J. Am. Chem. Soc. v 115
p. 8008 Bernstein

Rev J- 8018-m1

Supplementary Material for the paper entitled

Solvent and Substrate-Dependent Rates of Imine Metallations by Lithium Diisopropylamide (LDA): Understanding the Mechanisms Underlying "k_{rel}"

Max P. Bernstein and David B. Collum*
Contribution from the Department of Chemistry, Baker Laboratory
Cornell University
Ithaca, New York 14853-1301

*Equation numbers refer to equations in text.

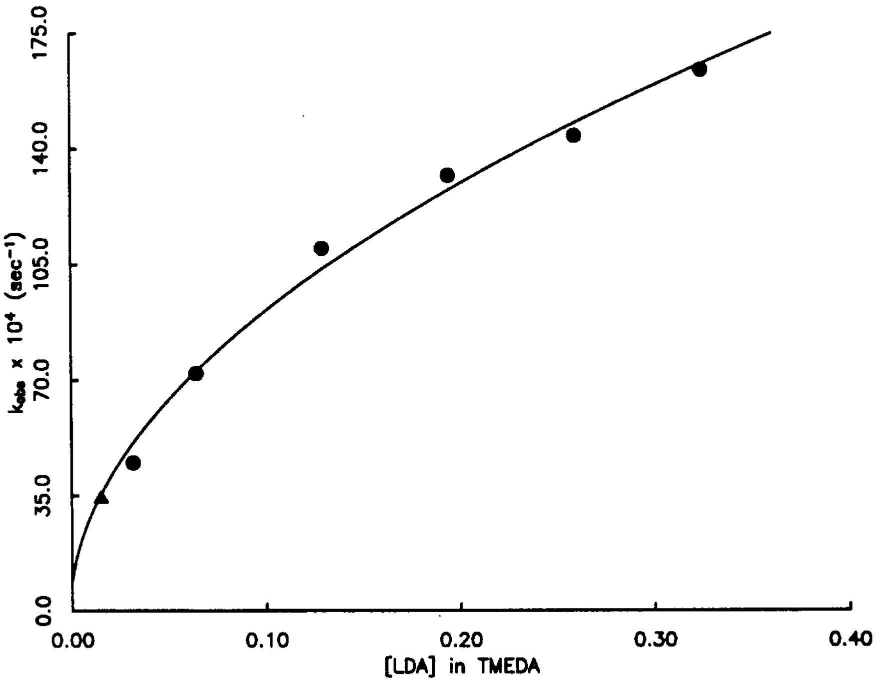

Figure I. Plot of k_{obsd} versus [LDA] in neat TMEDA for the metallation of imine **2-d_4** (0.004 M) at 0.0 ± 0.5 °C. The curve depicts the result of an unweighted non-linear least-squares fit to Equation 4 (n = 0.51 ± 0.01). The rate constant at the lowest LDA concentration, designated by a triangle (Δ), was not recorded under fully pseudo-first-order conditions and was not included in the fit.

