

Lithium Diisopropylamide-Mediated Enolizations: Solvent-Independent Rates, Solvent-Dependent Mechanisms

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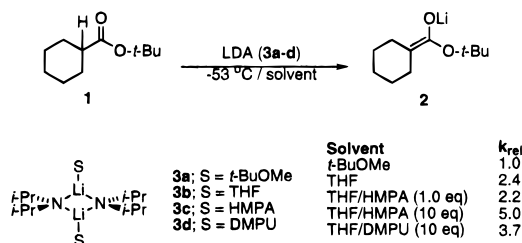
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Abstract: Rate studies of a lithium diisopropylamide-mediated ester enolization reveal solvation effects that are not in accord with expectation. Metalations in THF, *t*-BuOMe, HMPA/THF, and DMPU/THF (HMPA = hexamethylphosphoramide, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone) occur at nearly the same rates, yet proceed via four fundamentally distinct scenarios: (1) disolvated monomer in THF, (2) monosolvated dimer in *t*-BuOMe, (3) both monosolvated monomer and tetrasolvated dimer in HMPA/THF, and (4) mono- and disolvated monomers in DMPU/THF. The implication of reactive open dimers in *t*-BuOMe and triple ions in HMPA/THF underscores the importance of aggregate-based reactions.

Introduction

Lithium diisopropylamide (LDA) has attained a prominence in organic chemistry enjoyed by very few reagents,¹ playing a central role in the generation of enolates and related carbanions. It is also true, however, that detailed rate and mechanistic studies revealing the consequences of aggregation and solvation have been slow to develop.²

We have carried out a two-part investigation of LDA-mediated enolizations. In this paper we will describe detailed rate studies under pseudo-first-order conditions that focus upon the influence of four solvents: (1) *t*-BuOMe, a weakly coordinating solvent rapidly emerging as a safer alternative to Et₂O;³ (2) THF, the ethereal solvent most commonly employed in organolithium chemistry; (3) HMPA,⁴ the strongest (albeit most carcinogenic)⁵ monodentate ligand in organolithium chemistry;⁶ and (4) DMPU,⁴ a reputed noncarcinogenic substitute for HMPA.⁷ We jump ahead with a striking result: The enolizations of ester **1** by LDA in these four markedly different solvents proceed at nearly the same rates (eq 1).⁸ We will show that this congruence of metalation rates belies a remarkably solvent-dependent mechanistic landscape.^{9,10} This study is explicitly designed to exclude contributions from mixed aggregation effects. The following paper will describe semiquan-



tative investigations of how intervening mixed aggregates can cause significant dependencies of the reaction rates on the choice of solvent.^{11–13}

Results

LDA Solution Structures. Previous investigations have shown that LDA is a disolvated dimer (**3a** and **3b**) in ethereal solvents.^{14,15} Moreover, HMPA and DMPU quantitatively displace THF from dimer **3b** to afford dimers **3c** and **3d** (respectively) *without detectable deaggregation*.¹⁶

Rate Studies: General. The LDA used in the rate studies was doubly recrystallized¹⁷ and used as freshly prepared stock solutions. Pseudo-first-order conditions were established with

(1) d'Angelo, J. *Tetrahedron* **1976**, 32, 2979. Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Buncl, E., Durst, T., Eds.; Elsevier: New York, 1980; Vol. B, Chapter 4. Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, 2, 1. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vols. 2 and 3. Snieckus, V. *Chem. Rev.* **1990**, 90, 879.

(2) For leading references to structural, rate, and mechanistic studies of LDA, see ref 9.

(3) Little, C. J.; Dale, A. D.; Whatley, J. A.; Wickings, J. A. *J. Chromatogr.* **1979**, 169, 381 and references therein.

(4) HMPA = hexamethylphosphoramide, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone.

(5) Spencer, H. *Chem. Ind.* **1979**, 728.

(6) Recent rate studies exploring the role of HMPA: Leung, S. S.-W.; Streitwieser, A. *J. Org. Chem.* **1999**, 64, 3390. Reich, H. J.; Sikorski, W. H.; Gudmundsson, B. Ö.; Dykstra, R. R. *J. Am. Chem. Soc.* **1998**, 120, 4035 and references therein.

(7) (a) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, 65, 385. (b) Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. Ö.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, 120, 7201.

(8) The relative rate constants were determined using 0.1 M LDA in neat ethereal solvents.

(9) The results for LDA/THF-mediated enolizations have been communicated previously: Sun, X.; Kenkre, S. L.; Remenar, J. F.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, 119, 4765.

(10) For related studies of ketone enolization, see: Majewski, M.; Nowak, P. *Tetrahedron Lett.* **1998**, 39, 1661.

(11) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, 122, 2459–2463.

(12) For leading references to rate studies affording insights into solvation at the transition structure, see: (a) Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, 115, 8008. (b) Schmitz, R. F.; Dekanter, F. J. J.; Schakel, M.; Klumpp, G. W. *Tetrahedron* **1994**, 50, 5933.

(13) A particularly clear discussion of the relationship between ground state and transition state solvation in organolithium chemistry has been presented: Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, 105, 1. Also, see: Collum, D. B. *Acc. Chem. Res.* **1993**, 25, 448.

(14) Collum, D. B. *Acc. Chem. Res.* **1993**, 26, 227.

(15) Reviews of lithium amide structural studies: Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* **1991**, 37, 47. Mulvey, R. E. *Chem. Soc. Rev.* **1991**, 20, 167.

(16) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, 113, 5751. In light of the rate studies described herein, the NMR spectroscopic investigations of LDA in HMPA/THF showing exclusively disolvated dimer **3c** were repeated and the results confirmed.

(17) Bernstein, M. P.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Williard, P. G.; Liu, Q. Y.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, 114, 5100.

