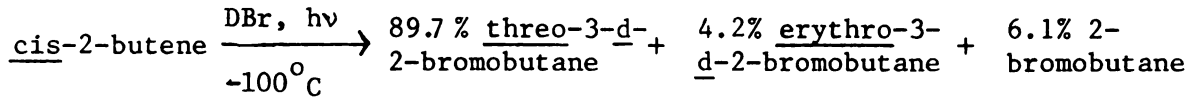


48- erythro

d_1-1-butene cis-d_1 trans-d_o

(79)

Each butene isomer was separated by GLC and analyzed by mass spectroscopy at 10.7 eV, just enough energy to ionize the molecule yet not enough energy to cause ion fragmentation. The deuterium content of each isomer was determined. From this data the actual purity of the two deuterated bromobutanes was calculated (see the Experimental section for details of the calculation), and the results are reported below in Figure 4.



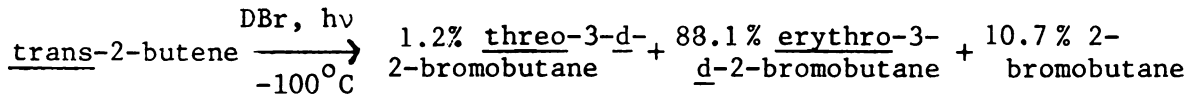
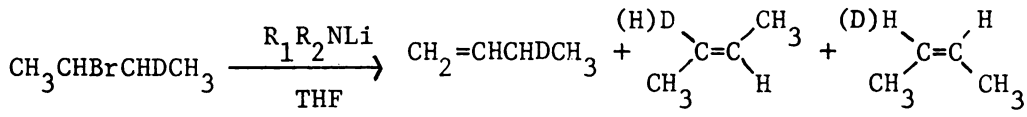


Figure 4. Isotopic Purity of Threo and Erythro 3-d-2-Bromobutane

Dehydrohalogenation of 47 and 48 was accomplished under experimental conditions identical with those used for the dehydrohalogenation of 2-bromobutane. The results of the elimination reactions with both 47 and 48 are presented in Tables XIII and XIV, respectively.

There are several clearly noticeable effects on butene product ratios for 47 and 48 when compared to undeuterated 2-bromobutane. The relative proportion of 1-butene formed in the amide elimination reaction of either 47 or 48 is greater than that observed for 2-bromobutane using the same amides. Secondly, the relative trans/cis-2-butene ratio from threo-3-d-2-bromobutane 47, is greater than the trans/cis-2-butene ratio obtained from the elimination reaction of 2-bromobutane with the corresponding lithium amides. Finally, the relative trans/cis-2-butene ratio from erythro-3-d-2-bromobutane 48,is smaller than the trans/cis-2-butene ratio obtained from the elimination reaction of 2-bromobutane with the corresponding lithium amides. Cis and trans-2-butene, isolated from the reaction of diethylamide and 21-Li with 47 and 48, were separated by GLC and analyzed by mass spectroscopy at 10.7 eV. The deuterium

Table XIII. Product Ratios for the Dehydrohalogenation of Threo-3-d-2-bromobutane with Lithium Amides in THF at 0°C.

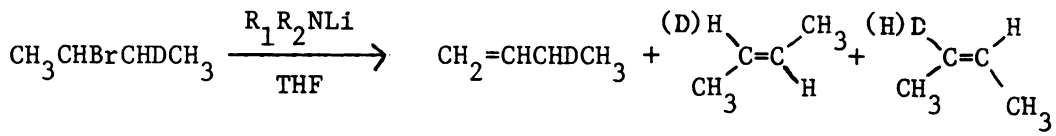


47 A B C

R_1R_2	A(%)	B(%)	C(%)	B/C
R_1=R_2= Et	63	32.9	3.8	8.6
R_1=R_2= i-Propyl	71.5	25	3.5	7.3
tetramethylpiperidine	92	6.1	1.8	3.4
R_1=R_2= $EtMe_2C$- 24	85.5	13	1.5	8.8
R_1=$EtMe_2C$-; R_2=Et_2MeC- 25	87.5	11	1.4	9.8
R_1=R_2= Et_2MeC- 26	78	20	2.0	13.5
R_1=Et_2MeC-; R_2=Et_3C- 27	62	35	2.5	14.2
R_1=R_2= Et_3C- 21	65	33	1.7	17. 3

All amides were prepared using 1 equivalent of TMEDA in hexane with n-butyllithium.

Table XIV. Product Ratios for the Dehydrohalogenation of Erythro-3-d-2-bromobutane with Lithium Amides in THF at 0°C.



48 A B C

R_1R_2	A(%)	B(%)	C(%)	B/C
R_1=R_2= Et	77.3	6.4	16.3	0.39
R_1=R_2= i-Propyl	83.6	4.0	12.4	0.33
tetramethylpiperidine	90.8	1.2	7.9	0.15
R_1=R_2= $EtMe_2C$- 24	89.3	3.1	7.9	0.39
R_1=$EtMe_2C$-; R_2=Et_2MeC- 25	91. 6	2.4	5.9	0.41
R_1=R_2= Et_2MeC- 26	86.4	6.2	7.2	0.86
R_1=Et_2MeC-; R_2=Et_3C- 27	79.6	8.8	11.6	0.75
R_1=R_2= Et_3C- 21	79.0	8.7	12.3	0.71

All amides were prepared using 1 equivalent of TMEDA in hexane with n-butyllithium.

The butene values are known with a precision of ±0.3%

isotope ratio was determined for each isomer and the results are shown in Table XV.

Table XV. Deuterium Content in Cis and Trans-2-Butene from the Dehydrohalogenation of Threo and Erythro-3-d-2-bromobutane.

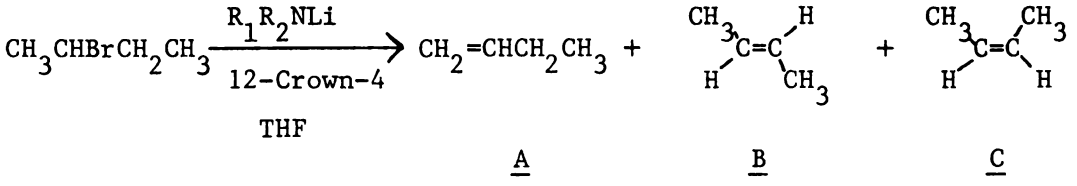
	$(Et_2)NLi$		$[(Et_3)C]_2NLi$	
	% trans-d-2-butene	% cis-d-2-butene	% trans-d-2-butene	% cis-d-2-butene
threo-3-d-2-bromobutane	87	13	89	11
erythro-3-d-2-bromobutane	10	90	12	88

Butene isomers separated by GLC. Mass spectral analysis at 13.5 eV

Another set of experiments was performed with 2-bromobutane and the amides in Table IX. These were designed to determine the exact orientational and geometrical effect of 1,4,7,10-tetraoxacyclododecane (12-Crown-4) on the dehydrohalogenation of 2-bromobutane with lithium amides. One equivalent of 12-Crown-4, a chelating ligand for lithium ions, was added to a 1 molar solution of 2-bromobutane, THF and a secondary lithium amide at $0^{\circ}C$. Yields of butenes were very low for most of the amides studied. Low temperature addition ($-78^{\circ}C$) of

12-Crown-4 to the amide solutions followed by 2-bromobutane, gave the best yields of butenes. The reaction solutions were stirred for 15 min at -78°C, warmed to 0°C and stirred for an additional 15 min. GLC analysis of the solution products was performed as before, without quenching. Quenching studies at -78°C with H_2O showed that for all the amides studied, except LiTMP, there was no dehydrohalogenation of 2-bromobutane within 30 min. LiTMP reacted very quickly (<10 min) with 2-bromobutane in the 12-Crown-4 THF solution at -78°C. The results obtained for the dehydrohalogenation of 2-bromobutane in 12-Crown-4 amide solutions are given in Table XVI, and show the same general trends which were observed in all the other lithium amide-haloalkane studies. There is an initial rise, then a fall in the 1-butene/2-butene ratio with increasing amide bulk. Concomitantly, one observes a fall, then a rise in the trans/cis-2-butene ratio with increasing amide bulk. The major difference apparent between the presence and absence of crown ether in these eliminations is that crown ether leads to poorer regioselectivity for 1-butene with the more hindered amides. A very notable exception occurs, however, with LiTMP, 12-Crown-4 (1 equivalent) and 2-bromobutane. This reaction shows excellent regioselectivity for 1-butene formation. The only other amide which showed a better regioselectivity with crown ether is LDA. The trans/cis-2-butene ratio variation with increasing amide bulk followed quite closely the results obtained without crown ether. The only exception occurs with very hindered amides, where the trans/cis-2-butene ratio is lower than that observed without any crown ether. Experiments performed with LiTMP, 2-bromobutane and varying amounts of lithium crown ether showed that as less 12-Crown-4 ether is added

Table XVI. Product Ratios for the Dehydrohalogenation of 2-Bromobutane with Lithium Amides Using 12-Crown-4 in THF at -78°C.



