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Lithium Reagents

Lithium Diisopropylamide: Solution Kinetics and Implications for Organic Synthesis

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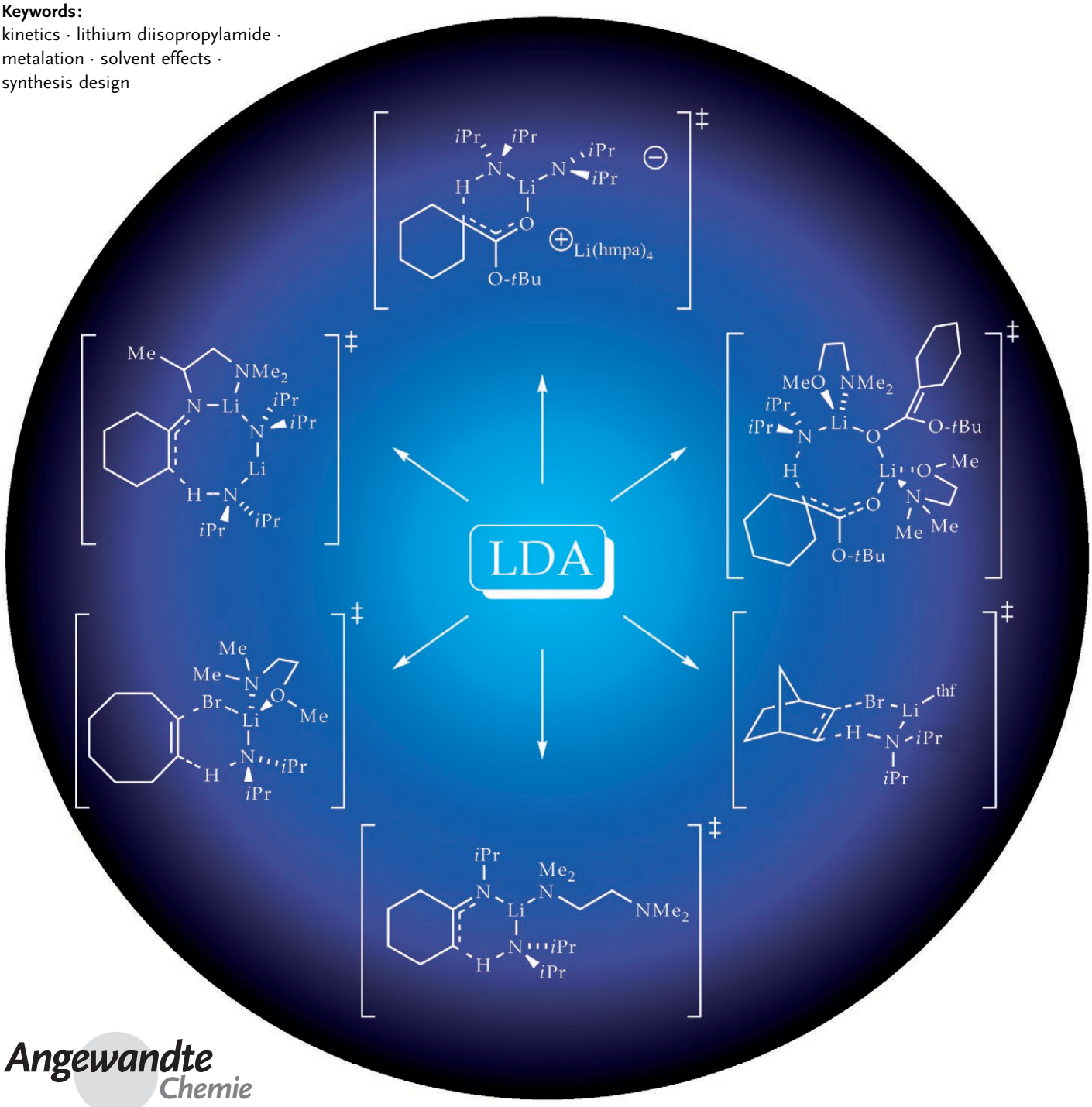
kinetics · lithium diisopropylamide · metalation · solvent effects · synthesis design



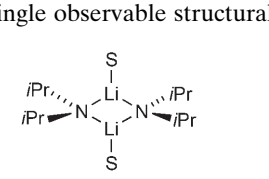
Lithium diisopropylamide (LDA) is a prominent reagent used in organic synthesis. In this Review, rate studies of LDA-mediated reactions are placed in the broader context of organic synthesis in three distinct segments. The first section provides a tutorial on solution kinetics, emphasizing the characteristic rate behavior caused by dominant solvation and aggregation effects. The second section summarizes substrate- and solvent-dependent mechanisms that reveal basic principles of solvation and aggregation. The final section suggests how an understanding of mechanism might be combined with empirical methods to optimize yields, rates, and selectivities of organolithium reactions and applied to organic synthesis.

From the Contents

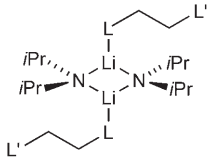
1. Introduction

During a natural product synthesis in 1980, we noted that alkylations of hydrazones displayed odd stereoselectivities when compared to alkylations of their ketone counterparts.[1,2] Lacking a satisfactory explanation and inspired by Seebach's contemporaneous crystallographic studies of lithium enolates,[3,4] we obtained two crystal structures of lithiated hydrazones displaying curious structural features that posed more questions than answers.[2] Subsequent rate studies led to mechanistic and stereochemical models[5] and, more important, left us captivated by organolithium aggregation and solvation. Over the next two decades, we studied a number of synthetically important organolithium reactions with the goal of understanding the mechanistic basis of reactivity and selectivity. Each case study was necessarily prefaced by determining the organolithium structures in solution and was often concluded with computational probes of experimentally elusive details. Solution kinetics, however, provided the compelling insights useful to a broader audience. One reagent has been particularly revealing: lithium diisopropylamide (LDA).

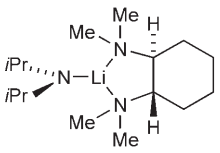
LDA has played a profound role in organic synthesis, serving as the base of choice for a broad range of deprotonations effected daily by synthetic chemists.[6] LDA is also an ideal template for studying organolithium reactivity. It exists as a single observable structural form—disolvated dimer **1**—in *all* monofunctional solvents.[7–12] Chelating ligands afford isostructural disolvated dimers **2**[8b,10] with the notable exception of TMCDA-solvated monomer **3**.[8b,13] The structural control is tactically important because rate studies based on either uncharacterized reagents or well-characterized mixtures are of limited value. The structural homogeneity is of pedagogic value because it allows the nonspecialist to focus on reaction coordinates rather than the reactant structures.



1a; S = thf
1b; S = *n*BuOMe
1c; S = R_2O
1d; S = Me_2NEt
1e; S = hmpa
1f; S = dmpu



2a; L = L' = OMe (dme)
2b; L = L' = NMe_2 (tmeda)
2c; L = OMe, L' = NMe_2
2d; L = OR, L' = NR'$_2$



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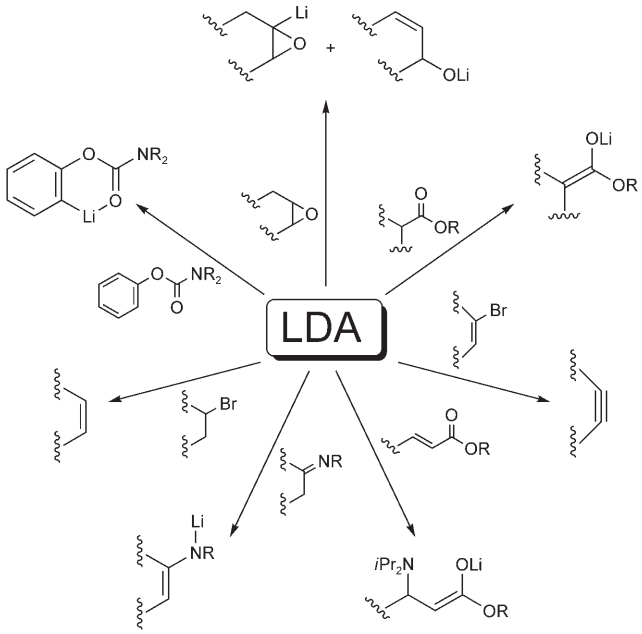
This Review focuses on mechanistic investigations of the LDA-mediated reactions summarized in Scheme 1. It is



Scheme 1. Representative reactions mediated by lithium diisopropylamide.

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organized as a series of maxims to underscore the principles governing reactivity rather than focus on the mechanistic complexity. Section 2 offers a tutorial on reaction kinetics, emphasizing the idiosyncrasies caused by solvation and aggregation. Section 3 describes general principles of reactivity, many of which we believe are not self-evident. Section 4 concludes the Review with guidelines that can be dovetailed into empirical approaches for optimizing the yields and selectivities of organolithium reactions.

