Regioselective Lithium Diisopropylamide-Mediated Ortholithiation of 1-Chloro-3-(trifluoromethyl)benzene: Role of Autocatalysis, Lithium Chloride Catalysis, and Reversibility

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Supporting Information

ABSTRACT: Ortholithiation of 1-chloro-3-(trifluoromethyl)benzene with lithium diisopropylamide (LDA) in tetrahydrofuran at −78 °C displays characteristics of reactions in which aggregation events are rate limiting. Metalation with lithium-chloride-free LDA involves a rate-limiting deaggregation via dimer-based transition structures. The post-rate-limiting proton transfers are suggested to involve highly solvated triple ions. Autocatalysis by the resulting aryllithiums or catalysis by traces (<100 ppm) of LiCl diverts the reaction through di- and trisolvated monomer-based pathways for metalation at the 2 and 6 positions, respectively. The regiochemistry is dictated by a combination of kinetically controlled metalations overlaid by an equilibration involving diisopropylamine that is shown to occur by the microscopic reverse of the monomer-based metalations.

INTRODUCTION

Equation 1 illustrates lithium-amide-mediated ortholithiations of 1 first studied by Schlosser and co-workers.1 Divergent regioselectivities derived from lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LiTMP) have been observed for ortholithiations and are often attributed to steric effects.2 Further experiments, however, show this to be too simplistic. The reactions are extraordinarily sensitive to the source of LDA: commercially purchased LDA prepared from styrene and lithium metal is approximately 10 times less reactive than LDA generated using n-BuLi and i-Pr₂NH, and the regioselectivities are similar but not identical. Monitoring reactions of analytically pure LDA3 using in situ IR and ¹⁹F NMR spectroscopies uncovers additional oddities. Addition of low concentrations of arene affords a linear disappearance of 1 and a slight drift in regioselectivity that continues after the metalation is complete (Figure 1A). Ortholithiation using higher substrate concentrations (Figure 1B) affords a sigmoidal disappearance of arene 1 and a distribution of regioisomers 2 and 3 that changes markedly over time. Traces of LiCl added to a reaction in progress causes a burst of reactivity that displays upward curvature (Figure 2).

We describe herein rate and mechanistic studies of the ortholithiation in eq 1 that support the simplified mechanistic scenario summarized in Scheme 1, studies which culminated in the best-fit numerical integrations displayed in Figure 1. The high regioselectivity of the reaction at −60 °C derives from an equilibration of aryllithiums (2a and 3a), which is discussed in detail.4,5 The really interesting part of this story, however, is what lurks beneath the 2:1 selectivity using LDA in tetrahydrofuran (THF) at −78 °C. The ortholithiation of 1 joins a growing class of LDA-mediated transformations in which the fragmentation of LDA dimer 4 is rate limiting.5 Reactions within this class proceed at −78 °C, conditions prevalent in organic chemistry,8 and are prone to both autocatalysis as well as catalysis by traces of LiCl and other exogenous lithium salts.8,9 The ortholithiation of 1 introduces two prominent dimensions absent in previous studies: (1) aryllithiums 2a and 3a are inequivalent autocatalysts, and (2) the uncatalyzed and catalyzed lithiations proceed via distinctly different fleeting structural forms of LDA (5 and 6).

The results section offers a view of how the mechanisms were determined. The data are highly interdependent but are necessarily presented linearly. Evidence supporting the conclusions paints a compelling picture when considered collectively. The discussion begins with a summary, which is followed by analyses of rate-limiting deaggregation, LiCl catalysis, autocatalysis, and aryllithium (ArLi) equilibration. The conclusion considers the implications from the divergent perspectives of mechanistic and synthetic organic chemists.

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RESULTS

Solution Structures. Structural assignments of LDA and aryllithiums are required to interpret the rate data. Previous studies of \(^{\text{\textsuperscript{7}}}{\text{Li}}, \text{\textsuperscript{15}}\text{N}\)|LDA using \(^{\text{\textsuperscript{7}}}{\text{Li}}\) and \(^{\text{\textsuperscript{15}}}{\text{N}}\) NMR spectroscopy\(^{10}\) reveal exclusively disolvated dimer \(^{4}\).\(^{11}\) The \(^{13}\text{C}\) NMR spectra of aryllithiums \(^{2}\) and \(^{3}\) display 1:1:1 triplets for the lithiated carbons.\(^{12}\) The triplet corresponding to \(^{2}\) is further split by \(^{19}\text{F}–^{13}\text{C}\) coupling, whereas no such coupling is observed for \(^{3}\). The \(^{19}\text{F}(^{1}\text{H})\) NMR spectra display singlets.\(^{13}\) Generating \(^{2}\) and \(^{3}\) with excess \(^{\text{\textsuperscript{7}}}{\text{Li}}, \text{\textsuperscript{15}}\text{N}\)|LDA shows no \(^{7}\text{Li}–^{15}\text{N}\) splitting in the \(^{7}\text{Li}\) resonances of \(^{2}\) and \(^{3}\), confirming the absence of mixed aggregation.\(^{10}\) Comparing 1 recovered from quenching metallocations using \(\text{D}_2\text{O}\) with authentic samples prepared from the corresponding aryl bromides\(^{14}\) confirm the assignments. Density functional theory (DFT) computations at the B3LYP/6-31G(d) level\(^{15}\) with single-point calculations at the MP2 level of theory implicate trisolvated monomers (2\(^{a}\) and 3\(^{a}\); Scheme 1) in accord with other monomeric aryllithiums.\(^{16}\) References to 2\(^{a}\) and 3\(^{a}\) are used instead of \(^{2}\) and \(^{3}\) when the structural details need to be specified. Under conditions of LiCl catalysis (<5.0 mol % LiCl), LiCl has been shown to exist exclusively as an 8:1 mixture of mixed trimer \(^{7}\) and dimer \(^{8}\).\(^{3,17}\)

Kinetics: General Protocols. Acceleration of ortholithiations by as little as 0.01 mol % LiCl (1.0 ppm) demands preparation of rigorously LiCl-free LDA from lithium metal and isoprene. The solid LDA was subsequently recrystallized from hexanes.\(^{3}\) Exogenous LiCl was generated in situ from Et\(_3\)N • HCl.\(^{18}\) Et\(_3\)N is a poor ligand\(^{19}\) that has no effect on LDA structure or reactivity. The disappearance of arene 1 is most conveniently followed using in situ IR spectroscopy (1325 cm\(^{-1}\)).\(^{20}\) \(^{19}\text{F}\) NMR spectroscopy was used to follow 1 (\(\delta = -62.21\) ppm), 2 (\(\delta = -61.71\) ppm), and 3 (\(\delta = -60.90\) ppm) concurrently. The initial rates of metalation\(^{21}\) were obtained from the first derivative of a polynomial fit to data from 0–5% conversion.\(^{22}\) On several occasions the reaction temperature was raised to \(-65\) °C (as noted) to avoid protracted reaction times.

