Lithium Diisopropylamide-Mediated Reactions of Imines, Unsaturated Esters, Epoxides, and Aryl Carbamates: Influence of Hexamethylphosphoramide and Ethereal Cosolvents on Reaction Mechanisms

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Abstract: Several reactions mediated by lithium diisopropylamide (LDA) with added hexamethylphosphoramide (HMPA) are described. The *N*-isopropylimine of cyclohexanone lithiates via an ensemble of monomer-based pathways. Conjugate addition of LDA/HMPA to an unsaturated ester proceeds via di- and tetra-HMPA-solvated dimers. Deprotonation of norbornene epoxide by LDA/HMPA proceeds via an intermediate metalated epoxide as a mixed dimer with LDA. Ortholithiation of an aryl carbamate proceeds via a mono-HMPA-solvated monomer-based pathway. Dependencies on THF and other ethereal cosolvents suggest that secondary-shell solvation effects are important in some instances. The origins of the inordinate mechanistic complexity are discussed.

Introduction

Hexamethylphosphoramide (HMPA) is one of the most prominent additives used to influence the yields, rates, and selectivities of organolithium reactions.[1] A preponderance of what is known about solvation of lithium ions by HMPA derives from the studies of Reich and co-workers.[2] Their spectroscopic analyses of lithium salts in the limit of slow exchange of free and lithium-ion-coordinated HMPA offer intimate details of HMPA-mediated deaggregation and ionization. Despite the sound understanding of how HMPA influences the structures of lithium salts, the oft-cited influence of HMPA on reactivity is not well understood and leaves many questions unanswered.[3] Does the marked tendency of HMPA to serially solvate organolithiums foreshadow a similar structural diversity in the rate-limiting transition structures? Do dramatic accelerations result from the capacity of HMPA to promote high solvation numbers and low aggregation numbers in the rate-limiting

transition structures? Why does HMPA sometimes fail to elicit high reactivities?[2]

We have begun addressing some of these questions in the context of lithium diisopropylamide (LDA),[4–9] a prevalent base in organic synthesis.[10] We describe herein investigations of four reactions mediated by LDA/HMPA—lithiation of imine **1** (eq 1),[7f,8b,11,12] 1,4-addition to unsaturated ester **3** (eq 2),[13,14] opening

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(13) (a) Herrman, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433. (b) Uyehara, T.; Asao, N.; Yamamoto, Y. *J. Chem. Soc. Chem. Commun.* **1987**, 1410. (c) Bellasoued, M.; Ennigrou, R.; Gaudemar, M. *J. Organomet. Chem.* **1988**, *338*, 149.

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of epoxide **5** (eq 3),[10,15−17] and ortholithiation-Fries rearrangement of carbamate **7** (eq 4).[18] All have found niches in organic synthesis, and all but the 1,4-addition have proved useful in studies of LDA structure−reactivity relationships.[19] The results support an emerging picture of unusual mechanistic diversity imparted by HMPA;[4,5] they are summarized at the start of the discussion for the benefit of the nonspecialist.


(1)

(2)

(3)

(4)
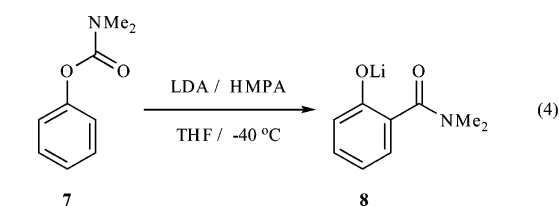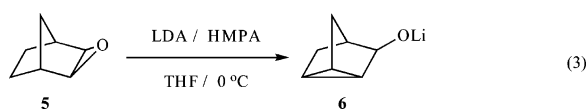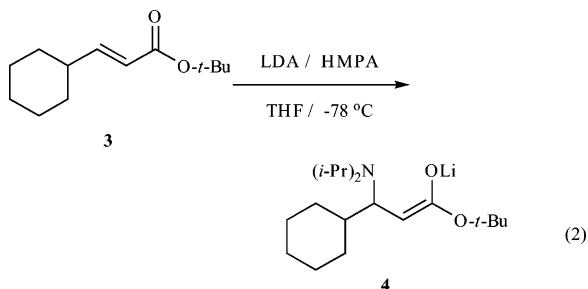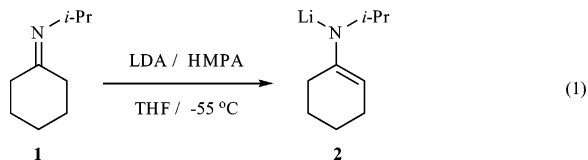
Background. Any examination of structure−reactivity relationships must be prefaced by a clear understanding of structure.[19,20] LDA offers an optimal template in that it forms exclusively disolvated dimer **9** over all THF concentrations and

