Ketone Enolization by Lithium Hexamethyldisilazide: Structural and Rate Studies of the Accelerating Effects of Trialkylamines

Pinjing Zhao and David B. Collum
Department of Chemistry and Chemical Biology
Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

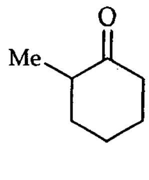
Supporting Information

Part I. NMR Structural Studies

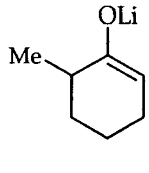
Procedure for Sample Preparation

Part II. *in situ* IR Kinetic Studies

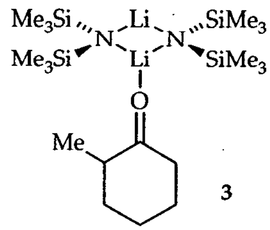
Structures in Supporting Information



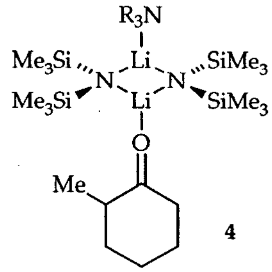
1



2



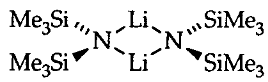
3



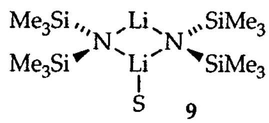
4

$[(Me_3Si)_2NLi]_n$

7 (n = 3 or 4)



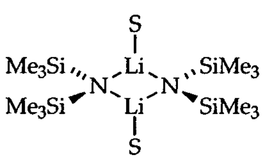
8



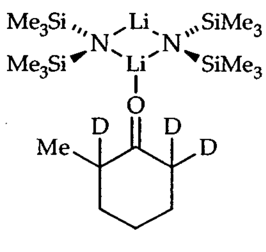
9

$2\ (Me_3Si)_2NLiS_3$

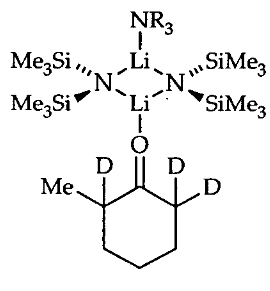
11



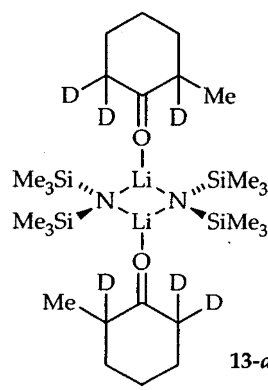
10



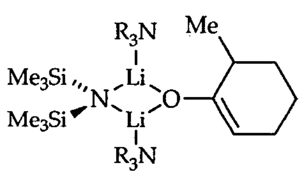
3-d_3



4-d_3



13-d_6



14

Part I. NMR Structural Studies

Procedure for Sample Preparation The stock solutions of [^{6}Li,^{15}N]LiHMDS (0.30 M in toluene), **1**-d_3 (1.2 M in toluene), and Me_2NEt (6.0 M in toluene) were prepared. The NMR tubes were capped with a serum stopper and flushed with Ar, charged with 200 μL of the LiHMDS solution, and submerged below the sample level in liquid nitrogen. The solution of ketone (100 μL) was layered and frozen sample to afford two separate frozen layers. The tube was placed in a dry ice/acetone bath to allow the solutions melt and mix. (In the absence of amine, the ketone enolization is very slow.) The sample was frozen in liquid nitrogen and layered with the solution of Me_2NEt (300 μL). The sample was allowed to warm and mix inside the NMR probe at -100 °C.

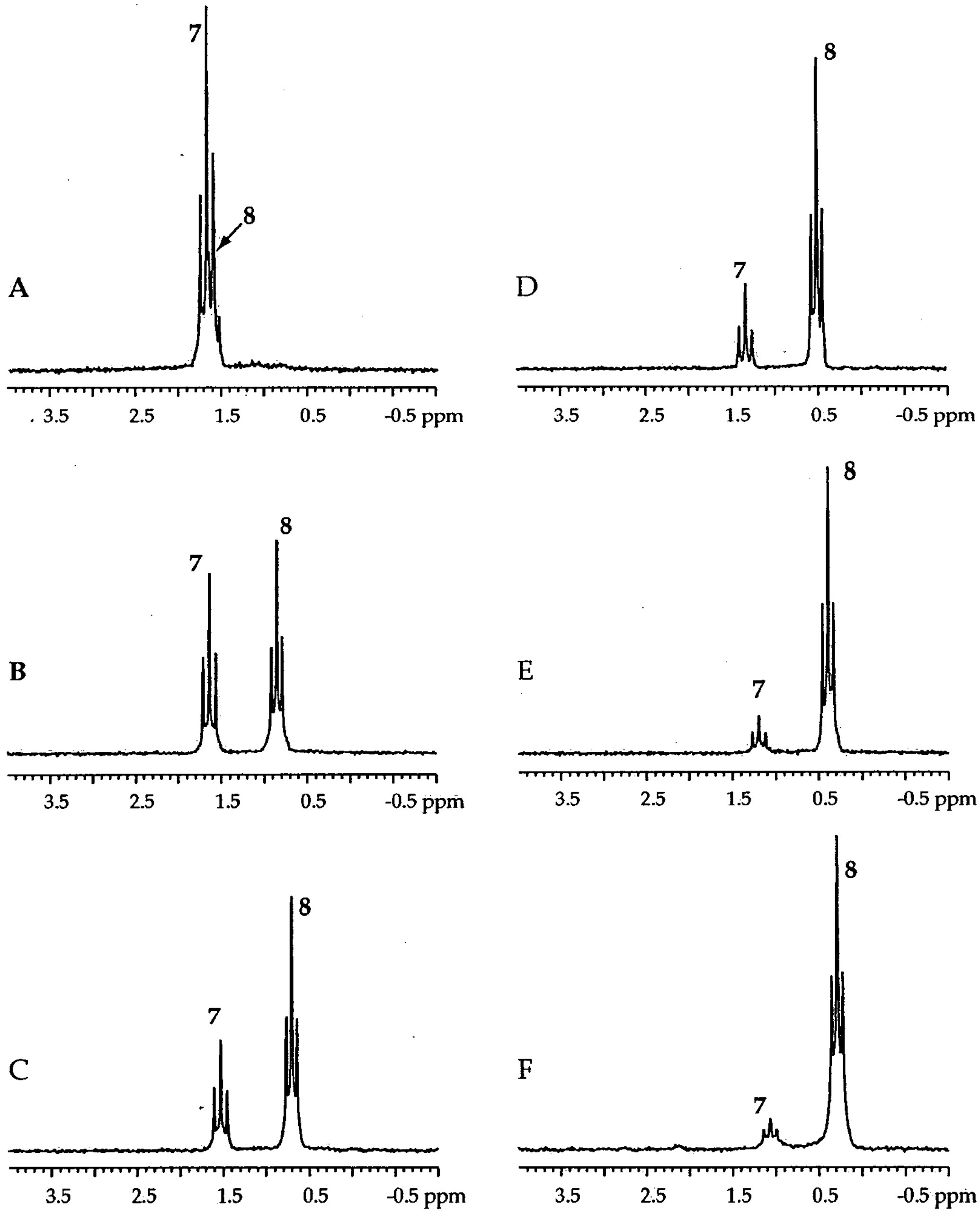


Figure 1. ^{6}Li NMR spectra recorded on 0.1 M [^{6}Li,^{15}N]LiHMDS in toluene/pentane mixtures at –100 °C. Higher oligomer **7** and dimer **8** were monitored at different toluene volume contents: (A) neat pentane; (B) 20% toluene; (C) 40% toluene; (D) 60% toluene; (E) 80% toluene; (F) neat toluene.

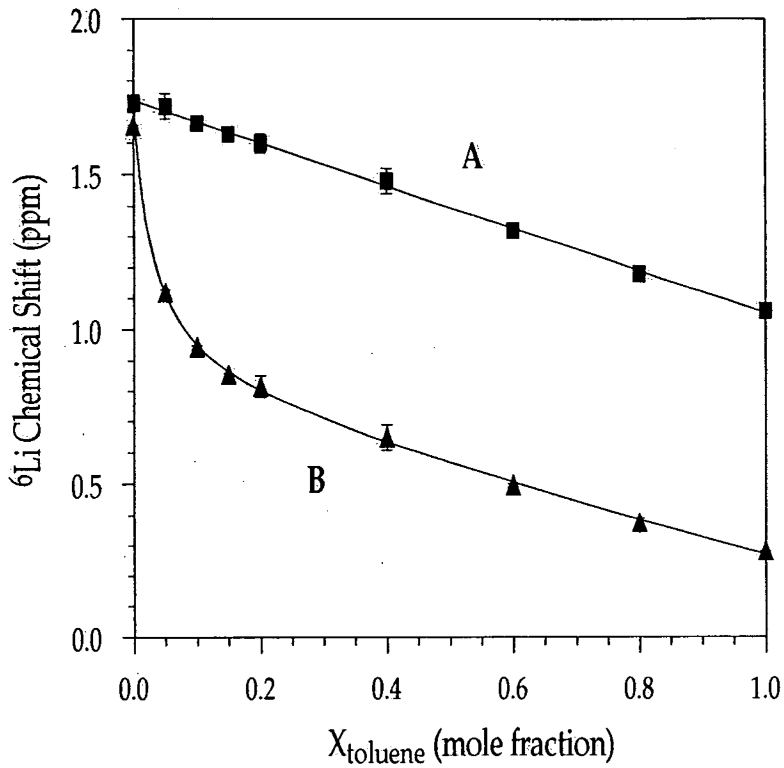


Figure 2. Plot of ^{6}Li chemical shift vs toluene mole fraction in the solution of 0.1 M [^{6}Li,^{15}N]LiHMDS in toluene/pentane at –100 °C. **Curve A** (correlating to higher oligomer **7**) depicts the results of an unweighted least-squares fit to $y = ax + b$, where $a = 1.736 \pm 0.008$, $b = -0.68 \pm 0.01$; **Curve B** (correlating to dimer **8**) depicts the results of an unweighted least-squares fit to $y = (a + bx)/(1 + cx) + dx$, where $a = 1.66 \pm 0.01$, $b = 22 \pm 3$, $c = 29 \pm 3$, $d = -0.54 \pm 0.03$.

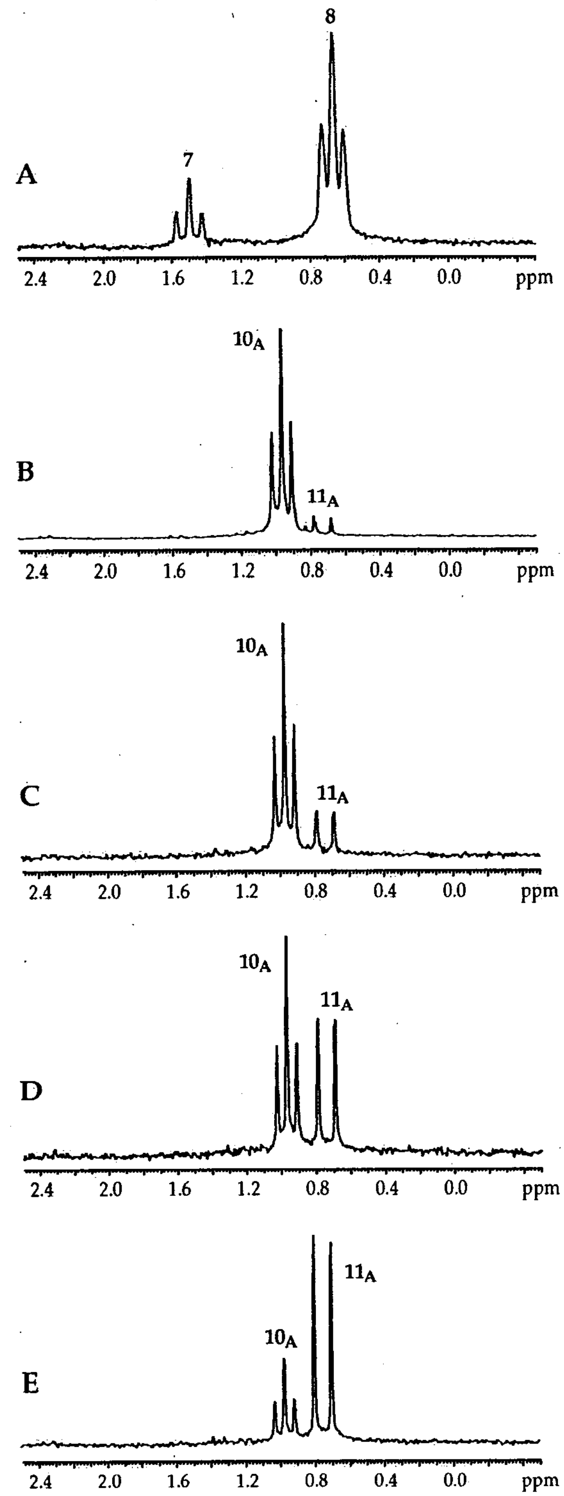


Figure 3. ^{6}Li NMR spectra recorded on 0.1 M [^{6}Li,^{15}N]LiHMDS with Me_2NEt (**A**) in 50% toluene/pentane at –100 °C. Dimer **10_A** and monomer **11_A** were monitored at different Me_2NEt concentrations: (A) 0 M (showing higher oligomer **7** and dimer **8**); (B) 0.15 M; (C) 0.30 M; (D) 0.60 M; (E) 1.2 M.