Uncatalyzed Ortholithiation: Rate-Limiting Deaggregation. Let us first examine the mechanism of the uncatalyzed metalation. Monitoring the metalation of 1 at early conversion, measuring the rates before the onset of autocatalysis, reveals a rate-limiting deaggregation of dimer 4. Thus, a plot of initial rate versus arene 1 concentration shows a clear zeroth-order dependence consistent with the absence of arene 1 in the rate-limiting

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Representative plots of concentration versus time monitored by \(^{19}\text{F}\) NMR spectroscopy for the ortholithiation of 1 and formation of 2 and 3 by LDA (0.10 M) in THF (12.2 M) at \(-60\) °C: (A) 0.005 M 1; (B) 0.050 M 1. The curves represent best-fit numerical integrations as described below.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Ortholithiation of 1 (0.010 M) with LDA (0.10 M) in THF (12.2 M) at \(-78\) °C monitored by IR spectroscopy (1325 cm\(^{-1}\)) with injection of 1.0 mol % LiCl (0.001 M).

![Scheme 1](https://example.com/scheme1.png)

**Scheme 1.**
The curve depicts an unweighted least-squares fit to \( y = a[\text{ArH}] + b \). \( a = (9 \pm 1) \times 10^{-3} \), \( b = (7 \pm 8) \times 10^{-9} \).

Figure 3. Plot of initial rate vs \([1]\) (initial arene concentration) for the ortholithiation of 1 with LDA (0.10 M) in THF (12.2 M) at \(-78^\circ C\) measured by IR spectroscopy. The behavior of doubly deuterated arene \(1\) (0.050 M) by LDA (0.10 M) at \(-78^\circ C\) measured by IR spectroscopy. The curve fits depict an unweighted least-squares fit to \( y = a[\text{THF}] + b \). \( a = (7 \pm 1) \times 10^{-3} \), \( b = (3.9 \pm 0.1) \times 10^{-9} \).

Figure 4. Plot of initial rate versus \([\text{THF}]\) in hexanes for the ortholithiation of 1 (0.050 M) by LDA (0.10 M) at \(-78^\circ C\) measured by IR spectroscopy. The curve depicts an unweighted least-squares fit to \( y = a[\text{LDA}] + b \). \( a = (1.2 \pm 0.2) \times 10^{-5} \), \( n = (1.16 \pm 0.09) \).

Figure 5. Plot of initial rate versus \([\text{LDA}]\) in THF (12.2 M) for the ortholithiation of 1 (0.050 M) at \(-78^\circ C\) measured by IR spectroscopy. The curve depicts an unweighted least-squares fit to \( y = a[\text{LDA}] + b \). \( a = (1.2 \pm 0.2) \times 10^{-5} \), \( n = (1.16 \pm 0.09) \).

The initial rates are independent of THF concentration (Figure 4) and display an approximate first-order dependence (1.16 \pm 0.09 order) on LDA concentration (Figure 5).\(^{24,25}\) Isotopic labeling studies (below) confirm post-rate-limiting proton transfer.

Uncatalyzed Ortholithiation: Kinetic Isotope Effects. Deuterium labeling studies confirm that the critical proton transfer (still measured at early conversion) is post-rate-limiting. The analysis was carried out using \(^{19}\)F NMR spectroscopy and is summarized in Scheme 2. By focusing on the unlabeled substrate (1) and monodeuterated substrates (1-2-\(d\) and 1-6-\(d\), we noted that the rates of disappearance of the three isotomers are indistinguishable (±5%) despite the suppression of specific pathways. Such equivalent intermolecular isotope effects\(^{26,28}\) are consistent with post-rate-limiting proton (deuteron) transfers. The ratios of rate constants corresponding to isotopically sensitive (but post-rate-limiting) branch points \((k_{H(2)}/k_{D(2)}, k_{H(2)}/k_{D(2)}, k_{H(2)}/k_{D(2)})\) were determined by measuring the respective 2/3 ratios at early conversion using \(^{19}\)F NMR spectroscopy. The regioselectivities make intuitive sense: deuteration at C2 (1-2-\(d\)) markedly promotes metalation at C6 (2:3 = 1:18), whereas deuteration at C6 (1-6-\(d\)) promotes metalation at C2 (2:3 = 34:1). The intramolecular isotope effects\(^{28,29}\) corresponding to \(k_{H(2)}/k_{D(2)}\) and \(k_{H(6)}/k_{D(6)}\) were calculated according to eqs 6 and 7 and found to be substantial and inequivalent.\(^{30}\)

\[
\frac{k_{H(2)}}{k_{D(2)}} = \frac{(k_{H(2)}/k_{H(6)})}{(k_{D(6)}/k_{D(2)})} = 31
\]

\[
\frac{k_{H(6)}}{k_{D(6)}} = \frac{(k_{H(6)}/k_{H(2)})}{(k_{D(2)}/k_{D(6)})} = 19
\]

The behavior of doubly deuterated arene 1-2,6-\(d_2\) diverges from that of the other three substrates and offers an interesting window into the mechanism.\(^{31}\) The curvatures exhibited by the
decays are highly dependent on arene concentration. At high concentration (0.10 M) we observe downward curvature characteristic of autocatalysis. As the concentration decreases, the downward curvature gives way to upward curvature that becomes exponential at <0.005 M, which is expected for first-order arene dependencies.

The upward curvature suggests that deuteration causes the metalation to become at least partially rate limiting. Moreover, the initial metalation rate at 0.050 M \(1\)-2,6-\(d_2\) is approximately 3-fold slower than that of the other three isotopomers (eq 8), showing that the metalation rate has an attenuated but detectable isotopic sensitivity. To understand the origins of this partial rate limitation we return to eq 3. A rate-limiting deaggregation demands that the fleeting intermediate denoted as \(A_2S_2^*\) (suggested computationally to be open dimer \(S\)) be trapped efficiently by \(ArH\) (\(k_2[ArH] \gg k_{-1}\)).

The much slower metalations of \(1\)-2,6-\(d_2\) cause deuterium transfer to become partially rate limiting (eq 9), where \(ArH\) is \(1\)-2,6-\(d_2\). The ratio \(a/b\) was constrained to \(1.6 \times 10^{-6}\) M s\(^{-1}\) to ensure saturation at the initial rate of \(1\) \((1.6 \times 10^{-6}\) M s\(^{-1}\)). [\(b = (2.62 \pm 0.08) \times 10^{-6}\).]

