Lithium Diisopropylamide-Mediated Ortholithiation and Anionic Fries Rearrangement of Aryl Carbamates: Role of Aggregates and Mixed Aggregates

Kanwal Jit Singh and David B. Collum*

Contribution from the Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

Received June 30, 2006; E-mail: dbc6@cornell.edu

Abstract: Structural and mechanistic studies of the lithium diisopropylamide (LDA)-mediated anionic Fries rearrangements of aryl carbamates are described. Substituents at the meta position of the arene (H, OMe, F) and the dialkylamino moiety of the carbamate (Me₂N, Et₂N, and i-Pr₂N) markedly influence the rates of ortholithiation and subsequent Fries rearrangement. Structural studies using ^6Li and ^15N NMR spectroscopies on samples derived from [^6Li,^15N]LDA reveal an LDA dimer, LDA dimer—arene complexes, an aryllithium monomer, LDA—aryllithium mixed dimers, an LDA—lithium phenolate mixed dimer, and homoaggregated lithium phenolates. The highly insoluble phenolate was characterized as a dimer by X-ray crystallography. Rate studies show monomer- and dimer-based ortholithiations as well as monomer- and mixed dimer-based Fries rearrangements. Density functional theory computational studies probe experimentally elusive structural and mechanistic details.

Introduction

Fries rearrangements are approaching their centenary year.1,2 The Lewis acid mediated version was discovered by Fries in 1908.3 A photochemical variant was first described in 1960,4 and the anionic variant appears to have been first reported by Melvin in 1981.5 The synthetic utility of the anionic Fries rearrangement exemplified by the tandem ortholithiation—Fries rearrangement of aryl carbamate 1 (eq 1)6 has come about from high yields and ortho specificity. The reaction has received attention from the pharmaceutical industry;7 its increasingly widespread use derives in large part from extensive development by Snieckus and co-workers.2

![Equation 1](image)

We describe herein structural and mechanistic investigations of the lithium diisopropylamide (LDA)-mediated Fries rearrangement illustrated in eq 1.6 Spectroscopic studies reveal that the reaction proceeds through a number of intermediates summarized in Scheme 1. The choice of solvent and substrate dictates which intermediates can be observed as the reaction proceeds. Rate studies of both the ortholithiation and the subsequent rearrangement reveal some surprising consequences of mixed aggregation.

Results

The results are presented sequentially as follows: (1) relative reactivities—qualitative studies reveal how the meta substituent (X) and the carbamate substituent (NR₂) influence the relative rates of ortholithiations and Fries rearrangements; (2) aggregate structures—IR and NMR spectroscopic studies establish the structures of the intermediates in Scheme 1; (3) rate studies—concentration-dependent rates reveal the mechanism(s) of the LDA-mediated ortholithiations and the subsequent Fries rearrangements; and (4) computational studies—density functional theory (DFT) calculations provide insights into experimentally elusive structural and mechanistic details.

(3) Fries, K.; Finck, G. Ber. 1908, 41, 2447.
elusive details. The transition structures depicted are also supported by previous computational studies of LDA-mediated lithiations.8

**Relative Reactivities.** Some qualitative observations pertaining to substituent effects provide a sense of how meta substituents on the arene and N-alkyl substituents on the carbamate moiety influence reactivity. The methods for measuring their relative reactivities are discussed below in the context of detailed rate studies.

Bulky carbamate substituents have limited influence on the rates of ortholithiation yet dramatically impact the rates of Fries rearrangement (Me2N ≫ Et2N ≫ i-Pr2N).b Consequently, arene 1a bearing an Me2N substituent and no anion stabilizing meta substituent affords a relatively slow (rate-limiting) ortholithiation followed by a rapid Fries rearrangement; the intermediate aryllithium (2a or 6a) is not detected (see below). Conversely, ortholithiation of the corresponding N,N-dipropyl carbamate 1c occurs at −40 °C to the exclusion of the Fries rearrangement (eq 2) but proceeds to low (<10%) conversion as shown by in situ IR spectroscopy. Quantitative ortholithiation of 1c using lithium tetramethylpiperidide at −40 °C and subsequent addition of i-Pr2NH reverses the ortholithiation, confirming the low conversion to aryllithium using LDA derives from an unfavorable equilibrium.