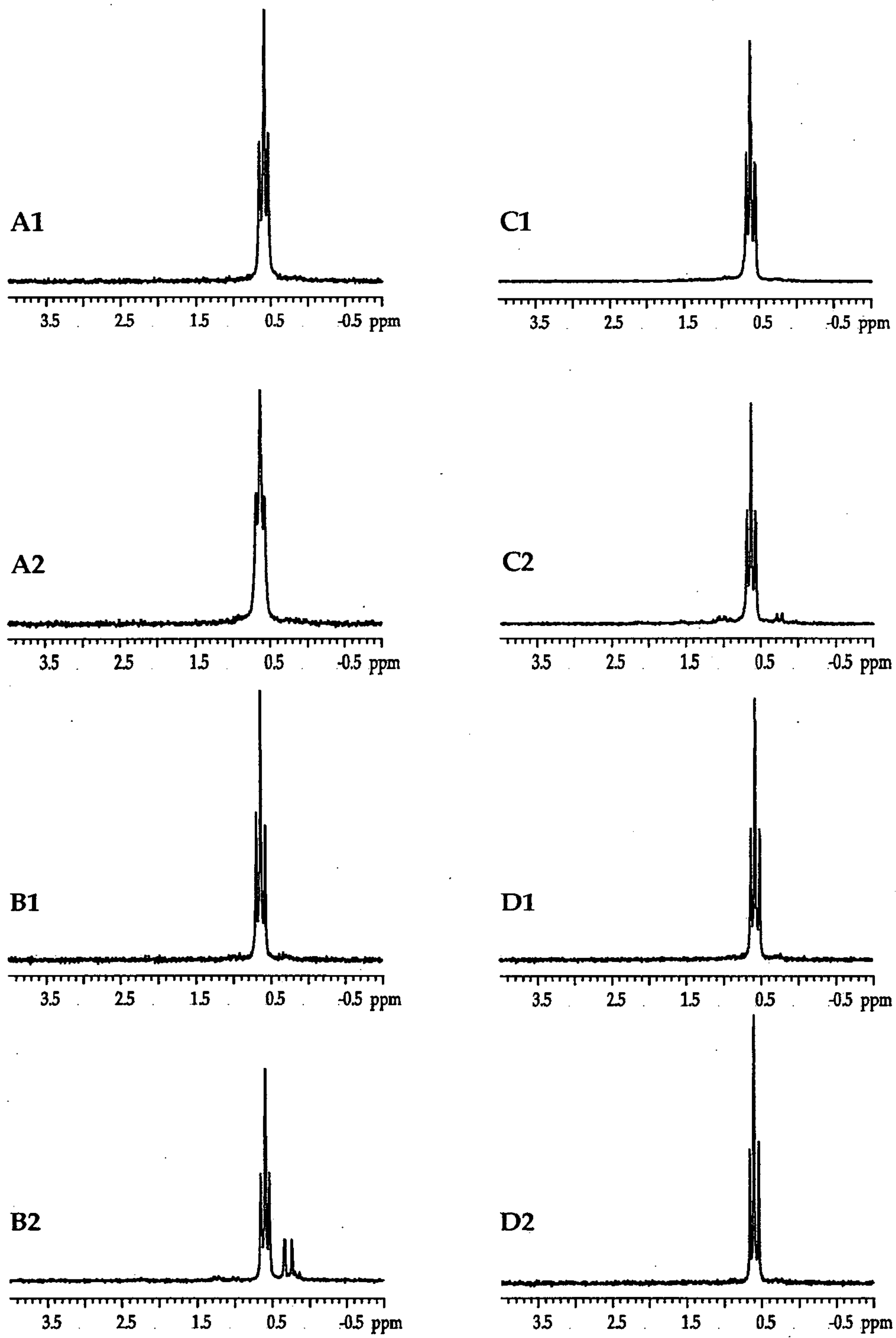


Figure 4. ^{6}Li NMR spectra recorded on 0.1 M [^{6}Li,^{15}N]LiHMDS in toluene at –100 °C with (1) 0.15 M and (2) 0.60 M dimethylamines: (A) *N,N*-dimethyl-1-ethylpropylamine; (B) *N,N*-dimethyl-*s*-butylamine; (C) *N,N*-dimethyl-*t*-butylamine; (D) *N,N*-dimethyl-*t*-amylamine.

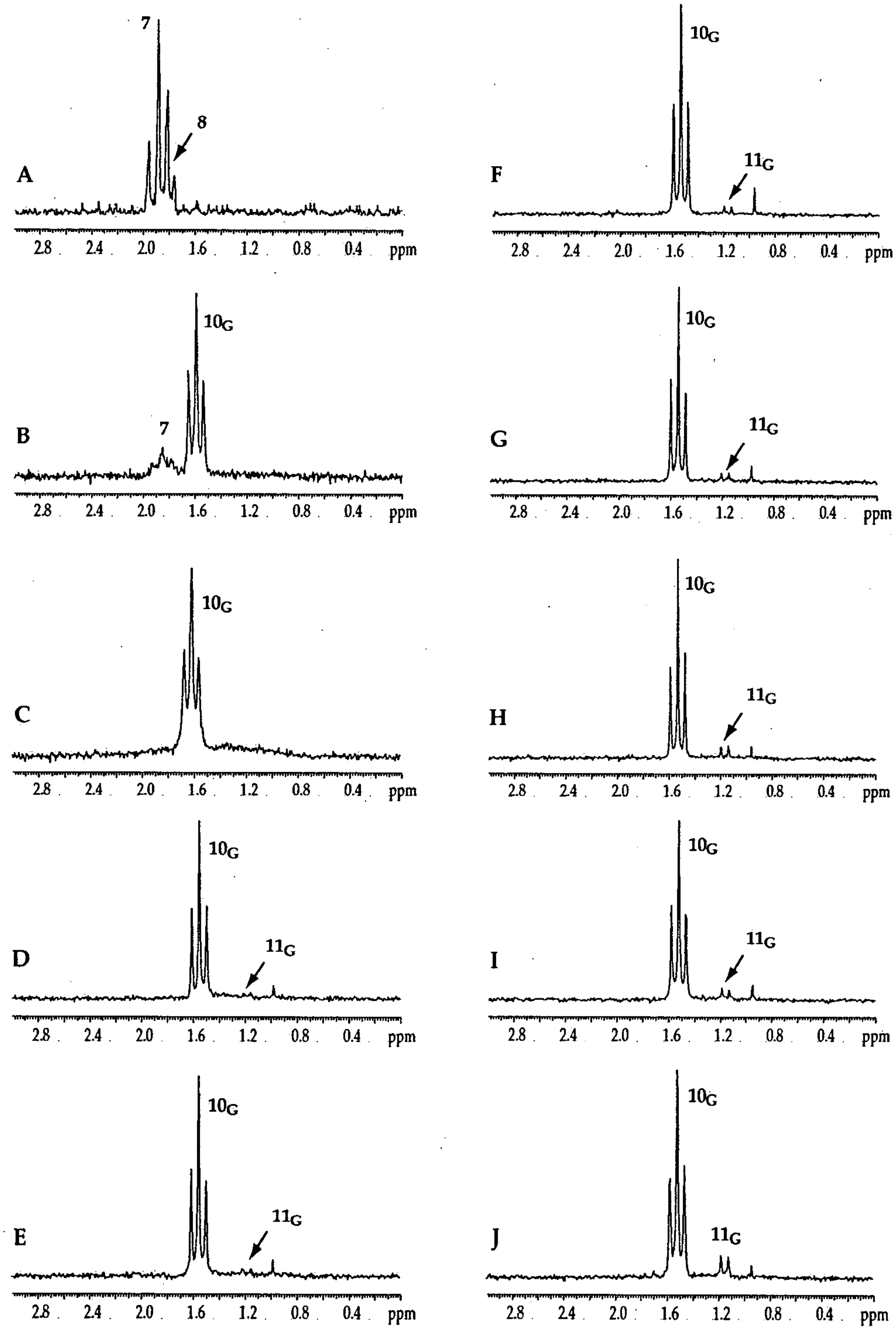


Figure 5. ^{6}Li NMR spectra recorded on 0.1 M [^{6}Li,^{15}N]LiHMDS in Et_3N (**G**)/pentane mixtures at –60 °C. Dimer $\mathbf{10_G}$ and monomer $\mathbf{11_G}$ were monitored at different Et_3N concentrations: (A) 0 M (showing higher oligomer **7** and dimer **8**); (B) 0.05 M; (C) 0.10 M; (D) 0.15 M; (E) 0.30 M; (F) 0.45 M; (G) 0.60 M; (H) 0.90 M; (I) 1.2 M; (J) 1.8 M.

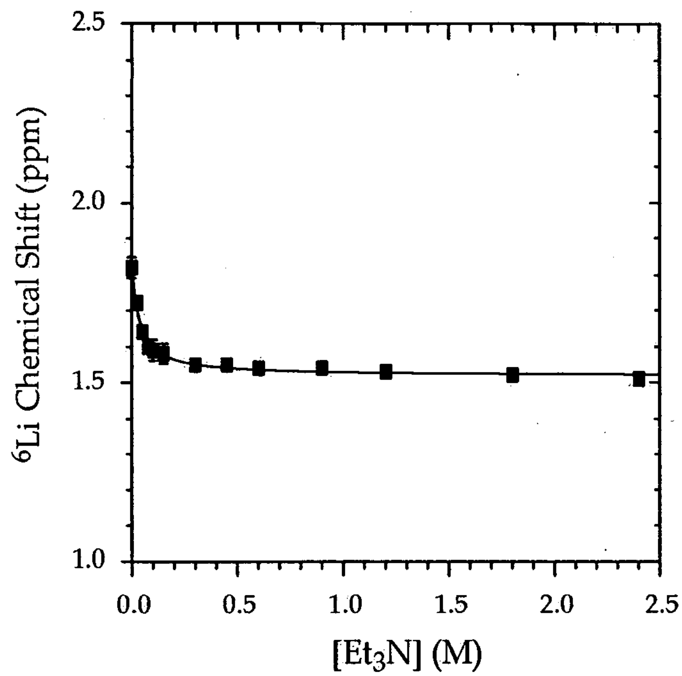


Figure 6. Plot of ^{6}Li chemical shift vs [Et_3N] for 0.1 M [^{6}Li,^{15}N]LiHMDS in pentane at –60 °C. The curve depicts the results of an unweighted least-squares fit to y = ax/(1 + bx) + c. The values of the parameters are as follows: a = -9 ± 1 (ppm·M^{-1}), b = K_{eq} = 28 ± 3 (M^{-1}), c = 2 ± 1 (ppm).