![Figure 6](image)

*Figure 6. Competitive ortholithiation of \(1\) (0.050 M) and \(1\)-2,6-\(d_2\) (0.050 M) with LDA (0.10 M) in THF (12.2 M) at \(-78^\circ\)C monitored by IR spectroscopy.*

![Figure 7](image)

*Figure 7. Plot of initial rate versus \(1\)-2,6-\(d_2\) for the ortholithiation of \(1\)-2,6-\(d_2\) by 0.10 M LDA in 12.2 M THF at \(-78^\circ\)C measured by IR spectroscopy. The curve depicts an unweighted least-squares fit to a first-order saturation function: \(-\Delta[ArH]/\Delta t = (a[ArH])/(1 + b[ArH])\) where \(ArH\) is \(1\)-2,6-\(d_2\). The ratio \(a/b\) was constrained to \(1.6 \times 10^{-6}\) M s\(^{-1}\) to ensure saturation at the initial rate of \(1\) \((1.6 \times 10^{-6}\) M s\(^{-1}\)). [\(b = (2.62 \pm 0.08) \times 10^{-6}\).]*
The curve depicts an unweighted least-squares fit to \( y = a(\text{THF})^n + b \), with 
\( a = 12.5 \pm 0.8, n = -0.8 \pm 0.2, \text{and } b = 0.1 \pm 0.8. \)

The elevated temperature was used to shorten the duration of the experiments. The curve affords what one might call an order of magnitude limitation, which approaches unity at the high concentration limit.

**Uncatalyzed Ortholithiation: Mechanisms of Proton Transfers.** The regioselectivity in this reaction provides a glimpse beyond rate-limiting deaggregation, a portion of the reaction coordinate considered largely invisible to kinetics. Monitoring the initial rates of formation of aryllithiums 2 and 3 using \(^{19}\text{F}\) NMR spectroscopy affords what one might call a relative rate law (eq 10). If, for example, 2 and 3 form via a single (shared) fleeting intermediate, then the regioselectivity (the post-rate-limiting branch) would be independent of LDA and THF concentrations. Indeed, the product ratios are independent of LDA concentration, showing a shared aggregation state. By contrast, although the overall metalation rates are THF-concentration independent, the product ratios show a greater tendency to form 3 at elevated THF concentration (Figure 8). A nonlinear least-squares fit shows that the metalation to form 3 requires one THF ligand beyond what is required for the metalation to form 2.

\[
\frac{[2]}{[3]} = c[\text{ArH}]^0[LDA]^0[\text{THF}]^{-1} \tag{10}
\]

Metalations at the lowest concentrations of 1-2,6-d\(_2\), conditions in which both the curvatures and isotope effects indicate that the rate-limiting step is deuterium transfer, allowed us to probe the events following the deaggregation step. A plot of \(k_{\text{obsd}}\) vs LDA concentration (Figure 9) shows near linearity (0.92 order), indicating that the metalation of 1-2,6-d\(_2\) is dimer-based as suspected. The corresponding plot of \(k_{\text{obsd}}\) versus THF concentration affords an altogether unexpected second-order THF dependence (Figure 10). Switching from hexane to 2,S-Me\(_2\) THF as the cosolvent to maintain a more constant polarity had no effect on the observed rates, again affording a second-order THF dependence. The combined data afford the rate law in eq 11 and the mechanism in eq 12 involving tetrasolvated dimers. We hasten to add that the two terms in eq 11 (the second order affiliated with the formation of 2 and the third-order solvent affiliated with formation of 3) and accompanying tetra- and pentasolvated terms in eq 12 do not derive from the measured solvent order in Figure 10 (which clearly approximates two) but rather from the relative solvent order illustrated in Figure 8 demanding differential solvation. We estimate from relative contributions of pathways leading to 2 and 3 that the measured solvent order should have been slightly above 2.

\[
\frac{[2]}{[3]} = c[\text{ArH}]^0[LDA]^0[\text{THF}]^{-1} \tag{10}
\]
Concerned that we might be getting deceived by the LDA order, we examined the influence of LiCl on the metalation rates. If the rate-limiting metalation proceeds via a pre-equilibrated monomer-based pathway, then LiCl should have no effect because LiCl serves to catalyze dimer/monomer exchange (vide infra). In the event, addition of LiCl to a metalation of 1,2,6-d$_2$ at low concentrations elicited a 10-fold acceleration, suggesting that the uncatalyzed and LiCl-catalyzed metalation are indeed different. Triple ions 10 and 11 are computationally viable candidates for the dimer-based reactions. Although the absolute energies of such highly ionized forms are of little value, 10 is 3.5 kcal/mol more stable than 11.$^{3,34}$

$$\frac{d[\text{ArH}]}{dt} = k_{(2)}[\text{ArD}]^2[A_2S_4]^3 + k_{(3)}[\text{ArD}]^2[A_2S_2]^3$$

$$A_2S_2 \xrightarrow{k_{(1)}} A_2S_4/S \xrightarrow{k_{(2)}} \text{ArLi}$$

Although the data implicate tetra- and pentasolvated dimers, we also explored various di- and trisolvated-dimer-based transition structures summarized in Figure 11. (We include those leading to the unobserved regioisomeric ArLi for comparison.) All are computationally reasonable, displaying absolute activation energies of 13–18 kcal/mol. The origins of the solvent-dependent regioselectivities fall within the error of the computations.$^{35}$

**LiCl Catalysis.** Traces of LiCl elicit marked rate accelerations that are accompanied by distinct upward curvatures, suggesting that LiCl catalysis brings arene 1 back into the rate law. Clean first-order decays are observed at >5 mol % LiCl (Figure 12). A plot of the initial rates versus LiCl concentration shows second-order saturation kinetics with the onset of saturation at low levels (<2.0 mol % LiCl) as noted in previous studies (Figure 13).$^{3,6}$

The saturation behavior in Figure 13 is not Michaelis–Menten kinetics, however, which would require stoichiometric LiCl to attain saturation.$^{36}$ It should also not be confused with the saturation kinetics noted for metalations of 1,2,6-d$_2$ shown in Figure 7 (although...

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**Figure 10.** Plot of $k_{\text{obsd}}$ versus [THF] in hexanes for the ortholithiation of 1,2,6-d$_2$ (0.002 M) by LDA (0.050 M) at $-65 \degree C$ measured by $^{19}$F NMR spectroscopy. The curve depicts an unweighted least-squares fit to $y = k[T\text{HF}]^n + c$. [$k = (3 \pm 1) \times 10^{-6}$, $n = 2.0 \pm 0.2$, and $c = (3 \pm 1) \times 10^{-5}$].