disolvated dimer **10** at ≥1.0 equiv of HMPA.[6a,21] (The absence of deaggregation is notable given that HMPA usually deaggregates organolithiums.[2])
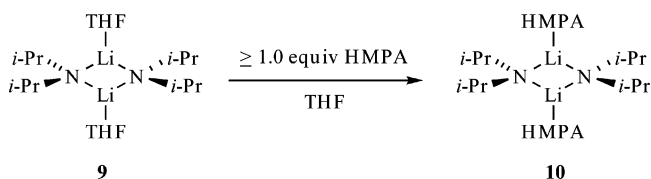
A brief survey of previous rate studies of LDA/HMPA-mediated reactions is instructive. LDA/HMPA elicits considerable mechanistic variability.[4,5] For example, enolizations of a hindered ester by LDA/THF and LDA/HMPA/THF proceed at similar rates by distinctly different mechanisms.[4b] The sole detectable pathway in neat THF involves disolvated monomers (**11**), whereas HMPA causes enolization to proceed via monosolvated monomers (**12**) and putative triple ions (**13**). (Three-dimensional depictions of transition structures throughout this paper derive from computational studies,[7,8] analogies with observable structural forms,[4,6,7f] and conjecture.)
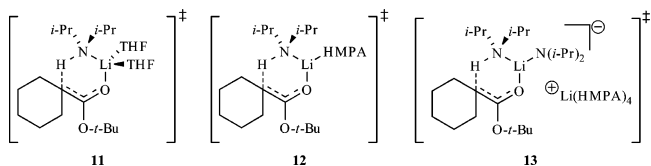
Dehydrobrominations of alkyl bromides proceed by mono-, di-, and trisolvated monomers (**14−19**) as well as triple ions (**20**).[5] The highly variable solvation numbers are unusual when compared with LDA-mediated reactions in standard ethereal solvents.[19]
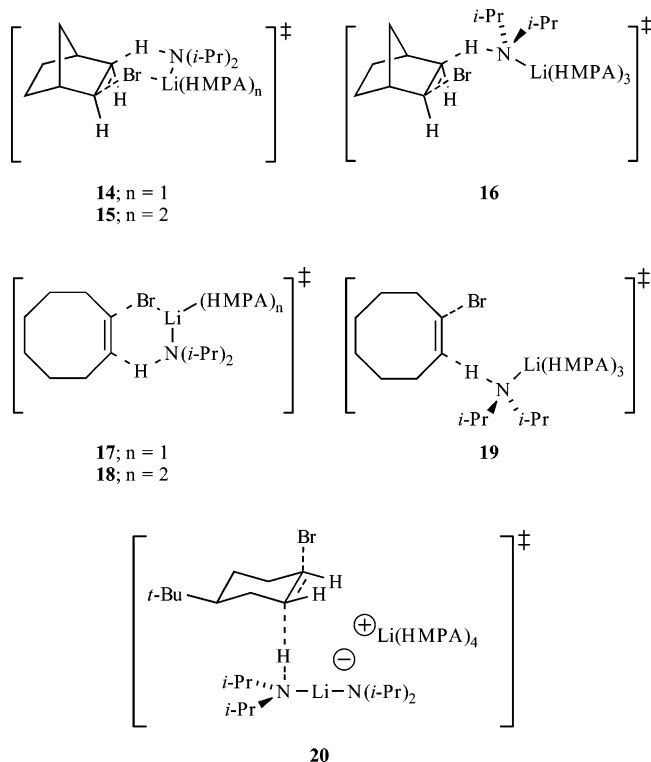
A seemingly minor point has baffled us. LDA/HMPA-mediated dehydrobrominations are insensitive to the proportions of THF in THF/hexane cosolvent. Conversely, enolization proceeding via putative triple ion **13** is *inhibited* by THF.[4b] A model based on the solvation of free (uncoordinated) HMPA by THF[22] with an affiliated net stabilization of the ground state was postulated,[4b] but this explanation was subsequently dismissed as incorrect or at least inadequate.[5] The dual role of ethers as both ligands and media continues to be vexing.[23,24]
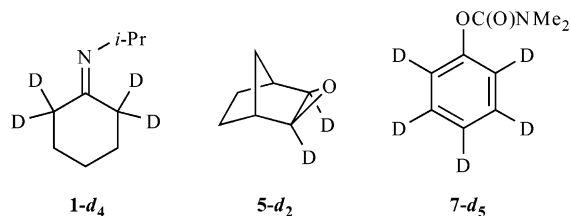
Results

General Methods. Reactions carried out under standard conditions using 1.0−4.0 equiv of [⁶Li,¹⁵N]LDA[6a] confirm that

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14; n = 1
15; n = 2

16

17; n = 1
18; n = 2

19

20

compd	δ [6]Li (mult, J_{LiN})	δ [15]N (mult, J_{LiN})
21	0.72 (s)	—
27a	0.88 (d, 5.2)	74.8 (q, 5.4)
27b	1.03 (d, 5.2)	76.7 (q, 5.2)
38	0.88 (d, 5.0)	76.0 (q, 5.0)
39	0.91 (d, 5.1)	75.0 (q, 5.0)
43	0.78 (d, 5.2)	76.4 (q, 5.2)

[a] Spectra were recorded in THF solutions of 0.10 M [[6]Li,^{15}N]LDA total lithium titer, 0.40 M total HMPA (bound and unbound), and 0.025 M substrate. Coupling constants are reported in hertz. Multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet, q = quintet. The chemical shifts are reported relative to 0.30 M [6]LiCl/MeOH at −90 °C (0.0 ppm) and neat Me$_2$NEt at −90 °C (25.7 ppm). Spectra also contained [[6]Li,^{15}N]LDA dimer **10**: [6]Li NMR δ 1.64 (t, 4.9); ^{15}N NMR δ 73.3 (q, 4.8).

Table 2. Rate data for the LDA/THF-mediated lithiations of **1** and **7** in the absence of HMPA reported previously are also included in Table 2 for comparison.[8b,26] Rate studies of LDA/THF-based lithiation of **5**[9a] in THF with no added HMPA have not been reported previously and are described below.

Imine Lithiations. Previous [6]Li and ^{15}N NMR spectroscopic studies indicate that lithiated imine **2** is a monomer in THF.[30] Analogous studies in which imine **1** is metalated by a modest excess of [[6]Li,^{15}N]LDA (2.0–4.0 equiv) in the presence of 0.40 M HMPA reveal LDA dimer **10** along with a species displaying a singlet consistent with (but not rigorously assigned to) monomer **21**. Mixed aggregates are not formed.