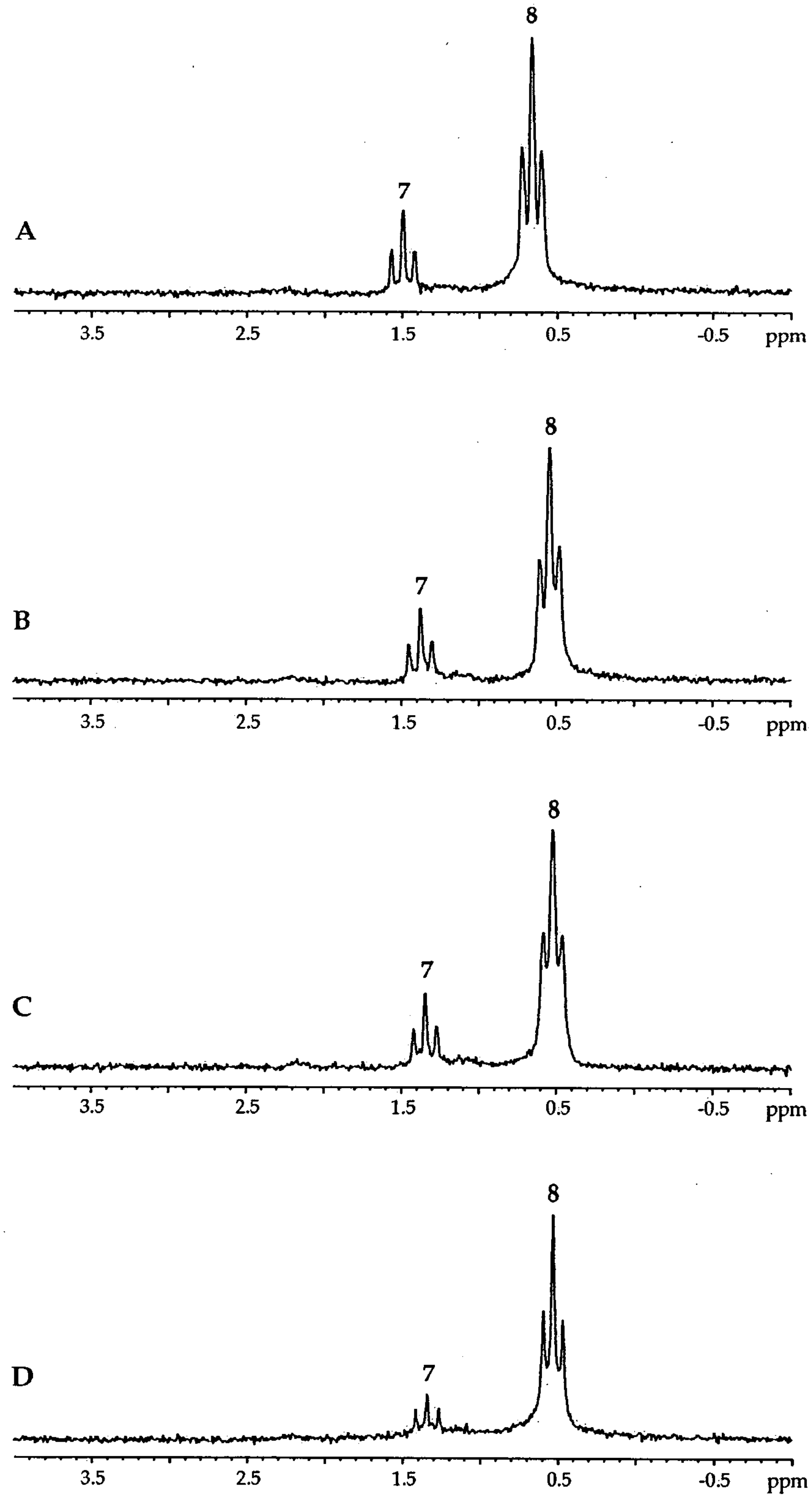


Figure 7. ^{6}Li NMR spectra recorded on 0.1 M [^{6}Li,^{15}N]LiHMDS in EtN*i*-Pr_2/toluene mixtures at –78 °C. Higher oligomer **7** and dimer **8** were monitored at different EtN*i*-Pr_2 concentrations: (A) 0 M; (B) 0.15 M; (C) 0.60 M; (D) 1.2 M.

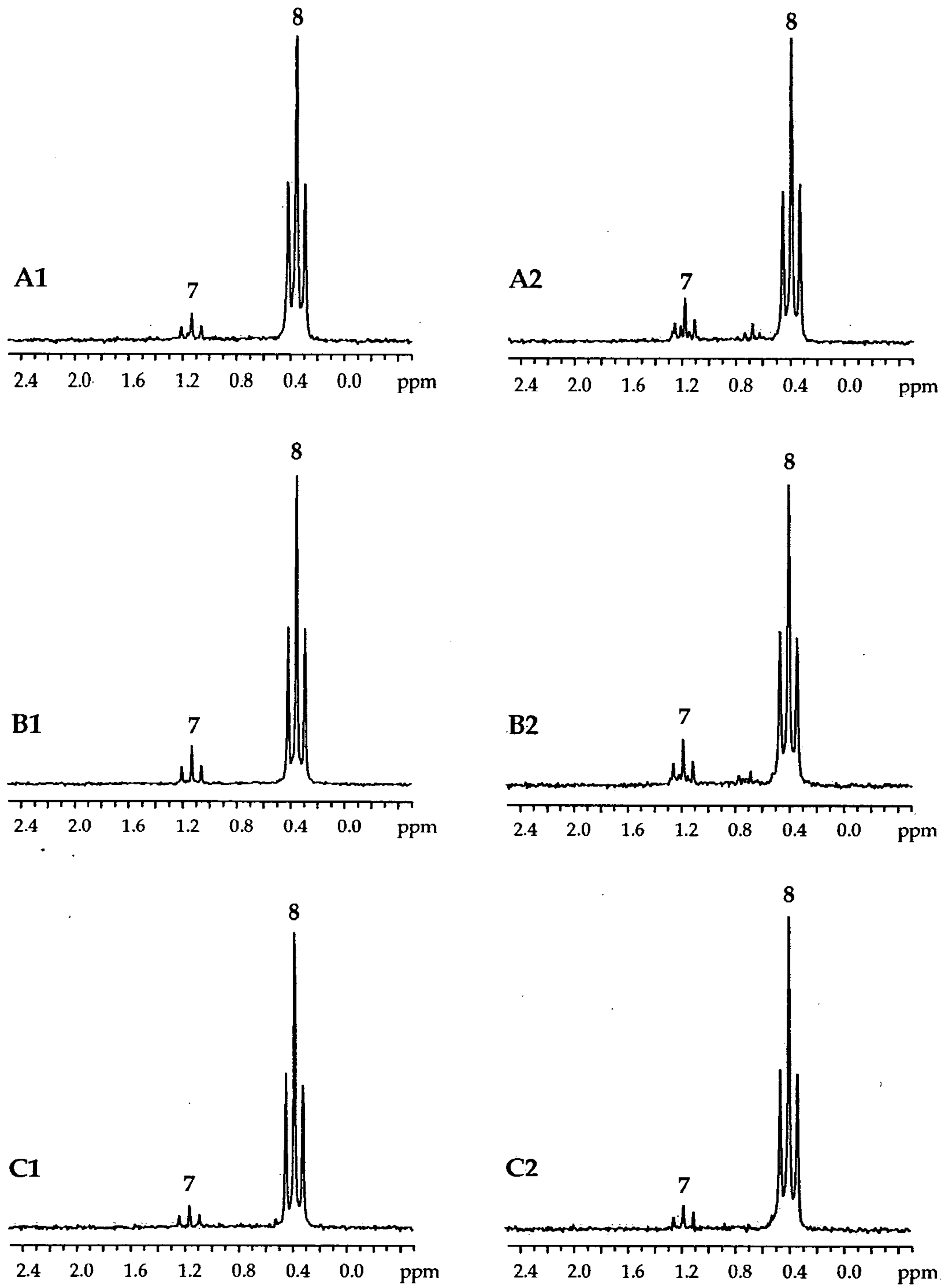


Figure 8. ^{6}Li NMR spectra recorded on 0.1 M [^{6}Li,^{15}N]LiHMDS in different amine/toluene mixtures at –78 °C: (A) *i*-Bu_3N (**O**); (B) *n*-BuN*i*-Bu_2 (**T**); (C) MeN*i*-Bu_2 (**J**). Higher oligomer **7** and dimer **8** were monitored at two amine concentrations: (1) 0.15 M; (2) 0.60 M.

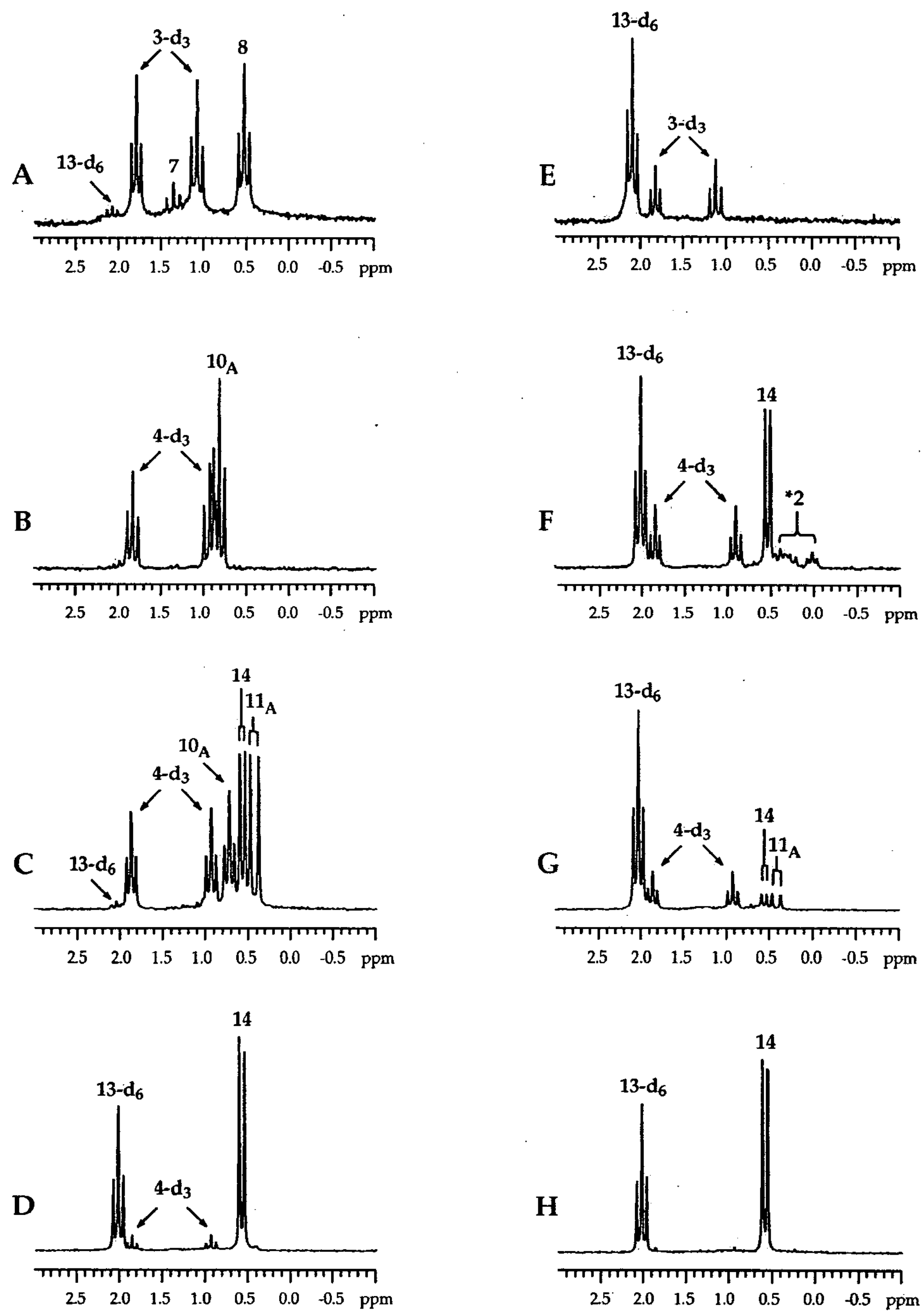
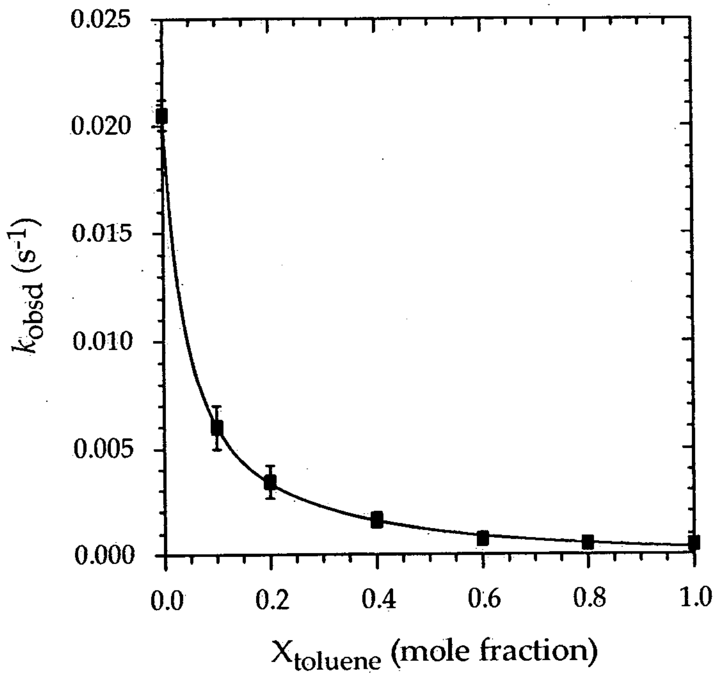