**Figure 11.** DFT computations [MP2/6-31G(d)//B3LYP/6-31G(d)] of dimer-based transition structures for the metalation of 1. The free energy of activation for the formation of 12 ($\Delta G^\ddagger$) is 19.3 kcal/mol calculated at $-78 \degree C$. The numbers affiliated with the arrows represent the relative free energies ($\Delta G$).
they are related). LiCl catalyzes a deaggregation. Analogous LiCl saturation behavior was observed for 1,4-additions of LDA to unsaturated esters, although the sigmoidal curvature evident at low LiCl concentrations (inset in Figure 13) that would signify a second-order LiCl dependence has not been observed. 3,37

The details of the deaggregation were examined at full saturation (5.0 mol % LiCl) as follows. Ortholithiation of 1 and 1-2,6-d2 reveals large and equivalent standard and competitive isotope effects (eqs 13 and 14) consistent with rate-limiting proton (and deuterium) transfer. Plotting initial rates versus LDA concentration affords a generic half-order dependence implicating a dimer/C0 monomer pre-equilibrium (Figure 14). 23 A plot of initial rates versus THF concentration using hexanes as cosolvent (Figure 15) shows a high (1.6 (0.3) order in THF. The curvature (a departure from a linear first-order dependence) was traced to medium effects using a now-routine protocol38 in which the hydrocarbon is replaced with the polar39 yet weakly coordinating 40 cosolvent, 2,5-dimethyltetrahydrofuran (Me2THF). Holding the polarity of the medium...
approximately constant afforded a THF order slightly above unity (1.1 \pm 0.1 order). The mechanism (eqs 15 and 16) and rate law (eq 17) include provisions for second-order saturation by LiCl. The odd mathematical form of eq 17 stems from the quadratic equation required by the deaggregation. The c term corresponds to the basal (uncatalyzed) rate. In the limit of full saturation, eq 17 reduces to eq 18.

\[
\frac{\Delta[\text{ArH}]}{\Delta t} = \frac{k_1[\text{ArH}]}{4k_{-1}[\text{LiCl}]} + \frac{1}{2}A_2S_2 + S \quad \text{AS}_2_k \rightarrow \text{AS}_2(\text{ArH})^* \quad \text{AS}_2 + \text{ArH} \\
\]

\[\frac{\Delta[\text{ArH}]}{\Delta t} = \left(\frac{k_1}{k_{-1}}\right)^{1/2}k_2[\text{ArH}][\text{THF}][\text{LDA}]^{0.5} \quad \text{(18)}\]

Comparing the regioselectivity in neat THF without catalysis (2.3 = 1.8:1) with that derived from LiCl catalysis (2.3 = 0.85:1) shows subtle differences that are mechanically important. Nonetheless, the regioselectivities under LiCl catalysis are, as noted for the uncatalyzed metalation, independent of LDA concentration and dependent on the THF concentration (Figure 16). In conjunction with the rate law, the results implicate an [AS_2 (ArH)]^+ stoichiometry for the formation of 3 and an [AS_2 (ArH)]^+ stoichiometry for the formation of 2. We examined the selectivities using DFT computations (Figure 17). All are computationally reasonable, displaying absolute activation energies of 12–15 kcal/mol. Disolvated monomer-based transition structure 21 and the corresponding trisolvate 24 are the most favorable, consistent with both the rate data and THF-dependent regioselectivities.

**Autocatalysis.** Autocatalysis is easily detected as downward curvature in plots of arene 1 versus time (Figure 1B). What makes detailed studies so challenging is that (1) 2 and 3 display different autocatalytic activities, (2) autocatalysis diverts dimer-based metalations prevalent in the absence of catalysis to monomer-based metalations, (3) the dimer- and monomer-based metalations display inherently different regioselectivities, and (4) an equilibration pathway superimposed on the autocatalysis converts 3 to 2.

The task of untangling the role of autocatalysis began with a routine control experiment to confirm its existence. After a kinetic run using 0.10 M LDA and 0.001 M arene 1 in neat THF, the IR baseline was zeroed and a second aliquot of 1 added (Figure 18). The loss of arene displays a distinct acceleration accompanied by substantially greater upward curvature (loss of downward curvature). Autocatalysis by ArLi (2 and 3) is analogous to the 100-fold more efficient catalysis by LiCl. Of particular note, the regioselectivities for the ArLi- and LiCl-catalyzed metalations are indistinguishable (2.3 = 0.85:1) and different from the 1.8:1 ratio observed for the uncatalyzed metalation. Moreover, plotting the initial rates versus ArLi concentration (Figure 19) shows saturation kinetics analogous to that observed for LiCl (Figure 13) but at much higher ArLi concentrations. The data shown in Figure 19 was generated using regioisomer d-6 because it was easily generated in 95% regioisomeric purity from d-6. Because of the 2.3 = 0.85:1 ratio from the 1.8:1 ratio observed for the uncatalyzed metalation. Moreover, plotting the initial rates versus ArLi concentration (Figure 19) shows saturation kinetics analogous to that observed for LiCl (Figure 13) but at much higher ArLi concentrations. The data shown in Figure 19 was generated using regioisomer d-6 because it was easily generated in 95% regioisomeric purity from d-6.

**Mechanism of Equilibration.** Conversion of ArLi 3 to 2 is observed over the course of the metalations and is readily effected.
through gentle warming. The equilibration is accelerated by added i-Pr₂NH, which was anticipated from rate studies of a reaction requiring an analogous equilibration.⁵ To study the mechanism in detail, we generated less stable regioisomer 3 from 1 in 20:1 selectivity using LiTMP. Equilibration during the ortholithiation is negligible because the highly hindered N,N,N',N'-tetramethylpiperidine byproduct does not mediate the exchange. Subsequent addition of i-Pr₂NH initiates the conversion of 3 to 2. The decay of ArLi 3 fits a first-order function (Figure 20). The pseudo-first-order rate constants show a first-order dependence on i-Pr₂NH (Figure 21) and a zeroth-order dependence on THF. The idealized⁶ rate law (eq 19) in conjunction with the assigned resting state of 3 as trisolvate 3a is consistent with the generic mechanism in eqs 20 and 21. The proton transfer is necessarily partially rate limiting in that the fleeting arene partitions to 1:1 mixture of 2 and 3. It is satisfying that transition structure \([\text{ArLi}](\text{THF})_3(i-\text{Pr}_2\text{NH})\)⁸ for protonation of 2 is stochiometrically the same as the transition structure \([(i-\text{Pr}_2\text{NLi})(\text{THF})_3(\text{ArH})]\) for metalation because the principle of microscopic reversibility⁴⁴ demands that they be the same transition structure.

\[
\frac{d[3]}{dt} = k'[\text{[i-Pr}_2\text{NH]}][\text{THF}]^0
\]  