J-8018-m2

J. Am. Chem. Soc. v 115
p. 8008 Bernstein

Supplementary material,
page 2

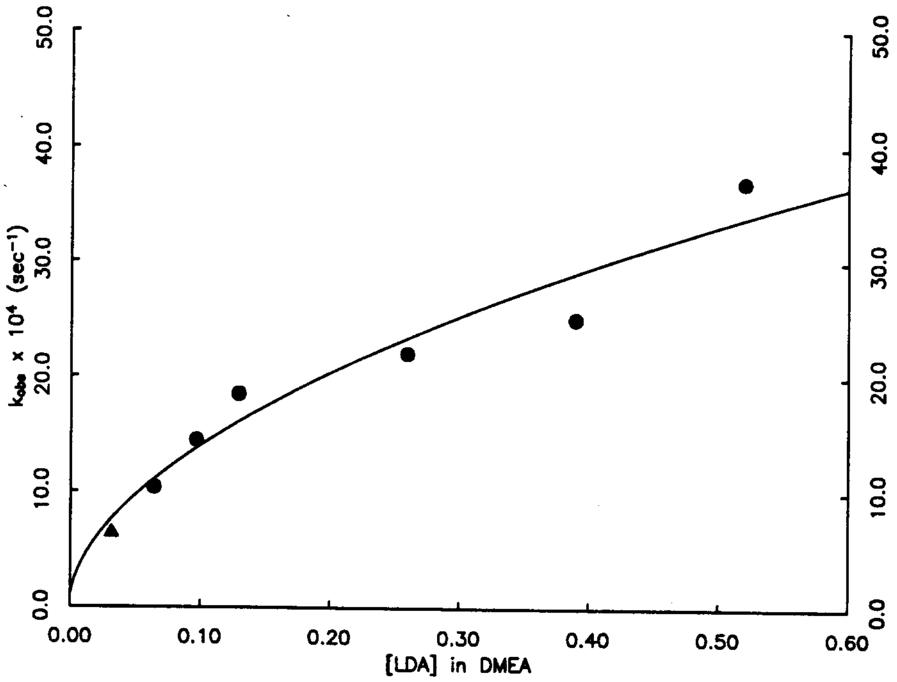

Figure II. Plot of k_{obsd} versus [LDA] in neat DMEA for the metallation of imine **2-d$_4$** (0.004 M) at 0.0 ± 0.5 °C. The curve depicts the result of an unweighted non-linear least-squares fit to Equation 4 ($n = 0.54 \pm 0.04$). The rate constant at the lowest LDA concentration, designated by a triangle (Δ), was not recorded under fully pseudo-first-order conditions and was not included in the fit.

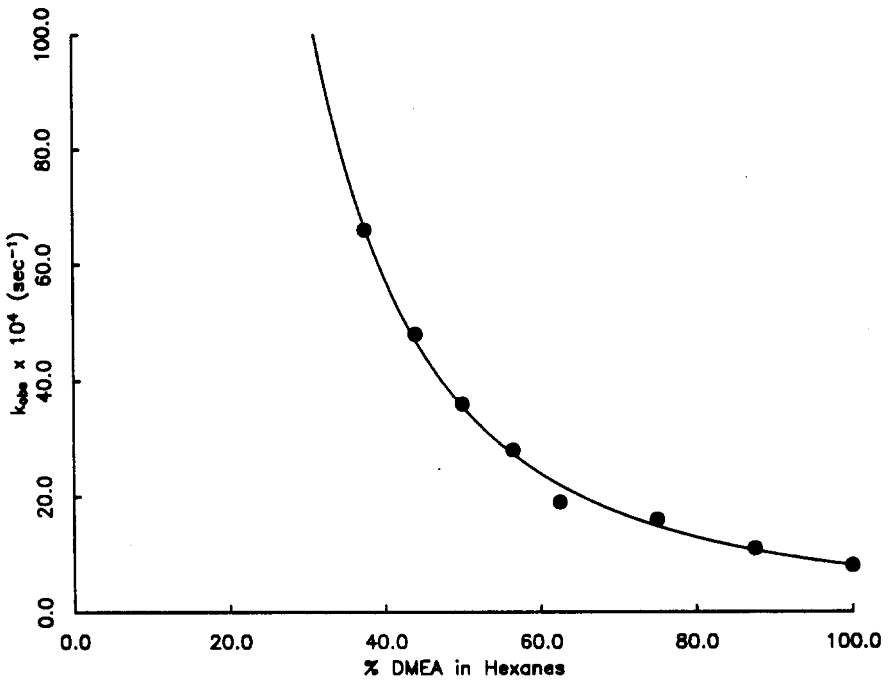

Figure III. Plot of k_{obsd} versus [DMEA] in hexane co-solvent for the metallation of imine 6 (0.004 M) by LDA (0.13 M) at 0.0 ± 0.5 °C. The curve depicts the result of an unweighted least-squares fit to Equation 8. The adjustable parameter, n, corresponds to the order in DMEA ($n = -2.20 \pm 0.01$). The parameter k_1 corresponds to the observed rate constant expected for the metallation via monomers ($k'' = 240 \pm 50 \times 10^{-4}$ sec^{-1}).