Figure 9. ^{6}Li NMR spectra of [^{6}Li,^{15}N]LiHMDS, Me_2NEt (**A**), and **1-*d₃*** in toluene at −100 °C with: (A) 0.2 equiv of **1-d_3**; (B) 0.2 equiv of **1-d_3** and 6.0 equiv of Me_2NEt; (C) 0.2 equiv of **1-d_3** and 12 equiv of Me_2NEt; (D) 0.5 equiv of **1-d_3** and 12 equiv of Me_2NEt; (E) 0.8 equiv of **1-d_3**; (F) 0.8 equiv of **1-d_3** and 1.5 equiv of Me_2NEt; (G) 0.8 equiv of **1-d_3** and 6.0 equiv of Me_2NEt; (H) 0.8 equiv of **1-d_3** and 12 equiv of Me_2NEt.

Part II. *in situ* IR Kinetic Studies

I. Table of rate constants for the enolizations of **1** (0.004M) by LiHMDS (0.10 M) in hydrocarbon solvents at –40 °C.

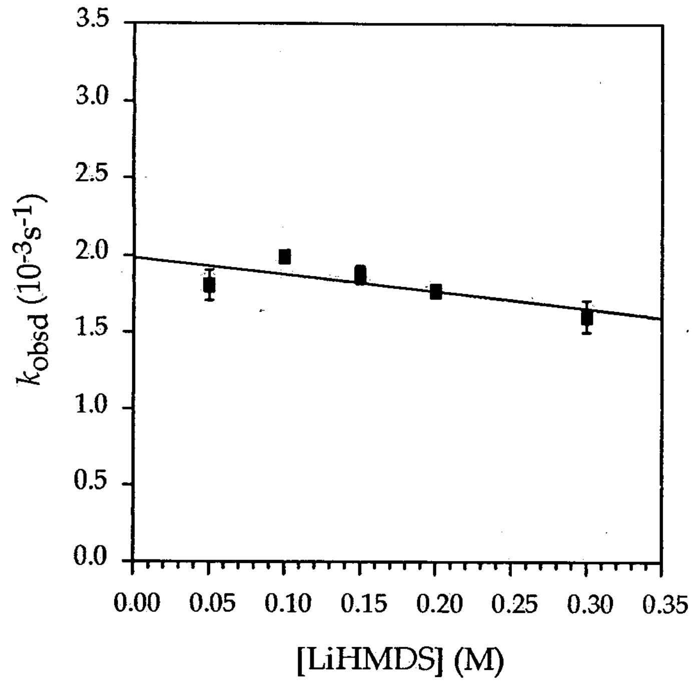
Solvent	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})	k_{rel}
Toluene	2.22 ± 0.05E-3	1.80 ± 0.04E-3	2.0 ± 0.1E-3	1
Mesitylene	3.84 ± 0.08E-3	4.0 ± 0.1E-3	3.9 ± 0.1E-3	2
1-Pentene	5.5 ± 0.2E-3	5.5 ± 0.1E-3	5.5 ± 0.2E-3	3
1-Hexene	5.5± 0.1E-3	5.9 ± 0.2E-3	5.7 ± 0.2E-3	3
3-Hexyne	6.0 ± 0.3E-3	6.6 ± 0.4E-3	6.3 ± 0.4E-3	3
Pentane	1.32 ± 0.03E-2	1.28 ± 0.04E-2	1.3 ± 0.1E-2	6
Cyclopentane	1.34 ± 0.05E-2	1.27 ± 0.05E-2	1.3 ± 0.1E-2	6
Hexane	1.348 ± 0.009E-2	1.34 ± 0.02E-2	1.34 ± 0.01E-2	7
Hexanes	1.87 ± 0.01E-2	1.925 ± 0.006E-2	1.90 ± 0.01E-2	10



II. Plot of k_{obsd} vs $X_{toluene}$ (X = mole fraction) in hexane for the enolization of **1-*d*₃** (0.004 M) by LiHMDS (0.10 M) at –60 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = (a + bx)/(1 + cx)$ ($a = 2.05 \pm 0.01 \times 10^{-2}$, $b = -1.3 \pm 0.2 \times 10^{-2}$, $c = 21.9 \pm 0.7$, $K_{eq} = 1 + c = 22.9 \pm 0.7$).

III. Table of data for plot in section **II**.

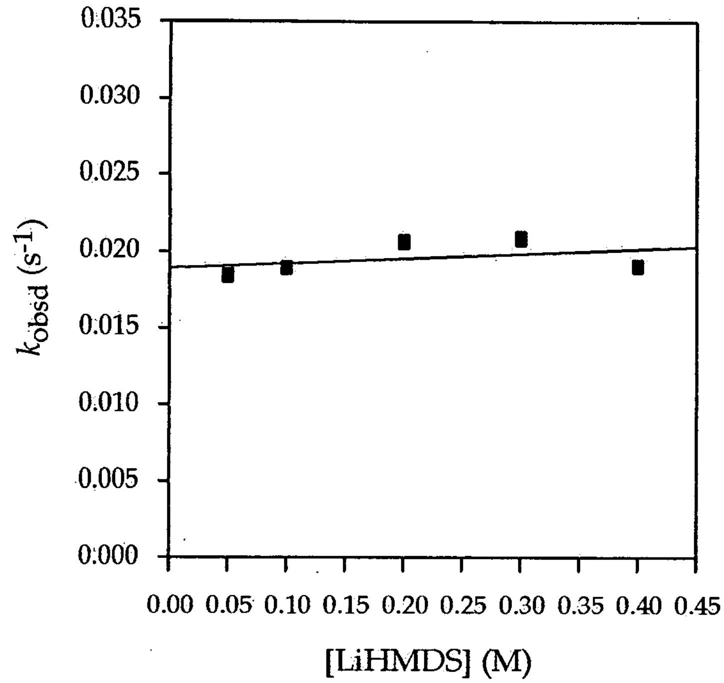
$X_{toluene}$	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0	2.00 ± 0.02E-2	2.1 ± 0.8E-2	2.1 ± 0.8E-2
0.1	6.70 ± 0.07E-3	5.2 ± 0.1E-3	6 ± 1E-3
0.2	2.7 ± 0.1E-3	4.0 ± 0.2E-3	3.4 ± 0.2E-3
0.4	1.8 ± 0.2E-3	1.3 ± 0.1E-3	1.6 ± 0.2E-3
0.6	7.3 ± 0.1E-4	--	--
0.8	5.33 ± 0.09E-4	--	--
1.0	4.79 ± 0.03E-4	--	--



IV. Plot of k_{obsd} vs [LiHMDS] in toluene for the enolization of **1** (0.004 M) by 0.10 M LiHMDS at –40 °C. The curve depicts the results of an unweighted least-squares fit to k_{obsd} = a[LiHMDS] + b (a = -1.1 ± 0.6 x 10^{-3}, b = 2.0 ± 0.1 x 10^{-3}).

V. Table of data for plot in section **IV**.

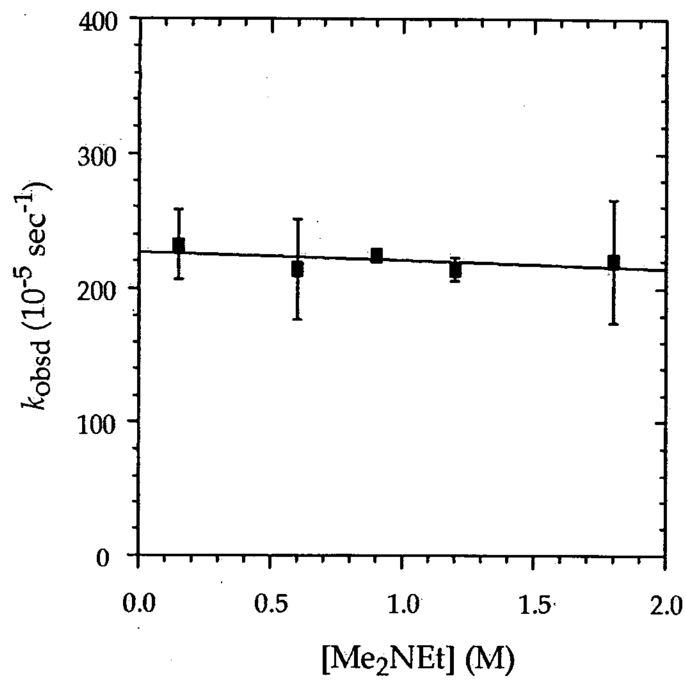
[LiHMDS] (M)	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0.05	1.76 ± 0.03E-3	1.95 ± 0.05E-3	1.8 ± 0.1E-3
0.10	2.00 ± 0.03E-3	1.98 ± 0.02E-3	1.99 ± 0.03E-3
0.15	1.81 ± 0.04E-3	1.93 ± 0.04E-3	1.87 ± 0.04E-3
0.20	1.81 ± 0.04E-3	1.72 ± 0.03E-3	1.76 ± 0.04E-3
0.30	1.72 ± 0.03E-3	1.46 ± 0.03E-3	1.6 ± 0.1E-3



VI. Plot of k_{obsd} vs [LiHMDS] in hexane for the enolization of **1** (0.004 M) by 0.10 M LiHMDS at –40 °C. The curve depicts the results of an unweighted least-squares fit to k_{obsd} = a[LiHMDS] + b (a = 3 ± 4 x 10^{-3}, b = 1.9 ± 0.1 x 10^{-2}).

VII. Table of data for plot in section **VI**.

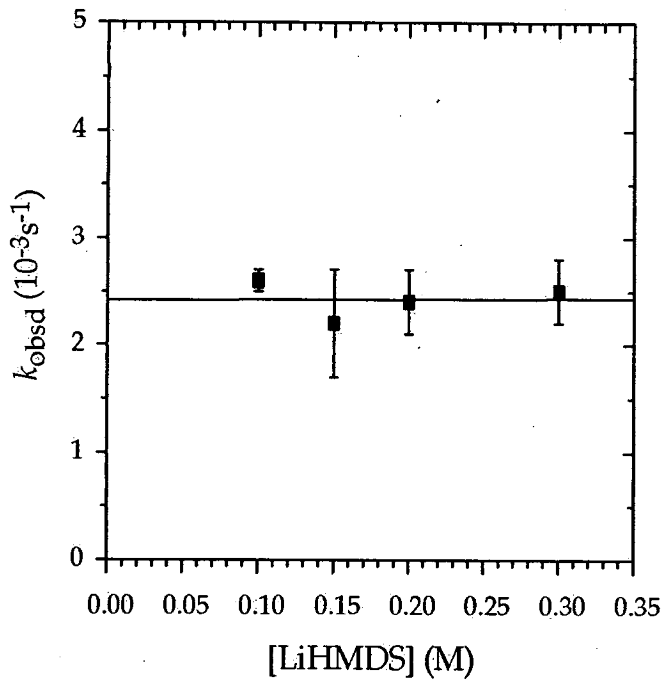
[LiHMDS] (M)	k_{obsd} (s^{-1})
0.05	1.84 ± 0.08E-2
0.10	1.89 ± 0.06E-2
0.20	2.06 ± 0.06E-2
0.30	2.08 ± 0.06E-2
0.40	1.9 ± 0.1E-2



VIII. Plot of k_{obsd} vs [Me_2NEt] in toluene for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) at –78 °C. The curve depicts the results of an unweighted least-squares fit to k_{obsd} = a[Me_2NEt] + b where a = 6 ± 6 x 10^{-5} ($s^{-1}\cdot M^{-1}$), b = 2.26 ± 0.07 x10^{-3} (s^{-1}).