2. Organolithium Solution Kinetics: A Tutorial

A picture is worth a thousand words. To a kineticist these pictures come as plots of concentrations versus time and plots of observed rate constants versus reagent and solvent concentrations.[14] We preface the tutorial on solution kinetics with a principle that is as old as kinetics itself.

2.1. The Rate Law Provides the Stoichiometry of the Rate-Limiting Transition Structure Relative to the Reactants.[15,16]

The rate law reveals *changes* in aggregation and solvation numbers required to reach the rate-limiting transition structure. Therefore, if one has a clear understanding of both the aggregation and the solvation numbers of the reactants, one obtains the aggregation and solvation numbers in the rate-limiting transition structure.

Rate studies in organolithium chemistry provide reaction orders and rate laws that are quite diverse. Equations (1)–(3)

$$A_2S_2 + \text{substrate} + S \xrightarrow{k} \text{product} \quad (1)$$

$$d[\text{product}]/dt = k_{obs}[\text{substrate}] \quad (2)$$

$$k_{obs} = k[A_2S_2]^a[S]^b \quad (3)$$

illustrate a generalized mechanism and rate law. A_2S_2 is shorthand for a disolvated dimer in which A refers to the iPr$_2$NLi fragment and S refers to a Lewis basic solvent. Variables a and b refer to their respective reaction orders. Table 1 summarizes ten potential mechanisms and affiliated rate laws for LDA-mediated reactions (observable substrate–LDA complexation, mixed aggregation, and multiple pathways introduce additional variations in rate behavior; see below). The pseudo-first-order rate constants (k_{obs}) reveal how the rates depend on the concentrations of LDA and coordinating solvent. Table 2 summarizes experimentally determined rate laws for LDA-mediated reactions to facilitate access to the primary literature; seven have been

Table 1: Relationship of the rate law [Eqs. (2) and (3)] to the stoichiometry of the transition structure.

Entry	a	b	k_{obs}	Stoichiometry
1	1/2	−1	$k[A_2S_2]^{1/2}[S]^{-1}$	$[A(\text{substrate})]^+$
2	1/2	0	$k[A_2S_2]^{1/2}[S]^0$	$[AS(\text{substrate})]^+$
3	1/2	1	$k[A_2S_2]^{1/2}[S]^1$	$[AS_2(\text{substrate})]^+$
4	1/2	2	$k[A_2S_2]^{1/2}[S]^2$	$[AS_3(\text{substrate})]^+$
5	1/2	3	$k[A_2S_2]^{1/2}[S]^3$	$[AS_4(\text{substrate})]^+$
6	1	−2	$k[A_2S_2]^1[S]^{-2}$	$[A_2(\text{substrate})]^+$
7	1	−1	$k[A_2S_2]^1[S]^{-1}$	$[A_2S(\text{substrate})]^+$
8	1	0	$k[A_2S_2]^1[S]^0$	$[A_2S_2(\text{substrate})]^+$
9	1	1	$k[A_2S_2]^1[S]^1$	$[A_2S_3(\text{substrate})]^+$
10	1	2	$k[A_2S_2]^1[S]^2$	$[A_2S_4(\text{substrate})]^+$

Table 2: Experimentally observed mechanisms for LDA-mediated reactions (see Scheme 1).

Substrate	Solvent (S)	Stoichiometry[a]	Ref.
RBr	THF	$[AS]^+$, $[AS_2]^+$, $[AS_3]^+$	[33, 34a]
RBr	HMPA[b]	$[AS]^+$, $[AS_2]^+$, $[AS_3]^+$	[34a]
RBr	MeOCH$_2$CH$_2$L[c]	$[AS]^+$	[33]
RBr	PMDTA[d]	$[AS]^+$, $[A_2S]^+$	[49]
RBr	TMCDA[d]	$[AS]^+$	[49]
RBr	MeOCH$_2$CH$_2$L[c]	$[AS]^+$, $[AS_2]^+$	[43]
enoate	HMPA[b]	$[A_2S_2]^+$, $[A_2S_4]^+$	[34b]
epoxide	MeOCH$_2$CH$_2$L[c]	$[AS]^+$, $[A_2S]^+$	[44]
epoxide	THF	$[AS]^+$, $[A_2S_2]^+$	[34b]
epoxide	HMPA[b]	$[A_2S_2]^+$	[34b]
ester	THF	$[AS_2]^+$	[25a,b]
ester	HMPA[b]	$[AS]^+$, $[A_2S_4]^+$	[25a]
ester	DMPU	$[AS]^+$, $[AS_2]^+$	[25a]
ester	tBuOMe	$[A_2S]^+$	[25a]
ester	MeOCH$_2$CH$_2$L[c]	$[A_2S]^+$	[48]
ArH	THF	$[AS]^+$	[29]
ArH	nBuOMe	$[A_2S]^+$	[29]
imine	THF	$[AS]^+$	[9, 32b, 35a,b]
imine	HMPA[b]	$[A_2S_4]^+$	[34b]
imine	TMEDA	$[AS]^+$, $[A_2]^+$	[10, 35b]
imine	Me$_2$NEt	$[AS]^+$, $[A_2]^+$	[35b]

[a] Substrate omitted for clarity. [b] THF cosolvent. [c] L = Et, OR, NR$_2$. [d] LDA exists as a monomer in TMCDA or PMDTA.

David B. Collum received a bachelor's degree in biology from the Cornell University College of Agriculture and Life Sciences in 1977. After receiving a PhD in 1980 from Columbia University working with Professor Clark Still, he returned to the Department of Chemistry at Cornell, where he is now a Professor of Chemistry. His previous work at Cornell addressed topics in natural products synthesis and organotransition-metal chemistry, but now focuses on understanding organolithium structure and mechanism.

Anne J. McNeil was born in Buffalo, NY in 1977. She received her BS in chemistry (1999) from the College of William and Mary, where her passion for physical organic chemistry emerged through her research with Prof. Robert J. Hinkle. Anne obtained her PhD in chemistry from Cornell University, where she investigated the structure and reactivity of lithium enolates derived from β-amino esters with Prof. David B. Collum. In November 2004, she began postdoctoral studies at MIT with Prof. Timothy M. Swager, where she is exploring the properties of encapsulated conjugated polymers.

documented with frequencies illustrated in Figure 1. We routinely refer to these as "idealized rate laws" because reaction orders determined by best-fit methods rarely afford integer values.

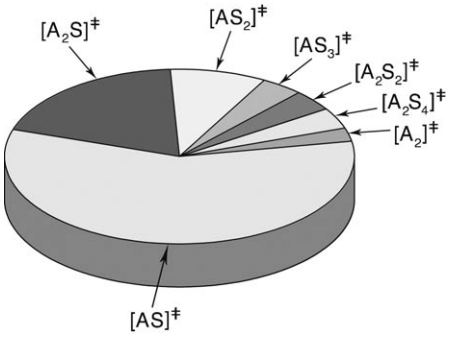


Figure 1. Frequency with which the various monomer- and dimer-based mechanisms shown in Table 2 have been observed.

Figure 2 illustrates a plot of LDA reaction orders versus solvent reaction orders that, although quite odd, is pedagogically useful. Inspection of the plot reveals how a change in solvent concentration or even a change in solvent dipolarity—tantamount to moving left to right along the *x* axis—might cause changes in mechanism and the affiliated rate laws. For each solvent order there can exist a monomer- and a dimer-based pathway. Thus, for any fixed solvent order there is a competition between monomer- and dimer-based chemistries.

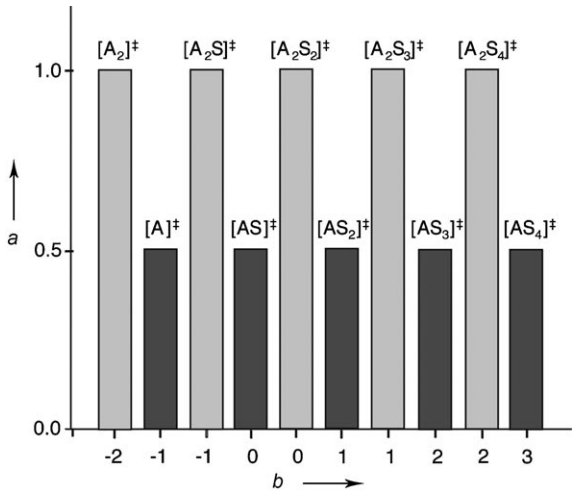


Figure 2. Plot of LDA reaction order (*a*) versus solvent reaction order (*b*) illustrating the relationship between reaction orders and stoichiometries of the transition structures.