© 1993 Am. Chem. Soc.
J. Am. Chem. Soc. v 115
p. 8008 Bernstein

Supplementary material,
page 3

J-8018-m3

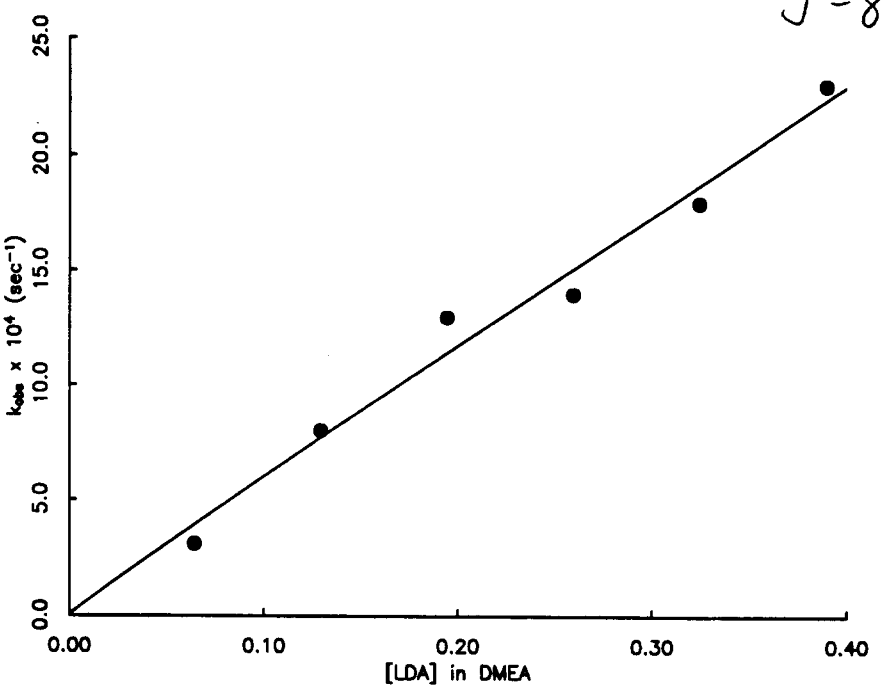

Figure IV. Plot of k_{obsd} versus [LDA] in neat DMEA for the metallation of imine **6** (0.004 M) at 0.0 ± 0.5 °C. The curve depicts the result of an unweighted non-linear least-squares fit to Equation 4 (n = 0.96 ± 0.03).

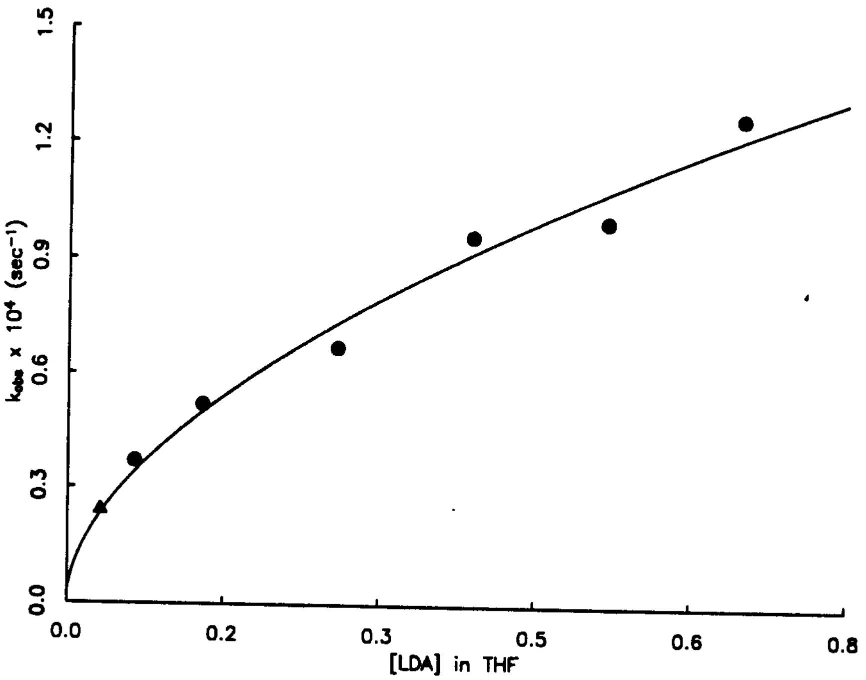

Figure V. Plot of k_{obsd} versus [LDA] in neat THF for the metallation of imine **6** (0.004 M) at 0.0 ± 0.5 °C. The curve depicts the result of an unweighted non-linear least-squares fit to Equation 4 (n = 0.55 ± 0.03). The rate constant at the lowest LDA concentration, designated by a triangle (Δ), was not recorded under fully pseudo-first-order conditions and was not included in the fit.