(19)

\[
\text{ArLiS}_3 + i-\text{Pr}_2\text{NH} \rightarrow [\text{ArLiS}_3(i-\text{Pr}_2\text{NH})]^\ddagger \rightarrow \text{ArH} + [\text{AS}_3]
\]  

(20)

\[
\text{ArH} + [\text{AS}_3]^\text{tor} \rightarrow 2 + 3
\]  

(21)

Mechanistic Hypothesis and Numeric Integrations. Rate and mechanistic studies were pieced together to form the mechanistic hypothesis shown in Scheme 1, which has been reformulated as Scheme 3 and described by the affiliated differential equations in eqs 22–28. (A₂⁺ represents an activated LDA dimer whereas ArLi₄(2) and ArLi₄(3) denote aryllithiums 2 and 3.) We have taken some liberties with the depiction of the model in Scheme 3 to optimize the visual presentation. Although the role of solvent has been elucidated for a number of steps, it is not germane to the numerical fits and has been omitted for clarity. We depict the critical autocatalytic step by affiliating \(k_2\) and \(k_{-2}\) with autocatalyst ArLi (either 2 or 3); it is
described numerically in the differential equations based on the equilibrium
\[ A_2 + ArH \rightleftharpoons A + ArLi + i-Pr_2NH \]
ArLi generically stands for ArLi(2) and ArLi(3). Because ArLi(4) is 6
times less catalytically active than ArLi(2), its rate contribution is scaled
accordingly in the curve fit. (We avoid treating the two autocatalysts
separately.) The equilibria in Scheme 3 are unbalanced to minimize
diffusional inequilibria. The results can be understood in the context of Scheme 1
by monomer-based pathways. LiCl catalysis, for example, causes large (100-fold) accelerations and affords
concentration dependencies and isotope effects consistent with di- and trisolvated-monomer-based metalations and rate-limiting proton transfers. Computational studies support di- and trisolvated-monomer-based transition structures 21 and 24 (Scheme 4), but others are plausible as well (Figure 17).

In the absence of LiCl, autocatalysis by 2 and 3 that form
during the reaction elicits acceleration as the reaction proceeds
(Figure 1B). Autocatalysis appears to divert the reaction
through the same monomer-based pathways as those shown in Scheme 4. This conclusion derives support from regioselectivities that suggest a commonality of intermediate(s) with LiCl-catalyzed metalation. Moreover, 2 is 6-fold more autocatalytically active than isomer 3. Both pale in comparison with LiCl, however.

Dissopropylamine formed during the reaction slowly equilibrates regioisomers 2 and 3. Such equilibriums are well-known, and participation by dissopropylamine has been documented. Detailed studies of such an equilibration appear to have been reported in only one instance. The nearly quantitative formation of 2 at equilibrium restricted rate studies to the unidirectional conversion of 3 to 2. The conversion is shown to be the microscopic reverse of the monomer-based metalation in Scheme 4, proceeding via trisolvated-monomer-based transition structure 24. It is not a particularly bold assertion that the protonation of 2 to give 1, although kinetically invisible to us, involves the microscopic reverse of the metalation via disolvate 21.

The independence pieces assemble to afford the mechanistic scenario summarized in Scheme 1. Additional insights about the role of solvation as well as steps that follow rate-limiting formation of open dimer 5 are not included in Scheme 1. The mechanism was reduced to the mathematically tractable model summarized in Scheme 3 and described by differential eqs 22-28. Best-fit numerical integrations are illustrated in Figure 1. On the one hand, the mechanistic model is not uniquely defined by the data; there are minor mechanistic variants that fit the data equally...
well. Nonetheless, the quality of the fits shows consistency with the proposed mechanism.

**Regioselectivities.** The regioselectivities of the metalations are highly sensitive to reaction conditions as underscored in Figures 1 and 2. A number of underlying factors are at play. In the absence of salt-catalyzed deaggregation, the metalations show a modest bias toward 2 that approaches 7:1 selectivity at low THF concentration (Figure 8), a bias that derives from the dimer-based metalations in Scheme 4. Autocatalyzed or LiCl-catalyzed metalations promote the formation of 3, moreso at high THF concentrations, owing to the monomer-based pathways. As the reactions proceed to full conversion, however, the equilibration becomes dominant, obscuring the kinetic selectivity and affording exclusively 2 in the limit of long reaction times.

The kinetically controlled regioselectivity appears to be dominated by steric effects with contributions from an eclectic mix of directing effects. Solvating lithium cations can be sterically very demanding. Not surprisingly, therefore, both dimer- and monomer-based metalations of 1 to form 2 require lower solvation numbers than do the analogous metalations to form regioisomer 3. Coordinating effects are also complex, however. Computations show viable transition structures with lithiums ligated by trifluoromethyl and chlorine and even with no ligation by substrate whatsoever. A natural tension arises between the tendency to maximally solvate lithium with strongly coordinating solvent and the tendency to coordinate the ortho-directing moieties.

**Peering Beyond Rate-Limiting Steps.** A rate-limiting LDA deaggregation may seem to constitute an opaque wall that renders the structures of fleeting intermediates and the mechanisms of proton transfers invisible (Scheme 5). This is incorrect. Admittedly, the intermolecular isotope effect, the influence of isotopic substitution on the reaction rate, will be unity if the proton transfer occurs after the rate-limiting step. By contrast, intramolecular isotope effects, isotope effects measured by a competition for abstraction between hydrogen and deuterium within the same molecule, will reflect the isotopic sensitivity of the post-rate-limiting metalation in the product distribution.

The concept behind intramolecular isotope effects also applies to competitive isotope effects in which two isotopically distinct substrates are competed. In this experiment, comparing 1 and 1-2,6-d2 (eq 9) reveals a large competitive isotope effect comparable to the values in Scheme 2, confirming that the post-rate-limiting metalation is isotopically sensitive. Of particular note, the accompanying biphasic kinetics (Figure 6), in which the less reactive isotopomer metalates only after the protio form has been consumed, is highly characteristic of a post-rate-limiting branch point.

Details of post-rate-limiting metalations are also reflected in their condition-dependent regioselectivities. We found, for example, that the proportions of 2 and 3 are LDA concentration-dependent.
monomer, and the quantities of LiCl required to attain full equilibration are stunningly small (<1.0 mol %; 1.0 ppm). Such catalysis has been observed previously, but the second-order saturation behavior evident in Figure 13 (see inset) was not observed. Our ongoing struggle to understand the details of LiCl catalysis is acute because LiCl exists exclusively as a mixture of mixed aggregates 7 and 8 at such low concentrations, and we do not know the fate of 7 and 8 under the reaction conditions. Let us make the seemingly plausible supposition, however, that the second order derives from a catalyzed deaggregation involving a transition structure of stoichiometry \([\text{(i-Pr}_2\text{NLi})_2\text{(LiCl)}_2]^n\) (mixed tetramer).