21

a number of mixed aggregates are formed, as described in the context of each case study.[25] [6]Li and ^{15}N NMR spectroscopic data are summarized in Table 1. To avoid autoinhibition often caused by mixed aggregation[4c,26] during the rate studies, pseudo-first-order conditions were established by using substrates at low concentrations (0.004 M). LDA, HMPA, and THF were maintained at high, yet adjustable, concentrations using inert cosolvents.[27] The loss of **5** was monitored using gas chromatography relative to an internal dodecane standard.[9] The loss of **1**, **3**, and **7** was monitored using in situ IR spectroscopy.[4,28] All follow first-order decays, affording pseudo-first-order rate constants (k_{obsd}) that are independent of the initial concentrations of substrate (±10%).[29] Isotope effects (k_H/k_D) determined using deuterated analogues **1**-d_4 and **7**-d_5 (Table 2) are consistent with rate-limiting proton transfers for **1** and **7**. The isotope effect obtained with epoxide **5**-d_2 is unusually small, emblematic of a proton-transfer that is *not* rate limiting.

LDA/THF-mediated metalations of imine **1** proceed via mono-solvated monomer (**22**).[8b,11] Conversely, the LDA/HMPA/THF-mediated metalation of imine **1** displays a stifling complexity. A plot of k_{obsd} versus HMPA concentration shows a first-order HMPA dependence in 2.0 M THF and a second-order HMPA dependence in 8.0 M THF (curves A and B, respectively, in Figure 1). The HMPA concentration-independent pathway—the nonzero intercepts in curves A and B—is *independent* of the THF concentration. The influence of THF can be illustrated from a different perspective in which the HMPA concentration is held constant and the THF concentration is varied (Figure 2). At low HMPA concentration, the rates are independent of the THF concentration (Figure 2, curve A),

1-d_4

5-d_2

7-d_5

Selected rate data are depicted in Figures 1−6, and the reaction orders constituting the rate laws are summarized in

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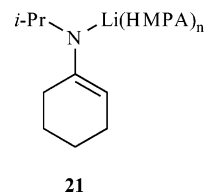
(24) Arene−lithium interactions have been discussed extensively by Dougherty and coworkers. Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303.

(25) For spectroscopic studies of LDA mixed aggregates in HMPA/THF mixtures, see refs 4c and 6b. For analogous computational studies, see ref 7e.

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(27) The concentration of LDA, although expressed as molarity, refers to the concentration of the monomer unit (normality). The concentrations of ethereal solvent and HMPA are expressed as total concentration of free (uncoordinated) ligand.

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Table 2. Summary of Rate Studies for the LDA-Mediated Reactions (eqs 1−4)

substrate	T (°C)	solvent	THF order	HMPA order	LDA order	k_H/k_D
1	20	THF	0	−	0.54 ± 0.02^a	10 ± 1^b
1	−55	THF/HMPA	2.4 ± 0.2	0	0.60 ± 0.03^c	−
			0	2.0 ± 0.3^d	0.54 ± 0.07^e	7.8 ± 0.1^e
3	−78	THF/HMPA	2.0 ± 0.3	0	1.0 ± 0.1^f	−
			$-^g$	1.87 ± 0.06^h	1.10 ± 0.06^i	−
5	20	THF	0	−	0.73 ± 0.04^j	3.6 ± 0.4^k
5	0	THF/HMPA	0	0	1.0 ± 0.1^a	1.3 ± 0.1^f
				-0.6 ± 0.2		
7	−40	THF	0	−	0.49 ± 0.01	16^k
7	−40	THF/HMPA	0	0	0.51 ± 0.04	14.2 ± 0.2^l

^{a} [LDA] = 0.10 M in 10.0 M THF/hexane. ^{b} See ref 8b. ^{c} [HMPA] = 0.10 M in 8.0 M THF/hexane. ^{d} [LDA] = 0.10 M; [THF] = 8.0 M in hexane cosolvent. ^{e} [HMPA] = 0.40 M in 8.0 M THF/hexane. ^{f} [HMPA] = 0.40 M in 10.0 M THF/hexane. ^{g} The order in THF could not be measured at high HMPA concentration due to insolubility. ^{h} [LDA] = 0.10 M; [THF] = 10.0 M in hexane cosolvent. ^{i} [HMPA] = 0.10 M in 10.0 M THF/hexane. ^{j} [LDA] = 0.10 M; [THF] = 10.0 M in hexane cosolvent. ^{k} See ref 43. ^{l} [LDA] = 0.10 M; [HMPA] = 0.50 M in 10.0 M THF/hexane.

Table 3. Relative Rate Constants for Reactions of LDA^a

substrate	T (°C)	k_{HMPA}:k_{THF}
1	−55	3:1
3	−78	4:1[25]
5	0	1:6
7	−40	1.5:1

^{a} LDA is 0.10 M in either 10.0 M THF/hexane or 0.40 M HMPA and 10.0 M THF/hexane.
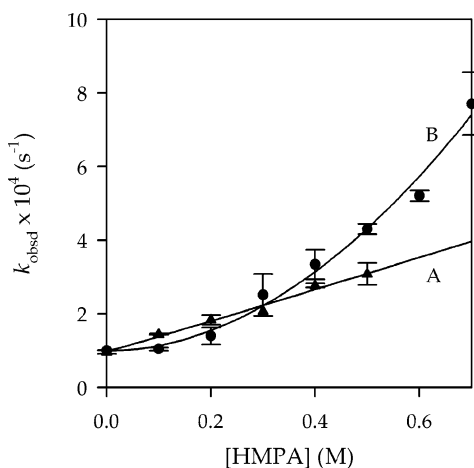

Figure 1. Plot of k_{obsd} vs [HMPA] for the lithiation of imine **1** (0.005 M) by 0.10 M LDA in THF/hexane at −55 °C: (A) 2.0 M THF; (B) 8.0 M THF. Curve A derives from a linear least-squares fit. Curve B depicts the result of an unweighted least-squares fit to $k_{obsd} = k[\text{HMPA}]^n + k'$ ($k = (1.3 \pm 0.1) \times 10^{-3}$; $k' = (1.0 \pm 0.2) \times 10^{-4}$; $n = 2.0 \pm 0.3$).

whereas at high HMPA concentration, an *exponential* (2.4 ± 0.4 order) dependence on the THF concentration is evident (Figure 2, curve B).