© 1993 Am. Chem. Soc.
J. Am. Chem. Soc. v 115
p. 8008 Bernstein

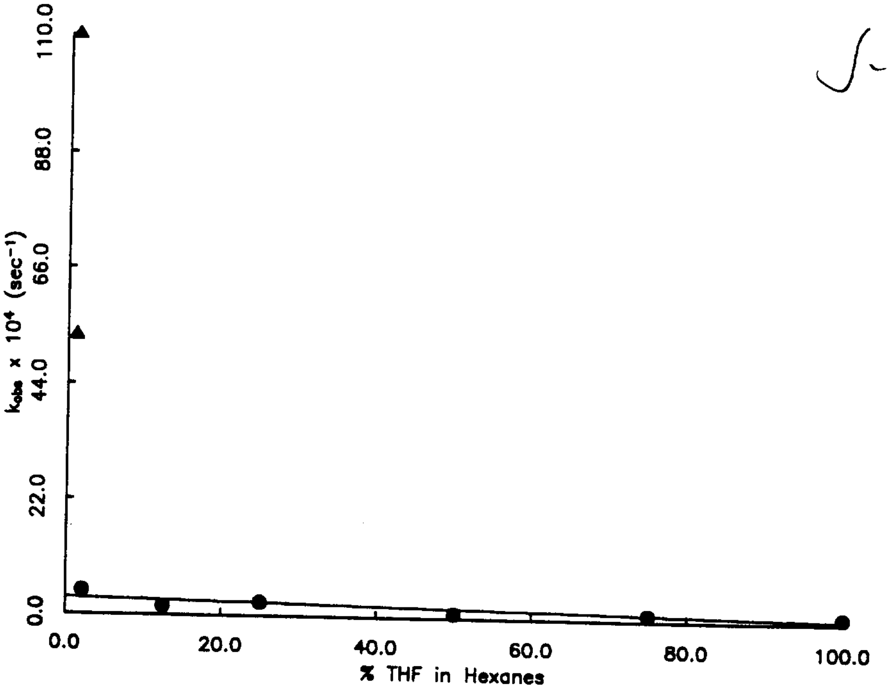

Figure VI. Plot of k_{obsd} versus [THF] in hexane co-solvent for the metallation of imine **6** (0.004 M) by LDA (0.13 M) at 0.0 ± 0.5 °C. The curve depicts the result of an unweighted fit to a linear equation. The rate constants at the lowest THF concentrations, designated by triangles (Δ), were not recorded under fully pseudo-first-order conditions and were not included in the fit.