R_1R_2	Equiv 12-Crown-4	A	B	C	B/C	Yield (%)GLC
R_1=R_2= Et	1.0	53	29	18	1.6	--
R_1=R_2= i-Propyl	1.0	71	19	10	1.9	74
tetramethylpiperidine	1.0	99	<0.5	∿0.5	---	102
" no TMEDA	1.0	99	<0.5	∿0.5	---	99
"	0.5	95	2.5	3.5	1.4	--
"	0.25	92	3	4.5	1.5	--
"	0.1	89	4	7	1.8	--
R_1=R_2= $EtMe_2C$-	1.0	88	5	7	1.4	75
R_1=$EtMe_2C$-;R_2=Et_2MeC-	1.0	81	13	6	2.2	40
R_1=R_2= Et_2MeC-	1.0	53	32	15	2.1	33
R_1=Et_2MeC-;R_2=Et_3C-	1.0	46	38	15	2.5	33
R_1=R_2=Et_3C-	1.0	40	45	15	3.0	36

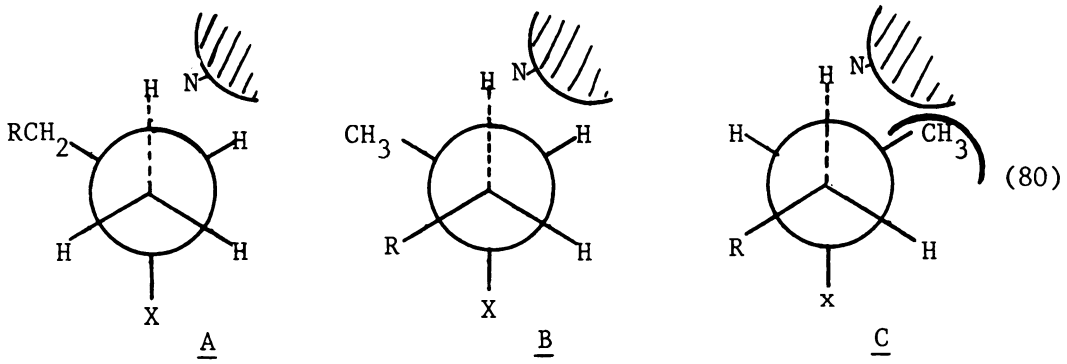
All amides prepared with 1 equivalent of TMEDA. Initial reaction temperature at -78°C for 15 min, then warmed to 0°C.

to the reaction solution, the regioselectivity of the dehydrohalogenation reaction is diminished. The presence or absence of TMEDA in the 12-Crown-4 dehydrohalogenation reaction of 2-bromobutane with LiTMP had no noticeable effect on the product butene ratios.

DISCUSSION

The E2 reaction of alkyl halides with secondary lithium amides has not been well studied, and there are few references to synthetic or physical organic investigations of dialkyl amide initiated E2 reactions.[59,64,65] A study was therefore initiated to investigate the stereo and regiochemical influence of secondary lithium amide base promoted dehydrohalogenation reactions.

Table IX lists the results of 2-bromobutane elimination reactions with dialkyl lithium amides. The rise in the 1-butene/2-butene ratio and concomitant fall in the trans/cis-2-butene ratio is what one might expect for the E2 reaction of increasingly hindered base species. Diethylamide, diisopropylamide, tetramethylpiperdylamide and the amide of 24 show progressively better terminal olefin regioselectivity. The Hoffmann product preference can be rationalized using a simple steric model, assuming an anti-elimination transition state (eq 80). This model is similar to one proposed by Bartsch for the E2 reaction using aggregated alkoxide bases of small to moderate steric dimentions.[47]



(80)

We have no a priori knowledge of the extent of amide base aggregation in THF solution. Whether or not the amide bases are associated, the simple steric model proposed in eq 80 seems adequate to explain the experimental results, at least for the less hindered amides. However,

as the amide bases become bulkier, transition states A and B for the formation of 1-alkene and cis-2-alkene, respectively, are less affected than that for trans-2-alkene formation, C, because of the possibility of tilting the base in A and B to relieve the steric interaction between the bulky base and the α and/or β-alkyl groups. Since these destabilizing steric interactions should increase in the order A < B < C as the effective base size increases, the relative percentage of 1-alkene should increase and the trans/cis-2-alkene ratio should decrease, as is observed for almost all of the alkyl halides studied (Table XVII).

Table XVII. Summary of Product Distribution Using Moderately Hindered Secondary Lithium Amides.

Alkyl Halide	$(Et)_2NLi$	$(i\text{-Propyl})_2NLi$	Lithium Tetramethylpiperidine	24-Li
2-Bromobutane				
a. 1-Butene	55%	67%	86%	90%
b. trans/cis 2-Butene	2.4	2.0	1.0	1.5
2-Iodobutane				
a. 1-Butene	37%	40%	61%	69%
b. trans/cis 2-Butene	1.9	1.7	1.1	1.5
2-Bromo-6-heptene	81%	87%	96%	93%
a. 1,6-Heptadiene	81	87	96	93
b. trans/cis 1,5-Heptadiene	3.0	3.0	3.0	2.0

The results obtained with or without TMEDA in the dehydrohalogenation reaction of 2-bromobutane were identical. TMEDA has no noticeable effect on the product distribution for the less hindered amides. One cannot predict the role TMEDA plays in influencing the product distribution for the very hindered amides, since TMEDA must be used to facilitate amide formation. If the THF solvent competitively coordinates with the amides' lithium ion, it would not be unreasonable to assume that this solvent would swamp any effect that TMEDA might have on the course of the dehydrohalogenation reaction.

Dehydrohalogentation of 2-alkyl halides with the very hindered amides 25-Li, 26-Li, 27-Li and 21-Li show markedly different behavior when compared with less hindered amides. Both orientational and geometrical control is reversed; the 1-alkene/2-alkene ratio decreases and the trans/cis-2-alkene ratio increases with increasing amide bulk. Table XVIII summarizes the results obtained in the dehydrohalogenation reactions of alkyl halides with very hindered lithium amides.

The simple steric model used in equation 80 to rationalize product butene ratios with moderately hindered amides no longer applies to the very hindered amide dehydrohalogenation reactions, for which other factors must come into play.

An explanation for this dichotomy might be that the simple steric model in eq 80 no longer is valid with very hindered amides. Another explanation might be that the steric model proposed in eq 80 is wrong and does not apply for any of the amides studied. In order to reconcile this apparent dichotomy, several different experiments were designed to explore the mechanism of the amide dehydrohalogenation reaction.

Table XVIII. Summary of Product Distribution Using Very Hindered Secondary Lithium Amides

Alkyl Halide	25-Li	26-Li	27-Li	21-Li
2-Bromobutane				
a. 1-Butene	89%	71%	57%	55%
b. trans/cis 2-Butene	1.75	3.8	3.7	4.0
2-Iodobutane				
a. 1-Butene	58%	38%	28%	28%
b. trans/cis 2-Butene	1.7	2.1	2.3	2.2
2-Bromo-6-heptene				
a. 1,6-Heptadiene	92%	85%	74%	76%
b. trans/cis 1,5-Heptadiene	2.5	2.5	3.0	2.8

Experiments were performed to determine if the dehydrohalogenation reaction was indeed a kinetically controlled reaction. No isomerization of the initially formed butenes occured by either unreacted amide or amide decomposition products. Control reactions using pure 1-butene and cis-2-butene with LiTMP and 21-Li showed that there was no isomerization of either butene. Another control reaction showed that amide decomposition products in THF do not cause dehydrohalogenation of 2-bromobutane. Olefin generation by a carbene mechanism was ruled out when 2-d-2-bromobutane retained its deuterium in the dehydrohalogenation reaction with LiTMP and 21-Li (eq 73).