Antonio Ramirez received a BS and a PhD degree in pharmacy from the University of Barcelona, Spain (1992 and 1997). As a graduate student he worked on the total synthesis of indole alkaloids under the guidance of Prof. Joan Bosch. He then obtained a fellowship from the Spanish Ministry of Education and moved to Cornell University, where he investigated the mechanism of different organolithium-mediated reactions with Prof. David B. Collum. Recently, Antonio joined the Process Research & Development Department at Bristol-Myers Squibb Co. in New Brunswick, NJ.

2.2. Rate Constants Are the Currency of Kinetics

A typical rate study in our laboratories occurs in two stages. In the first stage, we confront analytical problems and devise protocols for monitoring the reaction. We typically use gas chromatography, in situ IR spectroscopy, or NMR spectroscopy to monitor reactions.[17] Pseudo-first-order conditions are established by setting the substrate as the limiting reagent (Figure 3).[18] Several methods can be used to show

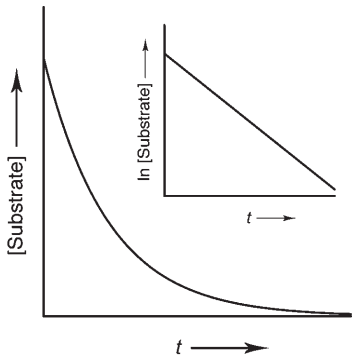


Figure 3. Plot of substrate concentration versus time under pseudo-first-order conditions following the function $[\text{substrate}]_t = [\text{substrate}]_{t=0}\exp(-k_{obs}t)$. The inset shows the linear fit to $\ln[\text{substrate}]_t = \ln[\text{substrate}]_{t=0} - k_{obs}t$.

that the reaction is first-order in substrate;[14] the most popular is the graphical method (Figure 3, inset) although best-fit methods are, in our opinion, superior.[19] A fit of concentration versus time affords pseudo-first-order rate constants, k_{obs}.

The second and decidedly more interesting stage involves monitoring the values of k_{obs} versus organolithium and solvent concentrations, revealing the aggregation and solvation state changes required to reach the rate-limiting transition structures. Insights derived from plots of k_{obs} versus reagent concentrations dominate the remainder of this Review.

2.3. Fractional Reaction Orders in LDA Reveal Deaggregations

The role of aggregation is gleaned from plots of k_{obs} versus LDA concentration. Reaction orders in organolithium reagents indicate the change in the aggregation number reflected in the rate-limiting transition structure.[4] Thus, a half-order dependence on the LDA concentration ($k_{obs} \propto [\text{LDA}]^{1/2}$; Figure 4, $a = 1/2$) indicates that the monomer—*one half* of the observable dimer **1**—is required. Conversely, a

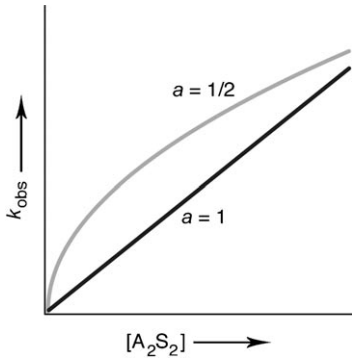


Figure 4. Plot of k_{obs} versus LDA concentration ($[A_2S_2]$) showing the reaction orders in LDA (*a*).

first-order dependence ($k_{obs} \propto [LDA]^1$; Figure 4, $a = 1$) implicates a dimer-based mechanism.

2.4. Solvents Are Ligands, Not Just Reaction Media

Rate studies offer distinct advantages over methods of direct observation[20] to probe the solvation of metal ions. By monitoring k_{obs} versus the concentration of the Lewis basic solvent using hydrocarbon cosolvents, the resulting reaction order provides the solvation number of the transition structure *relative* to the reactant. By example, a first-order solvent dependence affiliated with an LDA-monomer-based reaction (Figure 5, $b = 1$) indicates an association of one

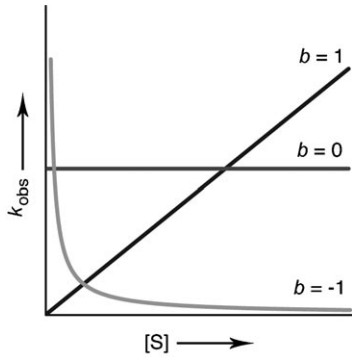


Figure 5. Plot of k_{obs} versus solvent concentration ([S]) showing reaction orders in solvent (*b*).

additional solvent molecule per monomer ($[AS_2(substrate)]^+$; see Table 1, entry 3). A first-order solvent dependence affiliated with a dimer-based reaction indicates an association of one additional solvent molecule per dimer ($[A_2S_3(substrate)]^+$; Table 1, entry 9). A zeroth-order dependence (Figure 5, $b = 0$) indicates that no additional solvent molecule is required beyond that already coordinated to the LDA ($[AS(substrate)]^+$ or $[A_2S_2(substrate)]^+$; Table 1, entries 2 and 8). In this instance, the coordinated solvent is still important (sometimes profoundly so),[10,21] but the existence and concentration of the uncoordinated solvent is not. An *inverse* solvent dependence (Figure 5, $b = -1$) is indicative of a mechanism demanding dissociation of one solvent ligand ($[A(substrate)]^+$ or $[A_2S(substrate)]^+$).

2.5. Multiple Reaction Pathways Are Common

When reactions afford two products, there are, by necessity, at least two reaction pathways. Nevertheless, even the simplest reactions affording a single product quantitatively can belie a deep-seated mechanistic complexity. The rate laws are simply combinations of the examples in Table 1 [Eq. (4)]. Parallel pathways are most often detected by

$$k_{obs} = \underbrace{k'[A_2S_2]^1[S]^0}_{[A_2S_2(substrate)]^+} + \underbrace{k''[A_2S_2]^{1/2}[S]^1}_{[AS_2(substrate)]^+} \quad (4)$$

monitoring the solvent concentration dependencies. For example, plots of k_{obs} versus solvent concentration (Figure 6) often display both solvent-concentration-*independent*

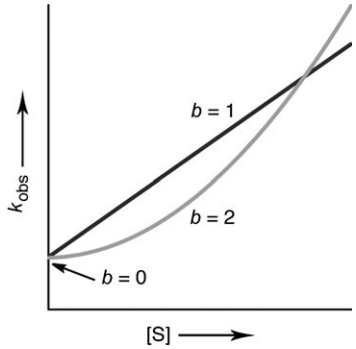


Figure 6. Plot of k_{obs} versus solvent concentration ([S]) showing solvent orders (*b*) for parallel reaction pathways.

ent rates (exemplified by a nonzero intercept, $b = 0$) and solvent concentration-*dependent* rates (causing slope and curvature). Noninteger solvent orders (for example, $1.0 < b < 2.0$) and significant deviations from the anticipated standard LDA reaction orders (for example, $0.5 < a < 1.0$, Figure 4) also implicate parallel pathways. Reaction orders in LDA measured in the limit of low and high solvent concentration can be different, signifying that a change in aggregation accompanies a change in solvent order.

2.6. Fleeting Intermediates Preceding the Rate-Limiting Step Are of No Kinetic Consequence

The sequence of equilibria that transform the observable disolvated dimer to the rate-limiting transition structure is likely to be complicated, and there may be a variety of intermediates along a number of possible paths. Fortunately, intermediates preceding the rate-limiting step are "invisible" to a kineticist unless they exist at observable concentrations (> 5 %). If they were consequential, rate data for even simple reactions would be intractable. It is often suggested, however, that transient complexes formed from the organolithium reagent and the substrate facilitate the reaction by a proximity effect, the so-called complex-induced proximity

effect (CIPE).[22] Stabilizing substrate–lithium interactions in the rate-limiting transition structure will influence the activation energy. However, the existence of a transiently formed, yet discrete, complex in advance of the rate-limiting transition structure is of no kinetic consequence, as illustrated in Figure 7. To argue the contrary is to argue a path dependence leading to the rate-limiting transition state, which is invalid.[23]

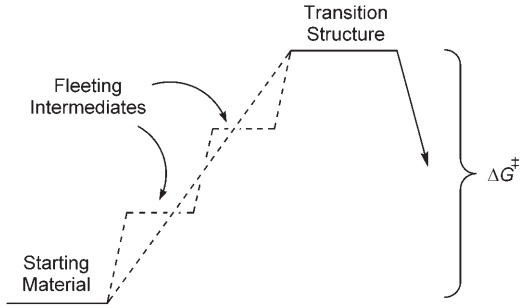
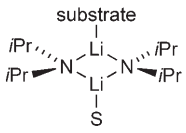


Figure 7. Inconsequence of fleeting intermediates on $\Delta G^{\ddagger}$.

2.7. Observable LDA–Substrate Complexation Markedly Influences the Rate Law

Dimeric LDA–substrate complexes (**4**), most often detected by in situ IR spectroscopy,[21,24] typically form in weakly coordinating solvents.[25] In contrast to the formation of transient complexes along the reaction coordinate, the formation of observable complexes significantly influences the concentration dependencies.[25] For example, the reaction of complex **4** via a monosolvated-dimer-based transition structure [Eq. (5)] follows a first-order dependence on complex **4**, and the rates will be *independent* of the free (uncomplexed) LDA and solvent concentrations [Eq. (6)].