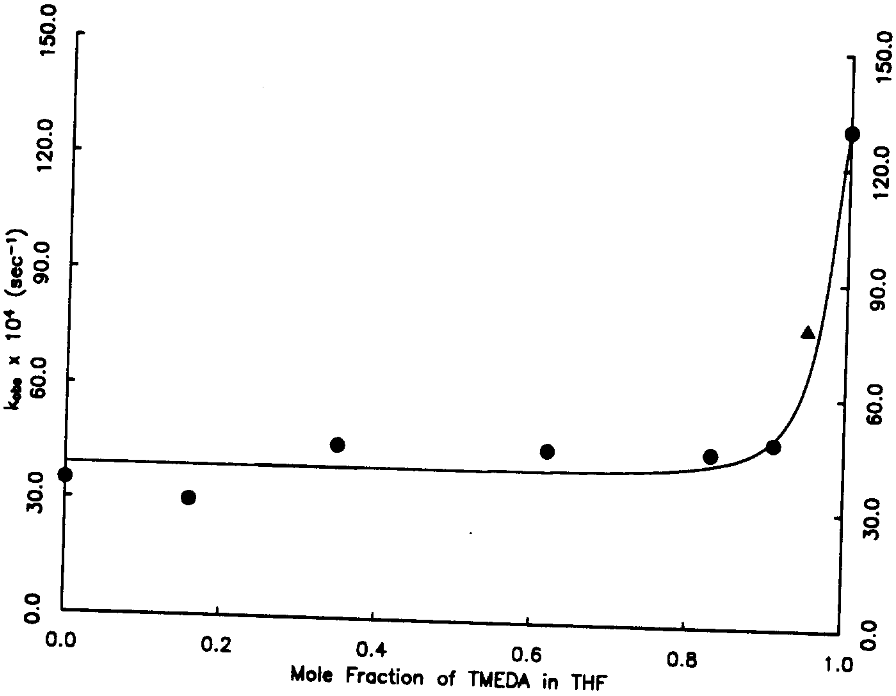

Figure VII. Pseudo-first-order rate constants for the metallation of imine **4-d_4** (0.004 $\underline{M}$) by LDA (0.13 $\underline{M}$) as a function of TMEDA and THF composition. The units on the x-axis correspond to solvent mole fraction [TMEDA]/{[TMEDA] + [THF]}. An unweighted least-squares fit to Equation 10 affords K_{eq}(THF/TMEDA) = 722 ± 244. The rate constant at the low THF concentration, designated by a triangle (Δ), was not recorded under fully pseudo-first-order conditions and was not included in the fit.

© 1993 Am. Chem. Soc.
J. Am. Chem. Soc. v 115
p. 8008 Bernstein

√- 8018-m5

TABULATED KINETIC DATA

PART 1. 2,2,6,6-Tetradeuterocyclohexanone *N*-Isopropylimine metallations (0.004 M).

Table I. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of [LDA] in neat THF.

[LDA], M	k x 10^4, sec^{-1}
0.065	6.8 ± 0.05
0.13	10.3 ± 0.15
0.26	15.1 ± 0.15
0.39	17.0 ± 0.27
0.52	20.4 ± 0.28
0.65	22.0 ± 0.05

Table II. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of [LDA] in neat TMEDA.

[LDA], M	k x 10^4, sec^{-1}
0.016	34 ± 3.0
0.033	45 ± 2.0
0.065	72 ± 3.4
0.130	110 ± 7.0
0.195	132 ± 5.0
0.260	144 ± 3.0
0.325	164 ± 8.0

J. Am. Chem. Soc. v 115
p. 8008 Bernstein

J- 8018-m6

Table III. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of [LDA] in neat DMEA.

[LDA], M	k x 10^4, sec^{-1}
0.033	6.4 ± 0.25
0.065	10.4 ± 0.09
0.098	14.5 ± 0.04
0.130	18.0 ± 0.10
0.260	21.9 ± 0.05
0.390	24.8 ± 0.03
0.520	37.4 ± 0.14

Table IV. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of [TMEDA] in Hexane. [LDA] = 0.13 M

[TMEDA], M	k x 10^4, sec^{-1}
0.00	2 ± 0.2
0.33	50 ± 3.2
0.66	70 ± 3.0
1.30	92 ± 3.0
2.60	111 ± 4.1
4.00	110 ± 1.8
5.30	98 ± 2.7
6.60	110 ± 7.0

Table V. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of [THF] in Hexane. [LDA] = 0.13 M

[THF], M	k x 10^4, sec^{-1}
0.0	1.6 ± 0.18
0.3	12.0 ± 0.65
2.5	10.0 ± 0.06
4.9	10.5 ± 0.07
7.4	11.0 ± 0.07
9.8	11.0 ± 0.07
12.3	9.0 ± 0.04

© 1993 Am. Chem. Soc.
J. Am. Chem. Soc. v 115
p. 8008 Bernstein

J- 8018-mm7

Table VI. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of % TMEDA in THF. [LDA] = 0.13 M

% TMEDA in THF	k x 10^4, sec^{-1}
0.0	10.3 ± 0.2
25.0	11.2 ± 0.1
50.0	10.1 ± 0.1
75.0	12.0 ± 0.9
90.0	19.5 ± 0.5
96.5	23.0 ± 0.3
98.3	45.0 ± 0.6
100.0	110.0 ± 7.0

Table VII. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of % DMEA in THF. [LDA] = 0.13 M

% DMEA in THF	k x 10^4, sec^{-1}
0.0	7.9 ± 0.1
25.0	8.8 ± 0.1
50.0	8.6 ± 0.1
75.0	8.3 ± 0.1
95.0	10.7 ± 0.2
97.5	15.0 ± 0.3
100.0	18.5 ± 0.9

Table VIII. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of % DMEA in TMEDA. [LDA] = 0.13 M

% DMEA in TMEDA	k x 10^4, sec^{-1}
0.0	92 ± 3.0
0.0	110 ± 7.0
12.5	89 ± 1.0
12.5	71 ± 1.1
25.0	82 ± 1.0
25.0	51 ± 3.0
37.5	44 ± 0.8
37.5	50 ± 0.5
50.0	50 ± 0.6
50.0	46 ± 0.4
62.5	42 ± 0.4
62.5	43 ± 0.3
75.0	31 ± 0.4
75.0	26 ± 0.3
87.5	25 ± 0.2
87.5	24 ± 0.3
100.0	18 ± 1.0
100.0	19 ± 0.9

PART 2. 2-Methylcyclohexanone, 1-Dimethylamino *N*-Isopropylimine metallations (0.004 M) .