2-Bromo-6-heptene was reacted with moderately and very hindered amides to determine if electron transfer occurs from the amides to the haloalkane. If electron transfer does occur, the free radical formed in the disproportionation of the radical anion would be quickly trapped as methylcyclohexane and 1,2-dimethylcyclopentane. Cyclization is much faster ($k = 10^{-5} - 10^{-6}\ s^{-1}$) than hydrogen radical abstraction to form olefins.[62] Less than 2% of cyclized products were formed with any of the lithium amides. Electron transfer from the amides to any of the three haloalkanes studied probably plays no significant role in olefin formation.

None of the above results pointed to anything but a concerted reaction mechanism for the dehydrohalogenation of any of the three alkyl halides studied. A simple and powerful tool was then applied to probe the transition states of these E2 reactions. Erythro-3-d-2-bromobutane, 48 and threo-3-d-2-bromobutane, 47 were synthesized and dehydrohalogenated with a series of lithium amides in THF. Figure describes how deuterium incorporation in the product butenes reflects

whether the amide elimination reaction of 47 and 48 proceed with syn or anti elimination stereochemistry.

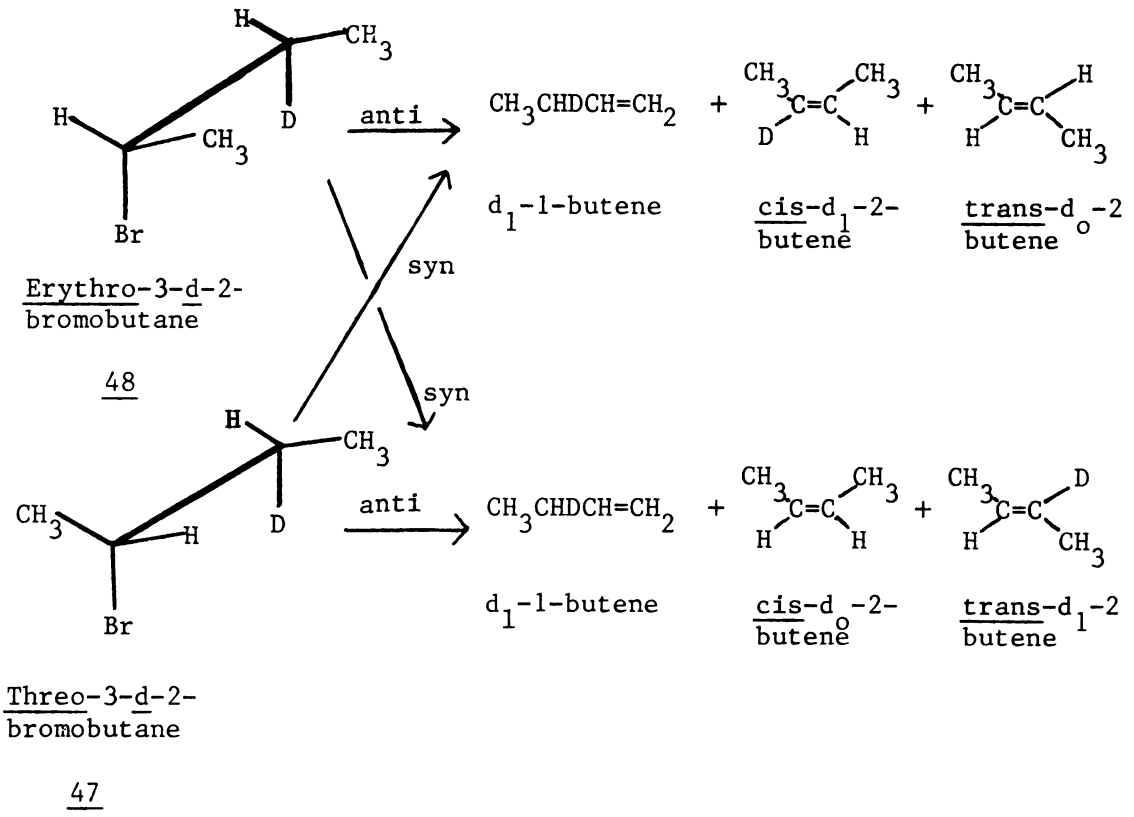
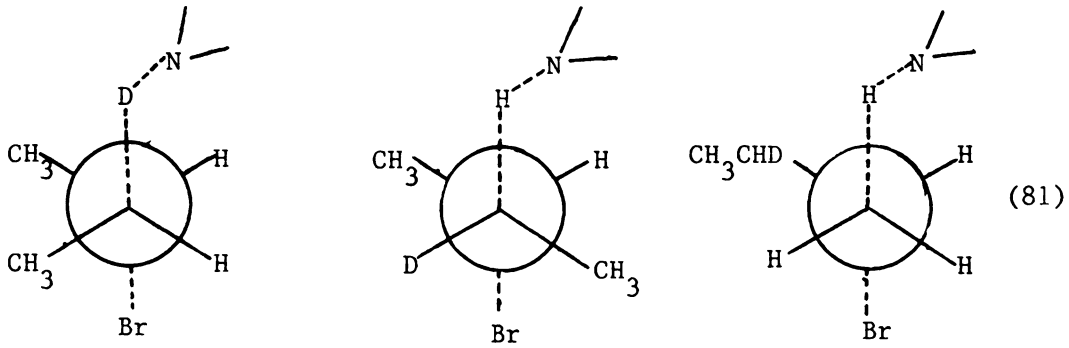


Figure 5. Syn and Anti Elimination Product Scheme for 47 and 48.

The magnitude of the isotope effect for an E2 elimination reaction depends on the bonding of the β-hydrogen atom in the transition state. If the hydrogen lies midway between the base and the β-carbon (central E2 like), the k_H/k_D ratio will be a maximum. Either less (E1 like) or more ($E1_{cB}$ like) C-H bond stretching will result in a lower isotope effect. A comparison of the data for the E2 reaction of 2-bromobutane (Table IX), threo-3-d-2-bromobutane 47 (Table XIII) and erythro-3-d-2-bromobutane (Table XIV) provides strong evidence favoring

anti-configuration with the hindered amides.

For threo-3-d-2-bromobutane, one would predict that an anti-transition state in the E2 elimination would look like the following (eq 81).



(81)

A ⟶ cis-d_0 B ⟶ trans-d_1 C ⟶ 1-d_1-butene

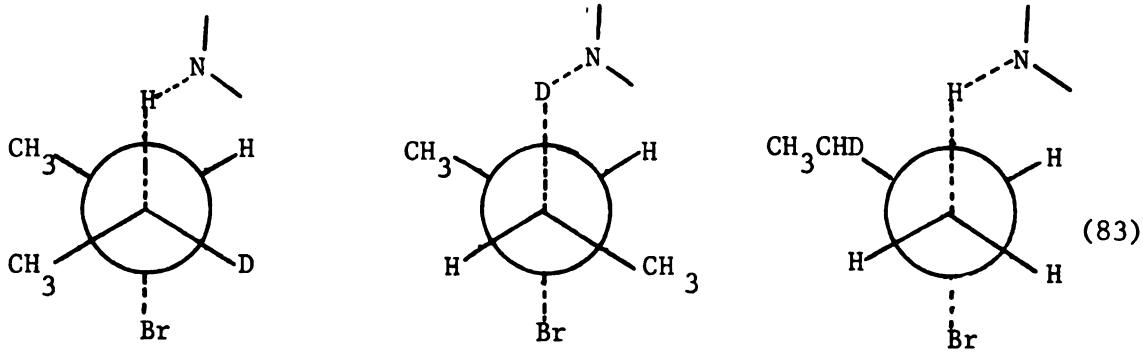
Assuming that the C-H(D) bond breaking step is rate limiting, retardation of the elimination step represented by A should be observed while the steps represented by B and C should proceed at a rate very similar to undeuterated 2-bromobutane. The retardation of step A (cis-2-d_0-butene formation) would result in an apparent rate increase in trans-d_1-2-butene and 1-d_1-butene formation. Thus an anti-E2 reaction with threo-3-d-2-bromobutane should result in an increase in the 1-butene/2-butene and trans/cis-2-butene ratios when compared with undeuterated 2-bromobutane. This is exactly what is observed in Table XIII. Both of these trends are observed with both moderately and very hindered amides. In fact, the very hindered amide E2 reactions show considerably higher trans/cis-2-butene ratios when compared with the same results from moderately hindered amide E2 reactions. Product analysis for deuterium content from the E2 reaction of diethylamide and 21-Li with 47

confirms, within experimental error, that the E2 reaction proceeds by an anti-elimination mechanism (eq 82).