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$$A_2S(\text{substrate}) \rightarrow [A_2S(\text{substrate})]^{+} \quad (5)$$

4

$$-\mathrm{d}[\text{substrate}]/\mathrm{d}t = k[\mathbf{4}][A_2S_2]^0[S]^0 \quad (6)$$

Contrast this with the reaction orders of −1 (solvent) and 1 (LDA) observed for the same monosolvated-dimer-based metalation when substrate–LDA complexation does *not* occur (Table 1, entry 7).[26] Nonetheless, the dimer-based substrate complex does not *cause* the dimer-based mechanism; complexation and dimer-based reactivity share a "common response"[27] to weak solvation.

The results could become particularly strange in the event that complex **4** reacts via a monosolvated monomer; the LDA-mediated lithiation would be inhibited by excess LDA [Eqs. (7) and (8)]. Although this scenario has not yet been detected, it is plausible.[28,29]

$$A_2S(\text{substrate}) + S \rightarrow [AS(\text{substrate})]^{+} + {}^{1}/_{2}A_2S_2 \quad (7)$$

4

$$-\mathrm{d}[\text{product}]/\mathrm{d}t = k[\mathbf{4}]\,[A_2S_2]^{-1/2}[S]^1 \quad (8)$$

2.8. Saturation Often Reveals a Change in Reagent Structure

Leveling out of the observed rate constant—so-called saturation kinetics (Figure 8)—indicates either 1) a change in the rate-limiting step, or 2) a change in the observable form of the reactant.[30] The two models are mathematically indistinguishable, yet the latter is more probable within organolithium chemistry.[10,21] Such saturation is commonly observed

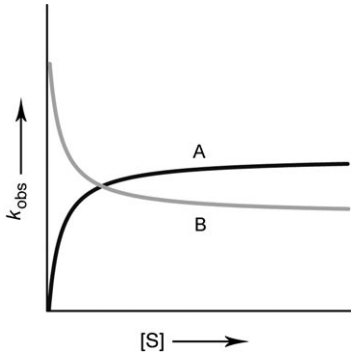


Figure 8. Plot of k_{obs} versus solvent concentration ([S]) showing saturation kinetics: $k_{obs} = c[S]/(1+d[S])$; c and d are adjustable parameters.

in plots of k_{obs} versus solvent concentration [Eq. (9)] owing to

$$\underbrace{A_2S_2}_{\text{observed at low [S]}} + n\,S \rightleftharpoons \underbrace{A_xS_{x+n}}_{\text{observed at high [S]}} \rightarrow \text{product} \quad (9)$$

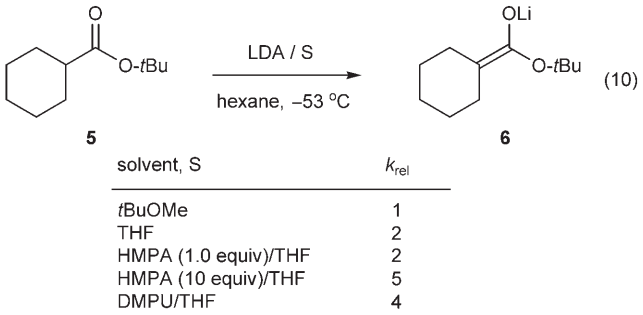
a solvent-dependent change in aggregation[31] or solvation number.[10,21] Such saturation behavior usually results in an increase in rate to an asymptotic limit (Figure 8, curve A), but can result in a *decrease* to an asymptotic limit if the more solvated form is less reactive (Figure 8, curve B).[21]

3. Structure–Reactivity Relationships

We now provide some basic principles of solvation and aggregation that have emerged from the rate studies. Recall that the rate laws only provide the stoichiometry of the rate-limiting transition structures. Transition structures depicted below showing key spatial relationships are based on structural analogies with solution and solid-state forms and extensive computational studies.[32,33]

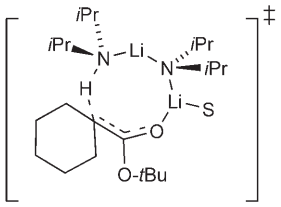
3.1. Relative Rate Constants Can Hide More Than They Reveal

Rate constants are the currency of kinetics, but relative rate constants can conceal as much as they reveal. Ester enolizations offer an excellent case in point [Eq. (10)].[25] Coordinating solvents spanning the range from poorly coordinating *t*BuOMe to strongly coordinating HMPA elicit marginal changes in rates. It might be tempting to conclude that solvent is an unimportant variable. Detailed rate studies,

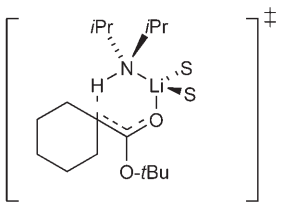


solvent, S	k_{rel}
*t*BuOMe	1
THF	2
HMPA (1.0 equiv)/THF	2
HMPA (10 equiv)/THF	5
DMPU/THF	4

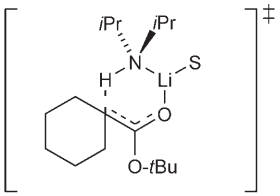
however, reveal that each solvent elicits a different mechanism exemplified by transition structures **7**–**10**. Moreover, a marginal increase in rate with a tenfold increase in the HMPA



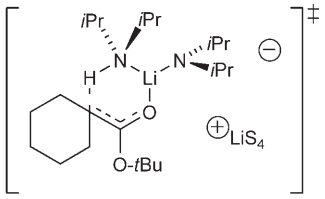
7; S = *t*BuOMe



8a; S = thf
8b; S = dmpu



9a; S = hmpa
9b; S = dmpu

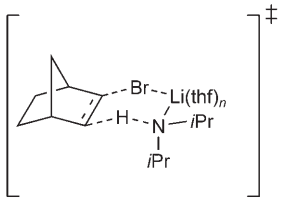


10; S = hmpa

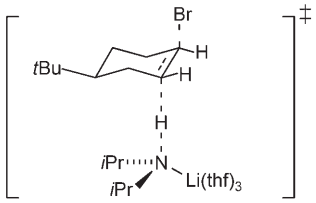
concentration belies a striking shift in prominence from monosolvated monomer **9a** to triple ion **10**. This shift is illustrated by the exponential curve labeled $b = 2$ in Figure 6. A profound shift from exclusively one mechanism in the limit of low solvent concentration (labeled $b = 0$ at the y intercept of the curve) to a predominantly different mechanism in the limit of high solvent concentration would be accompanied by only a several-fold increase in rate. In a more stereo- or regiochemically revealing instance, these modest rate changes could be affiliated with marked changes in selectivity.

3.2. Substrate-Dependent Mechanisms May Be the Rule, Not the Exception

The example above illustrates that solvent is an acute determinant of mechanism. It is incorrect, however, to presume that the organolithium/solvent combination is the overriding determinant of mechanism even within a class of reactions. We note, for example, that the mechanisms of dehydrobrominations change markedly with changes in the alkyl bromide. The *syn* elimination of *exo*-norbornyl bromide by LDA/THF proceeds via a combination of mono- and disolvated monomers **11a** and **11b** with a putative Br–Li interaction.[33] Conversely, a *trans*-diaxial elimination pro-



11a; $n = 1$
11b; $n = 2$

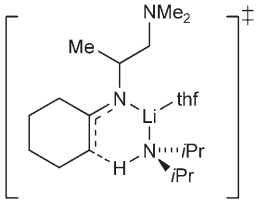


12

ceeds in the case of *tert*-butylcyclohexyl bromide via trisolvated monomer **12**. Presumably, the high solvation number occurs because concurrent Li–Br and N–H contacts are impossible.[34]

3.3. Dimers Can Be Much More Reactive Than Monomers

One of the widely held notions stemming from early rate studies of alkyl lithium reactions is that aggregates dissociate to monomers before reacting with the substrate.[4] Contrary to conventional wisdom, however, LDA-dimer-based reactions are prevalent (Figure 1). LDA/THF-mediated lithiations of imines bearing potentially chelating *N*-alkyl moieties proceed via monomer-based transition structure **13** at tractable rates



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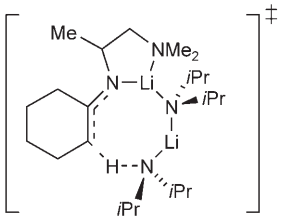


14

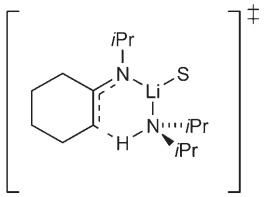
near ambient temperatures.[9] By contrast, the corresponding LDA/Me_2NEt-mediated lithiation occurs orders of magnitude faster at −78 °C ($k_{rel} > 10^3$) via a dimer-based transition structure (**14**).[35] Dimer-based reactions are also prominent in lithiations of epoxides, esters, and alkyl halides (Table 2).