IX. Table of data for plot in section **VIII**.

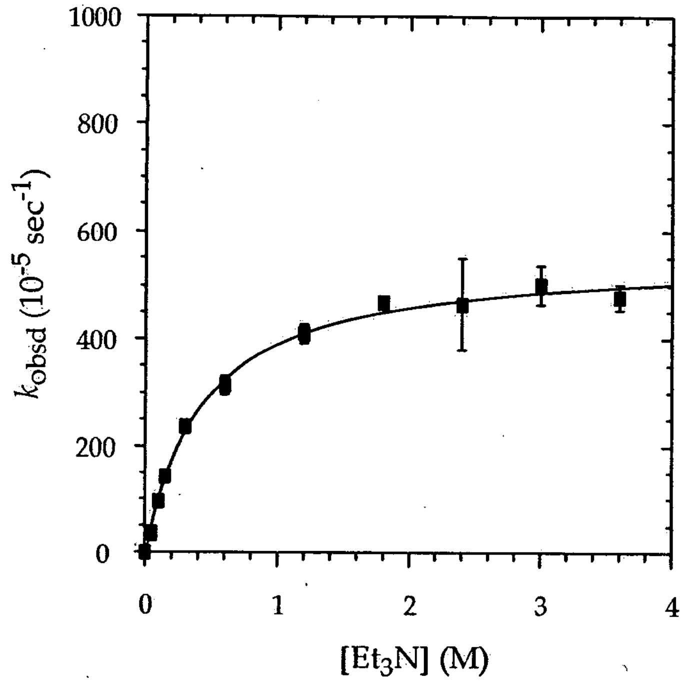
[Me_2NEt] (M)	k_{obsd}1 (s^{-1})	k_{obsd}2 (s^{-1})	k_{obsd}3 (s^{-1})	k_{obsd} (avg) (s^{-1})
0.15	2.14 ± 0.02E-3	2.50 ± 0.03E-3	1.85 ± 0.01E-3	2.3 ± 0.1E-3
0.60	1.87 ± 0.07E-3	2.40 ± 0.04E-3	1.80 ± 0.02E-3	2.1 ± 0.1E-3
0.90	2.2 ± 0.1E-3	2.2 ± 0.2E-3	--	2.2 ± 0.2E-3
1.2	2.07 ± 0.08E-3	2.2 ± 0.4E-3	--	2.1 ± 0.4E-3
1.8	1.89 ± 0.03E-3	2.52 ± 0.07E-3	--	2.2 ± 0.1E-3



X. Plot of k_{obsd} vs [LiHMDS] for the enolization of **1** (0.004 M) by 0.10 M LiHMDS in Me_2NEt/toluene at –78 °C. The curve depicts the results of an unweighted least-squares fit to k_{obsd} = a[LiHMDS] + b (a = 0 ± 2 x 10^{-4}, b = 2.4 ± 0.3 x 10^{-3}).

XI. Table of data for plot in section **X**.

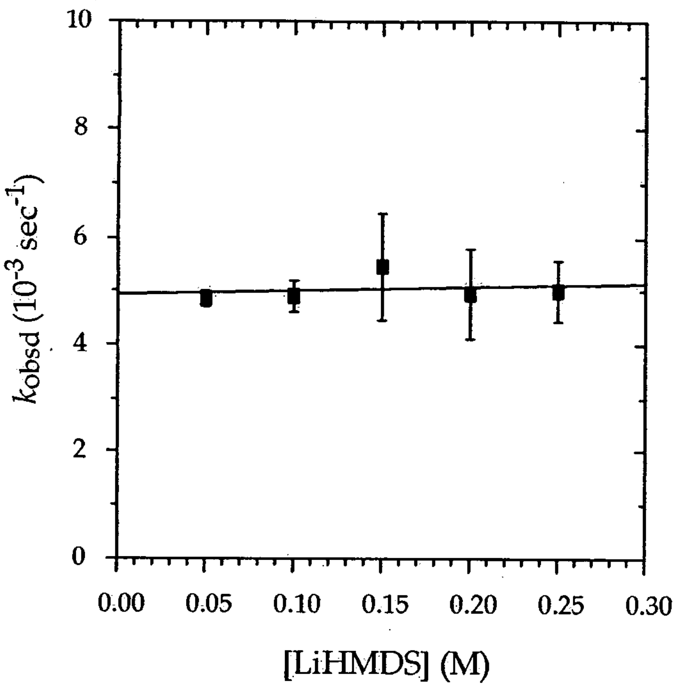
[LiHMDS] (M)	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0.10	2.5 ± 0.2E-3	2.7 ± 0.2E-3	2.6 ± 0.2E-3
0.15	2.5 ± 0.3E-3	1.8 ± 0.3E-3	2.2 ± 0.3E-3
0.20	2.6 ± 0.4E-3	2.0 ± 0.1E-3	2.4 ± 0.4E-3
0.30	2.7 ± 0.3E-3	2.3 ± 0.4E-3	2.5 ± 0.4E-3



XII. Plot of k_{obsd} vs [Et_3N] in toluene for the enolization of **1-*d*₃** (0.004 M) by LiHMDS (0.10 M) at –78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = a[Et_3N]/(1 + b[Et_3N])$ ($a = 1.25 \pm 0.08 \times 10^{-2}$, $K_{eq} = b = 2.2 \pm 0.2$, $k_2 = a/b = 5.7 \times 10^{-3}$).

XIII. Table of data for plot in section **XII**.

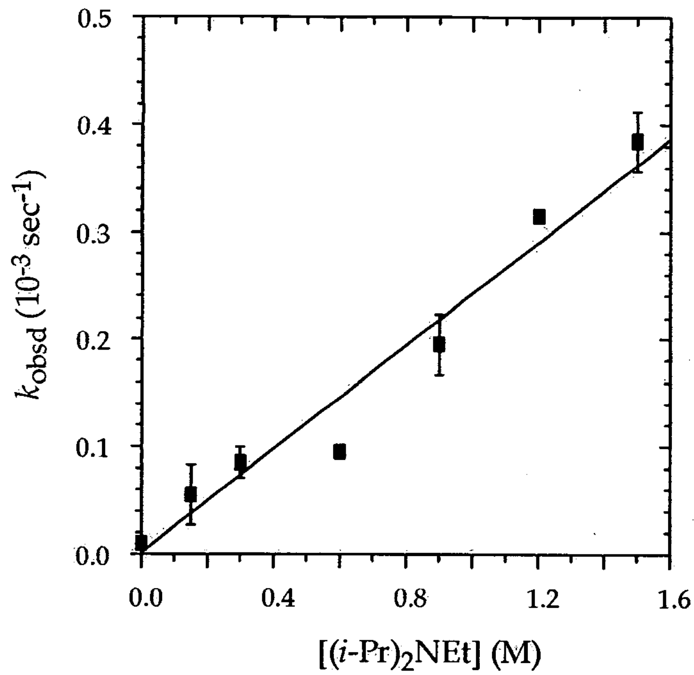
[Et_3N] (M)	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0.15	1.46 ± 0.02E-3	1.40 ± 0.02E-3	1.43 ± 0.02E-3
0.30	2.32 ± 0.04E-3	2.39 ± 0.03E-3	2.36 ± 0.04E-3
0.60	3.02 ± 0.07E-3	3.2 ± 0.1E-3	3.1 ± 0.1E-3
1.2	4.0 ± 0.2E-3	4.2 ± 0.1E-3	4.1 ± 0.2E-3
1.8	4.7 ± 0.1E-3	4.7 ± 0.2E-3	4.7 ± 0.2E-3
2.4	5.0 ± 0.4E-3	4.2 ± 0.1E-3	4.6 ± 0.4E-3
3.0	4.9 ± 0.2E-3	5.3 ± 0.2E-3	5.0 ± 0.2E-3
3.6	4.6 ± 0.2E-3	5.0 ± 0.1E-3	4.8 ± 0.2E-3



XIV. Plot of k_{obsd} vs [LiHMDS] for the enolization of **1-*d*$_3$** (0.004 M) by 0.10 M LiHMDS in Et_3N/toluene at –78 °C. The curve depicts the results of an unweighted least-squares fit to k_{obsd} = a[LiHMDS] + b (a = $2 \pm 3 \times 10^{-3}$, b = $4.8 \pm 0.4 \times 10^{-4}$).

XV. Table of data for plot in section **XIV**.

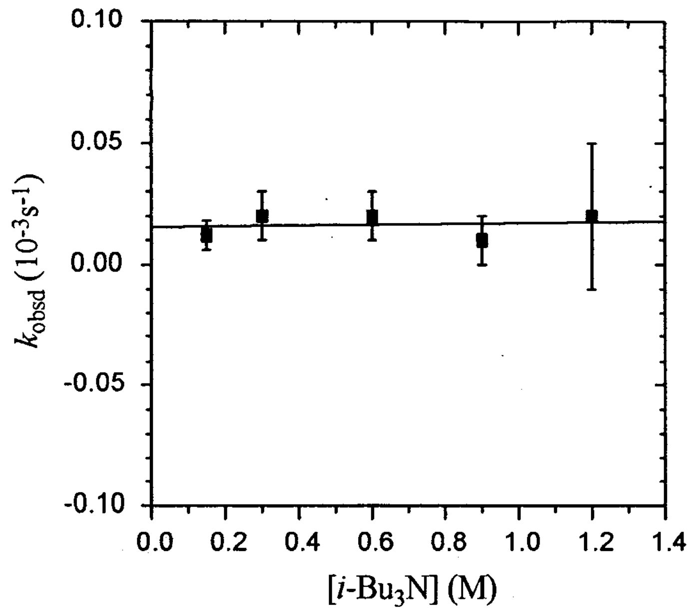
[LiHMDS] (M)	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0.05	4.7 ± 0.1E-3	4.9 ± 0.2E-3	4.8 ± 0.2E-3
0.10	4.8 ± 0.2E-3	5.3 ± 0.3E-3	5.0 ± 0.3E-3
0.15	5.8 ± 0.4E-3	4.4 ± 0.3E-3	5 ± 1E-3
0.20	5.3 ± 0.2E-3	4.0 ± 0.2E-3	4.6 ± 0.2E-3
0.25	5.2 ± 0.7E-3	4.4 ± 0.2E-3	4.8 ± 0.7E-3



XVI. Plot of k_{obsd} vs [*i*-Pr_2NEt] in toluene for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) at –78 °C. The curve depicts the results of an unweighted least-squares fit to k_{obsd} = a[*i*-Pr_2NEt] + b (a = 2.4 ± 0.2 x 10^{-4}, b = 0 ± 2 x 10^{-5}).