Table 1. Summary of Rate Studies for the LDA-Mediated Enolization of **1** (Eq 1)

subst.	ligand	temp, °C	LDA order	solvent order	k_H/k_D	putative mechanism
1	THF ^a	-53	0.53 ± 0.03 ^b	1.15 ± 0.06 ^b	22 ± 1	eqs 3 and 4
1 ^l	HMPA ^{d,e}	-35	0.49 ± 0.01 ^b	0 ^f	22 ± 1	eqs 6 and 7
1 ^l	HMPA ^{c,d}	-35	0.92 ± 0.04 ^g	1.97 ± 0.09 ^h	23 ± 1	eqs 8 and 9
1	DMPU ^{d,i}	-53	0.53 ± 0.01 ^b	0 ^f	18 ± 2	eqs 11 and 12
1	DMPU ^{d,j}	-53	0.50 ± 0.02 ^b	1.10 ± 0.13 ^h	24 ± 4	eqs 13 and 14
5	<i>t</i> -BuOMe ^a	0	0 ^k	0 ^k	7.9 ± 0.3	eq 16

^a Toluene cosolvent. ^b Obtained by a fit to the general expression $f(x) = ax^b$. ^c [HMPA] = 0.80 M. ^d THF cosolvent. ^e [HMPA] = 0.10 M. ^f Determined from the nonzero intercept in plots of k_{obsd} vs [S]. ^g Obtained by a fit to the general expression $f(x) = ax^{1/2} + bx^c$, such that c is the reaction order. ^h Obtained by a fit to the general expression $f(x) = a + bx^c$. ⁱ [DMPU] = 0.066 M. ^j [DMPU] = 1.56 M. ^k Zeroth-order is assigned due to the <10% change in rate over >10-fold changes in donor solvent concentrations. ^l The rate equation was determined using **1-d**₁.

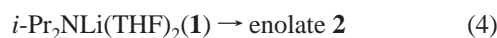
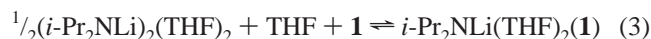
LDA at normal concentrations (0.04–0.40 M) by restricting the ester concentration to ≤0.004 M. Ester **1** offers an optimal window for monitoring enolizations at temperatures that are easily maintained in a commercially available thermostated bath. The IR absorbances of **1** (or **1-d**₁) at 1727 cm⁻¹ and enolate **2**¹⁸ at 1645–1655 cm⁻¹ were monitored using a ReactIR 1000 fitted with an immersible SiComp ATR probe.¹⁹ Ester–LDA complexes, exemplified by significant (10–30 cm⁻¹) shifts to lower frequencies,²⁰ are not observable except when explicitly noted otherwise. While LDA is a dimer under all conditions employed, “[LDA]” refers to the formal molarity of the monomer unit (normality). The solvent concentration refers to the concentration of *free* (uncoordinated) donor solvent in hexane (or THF) cosolvent. In all cases, loss of starting material follows a clean first-order decay to 5 half-lives. The resulting pseudo-first-order rate constants are independent of substrate concentration (0.004–0.04 M). Zeroing the IR baseline and monitoring a second injection affords no significant change in the rate constant, showing that autocatalysis, autoinhibition, and other conversion-dependent effects are not important under these conditions.²¹ All enolizations display substantial isotope effects consistent with rate-limiting proton transfers. The results of the rate studies are summarized in Table 1.

LDA/THF. The metalation of ester **1** shows a first-order dependence on the THF concentration and a half-order dependence on the LDA concentration (eq 2); details were provided previously.⁹ The data are fully consistent with a mechanism involving disolvated monomers (eqs 3 and 4).

Rate Equation:

$$-d[\mathbf{1}]/dt = k'[\text{LDA}]^{1/2}[\text{THF}][\mathbf{1}] \quad (2)$$

Monomer-Based Pathway:



LDA/HMPA/THF. LDA-mediated metalations of **1** in HMPA/THF are consistent with the idealized rate law illustrated in eq 5 and the two mechanisms depicted in eqs 6–9. Due to

(18) Under these conditions, the enolate exists partially as a mixed dimer with LDA. Galiano-Roth, A. S.; Kim, Y.-J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053. Also, see ref 11.

(19) ASI Applied Systems, Millersville, MD 21108.

(20) For leading references to detectable organolithium–substrate pre-complexation, see: Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1. For theoretical studies of substrate precomplexation, see: Bachrach, S. M.; Ritchie, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 3134 and references therein. For a general discussion of ketone–lithium complexation and related ketone–Lewis acid complexation, see: Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 1, p 283.

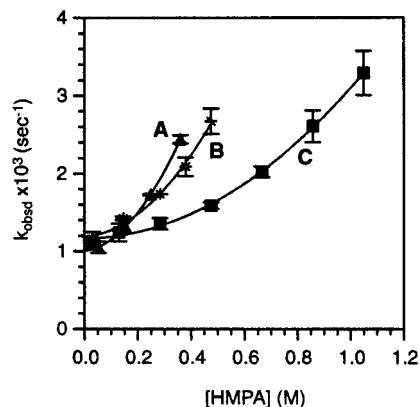


Figure 1. Plot of k_{obsd} vs [HMPA] in hexane cosolvent for the enolization of cyclohexanecarboxylic acid *tert*-butyl ester-*d*₁ (**1-d**₁, 0.004 M) by LDA (0.10 M) at -35 ± 0.5 °C. Curve A: THF (0.20 M) in cyclopentane cosolvent. Curve B: THF (2.0 M) in hexane cosolvent. Curve C: THF (9.8 M) in hexane cosolvent. The curves depict the results of unweighted least-squares fits to $k_{\text{obsd}} = k[\text{HMPA}]^n + k'$. The values of n are 1.82 ± 0.08, 1.88 ± 0.30, and 1.97 ± 0.09 for curves A, B, and C, respectively (Table 1).

the somewhat higher rates and limited solubility of HMPA under some conditions, the enolizations were more easily monitored using **1-d**₁ at -35 °C than using **1** at a substantially lower temperature. The pseudo-first-order rate constants show a second-order HMPA concentration dependence with a substantial nonzero intercept (Figure 1), consistent with two competing metalation pathways.