One advantage of dimer-based and other aggregate-based reactions is that aggregation energy is not completely forfeited. Further, the dimer-based lithiations offer more favorable (colinear) alignments of the N-H-C moiety than with the corresponding five- and six-center transition structures deriving from monomer-based lithiations.[32b] Why have aggregate-based reactions been so elusive in previous mechanistic studies? The answer may be remarkably simple: Kineticists are often forced to study reactions that proceed at tractable rates, and the resulting selection bias causes slow reactions to be more susceptible to detailed analysis. We believe that the fastest reactions are most likely to be

aggregate-based.[36] We are often reminded that if you find a lion that can talk, he will not tell you much about normal lions.[37] This paraphrased aphorism is worthy of a second read.

3.4. Deaggregation Does Not Require Further Lithium Ion Solvation

Fractional reaction orders in organolithium reagents, emblematic of deaggregation, have historically been affiliated with solvent concentration-dependent rates, suggesting that deaggregations require additional lithium ion solvation.[4] Highly solvent-dependent rates, yields, and selectivities observed empirically over decades have reinforced the central importance of solvation. We were initially surprised, therefore, that monomer-based lithiations of *N*,*N*-dimethylhydrazones and *N*-isopropylimines manifested solvent concentration-*independent* rates.[9,35] In light of well-documented three-coordinate lithium,[7] however, monosolvated monomers such as **15a** and **15b** are quite reasonable. In this instance, the



15a; S = thf
15b; S = Me_2NEt

coordinated solvent plays only a secondary role as an ancillary ligand. Solvent concentration-independent rates affiliated with deaggregations have been detected for virtually all reaction types (Table 2). In fact, of the greater than 70 rate laws recorded to date for various LDA/solvent/substrate combinations, more than 60% reveal a zeroth-order dependence on the coordinating solvent (Figure 1).

3.5. Generalized Medium Effects Are Minimal

Replacing hydrocarbons with more Lewis basic solvents increases the concentration of the coordinating solvent, but it also increases the polarity of the medium. Indeed, zeroth-order dependencies on THF concentration often show a gentle upward drift over the range from nearly neat hexane to neat THF. Using Me_4THF,[13] a polar but poorly coordinating cosolvent, instead of hexane as the cosolvent eliminates the drift (Figure 9).[9] Similarly, first-order dependencies can show slight upward curvatures traceable to medium effects.[18a] It may seem surprising that the polarity of the medium has only a minimal influence on reactions reputed to proceed via relatively ionic species.[38] We hasten to add, however, that aromatic hydrocarbons can cause significant deviations from ideality in some cases.[39]

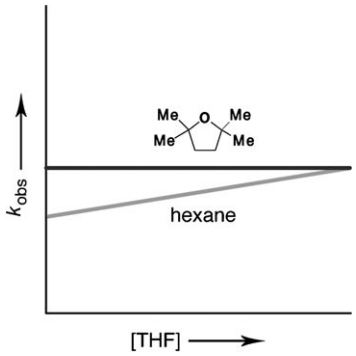
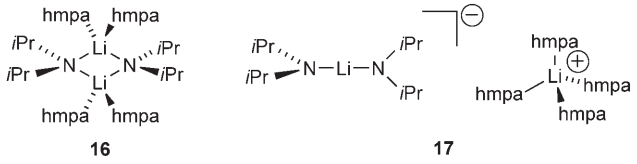
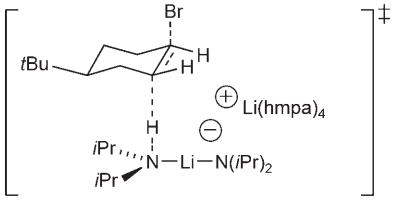


Figure 9. Plot illustrating the marginal influence of medium effects on reactivity through changes in inert cosolvents.

3.6. Highly Dipolar Solvents Promote Triple Ions

Investigations of LDA/HMPA-mediated enolizations[25] and dehydrobrominations[34] reveal high (second-order) dependencies on the HMPA concentration. This observation seems fully compatible with conventional views of HMPA as a strongly coordinating ligand. Taken in conjunction with first-order LDA concentration dependencies, however, the rate laws implicate tetrasolvated *dimers*. Although most organic chemists might affiliate HMPA with high solvation numbers,[40] few would identify either HMPA *or* high solvation numbers with an aggregate-based mechanism. Moreover, tetrasolvated cyclic dimer **16** is profoundly congested and



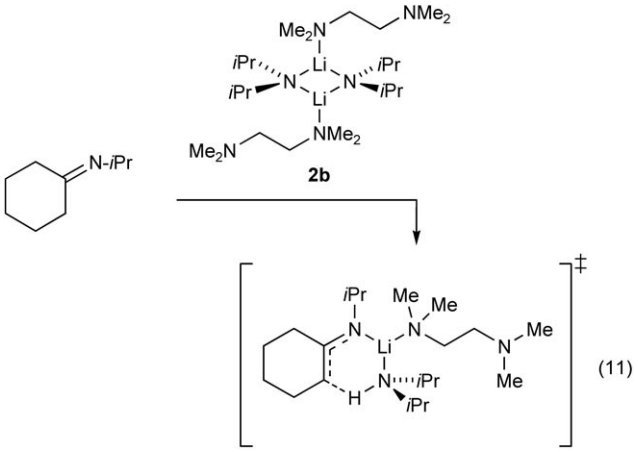


18

coordinatively saturated, leaving little room for the substrate. Accordingly, we developed a mechanistic model for enolizations based on triple ions of general structure **17**.[25] To the extent that triple ions are simply "-ate" complexes of lithium, analogy with other organometallic "-ate" complexes suggests high reactivity. Although LDA-based triple ions have not been directly observed, triple ions obtained from LiHMDS/HMPA[41] and LiTMP/HMPA[8a] mixtures are fully characterized. We noted that HMPA diverts ester enolizations through triple ion **10** with only a marginal increase in reaction rate compared with the monomer-based enolization in THF via **8a**. In contrast, the dehydrobromination via triple-ion-based transition structure **18** is accompanied by an approximate 1000-fold acceleration compared with **12**.[34]

3.7. Potentially Chelating Ligands Do Not Always Chelate

Our understanding of chelating ligands was first challenged during studies showing that LDA/TMEDA-mediated lithiations of simple imines are 10 times faster than the corresponding LDA/THF analogues.[10,35] Detailed structural and rate studies revealed that TMEDA does not function as a chelating ligand at any critical point along the reaction coordinate [Eq. (11)]. In fact, TMEDA proved indistinguishable from its nonchelating counterpart, Me_2NEt. Lithiation of imines bearing potentially chelating *N*-alkyl moieties confirmed this conclusion; dramatic accelerations ($>10^5$) using TMEDA/hexane instead of THF stemmed from dimer-based transition structure **14** (see Section 3.3), requiring dissociation of both weakly coordinated TMEDA ligands from LDA dimer **2b**.[35]



(11)

We were at a crossroads. Although the rate accelerations by TMEDA appeared normal, the underlying mechanisms certainly did not. We asked a seemingly odd question: Is TMEDA a good ligand for lithium?[42] What started as a literature survey evolved into a polemic. We concluded that TMEDA is not a universally strong ligand and that the influence of TMEDA on organolithium structures and reactivities was poorly understood. We had begun to question our most basic premises about solvation, aggregation, and reactivity.

3.8. Reactivity Does Not Necessarily Correlate with Solvation Energy

The lack of rigorous correlation between solvation energy and reactivity is best explained using the generic free energy diagram depicted in Figure 10A. We use the most prevalent mechanism, monosolvated monomers, emblematically. Strongly coordinating ligands are likely to stabilize both the ground state (ΔG°_{solv}) and the transition state ($\Delta G^\ddagger_{solv}$), eliciting a net cancellation of the influence of solvent.[16] Implicit in the widely held belief that high reactivity correlates with high solvation energy is that ΔG°_{solv} is less than $\Delta G^\ddagger_{solv}$ (Figure 10B). Indeed, there are instances in which the solvation number of the transition structure[16] is high relative to the reactant (as manifested by a high order in solvent), causing stabilizing ligands to accelerate the reaction. Many LDA-mediated lithiations, however, display either *zeroth* order or *inverse* orders in solvent (Figure 1, Table 2), rendering the relationship of ΔG°_{solv} and $\Delta G^\ddagger_{solv}$ unclear, but sometimes causing ΔG°_{solv} to be greater than $\Delta G^\ddagger_{solv}$ (Figure 10C). The next few sections will highlight the consequences of solvation in the ground and transition states.