The solvent dependencies are consistent with three independent terms in the idealized[31] partial rate law described by eq 5. We wondered whether the THF dependence derives from a sterically sensitive, primary-shell solvation by THF or a sterically insensitive secondary-shell effect.[4b,23,24] Compelling evidence of secondary-shell solvation was uncovered in a plot of k_{obsd} versus THF concentration using the weakly coordinating 2,5-dimethyltetrahydrofuran (2,5-Me$_2$THF) as cosolvent (Figure 2, curve C). When the polarity of the medium is held constant using a poorly coordinating cosolvent,[32] the apparent second-

(31) We define the idealized rate law as that obtained by rounding the observed reaction orders to the nearest rational order.
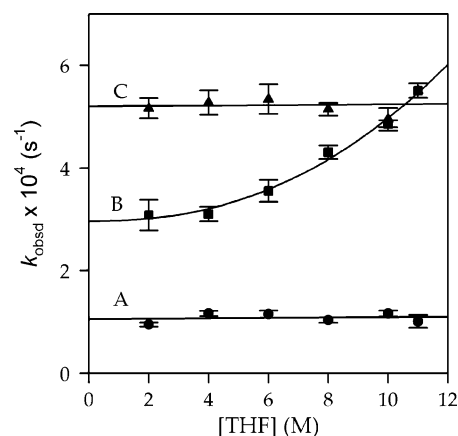

Figure 2. Plot of k_{obsd} vs [THF] for the lithiation of imine **1** (0.005 M) by 0.10 M LDA in hexane with HMPA at −55 °C: (A) 0.10 M free HMPA in cyclopentane; (B) 0.50 M free HMPA in cyclopentane; (C) 0.50 M free HMPA in 2,5-Me$_2$THF. Curves A and C derive from linear least-squares fits. Curve B depicts the result of an unweighted least-squares fit to $k_{obsd} = k[\text{THF}]^n + k'$ ($k = (7.6 \pm 0.8) \times 10^{-7}$; $k' = (3.0 \pm 0.1) \times 10^{-4}$; $n = 2.4 \pm 0.4$).

order THF dependence disappears.[33] Thus, although the rate law is formally described by eq 5, we choose to cull out the apparent secondary-shell solvation effects and provide the simplified version described by eq 6.

$$k_{obsd} = k_3 \pm k_4[\text{HMPA}] \pm k_5[\text{HMPA}]^2[\text{THF}]^2 \quad (5)$$

$$k_{obsd} = k_3 + k_4[\text{HMPA}] + k_5[\text{HMPA}]^2 \quad (6)$$

Plots of k_{obsd} versus LDA concentration reveal half-order LDA dependencies at both low and high HMPA concentrations consistent with monomer-based metalations (Figure 3). The fractional LDA orders in conjunction with HMPA and ethereal cosolvent dependencies are consistent with the idealized rate law[31] in eq 7. A literal interpretation of eq 7 implicates transition structures $[(i\text{-}\mathrm{Pr_2NLi})(\mathrm{HMPA})(\mathbf{1})]^{\ddagger}$, $[(i\text{-}\mathrm{Pr_2NLi})(\mathrm{HMPA})_2(\mathbf{1})]^{\ddagger}$, and $[(i\text{-}\mathrm{Pr_2NLi})(\mathrm{HMPA})_3(\mathbf{1})]^{\ddagger}$ for which we offer depictions **23**,

(32) (a) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567. (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863.

(33) Alternatively, plots of k_{obsd} versus HMPA concentration in an assortment of ethereal solvents display approximately second-order dependencies. The relative ether-dependent accelerations follow this order (with relative rates in parentheses): MeTHF (4) > 2,5-Me$_2$THF (3) > THF (1) ≈ Et$_2$O (1). The lack of correlation with measured binding constants (ref 32) further argues against a primary-shell effect.
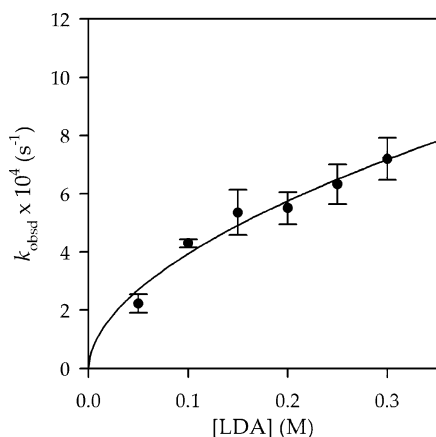
Figure 3. Plot of k_{obsd} vs [LDA] for the lithiation of imine **1** (0.005 M) in 0.40 M free HMPA/8.0 M THF/cyclopentane at $-55\ °C$. The curves depicts the result of an unweighted least-squares fit to $k_{obsd} = k[\text{LDA}]^n$ ($k = (1.4 \pm 0.2) \times 10^{-3}$; $n = 0.54 \pm 0.07$).
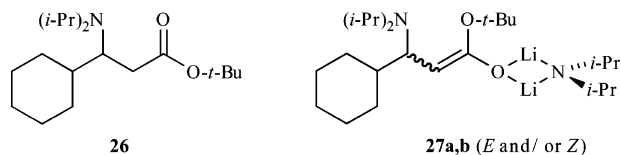

Figure 4. Plot of k_{obsd} vs [HMPA] for the Michael addition to ester **3** (0.004 M) by 0.10 M LDA in THF (10.0 M)/hexane at $-78\ °C$. The curve depicts the result of an unweighted least-squares fit to $k_{obsd} = k[\text{THF}]^n + k'$ ($k = (7.1 \pm 0.3) \times 10^{-3}$; $k' = (8.2 \pm 0.2) \times 10^{-2}$; $n = 1.87 \pm 0.06$).