To ascertain whether THF plays a role in either pathway we investigated the rates at three THF concentrations (0.20, 2.0, and 9.8 M) using hexane (or cyclopentane) as a cosolvent. We were particularly concerned that mixed solvates might be intervening. The y-intercepts for curves A, B, and C in Figure 1 (reflecting a putative monomer-based pathway as noted below) are essentially independent of the THF concentration. In contrast, the exponential term (reflecting a putative dimer-based pathway as noted below) is markedly *reduced* at high THF concentrations. We further found that (1) the approximate second-order HMPA dependence is maintained irrespective of the THF concentration, and (2) the THF concentration dependence does *not* follow a normal inverse first-order or second-order inhibition.^{22a} We will argue in the discussion that the inhibition derives from a long-range “medium effect” that may have little to do with lithium ion solvation.

(21) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. Caubere, P. In *Reviews of Heteroatom Chemistry*; MYU: Tokyo, 1991; Vol. 4, pp 78–139.

(22) (a) Fitting the three data sets in Figure 1 to $k_{\text{obsd}} = k' + k''[\text{HMPA}]^2$ affords three values of k'' at the three THF concentrations. A plot of k'' vs [THF] with fitting to $k'' = k'''[\text{THF}]^n$ affords $n = -0.33$. (b) Superposition of the absorbances for precomplex **6** and the resulting enolate causes the time-dependence of the absorbance to be described by $\text{abs}_{\text{total}} = \text{abs}_{\text{O(enolate)}}(1 - e^{-kt}) + \text{abs}_{\text{O(6)}}e^{-kt}$. Rearranging affords $\text{abs}_{\text{total}} = (\text{abs}_{\text{O(6)}} - \text{abs}_{\text{O(enolate)}})e^{-kt} + \text{abs}_{\text{O(enolate)}}$ (i.e., $f(x) = ae^{bx} + c$).

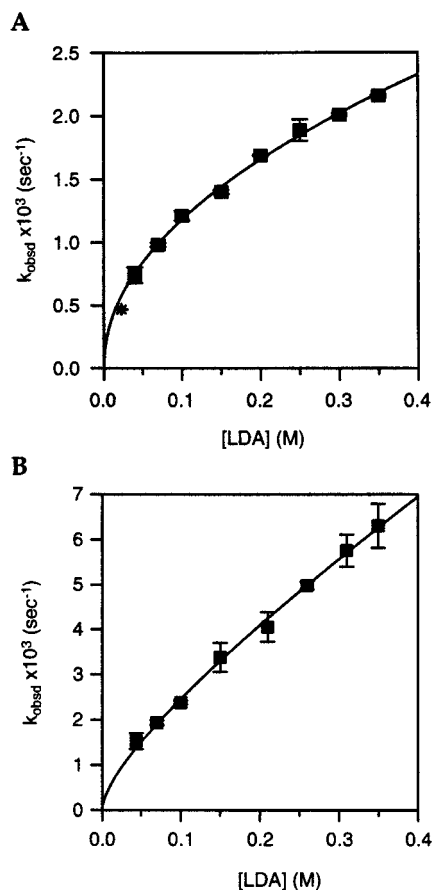


Figure 2. Plot of k_{obsd} vs [LDA] in THF (9.4 M) and hexane cosolvent for the enolization of cyclohexanecarboxylic acid *tert*-butyl ester-*d*₁ (**1-d**₁, ≤ 0.004 M) by LDA at -35 ± 0.5 °C. Curve A: [HMPA] = 0.10 M. The curve depicts the result of an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{LDA}]^n$. Curve B: [HMPA] = 0.80 M. The curve depicts the result of an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{LDA}]^{0.5} + k'[\text{LDA}]^n$ (Table 1). The asterisk (*) was not included in the fit.

Monitoring k_{obsd} vs [LDA] at low free [HMPA] (0.10 M) affords an approximate half-order dependence (Table 1 and Figure 2A), consistent with a spectroscopically invisible dimer–monomer preequilibrium. In conjunction with the substantial nonzero intercept in Figure 1, we conclude that the metalation at low HMPA concentration proceeds predominantly via a transition structure of stoichiometry $[(i\text{-Pr}_2\text{NLi})(\text{HMPA})_2(\mathbf{1})]$ (eqs 6 and 7). (The absence of a coordinated THF is addressed in the discussion.) Monitoring k_{obsd} vs [LDA] at high free [HMPA] (0.80 M) and fitting the data to the simple expression $k_{\text{obsd}} = k'[\text{LDA}]^n$ affords an intermediate fractional order ($n = 0.74 \pm 0.03$), suggesting a superposition of the half-order dependence described above and an emerging higher-order dependence at high [LDA]. Fitting the data to the more appropriate two-term expression $k_{\text{obsd}} = k'[\text{LDA}]^{1/2} + k''[\text{LDA}]^n$ affords $n = 0.92 \pm 0.04$ (Figure 2B). We conclude that the metalation pathway emerging at high [HMPA] proceeds via a transition structure of stoichiometry $[(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_4(\mathbf{1})]$ (eqs 8 and 9).