Table I. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of [LDA] in neat THF.

[LDA], M	k x 10^4, sec^{-1}
0.065	0.37 ± 0.008
0.13	0.52 ± 0.002
0.26	0.67 ± 0.006
0.39	0.96 ± 0.006
0.52	1.03 ± 0.012
0.65	1.27 ± 0.012

Table II. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of [LDA] in neat TMEDA.

[LDA], M	k x 10^4, sec^{-1}
0.065	14 ± 0.2
0.130	29 ± 1.3
0.130	27 ± 0.6
0.195	34 ± 0.7
0.260	51 ± 1.2
0.325	68 ± 1.7
0.390	89 ± 1.4
0.455	91 ± 4.0

Table III. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of [LDA] in neat DMEA.

[LDA], M	k x 10^4, sec^{-1}
0.065	3 ± 0.1
0.130	8 ± 0.2
0.195	13 ± 0.4
0.260	14 ± 0.6
0.325	18 ± 0.5
0.390	23 ± 0.8

Table IV. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of [THF] in Hexane. [LDA] = 0.13 M

[THF], M	k x 10^4, sec^{-1}
0.12	110.0 ± 8.0
0.14	53.0 ± 3.0
0.26	4.6 ± 0.2
1.54	1.7 ± 0.1
3.10	2.6 ± 0.1
6.15	1.0 ± 0.1
9.22	1.2 ± 0.1
12.30	1.0 ± 0.1

© 1993 Am. Chem. Soc.
J. Am. Chem. Soc. v 115
p. 8008 Bernstein

J-8018-m10

Table V. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of [TMEDA] in Hexane. [LDA] = 0.13 M

[TMEDA], M	k x 10^4, sec^{-1}
2.48	146.0 ± 4.0
2.48	140.0 ± 12
2.48	124.0 ± 14
3.30	80.0 ± 6.5
3.30	83.0 ± 19
4.13	47.4 ± 3.0
4.13	54.0 ± 1.5
4.95	32.6 ± 0.9
4.95	38.0 ± 0.9
5.78	32.0 ± 0.6
5.78	35.1 ± 0.5
6.60	27.0 ± 0.6
6.60	23.9 ± 0.6

Table VI. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of [DMEA] in Hexane. [LDA] = 0.13 M

[DMEA], M	k x 10^4, sec^{-1}
3.46	66 ± 3.0
4.06	48 ± 2.0
4.62	36 ± 1.5
5.21	28 ± 1.0
5.77	19 ± 0.6
6.92	16 ± 0.3
8.08	11 ± 0.1
9.23	8 ± 0.2

J- 8018-m11

Table VII. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of % TMEDA in THF. [LDA] = 0.13 M

% TMEDA in THF	$k \times 10^4$, sec^{-1}
0.0	0.52 ± 0.01
25.0	0.57 ± 0.01
50.0	0.44 ± 0.01
75.0	1.50 ± 0.01
90.0	2.30 ± 0.01
95.0	3.30 ± 0.30
97.5	8.80 ± 0.20
100.0	24.0 ± 0.60

Table VIII. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of % DMEA in THF. [LDA] = 0.13 M

% DMEA in THF	$k \times 10^4$, sec^{-1}
0.0	0.52 ± 0.01
25.0	0.38 ± 0.04
50.0	0.40 ± 0.01
75.0	0.49 ± 0.01
90.0	0.63 ± 0.01
95.0	1.19 ± 0.03
97.5	2.30 ± 0.10
100.0	8.00 ± 0.20

J- 8018-m12

PART 3. 2,2,6,6-Tetradeuterocyclohexanone *N,N*-dimethylhydrazone metallations (0.004M).