			% d_o-cis-butene	% d_1-trans-butene	
Diethylamide-Li	+	47 ⟶	13	87	
21-Li	+	47 ⟶	11	89	(82)

The contamination by undeuterated 2-butenes is a result of the 4% and 6% contamination of 48 (erythro isomer) and undeuterated bromobutane, respectively. Undeuterated 2-bromobutane results from the inability to remove all adsorbed H_2O from the red phosphorus starting material.

An identical amide elimination study for erythro-3-d-2-bromobutane was performed. The results (Table XIV) indicate that the E2 reaction also proceeds by an anti-elimination mechanism for all the amides studied. Equation 83 illustrates the transition states for anti-elimination of the erythro-3-d-2-bromobutane isomer.



(83)

A ⟶ cis-d_1 B ⟶ trans-d_o C ⟶ 1-d_1-butene

The erythro-3-d-2-bromobutane isomer should show a relative increase in 1-butene and cis-2-butene formation when compared with undeuterated 2-bromobutane. Thus an increase in the 1-butene/2-butene ratio and a

decrease in the trans/cis-2-butene isomer ratio is expected when compared with undeuterated 2-bromobutane. This is exactly what is observed experimentally. There is a very substantial decrease in the trans/cis-2-butene ratio for 48 when compared to the results observed with undeuterated 2-bromobutane. Product analysis of cis and trans-2-butenes for deuterium content was performed from the E2 reaction of diethylamide and 21-Li with 48. The results are listed in eq 84 and confirm, within experimental error, that the E2 reaction proceeds by an anti-elimination mechanism (eq 84).

		% d_1-cis-butene	% d_o-trans-butene
Diethylamide-Li + 48 ⟶		90	10
21-Li + 48 ⟶		88	12

(84)

Simple steric arguments are inadequate to rationalize why 1-butene selectivity decreases with increasing steric bulk. The expectation would be that the less hindered terminal methyl hydrogen is more accessible than the 3-methylene hydrogen of the alkyl halide. A kinetic study of the E2 reaction of 2-bromobutane with lithium amides showed that moderately hindered amides (diethylamde through 24-Li) reacted within 1.5 h at 0°C. With the very hindered amides, the elimination reaction required anywhere from 2.5 h for 25-Li to almost 4 days with 21-Li. An explaination for the slowdown in this E2 reaction for the very hindered amides is that they are just too hindered to effectively coordinate to the β-methyl or β-methylene hydrogen atom of the alkyl halide. Space filling models of very hindered amides show that the amide

nitrogen is effectively shielded by the alkyl sidechains, burying the anionic center within the hydrocarbon folds of the amide molecule. This shielding effect should limit the number of effective trajectories by which the amide could approach the alkyl halide to a rather narrow "window" through which the transition state geometry is exactly right to effect dehydrohalogenation by an anti- elimination mechanism.

Another plausible explanation might be that the very hindered amides are not as kinetically basic as the less hindered amides. Evidence for this proposal is found in the kinetic base study of lithium amides by their attack on THF (Chapter II).

The E2 reaction of 2-bromobutane and the lithium amides was investigated with 12-Crown-4 ether to determine if amide base aggregation played a significant role in influencing E2 elimination regiochemistry. The results obtained shed little light on the question of amide base aggregation in THF. The influence of 12-Crown-4 ether on amide base selectivity in the E2 reaction with 2-bromobutane was inconsistant with the models posed by Bartsch for alkoxide promoted E2 reactions in alcohol. There is an increase, then a decrease in the 1-butene/2-butene ratio with increasing amide bulk in the presence of 12-Crown-4. The 1-butene/2-butene ratio maximum and minimum are greater than and less than, respectively, the same ratios without added crown ether.

Based on Bartsch's observations that crown ether acts to reduce effective base size by dissociating alkoxide base aggregates, one could conclude from the results in Table XVI that the moderately hindered amides like diethyl and diisopropylamide are dissociated monomeric bases which are not influenced by crown ether. On the other hand, the very hindered amides appear to form aggregate pairs or oligomers whose

effective steric bulk and, in turn, regioselectivity, is reduced by the crown ether dissociation of amide base aggregates. However, it is hard to believe that very hindered amides form aggregates while moderately hindered amides apparently remain unassociated in THF solution. An even more difficult observation to rationalize is the greater regioselectivity of LDA and LiTMP for 1-butene formation with crown ether than without crown ether. Addition of crown ethers has never before been shown to improve regioselectivity in base promoted E2 reactions.

Based on the data obtained in Table XVI, no firm conclusions can really be made as to the aggregation state of the lithium amides in THF. Further studies directed towards determining the nature of the aggregation state of lithium amides in ethereal solution remain to be performed.

One other piece of information which might be used in elucidating the nature of the dichotomy in E2 reactions involving moderately and very hindered amides is the apparent deuterium isotope effect of deuterated and undeuterated 2-bromobutane. If we assume that the amide bases in THF are dissociated, stretching of the C_β-H bond in the transition state for the amide induced eliminations may increase with very bulky bases to a point where the base's steric effect is reduced. Table XVI lists data from which an apparent deuterium isotope effect can be calculated between 2-bromobutane and each of the two deuterated stereoisomers, 47 and 48. The values of k_H/k_D for threo and erythro-3-d-2-bromobutane were calculated (see Experimental section) and corrected for the deuterium content of each isomer. Table XIX lists the apparent isotope effects for each amide reaction shown in Table XVI.

Table XIX. Apparent Primary Deuterium Isotope Effect for 2-Bromobutane

R_1R_2	k_H/k_D threo $\longrightarrow$ cis-d_o	k_H/k_D erythro $\longrightarrow$ trans-d_o
R_1=R_2= Et	3.9	7.7
R_1=R_2= i-Propyl	3.0	7.8
tetramethylpiperidine	3.2	5.1
R_1=R_2=Me_2EtC-	2.8	2.2
R_1=Me_2EtC-;R_2=$MeEt_2C$-	2.7	3.7
R_1=R_2=$MeEt_2C$-	3.7	4.9
R_1=$MeEt_2C$-;R_2=Et_3C-	4.7	6.4
R_1=R_2=Et_3C-	7.0	6.8

Ratios are subject to an uncertainty of ±0.5.

Two things are immediately apparent. First, there is a substantially smaller isotope effect observed for moderately hindered amides using threo-3-d-2-bromobutane than with the erythro-isomer. Secondly, the isotope ratios for both stereoisomers initially decrease, then increase with increasing amide bulk.

The range of the deuterium isotope effects reflect changes in the transition state of the dehydrohalogenation reactions with hindered amides. For diethylamide through 24-Li, the decrease in k_H/k_D can be rationalized by arguing that the transition state shifts from a "central E2" to a more "$E1_{cB}$ like" transition state as the kinetic basicity of the amide bases increase. The range of the isotope effect for the threo-isomer is substantially smaller (3.9 to 2.8) than the isotope effect (7.8 to 2.2) for the erythro isomer with moderately hindered amides. One reason for this effect might be the steric interaction of the terminal methyl group of 2-bromobutane with the amide base in the deprotonation step of the E2 reaction. The transition state for the threo-isomer leading to cis-d_o-2-butene has the terminal methyl group eclipsing the β-methyl group. The amide anion has an unencumbered approach from one side of the bromobutane molecule. The lack of steric interference would permit the moderately hindered bases to bind tightly with the C_β-deuterium atom and break the C-D bond before a substantial stretching of the C_β-D bond could occur. This would in effect decrease the observed deuterium isotope effect because the transition state would become more "$E1_{cB}$ like". The erythro isomer on the other hand has the β-methyl group trans to the terminal methyl group in the transition state leading to trans- d_o-2-butene. This transition state blocks

the approach of the incoming amide anion in the deprotonation step. The steric interaction would not permit moderately hindered and kinetically weak bases like diethyl and diisopropylamide to bind as tightly with the β-deuterium atom in the trans-erythro transition state as in the cis-threo transition state. Thus, substantial stretching of the C_β-D bond would occur in the transtion state, giving rise to a more "E2-like" transition state with the erythro isomer. As the kinetic basicity of the amide anions increase (LiTMP, 24-Li and 25-Li), this should offset the steric interference of the β-methyl group. The kinetically powerful amide bases would break the C-D bond before any substantial stretching of the C-D could occur and this would explain the drop in the apparent isotope effect from 7.7 to 2.2 for diethylamide through 24-Li, respectively.