Rate Equation:

$$-d[\mathbf{1}]/dt = k'[\text{LDA}]^{1/2}[\mathbf{1}] + k''[\text{LDA}][\text{HMPA}]^2[\mathbf{1}] \quad (5)$$

Monomer-Based Pathway:

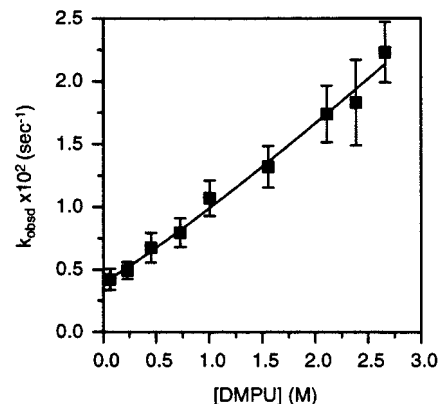
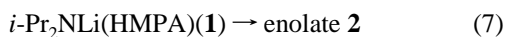
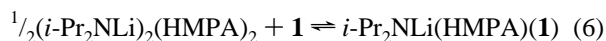
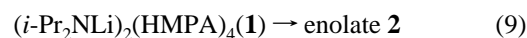
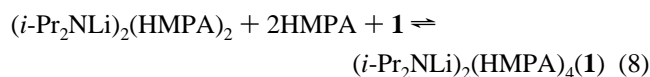


Figure 3. Plot of k_{obsd} vs [DMPU] in THF (8.2 M) and hexane cosolvent for the enolization of cyclohexanecarboxylic acid *tert*-butyl ester (**1**, 0.004 M) by LDA (0.10 M) at -53 ± 0.5 °C. The curve depicts the result of an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{DMPU}]^n + k'$ (Table 1).

Dimer-Based Pathway:

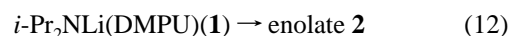
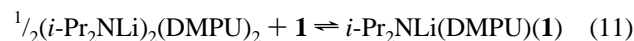


LDA/DMPU/THF. LDA-mediated metalations of **1** in DMPU/THF follow the idealized rate law in eq 10 consistent with two mechanisms depicted in eqs 11–14. The substantial nonzero intercept and linear dependence on [DMPU] (Figure 3) attests to concurrent [DMPU]-independent and [DMPU]-dependent pathways. Half-order LDA concentration dependencies at both low and high [DMPU] (Figure 4, Table 1) indicate that both pathways involve monomeric LDA fragments (eqs 11–14). The metalation rates show no measurable THF dependence, suggesting the absence of a coordinated THF on dimer **3d** and, in contrast to metalations in HMPA/THF, inconsequential cosolvent dependencies.

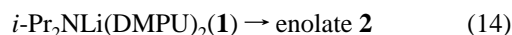
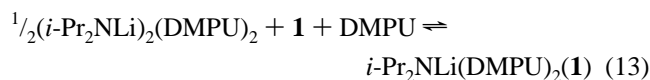
Rate Equation:

$$-d[\mathbf{1}]/dt = k'[\text{LDA}]^{1/2}[\mathbf{1}] + k''[\text{LDA}]^{1/2}[\text{DMPU}][\mathbf{1}] \quad (10)$$

Monomer-Based Pathway I:



Monomer-Based Pathway II:



LDA/*t*-BuOMe. Investigations of LDA-mediated enolizations in *t*-BuOMe and related poorly coordinating solvents are

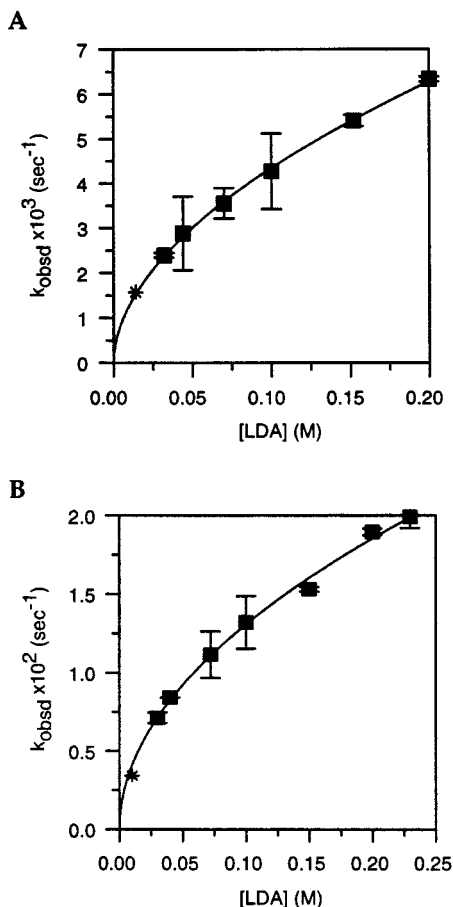
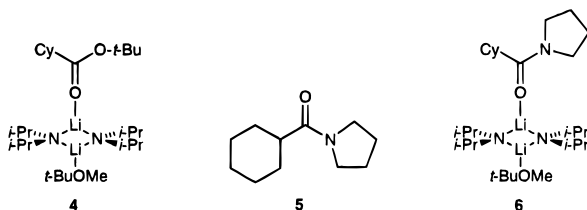


Figure 4. Plots of k_{obsd} versus [LDA] in THF (8.2 M) and hexane cosolvent for the enolization of cyclohexanecarboxylic acid *tert*-butyl ester (**1**, ≤ 0.004 M) at -53 ± 0.5 °C with (A) 0.066 M DMPU and (B) 1.56 M DMPU. The curves depict the results of unweighted least-squares fits to $k_{\text{obsd}} = k[\text{LDA}]^n$ (Table 1). The asterisks (*) were not included in the fits.