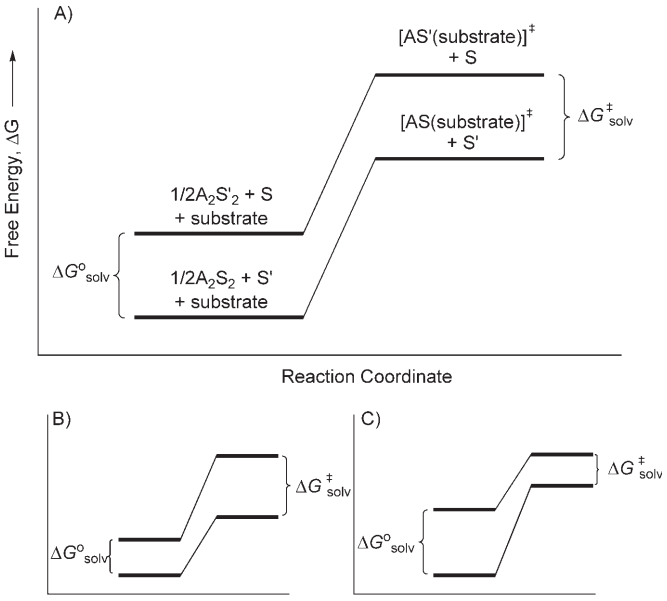


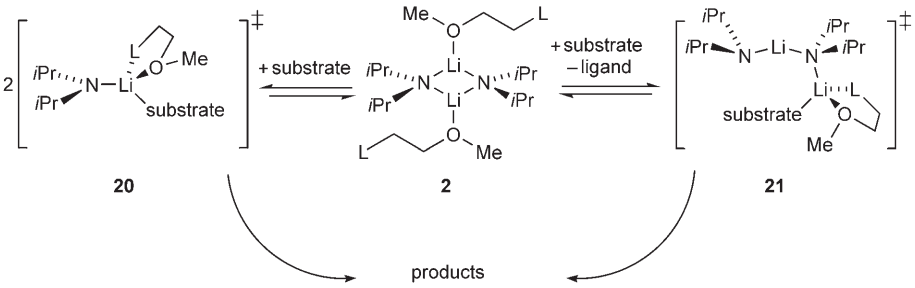
Figure 10. Thermochemical description of solvent-dependent rates.

3.9. Weakly Coordinating Solvents Can Accelerate Reactions

It is instructive to focus on the limit of weak solvation. Lithiations of N-functionalized imines requiring double dissociation of poorly coordinated Me_2NEt or TMEDA via transition structure **14** are extraordinarily fast.[35] It stands to reason that reactions requiring solvent dissociations should be favored in weakly coordinating solvents. In fact, because the only role of solvent in this case is to stabilize the LDA reactant, the lithiations are fastest (instantaneous at −78 °C) in noncoordinating hydrocarbons. Lithiations of epoxides and dehydrobrominations also show accelerations attributable to solvent dissociation.[43,44]

Facile solvent dissociation is attributed to high steric demands in the congested LDA dimer.[10,32,35] Such sterically driven accelerations, however, do not necessarily stem from mechanisms requiring solvent dissociation. In the early studies of the imine lithiations, for example, we found that LDA/THF and LDA/Me_2NEt mediate reactions via isostructural transition structures **15a** and **15b** (respectively), yet the rates using Me_2NEt are approximately 10 times higher.[10] A modified Job plot,[45] used to measure relative solvation energies in both the ground and transition states,[21,32,35b,43] confirmed that THF is a superior ligand to sterically demanding Me_2NEt. The accelerations derive entirely from

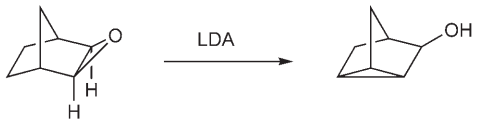
differential solvation energies of the dimer-based ground state rather than in the less congested monomer-based transition state (Figure 10C, $\Delta G^{\circ}_{solv} > \Delta G^{\ddagger}_{solv}$). This conclusion was supported computationally.[32] Probably the most dramatic and best understood inverse correlations of solvation energies and reactivities derive from LiHMDS/NR_3-mediated ketone enolizations.[21]



Scheme 2. Reactions mediated by hemilabile ligands via monomers and dimers.

3.10. Strongly Coordinating Solvents Do Not Always Accelerate Reactions

Indeed, LDA/HMPA-mediated reactions offer excellent cases in point. LDA/HMPA-mediated *syn* and *anti* dehydrobrominations and lithiations of imines are fast relative to their LDA/THF counterparts (Section 3.6).[34] Nonetheless, HMPA decelerates epoxide lithiations [Eq. (12)] when compared



(12)

solvent	k_{rel}
HMPA/THF	1
THF	8

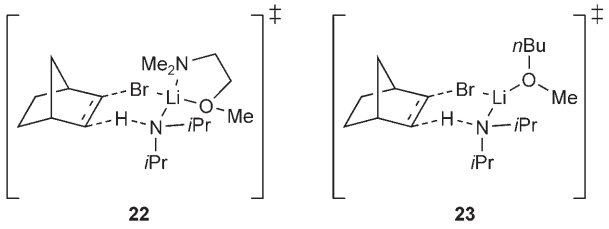
with THF alone and has little effect on the rates of ester enolizations.[34] Inhibition by HMPA has precedence, but it may not be widely appreciated.[46]

3.11. Rates Are Maximized by Stabilizing the Transition Structures, Not the Reactants

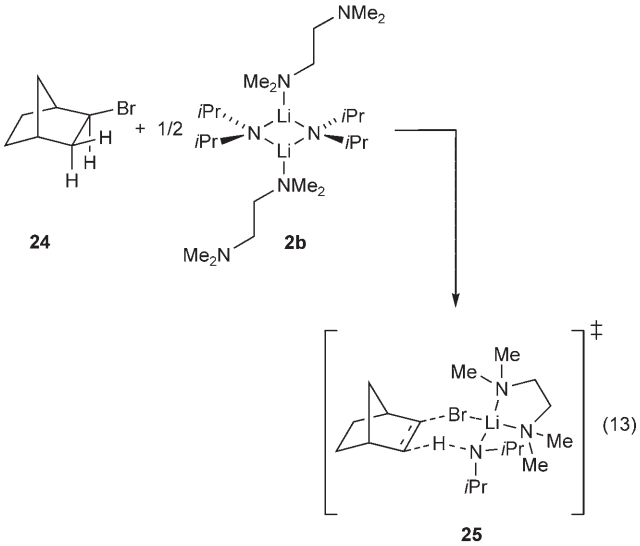
Although this statement is a truism in the purest sense almost unworthy of reiteration, a failure to understand it causes profoundly flawed reasoning. Discussions of solvent-dependent reactivities that consider the influence of solvent only in the transition states are, to put it bluntly, complete nonsense. (We facetiously call this the "universal ground-state assumption.")[33]

To achieve and better understand *selective* stabilization of the transition structure we turned to hemilabile ligands—bifunctional ligands bearing both a strongly and a weakly ligating group. Hemilabile ligands have been used by transition-metal chemists to exploit the stability of chelates while providing facile access to coordination sites.[47] We use them in the opposite sense, as illustrated generically in Scheme 2. A ligand that is η^1-coordinated in the reactant and η^2-coordinated at the rate-limiting transition structure (**20** or **21**) maximizes the benefits of chelation by eliminating counterproductive stabilization of the reactant.

LDA solvated by hemilabile diethers, diamines, and amino ethers (**2a**–**d**) is remarkably reactive. For example, dehydrobromination of norbornyl bromide by LDA/$MeOCH_2CH_2NMe_2$ (dimer **2c**) via transition structure **22** is 1100 times faster than with LDA/*n*BuOMe via **23**.[44] LDA/$MeOCH_2CH_2NMe_2$-mediated enolizations are 500 times



faster than enolizations with LDA/HMPA![48] Curiously, facile LDA/TMEDA-mediated *syn* dehydrobrominations are markedly accelerated by hemilability [Eq. (13)],[49] shedding further light on how TMEDA can influence organolithium structure and reactivity.



(13)

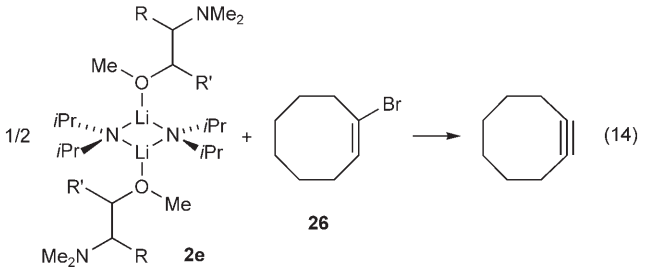
3.12. The Chelate Effect Is Not Well-Understood

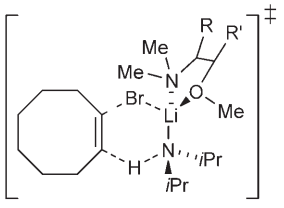
Our early efforts to study chelating ligands and potentially chelating substrates painted a muddled image of chelation. It became clear to us, however, that even the literature on transition-metal chemistry lacked incisive discussions of

chelation.[50] The problem stems, at least in part, from the choice of reference state. Chelates may be stable, but relative to what? We turned to hemilabile ligands to probe the chelate effect more systematically.