For the very hindered amides 25-Li through 21-Li, there is a gradual increase in the isotope effect for both deuterated 2-bromobutane isomers. This increase in the isotope effect would seem to indicate a steady increase in the stretching of the C_β-H bond, reflecting a shift towards a more symmetrical transition state. If the C_β-H bond stretching were to go too far, the transition state would become more El_{cB}-like. This is apparently not observed with the hindered amides.

This increased stretching of the C_β-H bond probably reflects a combination of both steric and kinetic base effects. It was previously shown in the amide base stability study and the E2 reaction rate study that as the amide bases become more hindered, their kinetic base strength decreases. The elimination reactions with kinetically slow, hindered amides probably proceeds with a central E2 transition state. This would permit the β-alkyl group to lower the energy of the very

hindered amide transition state by electron release to the developing double bond, so that 2-butene formation is favored in the elimination step. Also, one would expect that a more central or symmetrical E2 transition state would give a larger trans/cis-2-butene ratio when compared to the El_{cB}-like transition state, owing to the eclipsing effect between two alkyl groups in the transition state leading to cis-2-butene. This is also observed as the very hindered amide bases increase in bulk.

EXPERIMENTAL

2-Bromobutane, 2-iodobutane and 2-bromo-6-heptene were all at least 98% pure and stored in amber bottles over copper foil under refrigeration. N',N',N ,N-Teteramethylethylenediamine, tetramethylpiperidine, diisopropylamine and diethylamine were purchased from Aldrich and distilled over calcium hydride. Hindered amines 24, 25, 26, 27 and 21 were prepared and purified as described in Chapter I. Tetrahydrofuran and diethyl ether were dried over lithium aluminum hydride and stored over sieves under argon. n-Butyllithium was purchased from Aldrich and standardized as described in Chapter II. The lithium chelating macrocycle 12-Crown-4 was purchased from Aldrich and used without purification. Deuterium bromide was synthesized by in situ formation of phosphorus tribromide with bromine and red phosphorus and subsequent reaction with 99.8% pure deuterium oxide (Stohler Isotopes). All reference butenes were obtained from Matheson and were at least 99% pure. IR spectra were taken as neat films on NaCl plates with a Perkin-Elmer 237-B spectrophotometer. NMR spectra were taken on Varian T-60 and Bruker WR-250 spectrometer using tetramethylsilane (TMS) as the reference standard. Mass spectra were taken with a Finnigan EI-CI gas chromatograph - mass spectrometer. Analytical gas - liquid chromatography was performed with a Varian 920 gas chromatograph using a 40' x 1/8" aluminum column packed with 80/100 mesh Chromosorb W DMCS-AW treated with 20% SE-30 liquid phase. All preparative GLC analyses were performed on the same chromatograph using a 20' x 1/4" stainless steel column packed with the same support at $-20^{o}C$.

Dehydrohalogenation of 2-Bromobutane with Lithium Diisopropylamide in THF.

The following dehydrohalogenation procedure is representative of all the dehydrohalogenation reactions of 2-bromobutane, 2-iodobutane, erythro and threo-3-d-2-bromobutane and 2-bromo-6-heptene with hindered alkyl lithium amides in THF or diethyl ether.

A 10 mL round bottomed-flask, fitted with a rubber septum glass sidearm, Teflon stirring bar and gas inlet valve, was connected to a mercury bubbler and flame dried under argon. After cooling, 1.90 mL of n-butyllithium (3.0 mmol, 1.56 M) was injected by syringe into the reaction flask, followed by 0.45 mL (3.0 mmol) of TMEDA. The flask was cooled to $0^{o}C$ with an ice bath. Then 0.42 mL (3.0 mmol) of diisopropylamine was slowly injected into the reaction mixture. The cooling bath was removed and the solution stirred for 10 min. A warm water bath (40-$50^{o}C$) was placed beneath the reaction flask and the hexane solvent removed under vacuum. After the hexane was removed, the flask was cooled to $0^{o}C$ and 3 mL of THF solvent was added to the flask, followed by 0.33 mL (3.0 mmol) of 2-bromopentane and 0.345 mL pentane internal standard (3.0 mmol). After 1 h, a 10 microliter sample aliquot was withdrawn with a microliter syringe and injected into the GLC ($50^{o}C$). The three butenes eluted sequentially as 1-butene, trans-2-butene and cis-2-butene. Coinjection of authentic butene samples dissolved in THF confirmed the product identities. Elution of the product butenes and pentane standard required about 1.5 h.

The same experimental procedure was followed using 3 mmole of diethylamine (0.31 mL), diisopropylamine (0.42 mL), tetramethylpiperidine (0.51 mL), 24 (0.60 mL), 25 (0.64 mL), 26 (0.68 mL), 27 (0.72 mL) and 21 (0.76 mL). The reaction times for the dehydrohalogenation reactions

are reported in Table X. None of the reaction mixtures were quenched with water before GLC analysis.

Metallation of THF and Attempted Reaction of Metallated THF with 2-Bromobutane.

LiTMP (3 mmol) was prepared by the procedure outlined in Chapter II using TMEDA. After hexane solvent was removed from the amide solution, THF was added (3 mL) and the mixture stirred at 24°C for 2 days. 2-Bromobutane (3 mmol) was added to the metallated THF solution and the mixture was stirred for another 3 days at 24°C. Pentane standard (3 mmol, 0.345 mL) was added to the solution and a sample aliquot was analysed by GLC. Only trace amounts (<2%) of butenes were obtained.

Reaction of 2-Iodobutane with Hindered Lithium Amides in THF.

The procedure described for the dehydrohalogenation reaction of 2-bromobutane was applied to the same reaction with 2-iodobutane. All the amides were prepared (3 mmol scale) as described previously in Chapter II. Iodobutane (3 mmol,.37 mL) was added to the appropriate amide in THF solution at 0°C. The reaction times for the dehydrohalogenations ranged from 5 min for diethylamide to 1 h for 25-Li. Reaction rates for the very hindered amides were not determined. However, all the very hindered amides had completely reacted within 10 h of 2-iodobutane addition. Yields and relative butene ratios were determined by GLC as described previously with 3 mmol of pentane.

Preparation of 2-d-2-Bromobutane from 2-Butanone.

A 400 mL round-bottomed flask was fitted with a Teflon stirring bar, septum sidearm and a reflux condenser. The reflux condenser was connected to a mercury bubbler with a gas flow valve and rubber tubing. The entire system was flame dried and flushed with argon. Anhydrous ether (distilled over $LiAlH_4$) 200 mL, was added to the reaction flask, followed by 5.0 g of $LiAlD_4$ (98% Stohler Isotopes). The solution was stirred vigorously while 38 mmol of 2-butanone (34 mL, 27.0 g) was added by syringe at such a rate as to maintain a steady reflux. After ketone addition was complete, the solution was stirred overnight at 24°C. Water (9 mL) was carefully added to the solution to decompose any unreacted deuteride. The supernatant was carefully decanted and the aluminum hydroxide residue was washed five times with 50 mL aliquots of ether. The gel was vacuum filtered to remove any remaining traces of alcohol. The ether extracts were combined and dried over anhydrous K_2CO_3. The ether was removed under reduced pressure and the alcohol distilled through a 20 cm Vigreux column. By GLC (5% Carbowax 20M, Chromosorb W), the product alcohol was 95% pure, the remaining 5% unreacted ketone. Recovered alcohol yield was 66% (17 g).