complicated due to appreciable (but not quantitative) substrate precomplexation; the IR spectra of solutions containing LDA (0.1 M) and ester **1** (0.004 M) show absorbances corresponding to free and LDA-bound ester (**4**) at 1729 and 1703 cm^{-1} , respectively. Rather than deconvoluting such a complex case, we investigated the more strongly complexing carboxamide **5**. The IR spectra of solutions containing LDA (0.1 M) and **5** (0.004 M) show an absorbance corresponding to LDA-bound carboxamide (**6**; 1636 cm^{-1}) to the exclusion of free carboxamide **5** (1654 cm^{-1}). (The structure of **6** has been confirmed by ⁶Li and ¹⁵N NMR spectroscopy.)¹¹ Although the IR absorbances of precomplex **6** and the resulting enolate superimpose, they could be readily deconvoluted.^{22b}



IR spectroscopic analysis at 0 °C reveals that LDA complex **6** undergoes a first-order decay that is independent of both the [LDA] and [t-BuOMe] (Figures 5 and 6). The idealized rate

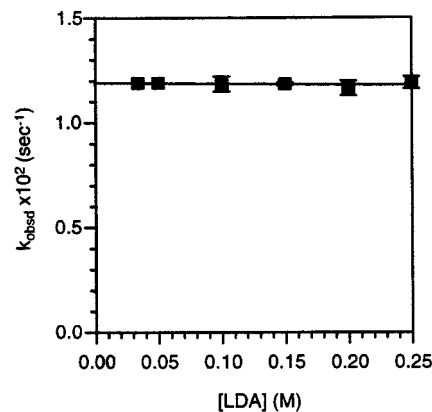


Figure 5. Plot of k_{obsd} vs [LDA] for the enolization of carboxamide **5** (0.003 M) by LDA in neat *t*-BuOMe at 0 °C. The curve depicts the result of an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{LDA}] + k'$ (Table 1).

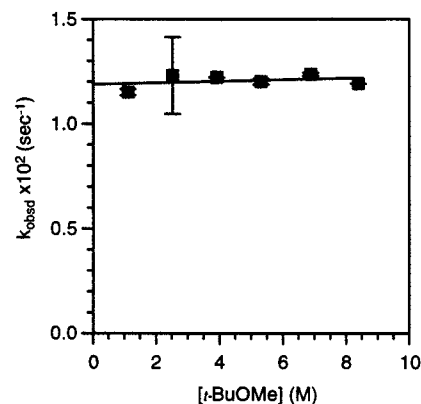
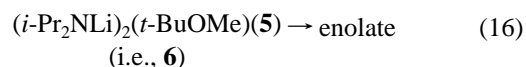


Figure 6. Plot of k_{obsd} vs [t-BuOMe] in hexane cosolvent for the enolization of carboxamide **5** (0.0025 M) by LDA (0.050 M) at 0 °C. The curve depicts the result of an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{t-BuOMe}] + k'$ (Table 1).

equation (eq 15) is consistent with a dimer-based pathway (eq 16).

$$-d[\mathbf{6}]/dt = k'[\mathbf{6}] \quad (15)$$

Dimer-Based Pathway:



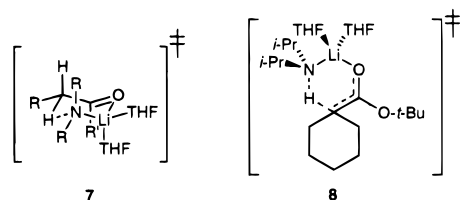
Discussion

The LDA-mediated ester enolizations show two remarkable features. First, the reaction rates are insensitive to a substantial range of solvating conditions (eq 1). Second, each change in solvent has associated with it a fundamental change in mechanism, dispelling any notions that reaction rates correlate with the coordinating power of the solvent or that analogous reaction rates implicate analogous reaction mechanisms.

LDA/THF. In 1976, Ireland depicted LDA/THF-mediated enolizations proceeding via disolvated monomeric transition structures (**7**).²³ While the proposal was based upon little hard evidence and the chairlike structure might be questioned,²⁴ the supposition appears to be correct, at least for the enolization of ester **1**. These rate studies paint a traditional picture of organolithium solvation and aggregation in which enolization

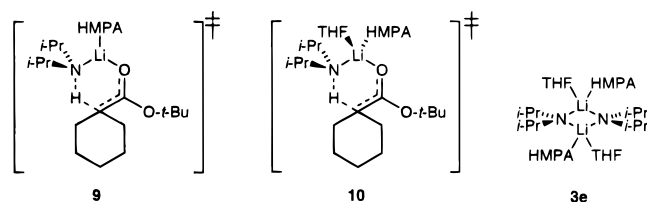
(23) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(24) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 2166.



proceeds via highly solvated, transiently formed monomers (e.g., transition structure such as **8**). However, any complacency imparted by such a “predictable” result is offset by investigations of other solvents.

LDA/HMPA/THF. Metalations in HMPA/THF mixtures appear to proceed via two very different pathways. The dominant metalation pathway at low [HMPA] manifests a zeroth-order in HMPA (the nonzero intercepts in Figure 1) and a fractional (half) order in LDA; a transition structure such as **9** is fully consistent with the data. However, in light of putative



disolvated monomeric transition structure **8** in THF, it seemed quite possible that a mixed solvated transition structure such as **10** might be intervening. We see two scenarios by which the intervention of mixed solvates might receive support and exclude both as follows:

(1) Assuming that the HMPA-solvated LDA dimer is indeed **3c**²⁰ (rather than a tetrasolvated dimer **3e** with two spectroscopically undetected THF ligands), then the intervention of a mixed-solvated monomer [*i*-Pr₂NLi(THF)(HMPA)(**1**)] would require a first-order dependence on the THF concentration. This would be manifested by a linear dependence of the nonzero intercept in Figure 1 on the [THF]. However, the intercept is nearly invariant over a 50-fold range in [THF].