24, and **25**, respectively; however, we advise caution against over interpreting such a three-term rate law.

$$-d^1/dt = \{k'[\text{LDA}]^{1/2} + k''[\text{HMPA}][\text{LDA}]^{1/2} + k'''[\text{HMPA}]^2[\text{LDA}]^{1/2}\}[\mathbf{1}] \quad (7)$$

22; S = THF
23; S = HMPA
24
25
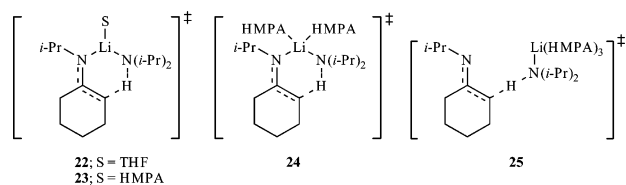
Conjugate Additions. LDA in THF solution undergoes conjugate addition to **3** in lieu of either α- or γ-deprotonation.[13a] However, the results are highly unusual and part of an emerging mechanistic story to be discussed in another context.[34] LDA/HMPA-mediated conjugate additions proceed smoothly and provide tractable rate data as follows.

Conjugate addition of LDA to unsaturated ester **3** in HMPA/THF (eq 2) affords β-amino ester **26** in 76% yield. Analogous addition with 2.0–4.0 equiv of [⁶Li,¹⁵N]LDA forms two mixed dimers that we believe are the two geometric isomers (**27a,b**). Enolization of amino ester **26** with 2.0–4.0 equiv of [⁶Li,¹⁵N]-LDA affords only one isomer. The stereochemical assignments of the *E* and *Z* isomers have not been made. Enolization with 1.25 equiv of LDA affords enolate **4** in an unknown aggregation state.[35]

26
27a,b (*E* and/ or *Z*)

Rate studies carried out under pseudo-first-order conditions afforded evidence of several mechanisms. A plot of k_{obsd} versus HMPA concentration reveals a second-order HMPA dependence

Figure 5. Plot of k_{obsd} vs [THF] for the Michael addition to ester **3** (0.004 M) by 0.10 M LDA with 0.10 M free HMPA at $-78\ °C$ in (A) 2,5-Me₂-THF as cosolvent; (B) hexane as cosolvent. Curve A derives from a linear least-squares fit. Curve B depicts an unweighted least-squares fit to $k_{obsd} = k[\text{THF}]^n + k'$ ($k = (3.8 \pm 0.5) \times 10^{-6}$; $k' = (3.8 \pm 0.3) \times 10^{-4}$; $n = 2.0 \pm 0.4$).

in 10.0 M THF (Figure 4). An HMPA concentration-independent pathway is evidenced by a significant nonzero *y*-intercept. Plots of k_{obsd} versus LDA concentration at both low and high HMPA concentrations reveal first-order dependencies, indicating that both the HMPA-independent and HMPA-dependent pathways are dimer based. In principle, transition structures $[(R_2NLi)_2\text{-}(HMPA)_4]^{\ddagger}$ (**30**) and $[(R_2NLi)_2(HMPA)_2]^{\ddagger}$ (possibly **28** or **29**) are consistent with the rate data. However, second-order dependencies on the THF concentration with distinct nonzero intercepts at both low and high HMPA concentrations (Figure 5, curve A) suggest two additional transition structures corresponding to $[(R_2NLi)_2(HMPA)_2(THF)_2]^{\ddagger}$ and $[(R_2NLi)_2(HMPA)_4\text{-}(THF)_2]^{\ddagger}$.[36] One could imagine describing the former transition structure as mixed-solvated triple ion **31**. The high solvation number of $[(R_2NLi)_2(HMPA)_4(THF)_2]^{\ddagger}$—formally a hexasolvated dimer—stretches our imaginations. A plot of k_{obsd} versus THF concentration at low HMPA concentration (0.10 M) using 2,5-Me₂THF as the cosolvent to hold the polarity of the medium

(34) Reactions of LDA with a number of substrates in THF at $-78\ °C$ display linear plots of substrate concentration versus time as well as odd sigmoidal behaviors, all of which are part of an ongoing study.
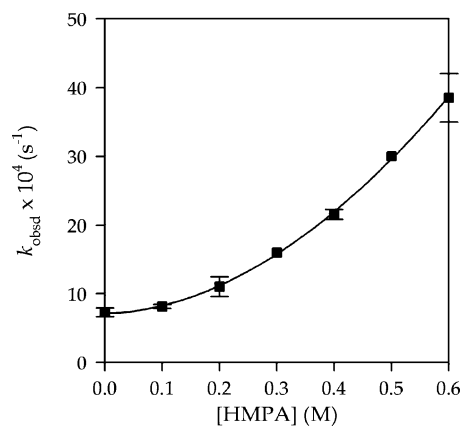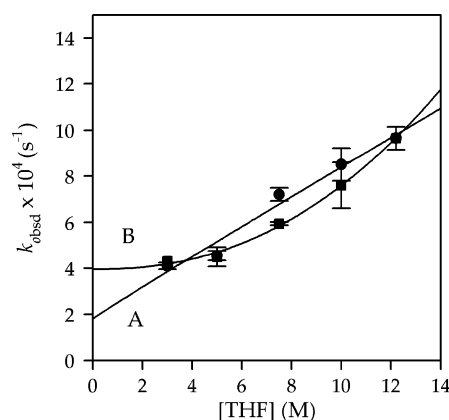
(35) Enolates bearing a β-NH₂ moiety form hexamers in solution: McNeil, A. J.; Toombes, G. E. S.; Gruner, S. M.; Lobkovsky, E.; Collum, D. B.; Chandramouli, S. V.; Vanasse, B. J.; Ayers, T. A. *J. Am. Chem. Soc.* **2004**, *126*, 16559.