The 2-d-2-butanol was converted to 2-d-2-bromobutane by a literature procedure.[66] Bromine (10 mmol, 0.51 mL) was added to a 25 mL round bottomed flask flushed with argon, fitted with a stirring bar, septum inlet and a gas inlet valve connected to a mercury bubbler. The reaction flask was cooled to -78°C and 9.6 g (3.36 mL) of PBr_3 (Kodak, 95%) was added dropwise by syringe over 5 min. Then 97 mmol (8.9 mL) of 2-d-2-butanol was added dropwise to the vigorously stirred reaction solution.

After addition of the alcohol was complete, stirring was continued for 10 h at $0^{o}C$. The organic layer was decanted and washed with 2 x 10 mL cold water and 2 x 10 mL cold saturated aqueous Na_2CO_3. The organic layer was separated and distilled (bulb to bulb) to obtain 7.0 g (60% yield) of 98% pure (GLC) 2-d-2-bromobutane. No proton resonance was observed corresponding to 2-H-2-bromobutane: NMR ($CDCl_3$) δ 1.0 (3 H, t, J=7), 1.7 (3 H, s), 1.83 (2H, q, J=7); mass spectrum, m/e (relative intensity) 138 (M^+), 58(100), 57(3).

Reaction of 2-d-2-Bromobutane with 21-Li in THF at $0^{o}C$.

Reaction of 2-d-2-bromobutane with amide 21-Li in THF was performed as described previously. The reaction time was 60 h at $0^{o}C$. Preparative GLC was performed on a 20' x 1/4" column at $-20^{o}C$ filled with 20% SE-30 on Chromosorb W. The three butene isomers were separated and collected at $-198^{o}C$ in glass collection tubes. The individual isomers were dissolved in D_6 benzene and NMR spectra were obtained with the flame sealed tubes. Product analysis of 1-butene showed no proton resonance at δ 5.3 - 6.0, corresponding to a secondary olefinic hydrogen of undeuterated 1-butene; NMR of 1-butene (2-d) δ 0.8 (3 H, t, J=6), 1.8 (2 H, q, J=6), 4.75 (2 H, bs). NMR of cis and trans-2-butene from 2-d-2-bromobutane shows a 4:1 integrated proton signal between the olefinic proton at δ 5.3 and the methyl doublet at δ 1.6. Undeuterated cis and trans-2-butene show a 2:1 integrated proton signal at the same position: mass spectrum, m/e (relative intensity) cis and trans-2-butene 57 (M^+), 100 (41).

Preparation of 2-Butyl p-Toluenesulfonate

2-Butanol (7 g, 95 mmol) was added to 125 mL of dry pyridine in a 250 mL Erlenmeyer flask. A one mol excess of toluene sulfonyl chloride (0.2 mol, 38.1 g) was added to the pyridine solution and the flask stoppered with a rubber stopper. The solution was stirred for 1 h at 22°C with a magnetic stirring bar. The solution was then placed in a refigerator overnight (12 h). The solution was then poured into a 2 L beaker filled with 1 L of chopped ice and water. The organic tosylate falls to the bottom of the beaker and is separated from the aqueous layer. The tosylate is washed 3 times with 200 mL of water to remove any remaining pyridine. The tosylate is recrystallized from petroleum ether at -78°C. The yield of product is 41 g (90%). The product is a liquid at room temperature; NMR δ 0.5 (3 H, t, J=6), 0.95 (2 H, d, J=6), 1.2 (2 H, q, J=6) 1.93 (3 H, s), 4.3 (1 H, q, J=6), 6.77 (2 H, d, J=9), 7.57 (2 H, d, J=9).

Preparation of 2-Butyl Trifluoroacetate.

2-Butanol (10 g, 0.14 mol) was added to 150 mL of dry pyridine in a 250 mL Erlenmeyer flask fitted with a stirring bar and rubber stopper. The solution was cooled to 0°C and 56.7 g (0.27 mol) of trifluoroacetic anhydride was added to the solution. The solution was stoppered and reacted overnight at 0°C. The reaction mixture was poured into 500 mL of ice water and the aqueous phase decanted. The ester was dried over 4 A molecular sieve and distilled (bulb to bulb) under vacuum to give 14 g of 99% pure (GLC) ester. Yield is 59%: NMR δ 0.93 (3 h, t, J=6), 1.33 (2 H, d, J=6), 1.63 (2 H, q, J=6), 6.0 (1 H, sext, J=6).

Reaction of 2-Butyl Tosylate and 2-Butyl Trifluoroacetate with Secondary Lithium Amides in THF.

Both 2-butyl tosylate (3 mmol, 0.57 mL) and 2-butyl trifluoroacetate (3 mmol, 0.47 mL) were reacted with lithium diethylamide and LiTMP (3 mmol in each) in THF (3 mL) at 0°C as previously described. Less than a 20% yield of total butenes was achieved for each trial (GLC) after 10 h reaction time.

Preparation of 1-Pentene-5-ol from Allyl Bromide and Ethylene Oxide.

This procedure was adapted from a previously reported synthesis.[67] A solution of a few iodine crystals and 2 g of allyl bromide in 50 mL of anhydrous ether was added to 57 g of magnesium (2.34 mol) in a flame dried 3-necked round-bottomed flask fitted with a mechanical stirrer, reflux condenser and a dropping funnel (pressure equalized). The entire apparatus was under argon and connected with a gas inlet valve to a mercury bubbler. The Grignard reaction sets in within 10 min. Once the reaction begins to reflux vigorously, 500 mL of anhydrous ether was added to the reaction vessel. The reaction flask was placed in an ice bath. Then a solution of 250 mL of ether, 125 mL (178 g, 1.45 mol) allyl bromide and 46 g ethylene oxide (1.43 mol) at 0°C was dripped into the reaction solution with vigorous stirring. The temperature of the reaction mixture should not rise above 10°C. After addition, the solution is stirred for 5 h at 0°C, then warmed to 50°C and refluxed for 1 h. The reaction solution was quenched carefully with 50 mL ice water. The reaction solution was vacuum filtered. The solid residue was washed with 3 x 50 mL ether. The filtrates were combined and the ether was

removed under low pressure. The product was distilled (50 mm, 56°-58°C) and gave 55 g (42% yield) of 98% pure (GLC) 1-pentene-5-ol.

Preparation of 5-Chloro-1-pentene from 1-Pentene-5-ol.

1-Pentene-5-ol (30 g, 0.35 mol) was added to 250 mL of dry pyridine and cooled to -5°C. Then 80 g of p-toluenesulfonyl chloride (80 g, .42 mol) was added to the solution and the mixture stirred overnight at 0°C. Water (10 mL) was added in two mL aliquots at 5 min intervals to the reaction solution at 0°C. Then 100 mL of ice water was added to the reaction mixture. The entire solution mixture was extracted with 3 x 100 mL of chloroform. The chloroform layers were combined and extracted twice successively with 1 M H_2SO_4, H_2O and Na_2CO_3. The tosylate was dried over anhydrous Na_2SO_4. The dried product was a liquid at 24°C and was used without further purification: NMR δ 1.5 - 2.2 (4 H, m), 2.33 (3 H, s), 3.93 (2H, t, J=6), 4.7 (1 H, m), 4.9 (1 H, m) 5.2-5.9 (1 H, bm), 7.16 (2 H, d, J=7), 7.67 (2 H, d, J=7).

Anhydrous lithium chloride (.32 mol, 13.4 g) was added to dry dimethylsulfoxide (130 mL) in a 300 mL round-bottomed flask equipped with a magnetic stirring bar. The mixture was stirred until all of the lithium chloride was dissolved. Then 63 g (0.26 mol) of 1-pentene-5-ol tosyl ester was poured into the reaction flask. The flask was stoppered and stirred for 2 days at 50°. Water (200 mL) was added to the solution and the solution cooled to 0°C. The 1-chloro-5-pentene separated from the solution and was decanted. The chloroolefin was distilled through a short path distillation column (bp 105-107°C, 750mm) and the recovered yield (19 g) was 70% of 98% pure product (GLC): NMR δ 1.7-2.4

(4 H, m), 3.47 (2 H, t, J=6), 4.9 (1 H, m), 5.1 (1 H, m), 5.4 - 6.0 (1 H, m).

Synthesis of 1-Heptene-6-ol.