XVII. Table of data for plot in section **XVI**.

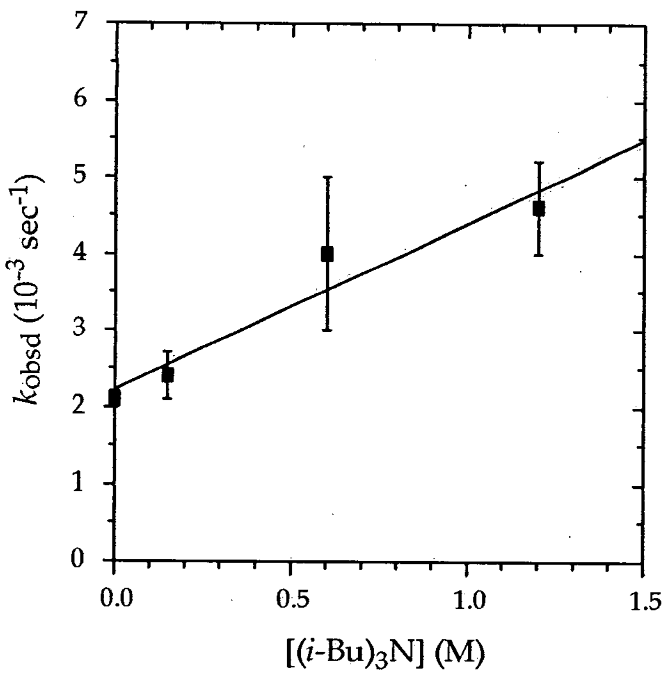
[*i*-Pr_2NEt] (M)	k_{obsd}1 (s^{-1})	k_{obsd}2 (s^{-1})	k_{obsd} (avg) (s^{-1})
0.15	7 ± 1E-5	4 ± 1E-5	6 ± 1E-5
0.30	9 ± 7E-5	7.9± 0.7E-5	8 ± 7E-5
0.60	9.3 ± 0.2E-5	1.0 ± 0.1E-4	1.0 ± 0.1E-4
0.90	2.1 ± 0.2E-4	1.8 ± 0.1E-4	2.0 ± 0.2E-4
1.2	3.1 ± 0.3E-4	3.2 ± 0.0E-4	3.2 ± 0.3E-4
1.5	4.0 ± 0.1E-4	3.7 ± 0.0E-4	3.8 ± 0.1E-4



XVIII Plot of k_{obsd} vs. [(i-Bu)$_3$N] (**O**) in toluene for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) at -78 °C. The curve depicts the results of an unweighted least-square fit to $k_{obsd} = a[(i\text{-Bu})_3N] + b$, where a = 2 ± 7 x 10^{-6} ($s^{-1}\cdot M^{-1}$), b = 1.5 ± 0.5 x 10^{-5} (s^{-1}).

XIX. Table of data for plot in section **XVIII**.

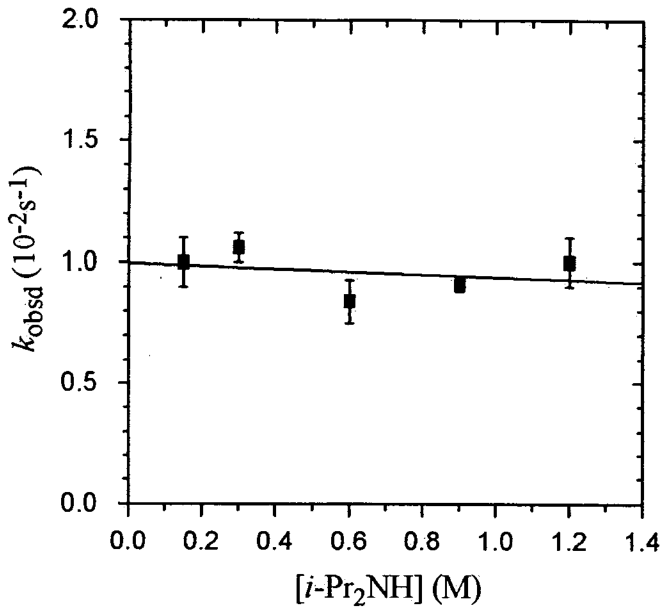
[i-Bu_3N] (M)	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0.15	7 ± 1E-6	1.6 ± 0.3E-5	1.2 ± 0.3E-5
0.30	1.5 ± 0.7E-5	2.9± 0.6E-5	2 ± 1E-5
0.60	2 ± 2E-6	2.8 ± 0.7E-5	2 ± 2E-5
0.90	2 ± 0.1E-6	0.0 ± 0.5E-5	1 ± 1E-6
1.2	4 ± 1E-6	4.4 ± 0.2E-5	2 ± 1E-5



XX. Plot of k_{obsd} vs [*i*-Bu_3N] in toluene for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) at –40 °C. The curve depicts the results of an unweighted least-squares fit to k_{obsd} = a[*i*-Bu_3N] + b (a = 2.2 ± 0.4 x 10^{-3}, b = 2.2 ± 0.1 x 10^{-3}).

XXI. Table of data for plot in section **XX**.

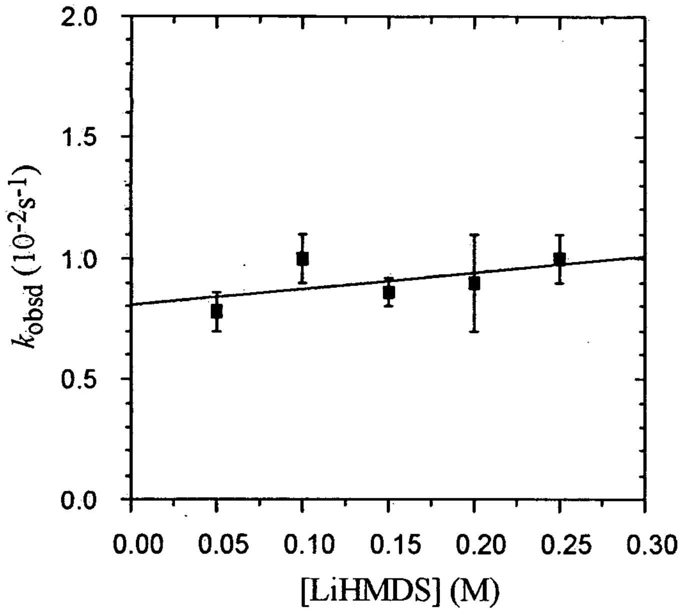
[*i*-Bu_3N] (M)	k_{obsd}1 (s^{-1})	k_{obsd}2 (s^{-1})	k_{obsd}3 (s^{-1})	k_{obsd} (avg) (s^{-1})
0	2.18 ± 0.08E-3	2.0 ± 0.1E-3	1.98 ± 0.08E-3	2.1 ± 0.1E-3
0.15	2.2 ± 0.1E-3	2.5± 0.1E-3	2.45 ± 0.05E-3	2.4± 0.1E-3
0.60	3.1 ± 0.1E-3	2.5 ± 0.1E-3	5.3 ± 0.2E-3	4 ± 1E-3
1.2	4.5 ± 0.3E-3	5.2 ± 0.2E-3	4.2 ± 0.1E-3	4.6 ± 0.3E-3



XXII. Plot of k_{obsd} vs [i-Pr_2NH] in toluene for the enolization of **4** (0.004 M) by LiHMDS (0.10 M) at –78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = ax + b$ ($a = -1 \pm 1 \times 10^{-3}$, $b = 1.00 \pm 0.08 \times 10^{-2}$).

XXIII. Table of data for plot in section **XXII.**

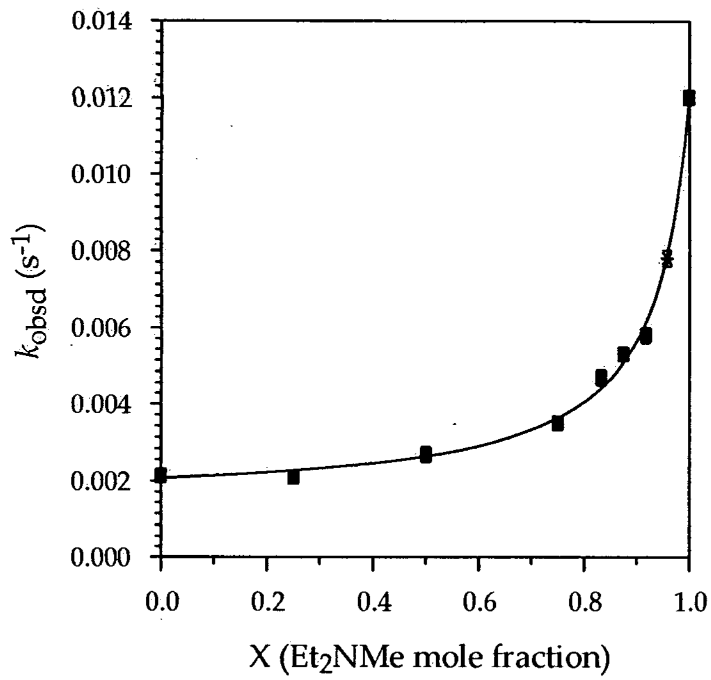
[i-Pr_2NH] (M)	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0.15	1.1 ± 0.1E-2	8.4 ± 0.3E-3	1.0 ± 0.3E-2
0.30	1.02 ± 0.03E-2	1.1 ± 0.1E-2	1.1 ± 0.1E-2
0.60	9 ± 1E-3	7.7 ± 0.4E-3	8 ± 1E-3
0.90	9.3 ± 0.4E-3	8.9 ± 0.5E-3	9.1 ± 0.5E-3
1.2	1.1 ± 0.1E-2	9.3 ± 0.5E-3	1.0 ± 0.1E-2



XXIV. Plot of k_{obsd} vs [LiHMDS] in *i*-Pr_2NH/toluene for the enolization of **4** (0.004 M) by LiHMDS at –78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = ax + b$ ($a = 7 \pm 6 \times 10^{-3}$, $b = 8.1 \pm 0.9 \times 10^{-3}$).

XXV. Table of data for plot in section **XXIV**.

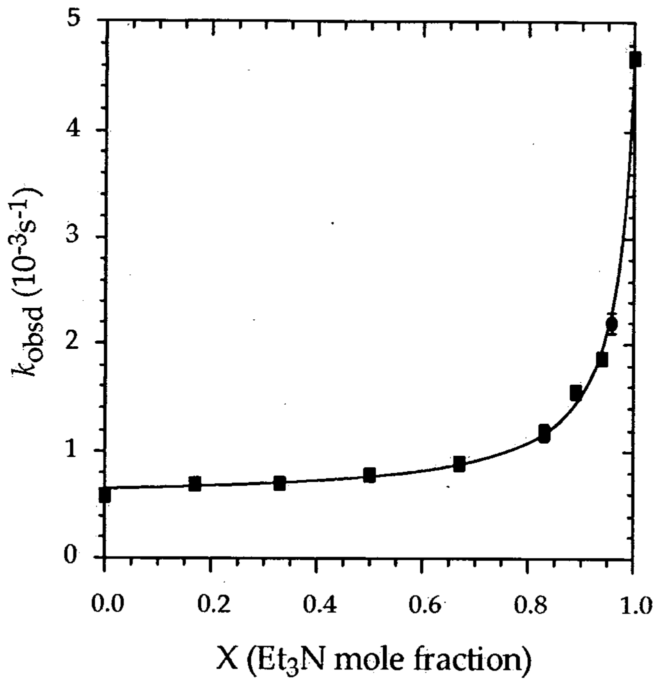
[LiHMDS] (M)	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0.05	7.8 ± 0.8E-3	7.8 ± 0.3E-3	7.8 ± 0.8E-3
0.10	1.1 ± 0.1E-2	9.3 ± 0.5E-3	1.0± 0.1E-2
0.15	9 ± 1E-3	8.2 ± 0.3E-3	9 ± 1E-3
0.20	7.4 ± 0.3E-3	1.01 ± 0.05E-2	9 ± 1E-3
0.25	1.1 ± 0.1E-2	9.1 ± 0.4E-3	1.0 ± 0.4E-2



XXVI. Plot of k_{obsd} vs X_{MeNEt_2} (X = mole fraction) in $Me_2NEt/MeNEt_2$ (1.2 M total)/toluene mixtures for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) at –78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = (a + bx)/(1 + cx)$ ($a = 2.1 \pm 0.1 \times 10^{-3}$, $b = -1.3 \pm 0.2 \times 10^{-3}$, $c = -0.938 \pm 0.006$. The point with * is not included in the fit.