We envision two fleeting intermediates that account for the catalysis and the accompanying second-order dependence on LiCl concentration. The first is ladder 28, which has ample precedent in structural lithium amide chemistry. The dissociation of LDA monomer from 28 (eq 29) has an energetic appeal because 28 would require dissociation of only one monomer rather than dissociating two high energy monomers from a dimer. The remaining three-rung ladder, 29, could be loosely considered a leaving group.

\[
\text{(i-Pr}_2\text{NLi})_2 + \text{LiCl} \rightarrow \text{i-Pr}_2\text{NLi}^+ + \text{LiCl}^-(29)
\]

Triple ions offer an even more provocative vehicle for deaggregating LDA dimer (Scheme 7). One could view chloride ion as simply a dipolar ligand, possibly akin to a sterically unhindered hexamethylphosphoramide analogue. Ongoing computational and spectroscopic studies show that LiCl catalyzes subunit exchanges in LDA dimers. Computed adducts archived in Supporting Information show 30 to be a minimum and transition structure 31 to be only 5 kcal/mol higher energy than 30. Adduct 30 is structurally similar to a halide adduct tentatively assigned spectroscopically.

Moreover, the Li—Cl—Li cationic triple fragment is well preceded and is computationally preferred relative to the simple lithium counterion. (The heptasolvation of the (THF)$_2$Li—Cl—Li(THF)$_4$ counterion is odd, but it is the preferred form computationally.) X—Li—X anionic triple fragments analogous to...
Many structurally distinct aggregated forms can be put to rest what had been a persistently circumstantial case of rate-limiting deuterium transfer. Point 4 seems to display a nearly fi ffest for dimer-based metalation. We are unsure, however, how tetramers (implicated triple ions) give us pause.

A different intermediate? There is no question that highly solvated arenes catalyzed deaggregation remain elusive, we are optimistic that mechanistic descriptions of salt-catalyzed LDA deaggregation will continue to evolve albeit obstinately. Dimer- versus Monomer-Based Metalations in Review. Throughout this paper we have described uncatalyzed and catalyzed metalations as dimer- and monomer-based, respectively. One might be troubled, however, by the seemingly parallel behavior of the two classes showing an oddly similar THF-tractable system in which to study the condensation of an aryllithium with LDA dimer, revealing a rate-limiting transition structure of stoichiometry [(i-Pr2NLi)2(2,6-Pr2ArLi)]5 (mixed trimers). It appeared that reactive LDA-lithiated carbamate mixed dimers interceded. Thus, we cannot say for certain whether the two instances of aryllithium-derived autocatalysis are completely analogous. Moreover, the studies described herein, showing that 2 is 6-fold more catalytically active than 3, underscore the two critical prerequisites to observe autocatalysis: a reaction must be sensitive to catalysis, and a product (or byproduct) must be a viable catalyst. Evidence is accruing that failures to observe autocatalysis may trace to one or both requirements. Although details of how aryllithiums catalyze LDA deaggregation remain elusive, we are optimistic that mechanistic descriptions of salt-catalyzed LDA deaggregation will continue to evolve albeit obstinately.

Evidence is accruing that highly reactive substrates can intercept LDA at various stages of deaggregation, rendering aggregation events rate limiting and the conditions decidedly non-equilibrating. Simplistic thinking early on led us to surmise that a rate-limiting deaggregation would be substrate independent and that all substrates above some threshold of reactivity would react at precisely the same rate. We realized, however, that intercepting different fleeting intermediates would necessarily lead to substrate-dependent rates even if the rates were independent of the substrate concentration. Substrates also may participate in a critical deaggregation or complexation event but with the key reaction of interest (proton transfer, for example) occurring as a post-rate-limiting step. In this scenario, even substrate concentration dependencies could be affiliated with an aggregation-limiting transformation.

Of course, LiX-catalyzed deaggregation adds a further layer of complexity in the form of a hypersensitivity to LiCl contaminants and accelerations elicited by autocatalysis. The appearance of autocatalysis and its virulence depend on both the catalytic efficacy of the lithium salt being formed and on a mechanistic advantage of the catalyzed deaggregation. Enolates, for example, are particularly poor autocatalysts’ compared with aryllithiums, aryllithiums display autocatalysis that depends on the substituents on the arene (as in 2 and 3), and the catalytic activity of all salts studied to date pale in comparison with LiCl.56

CONCLUSION

We conclude this paper in a somewhat unorthodox way by considering the consequences of the work from two very different perspectives. In the first, we address those interested in mechanistic organolithium chemistry. This viewpoint was most certainly the primary focus of the paper. In the second, we try to imagine what the ortholithiation of 1 might look like to a synthetic chemist peering through a largely empirical lens.

Mechanistic Organolithium Perspective. One could legitimately ask why LDA-mediated reactions in THF at −78 °C are proving so complex compared with their counterparts at elevated temperatures.55 To answer this question, we offer the ensemble of aggregates en route to LDA monomer in Scheme 8. The structures are not just figments of our imagination but rather computationally legitimate minima that will be described in the next paper of this series.6 The computed barriers separating them are, with the exception of the first solvation step,55 surprisingly high (>10 kcal/mol) relative to dimeric LDA in its resting state 4, and the barriers are at notably comparable energies.

For substrates of relatively low reactivity the equilibria in Scheme 8 are rapid on the time scales of reactions with the substrate. All species are available to react, and 25 years of accumulated rate studies confirm that many do.23 Now imagine monotonically increasing the reactivity of the substrate; instead of following the kinetics over shorter time scales, we simply reduce the reaction temperatures to monitor the reaction on convenient laboratory time scales. At some level of reactivity (at some temperature required to monitor reaction rates conveniently using standard analytical methods) the rates that substrates react with LDA aggregates become comparable to those at which the aggregates exchange. Through an odd twist of fate, this critical temperature for LDA/THF is at or near −78 °C.

Evidence is accruing that highly reactive substrates can intercept LDA at various stages of deaggregation, rendering aggregation events rate limiting and the conditions decidedly non-equilibrating. Simplistic thinking early on led us to surmise that a rate-limiting deaggregation would be substrate independent and that all substrates above some threshold of reactivity would react at precisely the same rate. We realized, however, that intercepting different fleeting intermediates would necessarily lead to substrate-dependent rates even if the rates were independent of the substrate concentration. Substrates also may participate in a critical deaggregation or complexation event but with the key reaction of interest (proton transfer, for example) occurring as a post-rate-limiting step. In this scenario, even substrate concentration dependencies could be affiliated with an aggregation-limiting transformation.