Table I. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of % TMEDA in THF. [LDA] = 0.13 M

% TMEDA in THF	k x 10^4, sec^{-1}
0.0	35 ± 2.2
25.0	30 ± 2.0
50.0	45 ± 2.8
75.0	45 ± 1.5
90.0	45 ± 3.0
95.0	48 ± 4.0
97.5	78 ± 6.2
100.0	130 ± 18

PART 4. Cyclohexanone N,N,-dimethylhydrazone metallations (0.004M).

Table I. Pseudo-first-order metallation rate constants measured at 0.0 ± 0.1 °C as a function of % TMEDA in THF. [LDA] = 0.13 M

% TMEDA in THF	k x 10^4, sec^{-1}
0.0	115 ± 18
20.0	126 ± 0.9
50.0	102 ± 0.6
80.0	148 ± 1.4
90.0	177 ± 3.0
95.0	274 ± 8.1
98.0	483 ± 17
100.0	680 ± 20

J. Am. Chem. Soc. v 115
p. 8008 Bernstein

J-8018-m13

DERIVATIONS

Equation 7:

$$\begin{tikzcd}[column sep=huge]
{[LDA]_n\ (n = 2, 3, 4\ldots)} \arrow[r, shift left, "\substack{K_{eq}\\ +2\ \mathrm{TMEDA\ (per\ dimer)}}"] \arrow[d, "\mathrm{imine}"', "k_1"] & {[LDA{\cdot}TMEDA]_2} \arrow[l, shift left] \arrow[d, "\mathrm{imine}"', "\substack{k_2\\ (= k_3[LDA_T]^{1/2})}"] \\
\mathrm{products} & \mathrm{products}
\end{tikzcd}$$

Scheme IV

If we approximate the concentration of the LDA unsolvated oligomers, $[(LDA)_n]$, as the concentration of unsolvated dimer, $[(LDA)_2]$, then

$$k'_{obsd} = k_1[(LDA)_2] + k_2[(LDA\cdot S)_2]$$

$$K_{eq} = \frac{[(LDA\cdot S)_2]}{[(LDA)_2][S]^2}$$

$$K_{eq}[S]^2 = \frac{[(LDA\cdot S)_2]}{[(LDA)_2]}$$

The total LDA *dimer* concentration ($[LDA]_T$) is described by

$$[LDA]_T = [(LDA)_2] + [(LDA\cdot S)_2]$$

Consequently,

$$k'_{obsd} = \frac{k'_{obsd}[LDA]_T}{[LDA]_T} = \frac{k'_{obsd}[LDA]_T}{[(LDA)_2] + [(LDA\cdot S)_2]}$$

$$k'_{obsd} = \frac{\{k_1[(LDA)_2] + k_2[(LDA\cdot S)_2]\}[LDA]_T}{[(LDA)_2] + [(LDA\cdot S)_2]}$$

Dividing through by $[\mathrm{LDA}]_T$ we obtain the pseudo-first-order observed rate constant (k_{obsd}) as follows:

$$k'_{obsd}/[\mathrm{LDA}]_T = k_{obsd} = \frac{k_1[(\mathrm{LDA})_2] + k_2[(\mathrm{LDA{\cdot}S})_2]}{[(\mathrm{LDA})_2] + [(\mathrm{LDA{\cdot}S})_2]}$$

Dividing numerator and denominator by $[(\mathrm{LDA})_2]$ yields

$$k_{obsd} = \frac{k_1 + k_2[(\mathrm{LDA{\cdot}S})_2][(\mathrm{LDA})_2]}{1 + [(\mathrm{LDA{\cdot}S})_2]/[(\mathrm{LDA})_2]}$$

Substituting $K_{eq}[S]^2$ for $[(\mathrm{LDA{\cdot}S})_2]/[(\mathrm{LDA})_2]$ we find

$$k_{obsd} = \frac{k_1 + k_2K_{eq}[S]^2}{1 + K_{eq}[S]^2}$$

where constant k_2 is a composite rate constant shown by the kinetics in the text to be adequately described by:

$$k_2 = k_3K''_{eq}[(\mathrm{LDA{\cdot}S})_2]^{1/2}$$

Since k_1 is small and since the derivation depends on the approximation of the LDA oligomers as dimers, we chose to include the approximation $k_{1'} \approx k_1/\{1 + K_{eq}[S]^2\}$ merely to define a non-zero y-intercept, affording

$$k_{obsd} = \frac{k_2K_{eq}[S]^2}{1 + K_{eq}[S]^2} + k_1' \qquad (7)$$

One should note that the observed rate constants and total [LDA] in the derivation of equation 7 are in terms of the LDA dimer concentration, while the measured rate constants in the text were based on the LDA titer (solution normality).