(36) Leading references to mixed solvation: Qu, B.; Collum, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 10820.

relatively constant (Figure 5, curve B) simply adds further confusion by revealing a first-order THF dependence rather than the second-order dependence noted in hexane.
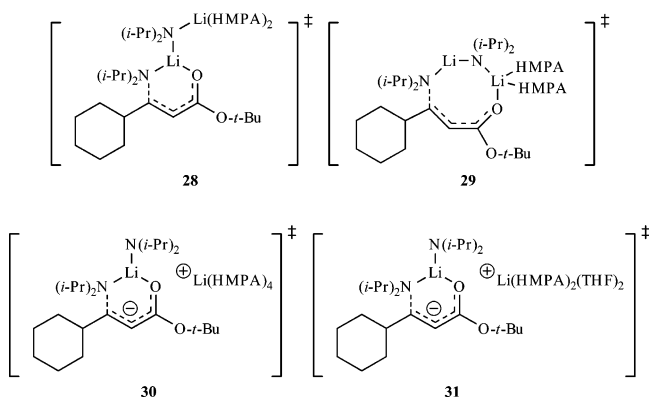

Epoxide Metalation. We examined the LDA/HMPA-mediated metalation of several epoxides and confirmed[16a,b] that epoxides **32** and **33** are unreactive even at ambient temperatures, above which the integrity of LDA/HMPA/THF becomes suspect.[37,38] Metalation of epoxide **5** in HMPA/THF (eq 3) affords alcohol **34** deriving from a transannular C−H insertion by a carbenoid intermediate in 80% isolated yield.
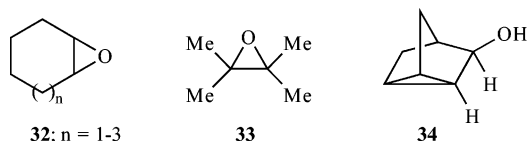
LDA/THF-mediated metalations of epoxide **5** display an odd (0.73 ± 0.04) fractional order in LDA and a clean zeroth-order dependence on the THF concentration. The idealized rate law (eq 8)[31] is consistent with reaction via mono-solvated monomers and disolvated dimers. (Previous studies of the LDA-mediated metalation of epoxide **5** using chelating ligands showed no evidence of a monomer-based pathway.) Transition structures **35**−**37** seem reasonable,[7,8,39] although the deviation from an optimal 180° C−H−N angle appears significant in **35**.[7,9a,40]

$$-d[\mathbf{5}]/dt = k_1[THF]^0[LDA]^{1/2}[\mathbf{5}] + k_2[THF]^0[LDA]^1[\mathbf{5}] \qquad (8)$$
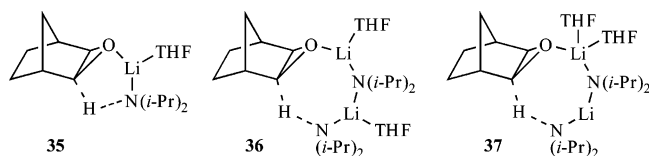
Metalation of epoxide **5** (0.25 M) using [⁶Li,¹⁵N]LDA (0.10 M) with HMPA (0.40 M) reveals a mixed dimer that is replaced by another mixed dimer. The latter was confirmed to be **38** by mixing [⁶Li,¹⁵N]LDA with alcohol **34**. The first-formed mixed
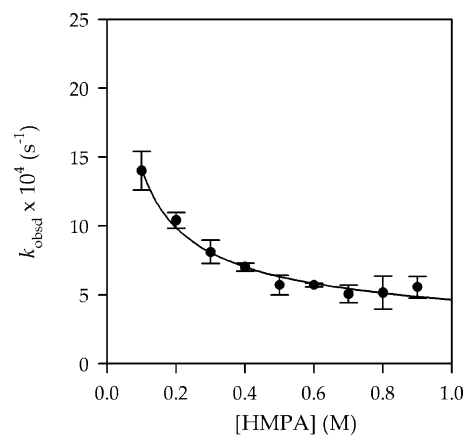

Figure 6. Plot of k_{obsd} vs [HMPA] for the deprotonation of epoxide **5** (0.004 M) by 0.10 M LDA in THF (10.0 M)/hexane at 0 °C. The curve depicts the result of an unweighted least-squares fit to $k_{obsd} = k[HMPA]^n + k'$ ($k = (3.3 \pm 1.9) \times 10^{-4}$; $k' = (1.3 \pm 2) \times 10^{-2}$; $n = -0.6 \pm 0.2$).

dimer is believed to be **39** derived from the observable lithiation before carbenoid formation/C−H insertion.[41] Quenching with D₂O failed to afford significant levels of deuterated **34**, which is not particularly surprising in light of Seebach's studies of D₂O quenches when *i*-Pr₂NH is present.[42] In the absence of HMPA, little or no metalated epoxide is observed (although some minor ⁶Li resonances are noted.)
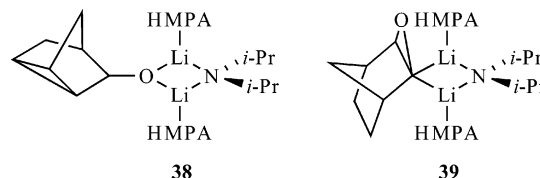
The intermediacy of **39** introduces an inordinate complexity that was unappreciated when the solution kinetics were investigated. Because we monitored the metalation using GC analysis of quenched samples, mixed dimer **39** registered as starting material rather than product. Consequently, the measured reaction orders listed in Table 2 are not easily interpreted. The small isotope effect ($k_H/k_D = 1.3 \pm 0.1$) makes sense if the metalation is reversible. The observed reaction displays a net inhibition by HMPA (Figure 6), but the metalated intermediate causes us to resist further interpretation of the rate data at this point. These suspect data are archived in Supporting Information.