The chemical half-life for conditions of a hypersensitivity to LiCl contaminants and accelerations elicited by autocatalysis. The appearance of autocatalysis and its virulence depend on both the catalytic efficacy of the lithium salt being formed and on a mechanistic advantage of the catalyzed deaggregation. Enolates, for example, are particularly poor autocatalysts’ compared with aryllithiums, aryllithiums display autocatalysis that depends on the substituents on the arene (as in 2 and 3), and the catalytic activity of all salts studied to date pale in comparison with LiCl.56

Scheme 8

![Scheme 8](image-url)
As we gather insights about LDA-mediated reactions under conditions in which aggregates are not at full equilibrium, we are constantly re-evaluating published conclusions. Case studies considered in isolation can be fully self-consistent whereas results from different case studies can conflict. As a simple example, LiCl-catalyzed deaggregation is sensitive to the substrate, appearing as a first-order dependence on LiCl concentration in one case and second-order dependencies in others. A fully self-consistent holistic view is beyond our gaze.

**Synthetic Chemistry Perspective.** Now consider the chemistry from the vantage point of a synthetic chemist who relies less on mechanism and more on empiricism and instinct. Schlosser and co-workers, for example, studied the metalation of arenes, either sec-BuLi or LiTMP affords 3 in 20:1 selectivity. Possibly not realizing that the hindrance of the aromatic system is eroded during protracted reaction times. You could have enjoyed the convenience and greater safety of commercial LDA with the activity of LDA prepared in situ by adding a few molar percent LiCl generated using Et3NHCl. By this time, your quest to prepare P3 via 3 would have led to other bases. Success is achieved: whereas sec-BuLi gives a 4:1 selectivity favoring 3, either sec-BuLi or LiTMP affords 3 in 20:1 selectivity. Possibly not realizing that the hindrance of the tetramethylpiperidine byproduct completely suppresses amine-mediated equilibration, you invoke a model based on purely steric effects, declare victory, and move on to the next step.

---

**Scheme 9**

\[
\begin{align*}
\text{Cl} & \quad \text{LDA} \\
\text{CF}_3 & \quad \text{Li} \quad \text{Cl} \\
\text{Cl} & \quad \text{Li} \quad \text{Cl} \\
\text{CF}_3 & \quad \text{Li} \quad \text{Cl} \\
\end{align*}
\]

As we gather insights about LDA-mediated reactions under conditions in which aggregates are not at full equilibrium, we are constantly re-evaluating published conclusions. Case studies considered in isolation can be fully self-consistent whereas results from different case studies can conflict. As a simple example, LiCl-catalyzed deaggregation is sensitive to the substrate, appearing as a first-order dependence on LiCl concentration in one case and second-order dependencies in others. A fully self-consistent holistic view is beyond our gaze.

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**EXPERIMENTAL SECTION**

**Reagents and Solvents.** THF and hexane were distilled from blue or purple solutions containing sodium benzophenone ketyl. The hexane contained 1% tetraglyme to dissolve the ketyl. Et3N·HCl was recrystallized from THF/2-propanol. Literature procedures were modified to prepare LDA as a LiCl- and ligand-free solid. Solutions of LDA were titrated using a literature method. Deuterated substrates were prepared as described below.

**IR Spectroscopic Analyses.** IR spectra were recorded using an in situ IR spectrometer fitted with a 30-bounce, silicon-tipped probe. The spectra were acquired in 16 scans at a gain of 1 and a resolution of 4 cm⁻¹. A representative reaction was carried out as follows: The IR probe was inserted through a nylon adapter and O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and a T-joint. The T-joint was capped by a septum for injections and a nitrogen line. After evacuating under full vacuum, heating, and flushing with nitrogen, the flask was charged with LDA (108 mg, 1.01 mmol) in THF and cooled in a dry ice–acetone bath prepared from fresh acetone. Preparation of the same solution but containing 0.5 mol % LiCl (0.005 M) requires the addition of a LiCl stock solution (0.50 mL) prepared from Et3NHCl (27.5 mg, 0.20 mmol) and LDA (25.0 mg, 0.23 mmol) in 2.0 mL THF. After recording a background spectrum, we added arenne I (0.76 mmol) with stirring. For the most rapid reactions, IR spectra were recorded every 3 s over the course of the reaction, monitoring the absorbance at 1325 cm⁻¹.

**NMR Spectroscopic Analyses.** All NMR samples were prepared using stock solutions and sealed under partial vacuum. Standard 2H, 13C, 15N, and 19F NMR spectra were recorded on a 500 MHz spectrometer at 73.57, 125.79, 50.66, and 470.35 MHz, respectively. The 2H, 13C, and 15N resonances are referenced to 0.30 M [6Li]LiCl/MeOH at −90 °C.
aqueous layers were separated, and the aqueous layer was washed with BrCF3 (5.0 mL, 37.0 mmol, 1 equiv) was added to the in situ generated LDA (q,2 JCF = 26 Hz, 1JC,F = 4.0 Hz), 123.8 (q, 1JC,F = 272 Hz), 123.4 (q, 1JC,F = 4.0 Hz).  

6-Deutero-1-chloro-3-(trifluoromethyl)benzene (1-6-d). The compound was synthesized as above from commercially available 6-bromo-1-chloro-3-(trifluoromethyl)benzene, and 1-6-d was collected at 135 °C as a colorless liquid (3.74 g, 18.2 mmol) in 49% yield. 1 H N M R 8.87 (d, 2 JCF = 16 Hz, 1JC,F = 4.0 Hz); 7.52 (m, 2H), 7.43 (m, 1H). 13 CN M R 135.3 (s), 132.6 (q, 2 JCF = 26 Hz, 1JC,F = 4.0 Hz), 123.4 (q, 1JC,F = 272 Hz), 123.5 (q, 1JC,F = 4.0 Hz).  

Numerical Integrations. The time-dependent concentration plots obtained using IR spectroscopy are fit to a mechanistic model expressed by a set of differential equations. The curve-fitting operation minimizes chi-square in searching for the coefficient values (rate constants). The Levenberg–Marquardt algorithm is used for the chi-square minimization and is a form of nonlinear, least-squares fitting. The fitting procedure implements numerical integration based on the backward differentiation formula to solve the differential equations, yielding functions describing concentration versus time.

**ACKNOWLEDGMENT**

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(11) (a) Kim, Y.-J.; Bernstein, M. P.; Galiano-Roth, A. S.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Collum, D. B.; Williard, P. G.
(28) Competitive and intramolecular isotope effects can be used to examine post-rate-limiting proton transfer. They differ in that the intramolecular isotope effect demands a symmetry-equivalent choice of H versus D within the same molecule whereas the competitive isotope effect requires an exchange mechanism to establish the choice of H versus D.