(2) If the HMPA-solvated LDA dimer is **3e** containing additional THF ligands (rather than **3c** as previously assigned),¹⁶ then the zeroth-order dependencies on both [HMPA] and [THF] would be fully consistent with transition structure **10**. However, spectroscopic,²⁵ crystallographic,²⁶ computational,²⁷ calorimetric,²⁸ and kinetic²⁹ studies have shown that LDA and related hindered lithium amide dimers contain *one* ligand per lithium irrespective of the choice of ligand. Even potentially bidentate ligands such as TMEDA and DME fail to force a four-coordinate lithium within the dimer framework.³⁰ It is therefore very unlikely that a bulky, strongly Lewis basic HMPA ligand would allow coordination of additional THF. Of particular importance, the THF inhibition (discussed below) does *not* follow a clean

(25) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751. Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863.

(26) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539.

(27) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 2112.

(28) Prikoszovich, W. (Novartis), personal communication.

(29) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772.

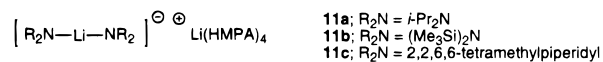
(30) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5573. Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707. Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G.; Schleyer, P. v. R.; Bernstein, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 1339.

inverse order dependence expected for a mechanism requiring a formal THF dissociation.^{23a}

This monomer-based pathway constitutes a rather surprising coincidence of thermochemistry. The substitution of a THF ligand on **3b** by an HMPA ligand to afford dimer **3c** represents a considerable perturbation on the stability of the reactants.^{31,7b} Substitution of the two THF ligands on transition structure **8** by an HMPA ligand to give transition structure **9** is also quite invasive. Nevertheless, in neat THF³² these two effects precisely cancel; the metalation rates in THF and THF with 1.0 equiv of HMPA are indistinguishable.

The lower coordination number of transition structure **9** compared to **8** is interesting. Despite some extensive efforts by Reich and co-workers,^{6,7b,33} many facets of exactly *how* HMPA accelerates reactions (and *whether* it does³³) remain unclear. One might surmise, for example, that HMPA promotes higher per-lithium solvation numbers. In this case, however, *HMPA allows the metalation to proceed via transition structures with lower solvation numbers*. Thus, one might view the highly dipolar HMPA as an adequate substitute for *two* THF ligands, in turn, avoiding a sterically and entropically problematic solvation event.

The dominant metalation pathway at high [HMPA] is exemplified by a second-order HMPA concentration dependence (Figure 1). In conjunction with a first-order dependence of the rates on the LDA concentration and spectroscopic studies revealing dimer **3c**,¹⁶ implicating reaction via tetrasolvated dimers (eqs 8 and 9). However, a tetrasolvated dimer appears to be far too coordinatively saturated to be a plausible reactive form.²⁴ We turn to previous computational^{24,27} and spectroscopic studies supporting triple ions (**11a**) as the reactive species.³¹



We have suggested on several occasions that lithium amide triple ions should be highly reactive in analogy to “ate” complexes of other main group elements.^{34,35} While treatment of LDA with excess HMPA fails to afford detectable concentrations of triple ion **11a**,¹⁶ the corresponding triple ions of LiHMDS³⁶ and LiTMP¹⁶ (**11b** and **11c**, respectively) have been observed. In more recent computational studies of ketone enolizations we explored the efficacy of aggregate-based metalations of ketones and *N,N*-dimethylhydrazones.²⁴ While transition structures based upon open dimers were suggested to be

(31) HMPA has been estimated to bind 300 times more strongly than THF in one case. Reich, H. J.; Kulicke, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 273.

(32) Since the metalations depend linearly upon the THF concentration in the absence of HMPA, it is only in neat THF that adding 1.0 equiv of HMPA does not measurably change the rate.

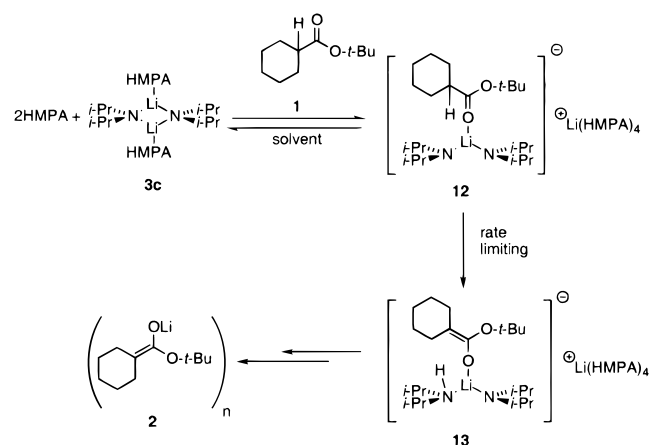
(33) HMPA can decelerate organolithium reactions. Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1989**, *111*, 3444. Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101. Reich, H. J.; Dykstra, R. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1469. Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14.

(34) Richey, H. G., Jr.; Farkas, J., Jr. *Organometallics* **1990**, *9*, 1778. Fabicon, R. M.; Parvez, M.; Richey, H. G., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 1412. Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233. Corriu, *Pure Appl. Chem.* **1988**, *60*, 99. Pelter, A.; Smith, K. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Vol 3, Chapter 14. Lipshutz, B. H. *Synthesis* **1987**, 325.

(35) The mixed triple ions analogous to **13** have also been investigated computationally and display limited Lewis acidity on the internal lithium. For leading references to lithium amide triple ions, see: Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9198.

(36) Romesberg, F. E.; Bernstein, M. P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 3475.

Scheme 1



favorable, there was no evidence that *tetrasolvated* open dimers are viable intermediates. In contrast, metalations via triple ions such as **11a**, while pressing the limits of the semiempirical methods, were found to be credible (as opposed to incredible).