XXVII. Table of data for plot in section **XXVI**.

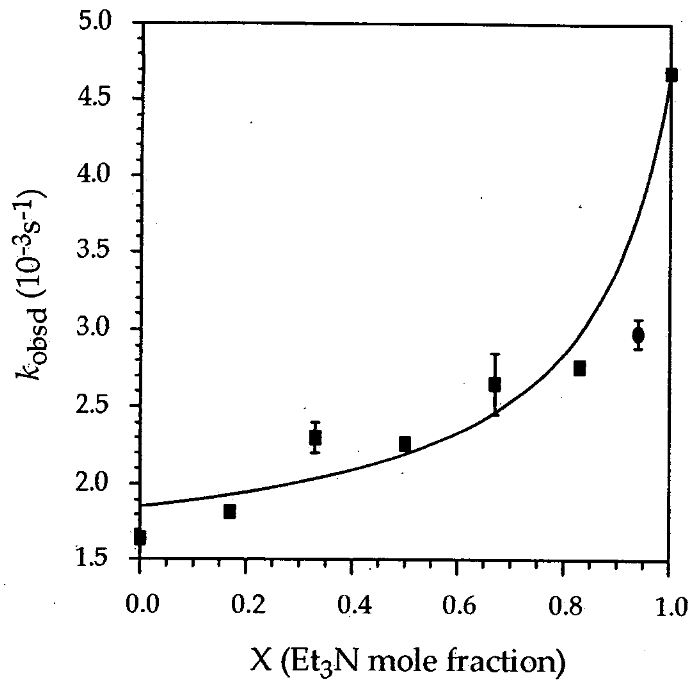
$MeNEt_2$ mol%	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0	2.20 ± 0.04E-3	2.07 ± 0.03E-3	2.1 ± 0.1E-3
25	2.03 ± 0.03E-3	2.18 ± 0.03E-3	2.1 ± 0.1E-3
50	2.87 ± 0.08E-3	2.44 ± 0.05E-3	2.7 ± 0.1E-3
75	3.6 ± 0.1E-3	3.4 ± 0.1E-3	3.5 ± 0.1E-3
83	4.85 ± 0.04E-3	4.5 ± 0.9E-3	4.7 ± 0.9E-3
88	5.4 ± 0.5E-3	5.2 ± 0.1E-3	5.3 ± 0.5E-3
92	6.1 ± 0.1E-3	5.6 ± 0.2E-3	5.8 ± 0.2E-3
96*	7.6 ± 0.3E-3	7.9 ± 0.1E-3	7.8 ± 0.3E-3
100	1.2 ± 0.1E-2	1.2 ± 0.1E-2	1.2 ± 0.1E-2



XXVIII. Plot of k_{obsd} vs X_{Et3N} (X = mole fraction) in $MeNEt_2/Et_3N$ (1.8 M total)/toluene mixtures for the enolization of **1-*d*₃** (0.004 M) by LiHMDS (0.10 M) at –78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = (a + bx)/(1 + cx)$ (a = $6.6 \pm 0.4 \times 10^{-5}$, b = $-5.2 \pm 0.5 \times 10^{-4}$, c = -0.971 ± 0.002. The point with * is not included in the fit.

XXIX. Table of data for plot in section **XXVIII**.

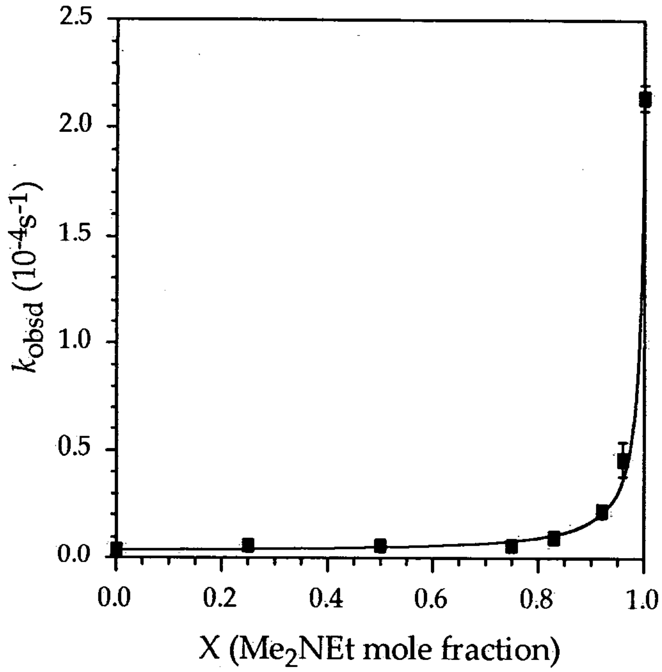
Et_3N mol%	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0	5.5 ± 0.2E-4	6.1 ± 0.7E-4	5.8 ± 0.7E-4
17	6.9 ± 0.2E-4	6.9 ± 0.2E-4	6.9 ± 0.2E-4
33	7.2 ± 0.1E-4	6.9 ± 0.1E-4	7.0 ± 0.1E-3
50	7.4 ± 0.1E-4	8.1 ± 0.1E-4	7.8 ± 0.1E-4
67	8.8 ± 0.1E-4	9.0 ± 0.2E-4	8.9 ± 0.2E-4
83	1.24 ± 0.08E-3	1.12 ± 0.02E-3	1.18 ± 0.08E-3
94	1.51 ± 0.07E-3	1.60 ± 0.01E-3	1.55 ± 0.07E-3
96*	1.88 ± 0.06E-3	1.86 ± 0.05E-3	1.87 ± 0.06E-3
100	4.65 ± 0.08E-2	4.71 ± 0.06E-2	4.68 ± 0.08E-2



XXX. Plot of k_{obsd} vs X_{Et_3N} (X = mole fraction) in $MeNEt_2$/2,2,6,6-tetramethylpiperidine (1.8 M total)/toluene mixtures for the enolization of **1-*d*$_3$** (0.004 M) by LiHMDS (0.10 M) at –78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = (a + bx)/(1 + cx)$ ($a = 1.9 \pm 0.1 \times 10^{-3}$, $b = -1.2 \pm 0.3 \times 10^{-3}$, $c = -0.86 \pm 0.05$). The point with * is not included in the fit.

XXXI. Table of data for plot in section **XXX**.

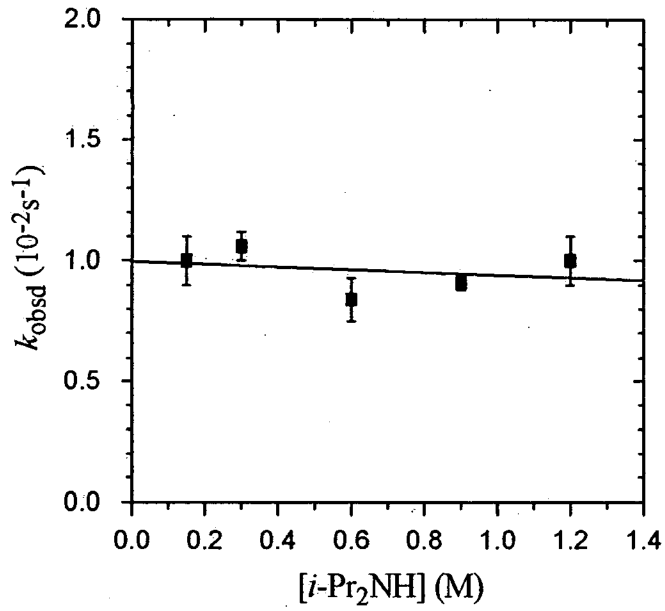
Et_3N mol%	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0	1.60 ± 0.01E-3	1.69 ± 0.01E-3	1.64 ± 0.01E-3
17	1.84 ± 0.06E-3	1.79 ± 0.03E-3	1.82 ± 0.06E-3
33	2.2 ± 0.3E-3	2.4 ± 0.2E-3	2.3 ± 0.3E-3
50	2.29 ± 0.01E-3	2.24 ± 0.01E-3	2.26 ± 0.01E-3
67	2.83 ± 0.02E-3	2.47 ± 0.02E-3	2.7 ± 0.1E-3
83	2.71 ± 0.03E-3	2.80 ± 0.03E-3	2.76 ± 0.03E-3
94*	3.07 ± 0.01E-3	2.89 ± 0.02E-3	3.0 ± 0.1E-3
100	4.65 ± 0.08E-2	4.71 ± 0.06E-2	4.68 ± 0.08E-3



XXXII. Plot of k_{obsd} vs X_{Me2NEt} (X = mole fraction) in Me_2NEt/*i*-Bu_2NH (1.2 M total)/toluene mixtures for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = (a + bx)/(1 + cx)$ ($a = 4 \pm 1 \times 10^{-5}$, $b = -2 \pm 1 \times 10^{-5}$, $c = -0.9925 \pm 0.0009$). The point with * is not included in the fit.

XXXIII. Table of data for plot in section **XXXII**.

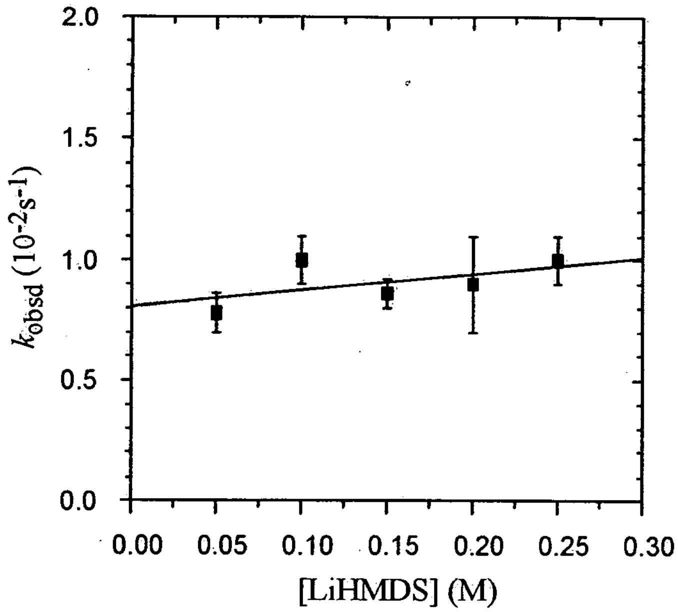
Me_3NEt mol%	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0	2.8 ± 0.8E-5	6 ± 1E-5	4 ± 1E-5
25	3.9 ± 0.9E-5	7 ± 1E-5	6 ± 1E-5
50	4 ± 2E-5	8 ± 2E-5	6 ± 2E-5
75	6 ± 1E-5	5 ± 2E-5	6 ± 2E-5
83	1.1 ± 0.3E-4	1.0 ± 0.1E-4	1.0 ± 0.3E-4
92	1.9 ± 0.3E-4	2.4± 0.4E-4	2.2 ± 0.4E-4
96*	5.4 ± 0.8E-4	3.8 ± 0.6E-4	5 ± 1E-4
100	2.07 ± 0.08E-3	2.20 ± 0.04E-3	2.1 ± 0.1E-3



XXXIV. Plot of k_{obsd} vs [i-Pr_2NH] in toluene for the enolization of **4** (0.004 M) by LiHMDS (0.10 M) at –78 °C. The curve depicts the results of an unweighted least-squares fit to k_{obsd} = ax + b (a = -1 ± 1 x 10^{-3}, b = 1.00 ± 0.08 x 10^{-2}).

XXXV. Table of data for plot in section **XX1a.**

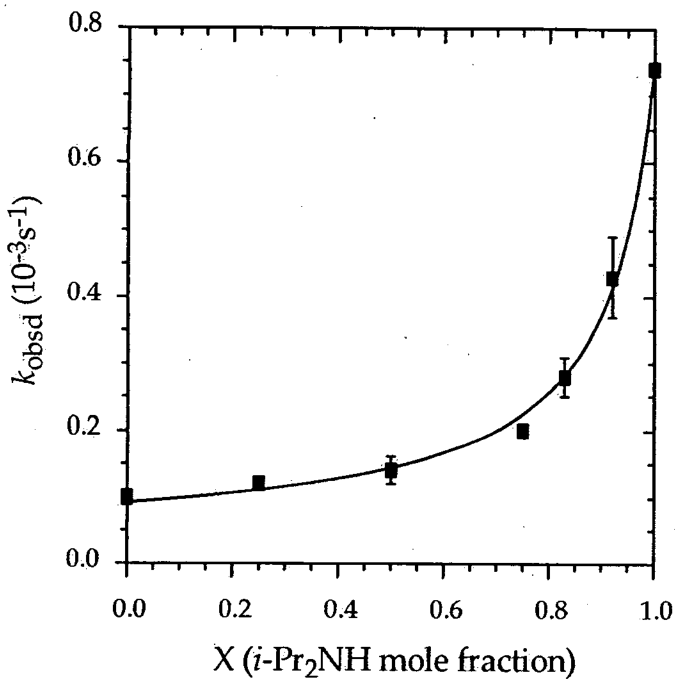
[i-Pr_2NH] (M)	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd}(avg) (s^{-1})
0.15	1.1 ± 0.1E-2	8.4 ± 0.3E-3	1.0 ± 0.3E-2
0.30	1.02 ± 0.03E-2	1.1 ± 0.1E-2	1.1 ± 0.1E-2
0.60	9 ± 1E-3	7.7 ± 0.4E-3	8 ± 1E-3
0.90	9.3 ± 0.4E-3	8.9 ± 0.5E-3	9.1 ± 0.5E-3
1.2	1.1 ± 0.1E-2	9.3 ± 0.5E-3	1.0 ± 0.1E-2



XXXVI. Plot of k_{obsd} vs [LiHMDS] in i-Pr_2NH/toluene for the enolization of **4** (0.004 M) by LiHMDS at –78 °C. The curve depicts the results of an unweighted least-squares fit to k_{obsd} = ax + b (a = 7 ± 6 x 10^{-3}, b = 8.1 ± 0.9 x 10^{-3}).