Carbamate Ortholithiation. Previous studies of the LDA/THF-mediated ortholithiation of carbamate **7** show a rate-limiting metalation via monosolvated monomer (**40**) followed by a rapid (post-rate-limiting) anionic Fries rearrangement. Formation of mixed dimer **42** causes a marked autoinhibition when only 1.0 equiv of LDA is used. Analogous behavior is observed in the presence of HMPA: mixed dimer **43** is observed to the exclusion of any intermediate aryllithium derivatives. Under pseudo-first-order conditions a large k_H/k_D confirms a rate-limiting proton transfer. (The particularly large isotope effect is characteristic of ortholithiations.[43]) A first-order HMPA

(37) (a) Stanetty, P.; Mihovilovic, M. D. *J. Org. Chem.* **1997**, *62*, 1514. (b) Aubrecht, K. B.; Collum, D. B. *J. Org. Chem.* **1996**, *61*, 8674. (c) 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 and references cited therein.

(38) Morgan and coworkers investigated the elimination of cyclopentene oxide by LDA/HMPA, apparently in the absence of base-labile ethereal ligands (ref 16a,b).

(39) For additional leading references to spectroscopic, crystallographic, and kinetic evidence of open dimers, see: Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 14411.

(40) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman & Hall: New York, 1980.

(41) For leading references to oxacarbenoids, see: Pratt, Lawrence, M.; Ramachandran, B. *J. Org. Chem.* **2005**, *70*, 7238; Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697.

(42) Seebach, D.; Aebi, J.-D. *Helv. Chim. Acta* **1985**, *68*, 1507.

concentration dependence and a half-order LDA concentration dependence implicate disolvated monomer-based metalation (**41**). A zeroth-order dependence on the THF concentration shows that medium effects are unimportant.
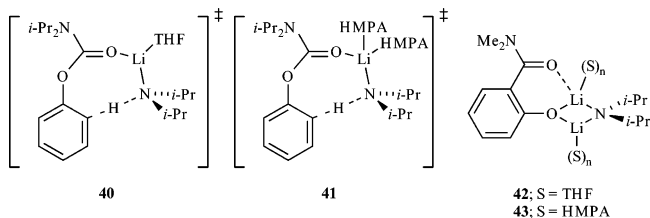
Discussion

We studied four LDA-mediated reactions—lithiation of imine **1** (eq 1), conjugate addition to unsaturated ester **3** (eq 2), α-deprotonation of epoxide **5** (eq 3), and ortholithiation of carbamate **7** (eq 4). All are important in organic synthesis, and HMPA has played a role in controlling reactivity in each case. The results are summarized below and discussed in more detail subsequently. We must reiterate an important point: The rate studies provide only the stoichiometries of the transition structures at the rate-limiting steps;[20] the three-dimensional renditions of the transition structures are based on computational studies,[7,8] analogies with observable structural forms,[6,21,32a] and conjecture. We routinely offer this caveat in the context of rate data, but it seems especially germane in the context of LDA/HMPA-mediated reactions.

Summary. The rate studies were prefaced by structural studies showing aggregate changes throughout the reaction coordinate when moderate excesses of LDA/HMPA are used. LDA/HMPA-mediated metalation of imine **1** affords an LDA-free lithiated imine believed to be monomer **21** based on prior studies.[30] Analogous reaction of epoxide **5** forms low concentrations of an intermediate lithiated epoxide as mixed dimer **39**. Subsequent carbenoid-derived insertion leads to LDA-alkoxide mixed aggregate **38**. Michael addition of LDA/HMPA to unsaturated ester **3** provides mixed dimer **27** as a putative E-Z mixture. Ortholithiation of aryl carbamate **7** affords an undetectable aryllithium that undergoes facile (post-rate-limiting) Fries rearrangement to give LDA—aryloxide mixed dimer **43** as the only observable product. Previous studies of mixed aggregation in LDA/HMPA mixtures are consistent with this picture of a highly salt-dependent penchant toward mixed aggregation.[4c,6b,7e]

Rate studies were carried out under pseudo-first-order conditions to preclude mixed aggregation effects. The intermediacy of metalated epoxide **39** proved disruptive to detailed rate studies. For the most part, however, the results are tractable and reveal considerable mechanistic diversity. The influence of THF in all LDA/HMPA-mediated reactions is discussed in a subsequent section.

Metalation of imine **1** by LDA/HMPA is mechanistically complex, displaying concentration dependencies implicating several monomer-based pathways (**23**−**25**). This complexity contrasts with analogous metalations in the absence of HMPA in which a single pathway involving a monosolvated monomer (**22**) is detected. LDA/HMPA-mediated conjugate addition to ester **3** proceeds via disolvated and tetrasolvated dimer-based pathways for which we depict **28** or **29** for the former and triple

ion **30** for the latter. LDA/HMPA-mediated metalation of epoxide **5** was only marginally informative because of the formation of an observable lithiated epoxide (**39**). Even metalation in the absence of HMPA, however, proved to be quite complex, implicating a combination of monosolvated monomer (**35**) and disolvated dimer (**36** or **37**). Last, the ortholithiation of carbamate **7** proceeds via a di-HMPA-solvated monomer (**41**).

Are Mixed and Secondary-Shell Solvation Important? Secondary-shell solvation—the influence of solvent as simply a medium—has received scant attention in organolithium chemistry.[4,23,24] Extensive investigations of LDA-mediated metalations have generally revealed that primary-shell solvation is critical but secondary-shell solvation is unimportant. In the case of LDA/HMPA-mediated reactions, one might presume that THF, normally a strongly coordinating solvent, would be relegated to the role of inert cosolvent. Indeed, LDA/HMPA-mediated dehydrohalogenations discussed as background (vide supra)[5] and metalations of epoxide **5** and aryl carbamate **7** described herein show no influence by THF whatsoever. In short, the reaction rates in HMPA/THF/hydrocarbon mixtures are independent of the THF concentrations.