Therefore, we propose the mechanism for LDA/HMPA-mediated enolization via triple ions illustrated in Scheme 1. Although computational studies suggest that the internal lithium of the anionic fragment of **12** is not very Lewis acidic,^{24,27,34} we have taken the liberty of depicting the ester as precomplexed to this site nonetheless.

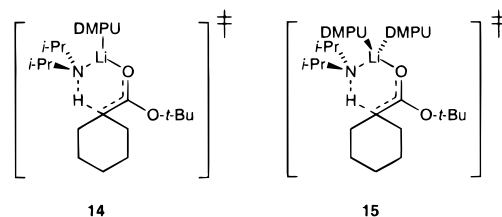
Since we have concluded that there are no coordinated THF ligands on dimer **3c**, then the origin of the THF-mediated inhibition of the putative triple ion-based metalation remains unexplained. One might argue that an estimated 5-fold inhibition is insignificant; however, it is not small when compared with the solvation effects illustrated in eq 1. Exactly what is this abstruse “medium” effect?³⁷ In the most general terms, it would seem that the polar medium must stabilize the ground state more than the transition state.³⁸ If we focus only on the *organolithium* species, it is not at all obvious that dimer **3c** in the ground state would be more stabilized by a polar medium than a transition structure derived from triple ion **12** (or any other transition structure for that matter). In fact, both rate and spectroscopic studies suggest that triple ions might be stabilized by a secondary solvation shell composed of THF ligands.³⁷ An explanation may reside in the exceptional dipolar character that makes HMPA so Lewis basic. The poor solubility of HMPA in hydrocarbons attests to a relative instability in nonpolar media. To whatever extent a polar medium stabilizes the dipole, the Lewis acidity and exothermicity of the complexation will be attenuated. This leads to a highly speculative, but striking conclusion: *the inhibition of the metalation in eqs 8 and 9 may arise from solvent–solvent interactions fully removed from the lithium ions.* Although Reichardt’s detailed survey of solvation effects on reaction rates includes seemingly analogous observations,³⁹ it is a sobering conclusion nonetheless.

LDA/DMPU/THF. The enolization of ester **1** by LDA in DMPU/THF solution proceeds via parallel pathways as evidenced by the linear dependence on [DMPU] with a substantial nonzero intercept. In conjunction with the half-order dependence on the LDA concentration at both low and high [DMPU], the solvent dependence implicates transition structures based upon mono- and disolvated monomers (**14** and **15**, respectively).

(37) Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524. Lucht, B. L.; Collum, D. B., unpublished.

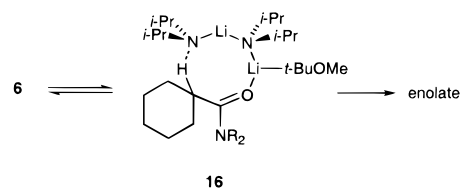
(38) While it is possible that both are destabilized, this seems unlikely.

(39) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: New York, 1988; Chapter 5.



It is often suggested that DMPU is a noncarcinogenic substitute for HMPA.⁷ Indeed, we see parallels in that both HMPA and DMPU promote metalations via monosolvated monomers whereas THF does not. In contrast, however, HMPA promotes reaction via putative triple ions (or at least some form of tetrasolvated dimers) while DMPU does not. In fact, we are inclined to describe DMPU as a strongly coordinating analogue of THF. It is also interesting in light of the results for HMPA that both DMPU-mediated metalation pathways are insensitive to the THF concentration.

LDA/*t*-BuOMe. Traditional reasoning would argue that enolizations in *t*-BuOMe, a poorly coordinating ligand,²⁵ should be very slow. To the contrary, the metalation rates are comparable to the other solvents studied (eq 1). IR spectroscopic analysis reveals measurable (but not quantitative) concentrations of dimer precomplex **4**. Rather than attempting to deconvolute this relatively complex case, we turned to carboxamide **5** that affords precomplex **6** quantitatively. Zeroth-order dependencies on both [LDA] (*free, uncomplexed LDA*) and [*t*-BuOMe] (eq 15) implicate an enolization via monosolvated dimers (eq 16). Therefore, the enolization originating from **6** is formally⁴⁰ a unimolecular process. We depict the metalation as proceeding via open dimer **16**. Lithium amide open dimers were first



invoked in 1988 by Schlosser and co-workers in the context of dehydrohalogenations by lithium diisopropylamide (LDA).⁴¹ Subsequent computational, spectroscopic, crystallographic, and kinetic studies have shown open dimers to be observable species and potentially important reactive intermediates.^{42,43} The appeal of this model is that open dimers allow for substrate precomplexation and liberation of a potentially basic lone pair on nitrogen without a complete loss of aggregation energy. A tendency of open dimers to emerge as key intermediates in poorly coordinating solvents⁴³ logically stems from the lower per-lithium solvation number.

It is instructive to briefly consider two consequences of quantitative substrate precomplexation:

(1) The Lewis acidity of the lithium cation is likely to be highly stabilizing at the transition state.⁴⁴ However, *any*

(40) Of course, all of the metalations described herein involve a potentially large number of steps leading from the reactants to the rate-limiting transition structures. However, they are all kinetically invisible.

(41) Matsuda, H.; Hamatani, T.; Matsubara, S.; Schlosser, M. *Tetrahedron* **1988**, *44*, 2865.

(42) For extensive leading references to discussions of lithium amide open dimers, see: Remenar, J. F.; Lucht, B. L.; Kruglyak, D.; Collum, D. B. *J. Org. Chem.* **1997**, *62*, 5748. For more recent examples, see: Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 4081.

(43) Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 789.