XXXVII. Table of data for plot in section **XX2a.**

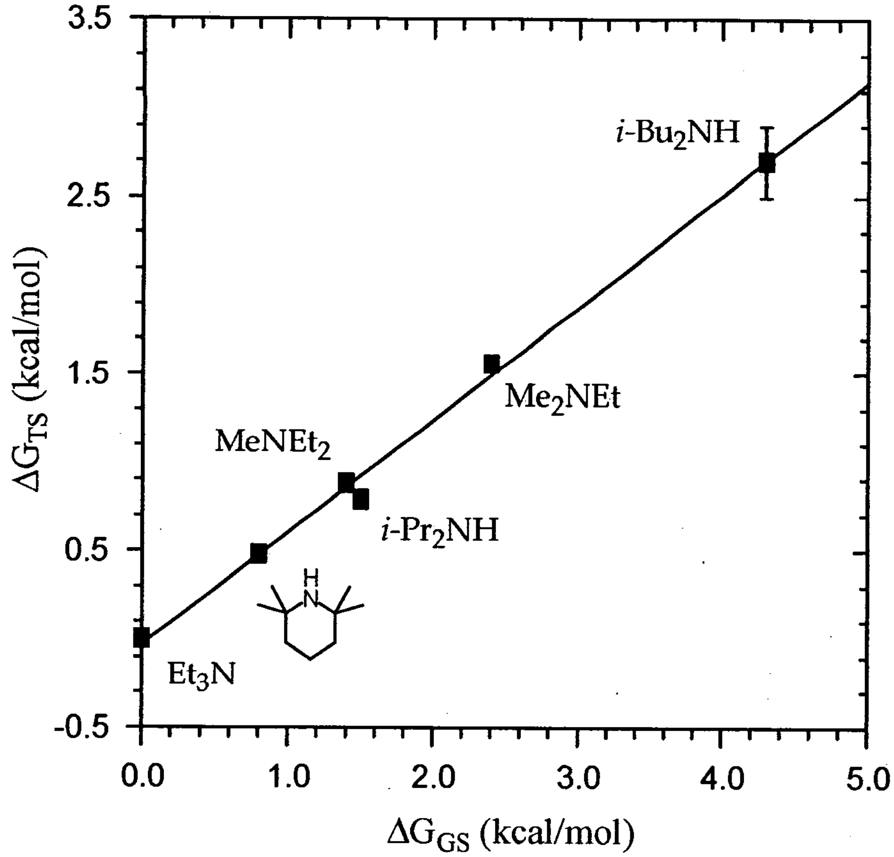
[LiHMDS] (M)	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	k_{obsd}(avg) (s^{-1})
0.05	7.8 ± 0.8E-3	7.8 ± 0.3E-3	7.8 ± 0.8E-3
0.10	1.1 ± 0.1E-2	9.3 ± 0.5E-3	1.0± 0.1E-2
0.15	9 ± 1E-3	8.2 ± 0.3E-3	9 ± 1E-3
0.20	7.4 ± 0.3E-3	1.01 ± 0.05E-2	9 ± 1E-3
0.25	1.1 ± 0.1E-2	9.1 ± 0.4E-3	1.0 ± 0.1E-2



XXXVIII. Plot of k_{obsd} vs $X_{i\text{-}Pr2NH}$ (X = mole fraction) in Me_2NEt/*i*-Pr_2NH (1.2 M total)/toluene mixturesfor the enolization of **1-*d*₃** (0.004 M) by LiHMDS (0.10 M) at –78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = (a + bx)/(1 + cx)$ ($a = 9 \pm 1 \times 10^{-5}$, $b = -3 \pm 1 \times 10^{-5}$, $c = -0.916 \pm 0.008$; $K_{eq} = 1 + c = 0.084 \pm 0.008$).

XXXIX. Table of data for plot in section **XXXVIII.**

i-Pr_2NH mol%	$k_{obsd}1$ (s^{-1})	$k_{obsd}2$ (s^{-1})	$k_{obsd}3$ (s^{-1})	k_{obsd} (avg) (s^{-1})
0	1.0 ± 0.1E-4	1.0 ± 0.1E-4	--	1.0 ± 0.1E-4
25	1.1 ± 0.1E-4	1.3 ± 0.1E-4	--	1.2 ± 0.1E-4
50	1.5 ± 0.1E-4	1.3 ± 0.3E-4	--	1.4 ± 0.3E-4
75	1.9 ± 0.4E-4	2.0 ± 0.4E-4	--	2.0 ± 0.4E-4
83	3.1 ± 0.2E-4	2.5 ± 0.2E-4	--	2.8 ± 0.2E-4
92	4.4 ± 0.1E-4	3.5 ± 0.2E-4	5.0 ± 0.1E-4	4.3 ± 0.2E-4
100	7.4 ± 0.1E-3	7.4 ± 0.2E-3	--	7.4 ± 0.2E-4



XL. Plot of ΔG^{o}_{TS} vs ΔG^{o}_{GS} for selected amine ligands at the enolization of **1-*d*$_3$** (0.004 M) by LiHMDS (0.10 M) in R_3N/toluene at –78 °C, using binary ligand systems listed in part **XXVI-XXXIX**. The curve depicts the results of an unweighted least-square fit to y = ax + b, where a = 0.64 ± 0.02, b = -0.03 ± 0.05 (kcal/mol).

XLI. Table of data for plot in section **XL**.

Ligand	K_{eq}	ΔG^{o}_{GS} (kcal/mol)	k_2 (s^{-1})	ΔG^{o}_{TS} (kcal/mol)
Et_3N	2.2 ± 0.2	0.00	5.7 ± 0.5E10^{-3}	0.00
Me_2NEt	1.2 ± 0.1E10^{3}	2.4 ± 0.3	1.0 ± 0.1E10^{-4}	1.56 ± 0.04
$MeNEt_2$	76 ± 6	1.4 ± 0.2	5.8 ± 0.3E10^{-4}	0.88 ± 0.02
i-Bu_2NH	1.7 ± 0.2E10^{5}	4.3 ± 0.5	6 ± 2E10^{-6}	2.7 ± 0.2
i-Pr_2NH	1.0 ± 0.1E10^{2}	1.5 ± 0.2	7.4 ± 0.0E10^{-4}	0.79 ± 0.01
2,2,6,6-tetramethyl-piperidine	16 ± 6	0.8 ± 0.4	1.64 ± 0.04E10^{-3}	0.48 ± 0.01

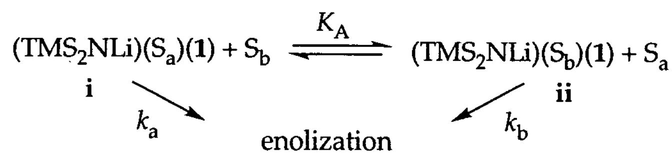
XLII. Isotope effects of ketone enolizations with LiHMDS and amine ligands (Chart 1 and 2 in text). Reactions were carried out using 0.1 M LiHMDS and 0.004 M 2-methycyclohexanone (**1** or **1**-d_3) in amine/toluene mixtures at –78 °C.

Amine Ligand	k_H	k_D	KIE
None[a]	2.0 ± 0.1E-4	2.0 ± 0.1E-5	10 ± 1
A[b]	2.1 ± 0.1E-3	1.0 ± 0.1E-4	20 ± 2
B[c]	8 ± 1E-3	2.13 ± 0.05E-4	40 ± 5
D[b]	1.2 ± 0.1E-2	6.28 ± 0.09E-4	19 ± 2
F[c]	3 ± 1E-2	2.5 ± 0.3E-3	12 ± 4
G[d]	2.4 ± 0.2E-2	7.4 ± 0.3E-4	30 ± 3
H[e]	2.5 ± 0.1E-2	9 ± 1E-4	26 ± 3
I[e]	9.6 ± 0.1E-3	5.1 ± 0.1 E-4	19 ± 1
N[b]	3.1 ± 0.1E-4	3 ± 1E-5	10 ± 3
O[f]	4.6 ± 0.5E-3	5.0 ± 0.1E-4	9 ± 1
P[e]	2.2 ± 0.1E-2	1.3 ± 0.1E-3	17 ± 1
R[c]	7 ± 1E-3	4.3 ± 0.2E-4	16 ± 2
U[c]	9.0 ± 0.1E-3	3.9 ± 0.1E-4	22 ± 1
Z[c]	1.1 ± 0.1E-2	7 ± 1E-4	16 ± 2
BB[c]	4.7 ± 0.2E-3	2.6 ± 0.2E-4	18 ± 2
EE[b]	6 ± 1E-3	3.7 ± 0.1E-4	16 ± 2
GG[b]	6.0 ± 0.1E-3	5 ± 1E-4	12 ± 2
HH[e]	8 ± 1E-3	6.0 ± 0.3E-4	13 ± 2
II[e]	2.8 ± 0.1E-3	1.16 ± 0.03E-4	23 ± 1
NN[b]	7 ± 2E-3	7.4 ± 0.1E-4	10 ± 3
OO[b]	4 ± 2E-5	6 ± 3E-6	7 ± 3
PP[e]	1.2 ± 0.1E-2	6.9 ± 0.1E-4	17 ± 1

[a] Reactions were carried out in neat toluene at –40 °C. [b] Reactions were carried out with 1.2 M amine lignad. [c] Reactions were carried out with 0.60 M amine lignad. [d] Reactions were carried out with 0.10 M Et_3N. [e] Reactions were carried out with 0.15 M amine lignad. [f] Reactions were carried out with 1.2 M *i*-Bu_3N at –40 °C.

XLIII. Derivation of expression for solvent binding constant determination (eq 10 and 15 in manuscript):

Scheme 3



For convenience, we let A = TMS_2NLi, B = ketone substrate (1) and describe Scheme 3 by eq 1-3.

$$A_2BS_a + S_b \overset{K_A}{\longleftrightarrow} A_2BS_b + S_a \quad (1)$$

$$A_2BS_a \xrightarrow{k_a} \text{product} \quad (2)$$

$$A_2BS_b \xrightarrow{k_b} \text{product} \quad (3)$$

$$[B]_{total} = [A_2BS_a] + [A_2BS_b] \quad (4)$$

$$d[\text{product}]/dt = k_{obsd}[B]_{total} = k_a[A_2BS_a] + k_b[A_2BS_b] \quad (5)$$

From eq 1 and 4,

$$[A_2BS_a] = [B]_{total}[S_a]/([S_a] + K_A[S_b]) \quad (6)$$

$$[A_2BS_b] = K_A[B]_{total}[S_b]/([S_a] + K_A[S_b]) \quad (7)$$

Substitution of $[A_2BS_a]$ and $[A_2BS_b]$ from eq 6 and 7 into eq 5 affords

$$k_{obsd} = (k_a[S_a] + k_bK_A [S_b])/([S_a] + K_A[S_b]) \quad (8)$$

Eliminating $[S_a]$ from the right side of eq 8 affords

$$K_{obsd} = \{k_a + k_bK_A([S_b]/[S_a])\}/\{1 + K_a([S_b]/[S_a])\} \quad (9)$$

Defining $[S_a]$ and $[S_b]$ in terms of mole fractions X_a and X_b for S_a and S_b (eq 10 and 11) and substituting into eq 8 affords eq 12.

$$X_a = [S_a]/([S_a] + [S_b]) \tag{10}$$

$$X_b = 1 - X_a \tag{11}$$

$$k_{obsd} = [k_a X_a + k_b K_A(1 - X_a)]/[X_a + K_A(1 - X_a)] \tag{12}$$