To a 100 mL round-bottomed flask fitted with a stirring bar, septum sidearm and reflux condenser, was added 4.6 g of magnesium shavings (0.19 mol). The flask was flamed dried and flushed with argon. Ether (20 mL) was added to the reaction flask, followed by 16.1 g of 5-chloro-1-pentene in 20 mL of ether at a rate where the solution refluxed gently. After the addition was completed, the solution was heated at reflux for 2 h. The solution was cooled to -10^{o}C and 6.4 g of acetaldehyde in 20 mL of ether was added dropwise. The addition must be done slowly enough to insure that the solution never exceeds 0^{o}C. The mixture was stirred for 2 h at 0^{o}C after acetaldehyde addition was completed. Ice (50 g) was added to the solution and the mixture acidified with 10% H_2SO_4. The reaction mixture was extracted with 3 x 10 mL of ether. The ether layers were combined and the ether was removed under reduced pressure. The residue was distilled through a short path distillation apparatus (20 mm, 62-63^{o}C). About 13.8 g of 1-heptene-2-ol (76% yield) was recovered: NMR δ 1.17 (3 h, d, J=7), 1.43 (4 h, bm), 1.8 - 2.2 (2 H, bm), 2.5 (1 H, bs, -OH), 3.7 (1 H, bm), 4.78 (1 H, m), 5.0 (1 H, m), 5.4 - 6.1 (1 H, m).

Synthesis of 2-Bromo-6-heptene from 1-Heptene-6-ol.

A solution of 14.1 g 1-heptene-6-ol and 30 mL dry ether was added by syringe into an ice bath cooled 50 mL round-bottomed flask containing

a stirring bar, septum side arm and 15.8 g (5.5 mL) of 95% phoshorus tribromide (56 mmol). After the alcohol was added, the solution was stirred at $0^{o}C$ overnight. Then 20 mL of cold staurated Na_2CO_3 was added slowly (vigorous CO_2 evolution) to the reaction mixture. The mixture was extracted with 3 x 30 mL of cold ether. The extracts were pooled and dried over anhydrous K_2CO_3. The ether was removed under reduced pressure and the residue distilled by short path distillation (50 mm, 46-47^{o}C). The yield was 58% (9.6 g, 98% pure by GLC): NMR δ 1.95 (2 H, sep, J=7), 4.0 (1 H, sex, J=6), 4.73 (1 H, m), 4.95 (1 H, m), 5.35 - 5.95 (1 H, bm), ^{13}C NMR (δ = ppm relative to TMS) δ 26.47, 27.0, 33.05, 40.56, 51.37, 114.94, 138.19; mass spectrum, m/e (relative intensity) 179 (M^+), 177 (M^+), 97 (82), 81 (57), 69 (41), 55 (100), 54 (70), 41 (78), 32 (63).

Reaction of 2-Bromo-6-heptene (46) with With Hindered Lithium Amides.

The reaction of 3 mmol of 46 (0.44 mL) with all the lithium amides in Table IX was carried out as described previously with 2-bromobutane. Analysis for heptadienes and either 1,2-dimethylcyclopentane or methylcyclohexane was carried out by GLC (40' x 1/8" aluminum column filled with 100 mesh Chromosorb W AW-DMSC coated with 20% SE-30). Product analysis was performed by coinjection of authentic heptadiene samples from Chemical Samples Co. Product analysis of 1,2-dimethylcyclopentane and methylcyclohexane was by mass spectrometry and sample coinjection: NMR analysis of sample cis and trans-1,5-heptadiene mixture; δ 1.6 (3 H, t, J=2), 2.03 (4 H, s), 2.06 (2 H, bm superimposed over s), 4.75 (1 H, m), 5.0 (1 H, m), 5.3 (2 H, m), 5.4 - 6.1 (1 H, m); mass spectrum m/e (relative intensity) 96 (M^+), 81 (31), 67 (43), 55 (76), 54 (100), 41 (29).

NMR 1,2-dimethylcyclopentane δ 0.8 (3 H, s), 0.93 (3 H, s), 1.0 - 2.0 (8 H, bm); mass spectrum, m/e (relative intensity) 98 (M^+), 83 (19), 70 (90), 69 (36), 56 (100), 55 (77), 42 (35), 41, (78).

Synthesis of Deuterium Bromide.

In a 100 mL flask fitted with a stopcock septum side arm was placed 2.5 g of red phosphorus and sufficient D_2O to thoroughly wet the flask walls. The flask was evacuated to less than one micron and then 5.1 mL of 99.8% D_2O was added, followed by 30 g (0.37 mol) of Br_2, added dropwise. The bromine reacted with considerable violence; flashes of light occured as it hit the solution. Addition required about 2 h. The DBr was collected in a dry ice-acetone cooled trap and then transfered to a vacuum line system and distilled through a -110°C trap (pentane, liquid N_2) into a liquid nitrogen cooled one. The material in the liquid nitrogen flask was condensed onto about 0.5 g of 1-octene to remove traces of elemental bromine. Four more distillations through a -110°C trap gave 98 mmol of DBr which was condensed into a thick walled pyrolysis tube and sealed under vacuum. The yield was 8.6 g (41% yield based on 0.24 mol of PBr_3).

Threo and Erythro-3-d-2-Bromobutane Synthesis.

Into an evacuated quartz flask fitted with a Teflon stirring bar and connected to a high vacuum line was condensed 10.9 g (119 mmol) of DBr and 5.54 g (99 mmol) of cis-butene using liquid nitrogen. The flask was covered with aluminum foil and the contents degased by warming to -78°C, cooling to -198°C, and applying high vacuum (<1 micron). This

was repeated twice. The reaction mixture was maintained at between -105 and -95°C using a 3 L Dewar flask filled with pentane and cooled by periodic addition of liquid nitrogen. The pentane cooling solvent was stirred using a magnetic stirring bar. The reaction mixture was irradiated with a Hanovia medium pressure utility mercury arc lamp at a distance of between 12 and 18 inches. Initially, no reaction occured; however, a rapid exothermic reaction soon set in as observed by a pressure rise in the reaction flask. The pressure was maintained below 25 mm by adusting the distance of the mercury lamp. At no time should the cooling bath temperature rise above -90°C. After the reaction was complete, irradiation of the reaction mixture caused no pressure increase. The irradiation required about 15 to 25 min. The mixture was distilled through a -100 °C trap to remove excess DBr. The liquid remaining in the -100°C trap was removed from the vacuum line and carefully washed with aqueous K_2CO_3 and distilled by a short path distillation to give 10.6 g (80% yield) of threo-3-d-2-bromobutane, bp 91°C. GLC analysis showed the product to contain less than 1% non-bromobutane impurities. A dehydrohalogenation procedure (vide infra) gives the stereoisomeric purity of the threo-sample.

The erythro-3-d-2-bromobutane diasteriomer was prepared in a similar manner from 60 mmol of DBr and 45 mmol trans-2-butene. The yield of the erythro diastereomer was 4.5 g (33 mmol, 73%). The same dehydrohalogentation procedure as above was used to determinine the stereoisomeric purtity of the erythro isomer.

Determination of the Stereoisomeric Purity of Threo and Erythro-3-d-2-Bromobutane.

To two mL of dimethyl sulfoxide (reagent grade), containing 400 mg potassium t-butoxide was added 200 µl (1.84 mmol) threo-3-d-2-bromobutane. The reaction mixture was kept at 30°C during the reaction. Gases were evolved and were collected in a liquid N_2 trap. The product butenes were condensed into an evacuated 50 mL Schlenk tube containing 1 mL of THF. The butenes dissoved in the THF and the solvent mixture was injected into the GLC. The butene isomers were separated and collected in glass capillary tubes. The proportion of butenes consisted of 36.2% 1-butene, 57.8% trans-2-butene and 5.9% cis-2-butene. The yield was not determined.

The same dehydrohalogenation reaction was repeated with the erythro isomer. The proportion of butenes consisted of 54.0% 1-butene, 22.4% cis-2-butene and 23.6% trans-2-butene.