(44) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560.

stabilization of the ground state will tend to offset stabilization at the transition state. A strongly complexing substrate could, at least in principle, retard an organolithium reaction. Moreover, if precomplexing the substrate displaces a ligand that is necessary for adequate stabilization of the rate-limiting transition structure, then one bimolecular step replaces another with no obvious advantage. Therefore, **6** does not offer unusual advantages due to atomic proximities; even transiently formed precomplexes offer the requisite atomic proximities. What complex **6** does offer is a close *stoichiometric* relationship between the ground state and the rate-limiting transition state.

(2) Increasing the ligand or LDA concentration does not increase the metalation rate. While the independence of the metalation on the LDA concentration may be initially nonintuitive, it is a direct result of precomplexation. If, hypothetically, the metalation starting from precomplex **6** had proceeded via a monomer, then the excess LDA would *inhibit* the metalation ($\text{rate} \propto 1/[\text{LDA}]^{1/2}$). Such inhibitions were observed for *s*-BuLi/TMEDA-mediated orthometalations by Beak and Smith.⁴⁵ It is important to recognize that organolithium reactions are not necessarily facilitated by more organolithium reagent.

Summary and Conclusions

It is no longer surprising to us when detailed investigations of organolithium structures and reactivities afford unanticipated results; the complex interplay between solvation and aggregation naturally renders simple, straightforward results improbable. Nevertheless, the investigations of LDA-mediated ester enolization in four different solvent combinations (*t*-BuOMe, THF, HMPA/THF, and DMPU/THF) afforded an unusual number of results that do not follow conventional wisdom. These are as follows:

(1) The enolization rates are essentially independent of solvent. While one might quibble over whether a factor of 5 is truly “solvent-independent” as the title of the paper suggests, a 5-fold change is small when a factor of 10^3 would not have been surprising.

(2) LDA/THF-mediated enolizations most closely follow conventional wisdom by proceeding via disolvated monomers.

(3) Addition of 1.0 equiv of HMPA to LDA in THF causes *no measurable change in rate despite a pronounced change in mechanism*. Addition of 10 equiv of HMPA affords only a 3-fold overall rate increase compared to neat solutions containing 1.0 equiv of HMPA despite the emergence of a new pathway that is *second-order in HMPA*. It is noteworthy that such a potentially important, highly [HMPA]-dependent path is readily obscured by a seemingly insignificant “ k_{rel} ”. This highly [HMPA]-dependent pathway via putative triple ions, the most efficient metalation of those studied, is an *aggregate-based pathway*. We suspect that many of the reactions that are too fast to study given the technology currently available to us proceed via aggregates.

(4) DMPU exhibits behavior similar to both THF and HMPA. However, the tendency to mediate only monomer-based metalations suggests that the analogy to THF is stronger.

(5) The poorly coordinating *t*-BuOMe allows for efficient metalations by promoting the *dimer*-based pathway. Support for open dimer intermediates seems compelling to us. While efficient metalations in poorly coordinating solvents may be surprising, one only need to note the analogy with the transition elements in which ligand lability is often critical. The flawed

notion that only strongly coordinating ligands promote high reactivity appears to be uniquely pervasive in the alkali metal literature.

Overall, the solvent-independent rates obscure a remarkable mechanistic landscape: four solvents afford four mechanistic scenarios. In a sense, rate studies are key to developing a mechanistic “basis set”: a set of principles from which we can describe all organolithium reactions. Do these mechanisms make a difference if the rates do not change? Absolutely! It is certain that the regio-, stereo-, and chemoselectivities of LDA-mediated metalations will depend critically upon the mechanism regardless of the rates. However, we must also include a disclaimer: for other reactions of LDA, even other LDA-mediated enolizations, the relative importance of these pathways may differ markedly and other undocumented mechanisms may be operative. Most importantly of all, this investigation reinforces a fundamental principle: “*isolated yields*” and “*relative rate constants*” cannot be used to probe organolithium reaction mechanisms.¹³

Experimental Section

Reagents and Solvents. THF, toluene, and hexane were distilled from blue or purple solutions containing sodium benzophenone ketyl. The hexane and toluene stills contained 1% tetraglyme to dissolve the ketyl. HMPA and DMPU were freshly distilled under vacuum from CaH₂. The LDA was prepared from *n*-BuLi⁴⁶ and purified by recrystallization from hexane as described previously.¹⁷ Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques. Solutions of *n*-BuLi and LDA were titrated using a literature method.⁴⁷

IR Spectroscopic Analyses. Spectra were recorded using a ReactIR 1000 from ASI Applied Systems fitted with a 30-bounce, silicon-tipped (SiComp) probe optimized for sensitivity.¹⁹ The spectra were acquired in 16 scans at a gain of one and a resolution of eight using system ReactIR 2.1 software. A representative reaction was carried out as follows: The IR probe was inserted through a nylon adapter and FETFE O-ring seal (Ace Glass) into an oven-dried, cylindrical flask fitted with a magnetic stir bar and T-joint. The T-joint was capped by a septum for injections and an argon line. Following evacuation under full vacuum and flushing with argon, the flask was charged with a solution of LDA (160 mg, 1.5 mmol) in THF (7.5 mL) and hexane (2.5 mL) and cooled in a Neslab model ULT80 cooling bath to an internal reaction temperature of -35.0 ± 0.5 °C as determined with a thermocouple. After addition of HMPA (3.0 mmol in 5.0 mL of THF), further thermal equilibration, and recording of a background spectrum, ester **1-d**₁ (12 μ L, 0.06 mmol) was added neat with stirring. IR spectra were recorded over the course of the reaction. To account for mixing and temperature equilibration, spectra recorded in the first 3.0 min were discarded. All reactions were monitored to >5 half-lives. Data manipulation and statistical analyses were carried out using the system 2.1 ReactIR software in conjunction with the nonlinear least-squares fitting protocols in the Scientist package provided by Micromath.

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Supporting Information Available: Rate data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(47) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.