(30) The calculated isotope effects in eqs 6 and 7 derive from the regioselectivities derived from 1-2-6-d$_1$ and 1-6-2-d$_1$. If the isotope effects are calculated using 1-2,6-d$_2$ instead of 1, the isotope effects are calculated as follows:

\[
\frac{k_{1(2)}/k_{1(2,6)}}{k_{1(2)/k_{1(2,6)}}} = 50
\]

\[
\frac{k_{1(6)}/k_{1(2)}}{k_{1(6)/k_{1(2,6)}}} = 12
\]

(31) The method used to prepare 1-2,6-d$_2$, which involves initial metalation by LDA and quenching with MeOD (1.0 equiv) followed by alternating pulses of n-BuLi with intermediate workups, may have a general utility for exhaustive deuteration of the acidic sites on amines.


(33) (a) Isotopic perturbation is insufficient to resolve the resonances of 1 and 1-2,6-d$_2$ by $^2$H NMR spectroscopy. (b) The IR absorbances of 1 (1428 cm$^{-1}$) and 1-2,6-d$_2$ (1384 cm$^{-1}$) could be monitored, but with some error introduced by absorbances of the aryllithiums. (b) Hindermann, D. K.; Corwell, C. D. J. Chem. Phys. 1968, 48, 4148. (c) Forsyth, D. A.; Yang, J.-R. J. R. Am. Chem. Soc. 1986, 108, 2157. (d) Lambert, J. B.; Greifenstein, L. G. J. Am. Chem. Soc. 1973, 95, 6150.

(34) For an attempted comprehensive bibliography of anionic triple ions of lithium salts (X = Li$^-$) see: Ma, Y.; Ramirez, A.; Singh, K. J.; Keresztes, I.; Collum, D. B. J. Am. Chem. Soc. 2010, 132, 10821 and references cited therein.


(36) Determining initial rates (slopes) of a curved decay can be strongly dependent on the percent conversion, requiring a compromise between adequate sample size and loss of linearity. This problem is mitigated by fitting a significant part of the decay, a portion that includes some curvature, to a third-order polynomial ($a t^3 + b t^2 + c$), making sure not to include too much curvature. The parameter $b$ represents the rate at time zero. (One may verify this by taking the first derivative with respect to $t$ and setting $t = 0$. Initial rate = $f'(0) = b$.) The experimental observable (NMR intensity, IR absorbance, etc.) is converted to concentration to ensure a valid comparison between initial rates of varying concentrations.

(37) For a review of rate studies of LDA-mediated reactions see: Collum, D. B.; McNeil, A. J.; Ramirez, A. Angew. Chem., Int. Ed. 2007, 46, 3002.

(38) The concentration of LDA, although expressed in units of molarity, refers to the concentration of the monomer unit (normality). The concentration of THF is expressed as total concentration of free (uncoordinated) ligand.

(39) The minor deviation above first order has the appearance of experimental error. A forthcoming study, however, describes experimental evidence of LDA-tetramer-based reactivities.

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

(41) Equation 17 appears to become undefined at $[\text{LiCl}]_0 = 0$, but this is not the case as described previously.


(44) The principle of microscopic reversibility seems to have been the source of frequent controversies and must be applied with caution. It is not obvious to us, for example, that the following authors, all warning of the risks, would agree with each other’s assertions: (a) Blackmond, D. G. Angew. Chem., Int. Ed. 2009, 48, 2648. (b) Krapka, R. M.; Kaplan, H.; Laidler, K. J. J. Chem. Soc., Faraday Trans. 1966, 62, 2756. (c) Chandrasekhar, S. Res. Chem. Intermed. 1992, 17, 173. (d) Burwell, R. L.; Pearson, R. G. J. Phys. Chem. 1966, 70, 300.


(49) A four-run LDA/LiX ladder has been characterized: Williard, P. G.; Hintze, M. J. Am. Chem. Soc. 1987, 109, 5539.


(52) The most stable lithium cation \([\text{Li}[\text{THF}]_3]^+\) and most stable triple ion \([\text{THF}][\text{LiCl}][\text{THF}]^+\) are related as follows:

\[
\Delta G = -5.0 \text{ kcal/mol}
\]

For related computations, see: Yakimansky, A. V.; Muller, A. H. E.; Van Beylen, M. Macromolecules 2000, 33, 5686.


(55) THF exchange on LDA is too fast to monitor by NMR spectroscopy, but it is calculated to occur with activation barriers of <4 kcal/mol.\(^6\)

\[
\text{O} \quad \text{N(i-Pr)}_2 \quad \text{LDA} \quad \text{THF} / -78^\circ \text{C} \quad \text{O} \quad \text{N(i-Pr)}_2
\]

During the following carbamate metatation\(^6\) two concerns lingered: the metatation displayed an unexpectedly small isotope effect \((k_{H}/k_{D} = 3 - 4)\), and a plot of rate versus concentration showed a first-order arene dependence but with a downward curvature that looks suspiciously like an incomplete version of the saturation curve in Figure 7. Indeed, we have now found a large competitive isotope effect \((k_{H}/k_{D} > 30)\), suggesting that the first-order dependence does not involve proton transfer and that deuterium transfer is partially rate limiting.

(57) Trapping experiments can be unreliable measures of the rates because they generate catalytically active lithium salts. Trimethylchlorosilane, for example, generates LiCl, rendering LiCl-sensitive arene lithiations nearly instantaneous. We chose benzaldehyde for our hypothetical example because alkoxides are not active deaggregation catalysts.\(^6\)

(58) Warming to –20°C in the presence of spiro[2.4]hepta-4,6-diene shows no evidence of trapping products. We do, however, see evidence of n-BuLi adducts if metatizations with n-BuLi are allowed to inadvertently warm. Leading reference to benzene formation: Riggs, J. C.; Ramirez, A.; Cremeens, M. E.; Bashore, C. G.; Candler, J.; Wirtz, M. C.; Coo, J. W.; Collum, D. B. J. Am. Chem. Soc. 2008, 130, 3406.


(60) The observed selectivities for the metatization of 1 by n-BuLi and sec-BuLi show approximately 3-fold higher proportions of 2 relative to 3 as the arene concentration goes from 0.05 equiv of 1 to 1.0 equiv of 1. This result appears to be a kinetic consequence of mixed aggregates favoring formation of 3. For references to structures and reactivities of n-BuLi/RLi ensembles, see: Chase, P. A.; Lutz, M.; Spek, A. L.; Gossage, R. A.; van Koten, G. Dalton Trans. 2008, 5783.