The olefins were analysed with a Finnigan EI-CI GLC - mass spectrometer at 11.4 eV. The mass spectrum of C_4H_8 at this electron energy consists solely of a peak for the parent ion; there were no P-1 or P-2 peaks. Table XX lists the results of the deuterium content analysis. Deuterium percentage was computed using the following formula.

$$\text{Percent Deuterium} = \frac{[\text{Mass } 57 - (\text{Mass } 56)\ (0.042)]\ 100}{\text{Mass } 56 + \text{Mass } 57 - \text{Mass } 56\ (0.042)}$$

Table XX. Mass Spectra of 2-Butenes from 3-d-2-Bromobutanes

Olefin	Source	Mass 56	Mass 57	Mass 58	Deuterium
cis-	Matheson	100	4.2	0	0%
trans-	threo-sample	7.34	100	0	93.1%
cis-	threo-sample	100	26.72	0	18.4%
trans-	erythro-sample	100	7.74	0	3.4%
cis-	erythro-sample	7.76	100	0	92.8%

The composition of these butene samples can be used to determine the percentage of undeuterated and diastereotopic impurities in the threo and erythro-3-d-2-bromobutane samples. Assuming that the dehydrohalogenation reactions proceed quantitatively with perfect trans-stereospecificity,[47] a pure erythro-sample should produce trans-2-butene-d_o and cis-2-butene-d_1. Similarly, a pure threo-sample should produce trans-2-butene-d_1 and cis-2-butene-d_o.

The first three rows in Table XXI give the experimental data for butene composition. These are taken from the butene compositions of the t-butoxide mediated dehydrohalogenation of threo and erythro-3-d-2-bromobutane and from the deuterium analysis in Table XX. In Table XXI, deuterated compounds are listed in separate columns and 1-butene is normalized to 100.

Table XXI. Butenes Produced by Dehydrohalogenation of Erythro and Threo-3-d-2-Bromobutane

	1-butene	trans-d_1	trans-d_o	cis-d_1	cis-d_o
(1) 2-bromobutane	100		163		47
(2) threo-sample	100	148.6	11	2.9	13.3
(3) erythro-sample	100	1.31	40	40.5	3.1
Composition calculation for pure threo-sample					
(4) threo-sample	100	148.6	11	2.9	13.3
(5) (0.0716) (line 3)	7.16	.09	2.86	(2.9)	0.22
(6)	92.84	148.5	8.14	0	13.08
(7) (0.050) (line 1)	5.0	0	(8.14)	0	2.34
(8)	87.84	148.5	0	0	10.74
(9) Normalize line 8	100	169	0	0	12.22

Table XXI (cont.)

	1-butene	trans-d_1	trans-d_o	cis-d_1	cis-d_o	Sb_n
Composition calculation for pure erythro sample						
(10) erythro-sample	100	1.31	40	40.5	3.1	184.9
(11) (0.00775) (line 9)	0.77	(1.31)	0	0	0.1	
(12)	99.23	0	40	40.5	3.0	
(13) (0.06383) (line 1)	6.38	0	10.4	0.0	(3.0)	19.78
(14)	92.8	0	29.6	40.5	0	
(15) Normalize line 14	100	0	31.89	43.64		
Recalculate composition for threo-sample, using corrected erythro-composition						
(16) line 4	100	148.6	11	2.9	13.3	275.8
(17) (0.06645) (line 15)	6.6	0.0	2.1	(2.9)	0	11.6
(18)	93.4	148.6	8.9	0	13.3	
(19) (0.0546) (line 1)	5.5	0	(8.9)	0	2.56	17.0
(20) Normalize difference	87.9 (100)	148.6 (169.1)	0	0	10.7 (12.2)	

Since cis-2-butene-d_1 should only be produced from the dehydrohalogenation of erythro-3-d-2-bromobutane, any present in the threo sample must be due to erythro impurity. The erythro sample experimental data (row 3, Table XXI) was multiplied by a factor (0.0716) that was chosen so that substraction of these products from the threo sample experimental data (row 4) would leave no cis-2-butene-d_1. Row 6 gives the difference. trans-2-Butene-d_o must arise from either erythro-3-d-2-bromobutane or undeuterated 2-bromobutane. Since all the erythro-contribution has already been removed from line 6, the remainder of the trans-2-butene must have come from undeuterated 2-bromobutane. Multiplication of the 2-bromobutane data (row 1) by (0.05) and subtration from row 6 removes all trans-2-butene d_o contribution. The results (row 8) relates the composition that would be obtained by dehydrohalogenation of a diastereomerically pure sample of threo-3-d-2-bromobutane. In line this composition is normalized such that 1-butene is 100.

A similar process was used on the erythro experimental data. The process was completely analogous to that used for the threo data, except that the corrected threo data (line 9) was used instead of the raw data. (Line 10) - (0.00775) (line 9) gives line 12 in which all threo contribution is removed. (Line 12) - (0.06383) (line 1) gives line 14, the composition that would come from a pure erythro-sample. Line 15 is this composition normalized such that 1-butene is 100.

Assuming all dehydrohalogenations are quantitative, the composition of the erythro sample can now be determined. Let the sum of all butenes in any line of Table XXI be denoted by the symbol Sb_n where n is the line under consideration. Sb_{10} represents all material obtained

from the erythro sample. Sb_{11} is the threo contribution, hence the percentage of threo present in this sample is $100Sb_{11}/Sb_{10}$. Similarly. the percentage undeuterated 2-bromobutane is $100Sb_{13}/Sb_{10}$. When numerical values from Table XXI are substituted into these expressions, it is found that this sample contained 1.2% threo and 10.7% undeuterated 2-bromobutane with the remainder consisting of erythro.

The data in lines 4 through 8 cannot be used for the determination of the threo sample composition because the erythro data that was subtracted contained contributions due to both threo and undeuterated 2-bromobutane. However, when the corrected erythro composition (line 15) was used instead of the experimental data (line 3), the composition could be determined. Lines 16 through 20 are analogous to lines 4 through 8, except corrected erythro data was used in this computation. The percentage erythro present is $100Sb_{17}/Sb_{16}$ and the percentage undeuterated 2-bromobutane is given by the expression $100Sb_{19}/Sb_{16}$. When numerical values are substituted into these expressions, it is found that this sample contained 4.2% erythro and 6.1 % undeuterated 2-bromobutane with the remainder consisting of threo.

Determination of the Kinetic Isotope Effect for Dehydrohalogenation of Threo and Erythro-3-d-2-Bromobutane with Hindered Lithium Amides in THF.

The primary kinetic isotope effect may be computed using the assumption that 1-butene is formed at the same rate in 2-bromobutane and its 3-deuterated counterparts. A second assumption is that the E2 reaction goes to completion with the deuterated isomers. The composition of the butene products from deuterated bromobutanes and 2-bromo

butane were normalized to 1-butene as 100. The kinetic isotope effect was calculated for each lithium amide dehydrohalogenation reaction as cis-2-butene$_{(undeuterated)}$/cis-2-d_o(erythro) and trans-2-butene$_{(undeuterated)}$/trans-2-butene-d_o (threo). The k_H/k_D value calculated was corrected for deuterium content; 12% d_o for the erythro isomer and 10% for the threo isomer.

Reaction of Lithium Amides with Threo and Erythro 3-d-2-Bromobutane in THF at 0°C.

The alkyl lithium amides were prepared as previously described. For the threo study, the reactions were run on a 3 mmol scale while the erythro-study was performed on a 2 mmol scale. Threo (325 µl) and erythro (216 µl) 3-d-2-bromobutane reaction were run for 1 day using the less hindered amides (diethylamide through 25-Li). Amides 26 through 21-Li were reacted for periods described in Table X. At least 3 injections of each sample were made and the cis/trans-2-butene ratios were performed with at least one peak adjusted to full scale deflection on the strip chart recorder. This was done to minimize the signal to noise ratio.

Reaction of Alkyl Lithium Amides with 2-Bromobutane in THF - 12-Crown-4 Ether Solution at -78°C.

The alkyl lithium amides were prepared as before (3 mmol). After hexane solvent was removed, the reaction flask was cooled to 0°C and 1.5 mL of THF was added to the amide. After the amide dissolved (about 1 min), the flask was cooled to -78°C. Then 1.5 mL of standard 2.0 M

solution of 12-Crown-4 in THF was added by syringe within 30 sec. The solution was stirred at -78°C for 1 min and immediately 0.33 ml of 2-bromobutane was added by syringe. The mixture was stirred at -78°C for 30 min, then warmed to 0°C for 2 h. The sample aliquots were analyzed by GLC using pentane internal standard. Care should by taken not to add pure 12-Crown-4 to the amide solution at 0°C, since the crown ether greatly accelerates metallation of THF. Pure 12-Crown-4 added to THF at -78°C will not dissolve, even after 2 h.

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