Bifunctional (hemilabile) ligands of general structure $MeO(CH_2)_nL$ and *n*BuOMe, an isostructural ethereal counterpart, have indistinguishable affinities for LDA.[43] By avoiding chelation in the reactants, the accelerations offer quantitative measures of the chelate stabilities exclusively in the transition structures. It was readily shown, for example, that five-membered chelates are the most stable, six-membered chelates display limited stability, and all other ring sizes offer no measurable stability. Dialkyl amino moieties ($L = R_2N$) are more strongly coordinating than their alkoxy counterparts (despite the preference for the MeO-bound form on LDA dimer **2**), with the least hindered Me_2N moiety optimal.

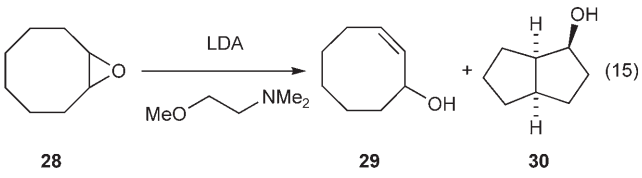
We suspected that substituents along the carbon backbone of the hemilabile ligand would markedly affect the relative propensities of the ligands to chelate at the transition structures, possibly increasing the stability of the chelate owing to the Thorpe–Ingold effect.[51] We were wrong. Using the elimination of HBr from cyclooctenyl bromide (**26**) as a model [Eq. (14)],[43a] we surveyed dozens of diethers and amino ethers to reveal that substituents destabilize the chelated transition structures (**27**) more than they destabilize η^1-coordinated reactants (**2e**). Computational studies suggest that the steric congestion (buttressing) in **27** is pronounced.



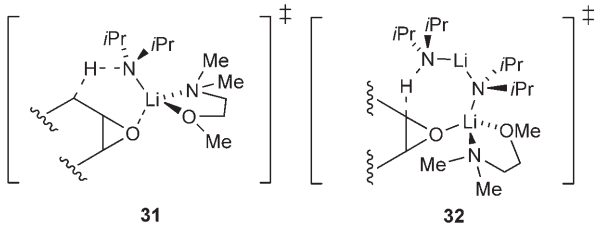


3.13. Selectivity Can Be Controlled Through Changes in Solvent Concentrations

Controlling selectivity is one of the holy grails of organic synthesis. Understanding how solvent concentrations influence rates leads to an understanding of how solvent concentrations dictate selectivities. By example, the LDA-mediated reaction of cyclooctene oxide bifurcates between α and β elimination, depending on the concentration of the hemilabile amino ether [Eq. (15)].[44] Rate studies reveal that the β elimination of epoxide **28** proceeds via monomer-based transition structure **31**, whereas the α elimination occurs via monosolvated dimer **32**. The preference for α elimination at low solvent concentrations stems from the lower solvation number (per lithium atom) of **32**.



MeO NMe$_2$	29/30
1.0 equiv	1:5
10.0 equiv	1:1

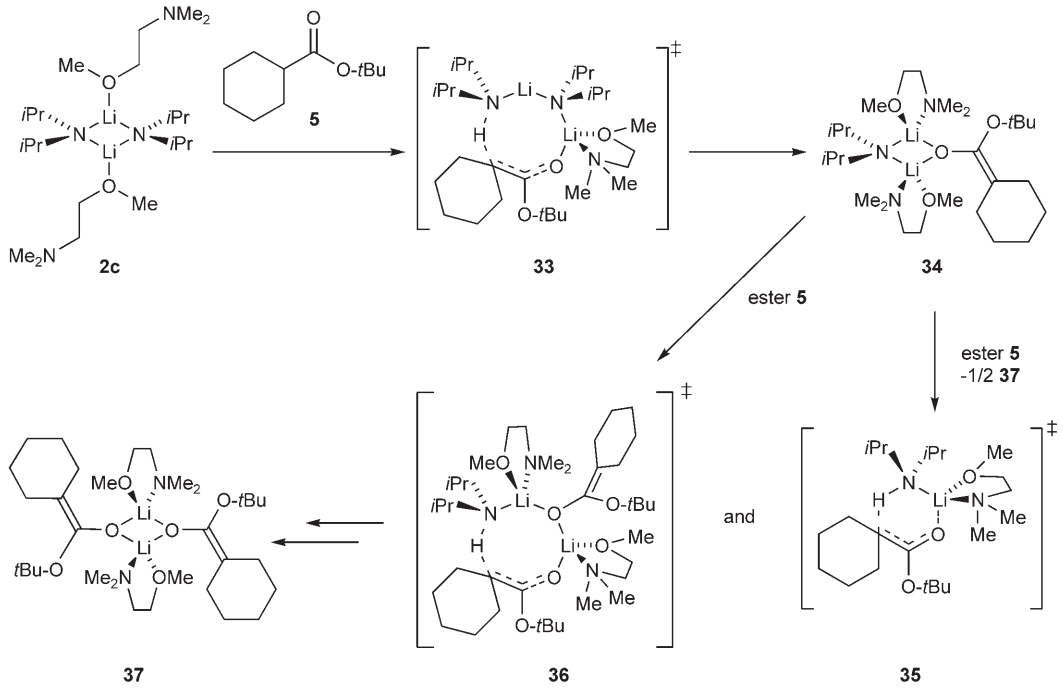


3.14. Mixed Aggregation Can Change Reaction Mechanisms, Rates, and Selectivities

During the course of an LDA-mediated lithiation, new lithium salts (LiX) are generated, and LDA is consumed. Spectroscopic studies show that LDA–LiX mixed aggregates (usually mixed dimers) form, often quantitatively.[52] These mixed aggregates are quite likely to influence selectivities and necessarily alter the rates and mechanisms as poignantly highlighted by Seebach in 1984.[53] For example, LDA/THF-mediated enolizations of 3-pentanone show a distinct erosion of the *E*/*Z* selectivity as a function of percent conversion that was traced to intervening LDA–lithium enolate mixed dimers and trimers.[52a]

In most of our rate studies we have avoided the consequences of mixed aggregation by maintaining the organolithium reagent in large excess. Nonetheless, qualitative probes of LDA-mediated ester enolizations[52b] and arene ortholithiations[52c] using equimolar solutions of LDA and substrate show that the lithiations tend to stall at 50% conversion. Although mixed-aggregate-derived autoinhibition appears to be common, the magnitude is sensitive to the choice of solvent.[52b,c]

The painstaking job of untangling precisely *how* mixed aggregation influences reactivity and selectivity is enormously important[53] and is likely to demand a large portion of our efforts in the future. Initial results are provocative. Scheme 3 illustrates the influence of an LDA–lithium enolate mixed aggregate on the mechanism of ester enolization. At the start of the reaction—before the appearance of mixed aggre-



2c **33** **34** **37** **36** **35**

Scheme 3. Aggregates and mixed aggregates involved in enolization.

gates—the enolization proceeds via open dimer **33**. At 50% conversion, mixed aggregate **34** becomes the only observable aggregate, and the reaction stalls. Rate studies at higher temperatures uncovered two pathways through which mixed dimer **34** reacts with ester **5**: 1) a mixed-dimer-based enolization bearing two coordinated amino ethers as depicted in **36** favored with a large excess of homoaggregated enolate, and 2) a monomer-based enolization via transition structure **35** requiring dissociation (deaggregation) of the lithium amide and enolate fragments promoted at low homoaggregated enolate concentrations. Of course, the intervention of mixed-dimer-based transition structure **36** represents a conspicuous mechanistic event. It is the monomer-based enolization demanding dissociation of the enolate fragment, however, that provides the most interesting and unanticipated views into mixed-aggregation effects.