J. Am. Chem. Soc. v 115
p. 8008 Bernstein

J-8018-m15

Equation 10:

$$\begin{tikzcd}[column sep=huge]
S_2 + 1/2[LDA{\cdot}S_1]_2 \arrow[r, shift left, "{K_{eq}(s_2/s_1)\quad \Delta G^o(C)}"] \arrow[d, "{k_{obsd}(s_1)\quad \Delta G^o(A)}", "\mathrm{iv}"'] & 1/2[LDA{\cdot}S_2]_2 + S_1 \arrow[l, shift left] \arrow[d, "{k_{obsd}(s_2)\quad \Delta G^o(B)}", "\mathrm{v}"'] \\
\text{products} & \text{products}
\end{tikzcd}$$

Scheme VII

$$K_{eq} = \frac{[(LDA{\cdot}S_2)_2][S_1]^2}{[(LDA{\cdot}S_1)_2][S_2]^2}$$

$$\frac{[(LDA{\cdot}S_2)_2]}{[(LDA{\cdot}S_1)_2]} = K_{eq}\ \frac{[S_2]^2}{[S_1]^2}$$

$$k'_{obsd} = k_{obsd}(S_1)[(LDA{\cdot}S_1)_2] + k_{obsd}(S_2)[(LDA{\cdot}S_2)_2]$$

The total LDA *dimer* concentration ($[LDA]_T$) is described by

$$[LDA]_T = [(LDA)_2] + [(LDA{\cdot}S)_2]$$

Consequently,

$$k'_{obsd} = \frac{k'_{obsd}[LDA]_T}{[LDA]_T} = \frac{k'_{obsd}[LDA]_T}{[(LDA{\cdot}S_1)_2] + [(LDA{\cdot}S_2)_2]}$$

$$k'_{obsd} = \frac{\{k_{obsd}(S_1)[(LDA{\cdot}S_1)_2] + k_{obsd}(S_2)[(LDA{\cdot}S_2)_2]\}[LDA]_T}{[(LDA{\cdot}S_1)_2] + [LDA{\cdot}S_2]_2}$$

© 1993 Am. Chem. Soc.
J. Am. Chem. Soc. v 115
p. 8008 Bernstein

S-8018-m16

Dividing through by $[LDA]_T$ we obtain the pseudo-first-order observed rate constant, k_{obsd}, as follows:

$$k_{obsd} = \frac{k_{obsd}(S_1)[(LDA{\cdot}S_1)_2] + k_{obsd}(S_2)[(LDA{\cdot}S_2)_2]}{[(LDA{\cdot}S_1)_2] + [(LDA{\cdot}S_2)_2]}$$

Dividing numerator and denominator by $[(LDA{\cdot}S_1)_2]$

$$k_{obsd} = \frac{k_{obsd}(S_1) + k_{obsd}(S_2)\{[(LDA{\cdot}S_2)_2]/[(LDA{\cdot}S_1)_2]\}}{1 + [(LDA{\cdot}S_2)_2]/[(LDA{\cdot}S_1)_2]}$$

Since

$$\frac{[(LDA{\cdot}S_2)_2]}{[(LDA{\cdot}S_1)_2]} = K_{eq}\frac{[S_2]^2}{[S_1]^2}$$

$$k_{obsd} = \frac{k_{obsd}(S_1) + k_{obsd}(S_2)K_{eq}[S_2]^2/[S_1]^2}{1 + K_{eq}[S_2]^2/[S_1]^2}$$

$$k_{obsd} = \frac{k_{obsd}(S_1)[S_1]^2 + k_{obsd}(S_2)K_{eq}[S_2]^2}{[S_1]^2 + K_{eq}[S_2]^2}$$

Finally, we replace $[S_2]$ in terms of $[S_1]$. The constants $a = [S_2]_{neat}$ and $b = [S_2]_{neat}/[S_1]_{neat}$ are needed to adjust for the differential molar volumes.

$$k_{obsd} = \{k_1[S_1]^2 + k_2K_{eq}(a-b[S_1])^2\}/\{[S_1]^2 + K_{eq}(a-b[S_1])^2 \qquad (10)$$