On occasion, however, supposedly inert cosolvents can influence organolithium structure and reactivity.[23,24] For example, monomer-based ester enolization (see **12**) is not measurably influenced by THF, whereas the putative triple-ion-based pathway (see **13**) is *inhibited* by THF. There is no evidence that primary-shell solvation by THF is the culprit. Similarly, LDA/HMPA-mediated metalation of imine **1** via putative monomer **25** is markedly *accelerated* by THF whereas lower-solvated analogs **23** and **24** are not influenced by the THF concentration. By using THF/2,5-Me₂THF cosolvent mixtures (rather than THF/hexane) we observe a loss of the THF concentration dependence, suggesting that the influence of the cosolvent is purely through secondary-shell (medium) effects. It is tempting, plausible, and convenient to conclude that the influence of the ethereal cosolvent is due *exclusively* to secondary-shell solvation. It may not be that simple, however.

The LDA/HMPA-mediated conjugate addition to ester **3** proceeds via a disolvated dimer-based pathway (**28** or **29**) and a tetrasolvated dimer-based pathway (**30**). Both have an affiliated second-order THF dependence in THF/hexane mixtures. The role of THF, however, is very strange. By holding the polarity of the medium fixed and varying the THF with 2,5-Me₂THF as the cosolvent, the second-order THF dependence gives way to a first-order dependence. Given the pronounced steric demands of both LDA and HMPA and consequent buttressing, one cannot rule out primary-shell solvation by HMPA *and* THF. Are we suggesting that there is *both* primary- and secondary-shell solvation by THF? Possibly, but not with any conviction. We must confess that, despite continued efforts to distinguish primary and secondary-shell solvation effects, the latter remains largely inscrutable.

Is Such Mechanistic Complexity Unusual? Surveying mechanisms underlying LDA/HMPA-mediated reactions, one cannot help but notice the large variation of both monomer- and dimer-based pathways. An inventory of LDA/HMPA-mediated reactions reported to date includes reactions based on [(*i*-Pr₂NLi)(HMPA)₁₋₃]‡ and [(*i*-Pr₂NLi)₂(HMPA)₂₋₄]‡, six total (not including putative mixed solvated forms). If each case study is viewed in isolation, the results seem reasonable. We have no

(43) Singh, K.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 13753.

reason to doubt the veracity of the data and, consequently, do not doubt the diversity of the behavior. Nevertheless, the case studies taken together afford a complexity that is daunting, vexing, and unique to LDA/HMPA-mediated reactions.

Is HMPA Special? The short answer is yes. HMPA presents a profound conflict between a marked Lewis basicity affiliated with the P=O dipole[2a,44−46] and the exceptional steric demands of the splaying dimethylamino groups.[7] Semiempirical computational studies of lithium amide solvation that compare HMPA with $(H_2N)_3P=O$ attest to the high affinity of phosphoramides for lithium ion.[7] However, the exothermicity of serial solvation tapers off gradually for $(H_2N)_3P=O$ yet drops off markedly for HMPA. Reich and co-workers have observed this experimentally in the serial solvation of Li cations by HMPA in ethereal solvents: Three HMPA substitutions occur quantitatively; a fourth HMPA substitutes reluctantly.[2] We also cannot ignore the idea expressed previously that solvation of uncoordinated HMPA could contribute significantly to its penchant for binding to lithium cations. Solvent−solvent interactions in solutions of HMPA have been discussed.[23]

Conclusion

LDA/HMPA elicits marked increases in mechanistic complexity compared with LDA in the absence of HMPA. This increased complexity may derive from the pronounced steric demands of both the LDA and HMPA. We have documented a plethora of mechanisms for LDA/HMPA-mediated reactions and have asked as many questions as we have answered. It is curious that the influence of HMPA on reaction rates can, as exemplified by the relative rate constants in Table 1, border on insignificant. The often marginal influence on reaction rates of LDA-mediated metalations incongruent with the significant influence HMPA imparts on mechanism and its importance in organic synthesis.

Experimental Section

Reagents and Solvents. Ethereal solvents, hydrocarbons, and HMPA were vacuum transferred from calcium hydride. The hydrocarbon stills contained 1% tetraglyme to dissolve the ketyl. Imines **1** and **1-d_4**[11] were distilled.[11] Epoxides **5** and **5-d_2**[9] were recrystallized. Unsaturated ester **3** was prepared as described in Supporting Information. LDA was prepared as a solid from commercial *n*-BuLi and purified using a standard literature procedure.[6a] Air- and moisture-sensitive materials were manipulated under argon or nitrogen following standard glovebox, vacuum line, and syringe techniques.

Kinetics. The rate studies were carried out using methods based on in situ IR spectroscopy[4,28] or gas chromatography[9] as described in detail previously.

Supporting Information Available: NMR spectra, rate data, and experimental protocols. This material is available free of charge via the Internet at http://pubs.acs.org.

JA074554E

(44) For discussions of steric effects on lithium ion solvation by HMPA, see: (a) Ishiguro, S. *Pure Appl. Chem.* **1994**, *66*, 393. (b) Dack, M. R. J.; Bird, K. J.; Parker, A. J. *Aust. J. Chem.* **1975**, *28*, 955. (c) Ishiguro, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1465.
(45) Burford, N.; Royan, B. W.; Spence, R. E. v. H.; T. Cameron, S.; Linden, A.; Rogers, R. D. *J. Chem. Soc., Dalton Trans.* **1990**, 1521.
(46) HMPA has been estimated to bind 300 times more strongly than THF in one case (ref 2a).