Lithium salts, whether explicitly added or generated during the reaction, cause pronounced changes in stereo- and regioselectivities.[3c,8a,20] For many years we believed it to be a truism that salts influence selectivities only if the salts are affiliated intimately with the organolithium reagent and substrate at the product-determining transition structure. We were wrong. Mixed aggregate **34** diverts the reaction from a dimer-based to a monomer-based pathway. How could the dimer and mixed dimer result in enolate-free mechanisms that are different? One can envision the influence of mixed aggregation on the enolate-free pathways by considering the monomer- and dimer-based transition structures **35** and **33** as an equilibrium [Eq. (16)]. Their relative efficacies depend on

$$^{1}/_{2}A_2S_2 + [AS(\text{substrate})]^{\ddagger} \rightleftharpoons [A_2S(\text{substrate})]^{\ddagger} + S \qquad (16)$$

2c **35** **33**

the free LDA dimer (**2c**) and solvent concentrations. To the extent that formation of mixed aggregate **34** serves to reduce the concentration of LDA dimer according to the principle of detailed balance,[54] one predicts a relative promotion of the monomer-based pathway [Eq. (16)]. Extraneous lithium salts can influence the mechanisms and, in turn, selectivities without being intimately affiliated with the substrate or lithium-based reagent at the product-determining transition structure.

4. Optimizing Rates and Selectivities

What is the practitioner of organolithium chemistry to do with this information? How does one apply this knowledge to the optimization of yields and selectivities of other organolithium reactions? To answer these questions we have assembled a list of suggestions. Many are known to experienced organic chemists; we simply provide some mechanistic nuances. Others are not at all obvious from a casual reading of the literature. These suggestions are presented with a brief summary as to how changes in protocol might elicit favorable responses and why.

4.1. Use Rates Rather Than Isolated Yields to Probe Mechanism

As noted in a previous review,[42] yields are a poor measure of mechanism. Improving a yield from 60 to 80% could result from a trivial change in rates, providing little if any useful information. In contrast, improving a yield from less than 1% to 20% may signal a profound change in rates. There is little reason to avoid measuring either rate constants

or initial rates (slopes) given quantitative analytical methods (GC, HPLC, in situ IR spectroscopy) and user-friendly linear and nonlinear regression software. Detailed tutorials describing how to execute nonlinear least-squares analyses using two commercially available statistical packages are included in the Supporting Information. They require 30 minutes to complete.

4.2. Change the Solvent Concentration, Not the Solvent

Changing a solvent is standard protocol when using a purely empirical approach to optimization. Unfortunately, the contributions from relative ground-state and transition-state effects often cannot be deconvoluted (Section 3.8). In contrast, changing a solvent *concentration* reveals the role of the solvent. If decreasing a solvent concentration by using a hydrocarbon cosolvent causes the rates to drop proportionately (signifying a first-order dependence) or exponentially (signifying a higher-order dependence), it might be productive to try strongly coordinating solvents or even bidentate (hemilabile) ligands. If the rates increase, however, then requisite solvent dissociation is implicated, and using either weakly coordinating solvents or completely omitting coordinating solvents may offer advantages. In the event that these changes in rates are accompanied by changes in selectivity, you can begin to understand the mechanistic basis of the selectivity. Moreover, it is trivial to ascertain the solvent orders of the product-forming steps by simply noting the concentration-dependent changes in ratios.[44]

4.3. Minimize Donor Solvent Concentrations

Recall that zeroth-order dependence on donor solvents is prevalent. Such a dependence suggests that although the structure of the solvent may be important, the *concentration* of the uncoordinated solvent is not. The practical consequences of solvent concentration-independent rates could be considerable. It is likely to be much more cost-effective, for example, to use a hydrocarbon cosolvent as the medium and relegate expensive coordinating solvents to the role of stoichiometric ligands. These cost savings could become quite large on process and plant scales.[55]

4.4. Beware of Polar Cosolvents

THF is a strongly coordinating solvent that will displace most ligands from lithium, dictating both structure and reactivity.[7,8b,35a] Specialized ligands (such as sparteine) often cannot compete with neat THF.[8b,56] Therefore, hydrocarbon cosolvents maximize the probability that added ligands will participate in the reaction coordinates. Omitting the ethereal solvent may also eliminate the poorly understood cooperative solvation that may be prevalent in ligand/ether mixtures.[57]

4.5. Change Organolithium Concentrations and Stoichiometries

Although it seems self-evident that excess organolithium reagent would facilitate a recalcitrant reaction, that is not necessarily true. If an organolithium–substrate complex forms appreciably (Section 2.7), the reaction could be either insensitive to or even *inhibited* by excess organolithium reagent.[21,29] Furthermore, if autoinhibition or autocatalysis are operative owing to mixed aggregation (Section 3.14), the rates, percent conversions, yields, and selectivities may depend markedly on the number of equivalents of reagent added.

4.6. Embrace Two-Point Curves

Imagine you measure a rate and then show that a fivefold increase in the organolithium concentration elicits a fivefold acceleration. Also imagine that a fivefold increase in the solvent concentration causes a fivefold *deceleration*. What do these three experiments tell us? 1) Increasing the organolithium concentration may be productive (leaving mixed-aggregation effects aside). 2) The apparent first-order dependence on organolithium reagent (Figure 4, $a = 1$) suggests that an organolithium–substrate complex does not form appreciably (Section 2.7). 3) *If* the organolithium is likely to be aggregated (an educated guess can usually be gleaned from the structural organolithium literature),[4,7,20b] then the rate-limiting transition structure is likely to involve an aggregate as well. 4) The apparent inverse first-order dependence on the solvent concentration—a two-point version of curve $b = -1$ in Figure 5—implicates a requisite solvent dissociation, probably owing to a stabilizing substrate–lithium interaction at the transition structure. 5) Weakly coordinating or noncoordinating solvents might accelerate the reaction. Thus, we can obtain significant information from only three experiments.

4.7. Monitor Selectivities over the Course of the Reaction

Selectivities and reaction rates can change over the course of a reaction owing to the buildup of lithium salts and intervening mixed aggregates (Section 3.14). To test for mixed-aggregation effects, selectivities should be monitored as a function of percent conversion. If the reaction is too fast to monitor while in progress, the selectivities should be monitored by adding the substrate incrementally. It is critical to know whether the selectivities are increasing, decreasing, or unchanged as the reaction progresses.

4.8. Add Lithium Salts

If mixed-aggregation effects are detected using the probes noted above, try adding other lithium salts.[3c,20a] For example, if the selectivity of a 1,2-addition to a ketone improves with percent conversion, tertiary alkoxides should be added at the outset. If the selectivity erodes with percent conversion, lithium halides may improve selectivity by occluding the

interfering lithium salts being formed. Even if the selectivities are unchanged with percent conversion, add lithium halides, lithium alkoxides, or even highly functionalized salts such as β-amino lithium alkoxides.[53] Moreover, to the extent that homoaggregate–mixed-aggregate equilibria are solvent-dependent,[7,52b] solvent-dependent rates and selectivities may reflect solvent-dependent mixed-aggregation effects. In our experience, mixed-aggregation effects are most probable in weakly coordinating solvents.[8d,52b]

4.9. Try Hemilabile Ligands

Admittedly, we are biased, but the facts speak for themselves. A number of LDA-mediated lithiations have been shown to be orders of magnitude faster using LDA/$MeOCH_2CH_2NMe_2$ in hydrocarbons when compared with the more conventional LDA/THF or LDA/HMPA mixtures. Although both DME and TMEDA function as hemilabile ligands in some settings, vicinal amino ethers such as $MeOCH_2CH_2NMe_2$ may prove superior. Can hemilability be exploited to accelerate other organolithium reactions?[58]

5. Summary and Outlook

> *"I believe that, for those who seek to discover new reactions, the most insightful lessons come from trying to trace important reactivity principles back to their origins."*
> K. Barry Sharpless, 1983[59]

Organolithium chemistry is of unquestionable importance in organic synthesis and is no longer limited to academia. A comprehensive survey of scaled procedures used by Pfizer Process during the last twenty years shows that 68% of all C–C bond formations are carbanion-based.[60] Process chemists at Schering-Plough recently reviewed applications of organolithium chemistry used to carry out asymmetric transformations by the pharmaceutical industry.[61] Organolithium reagents are indeed "unavoidable".[6b] We submit that understanding the underlying structures and mechanisms is also becoming important.

In the first portion of this Review we provide a tutorial on solution kinetics for the nonspecialist. We illustrate how one can use simple principles to understand seemingly elusive mechanistic issues. We believe a brief look at the principles of kinetics is timely. Physical organic chemistry is, once again, moving to the forefront, fueled by new analytical methods. Mechanistic studies are commonplace in pharmaceutical process laboratories.[17,55] This has not always been true.

The second portion of this Review describes what rate studies of LDA-mediated reactions have taught us about solvation and aggregation as determinants of reactivity. Many longstanding notions about organolithium structure–reactivity relationships have not held up to scrutiny. It is now clear that strong solvents do not necessarily lead to lower aggregates, and neither lower aggregates nor strong solvents necessarily correlate with high reactivity. A picture of considerable complexity is emerging, but it is a self-consistent picture.

The third section of the Review describes some strategies for optimizing rates, yields, and selectivities of organolithium reactions. By simply considering mechanisms that *might* be operative helps focus the experiments. The tools and tactics familiar to kineticists can be used without becoming a practicing kineticist.

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