Electron-withdrawing substituents at the meta position markedly accelerate the ortholithiation. By example, carbamate 1g ortholithiates with excess LDA instantly even at −78 °C.


Conversely, Fries rearrangement starting from mixed dimer 6g is 10-fold slower than from 6d. Presumably both rate effects derive from inductive stabilization of the aryllithium.9

**Aggregate Structures.** LDA, [6Li][LDA], and [6Li, 15N][LDA] were prepared as white crystalline solids.10 Spectral data for the key structural forms depicted in Scheme 1 are summarized in Table 1. Representatives of the structural forms in Scheme 1 were documented through changes in substituents.6Li and 15N assignments stem from 6Li, 13C, and 15N NMR spectroscopies11 augmented by 1J(6Li,15N)-resolved12 and 6Li,15N HMQC spectroscopies.13 In situ IR spectra were recorded using a silicon-based probe.14 LDA was previously shown to be disolvated in 0.70 M THF/hexane solution at −40 °C but reveals the absorbance of uncoordinated 1d at 1736 cm−1 along with an absorbance at 1714 cm−1, consistent with LDA—carbamate complex 5d. Uncoordinated carbamate 1d is the sole observable form in ≥3.0 M THF. By contrast,

### Table 1. 6Li and 15N NMR Spectral Dataa

<table>
<thead>
<tr>
<th>structure</th>
<th>%Li, δ (mult, JLiN)</th>
<th>%15N, δ (mult)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>0.43 (d, 4.9)</td>
<td>78.1 (q)</td>
</tr>
<tr>
<td>6b</td>
<td>1.39 (d, 4.9)</td>
<td>78.1 (q)</td>
</tr>
<tr>
<td>7b</td>
<td>0.44 (d, 4.9)</td>
<td>77.6 (q)</td>
</tr>
<tr>
<td>6c</td>
<td>1.51 (d, 5.1)</td>
<td>77.9 (q)</td>
</tr>
<tr>
<td>7c</td>
<td>0.50 (d, 5.0)</td>
<td>76.4 (q)</td>
</tr>
<tr>
<td>6d</td>
<td>1.68 (d, 5.1)</td>
<td>78.3 (q)</td>
</tr>
<tr>
<td>6e</td>
<td>1.70 (d, 5.1)</td>
<td>76.5 (q)</td>
</tr>
<tr>
<td>6f</td>
<td>1.69 (d, 5.0)</td>
<td>76.7 (q)</td>
</tr>
<tr>
<td>7d</td>
<td>0.62 (d, 5.0)</td>
<td>77.2 (q)</td>
</tr>
<tr>
<td>6g</td>
<td>1.71 (d, 5.3)</td>
<td>76.3 (q)</td>
</tr>
<tr>
<td>7g</td>
<td>0.40 (d, 4.8)</td>
<td>79.1 (q)</td>
</tr>
<tr>
<td>6h</td>
<td>1.22 (s)</td>
<td></td>
</tr>
<tr>
<td>6i</td>
<td>0.73 (br)</td>
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<tr>
<td>6j</td>
<td>1.79 (d, 5.3)</td>
<td>76.4 (q)</td>
</tr>
<tr>
<td>6k</td>
<td>1.99 (d, 5.2)</td>
<td>75.3 (q)</td>
</tr>
<tr>
<td>7d</td>
<td>0.90 (d, 5.6), 0.97 (d, 3.9)</td>
<td>71.23 (q)</td>
</tr>
</tbody>
</table>

*a Spectra were recorded on samples containing 0.1 M total lithium concentration (normality). Multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quintet; m, multiplet; br, broad. The chemical shifts are reported relative to 0.3 M 6LiCl/MeOH (0.0 ppm) and neat Me2NEt (25.7 ppm) at −90 °C. All J values are reported in Hz. Unless otherwise indicated, solvent is 11.1 M THF: pentane. b Solvent is 2.3 M i-BuOMe. c Solvent is 6.3 M t-BuOMe.

We studied the complexation of carbamates to LDA using carbamate 1d emblematically because of its role in the rate studies described below. IR spectra recorded on mixtures of 0.20 M LDA and 0.004 M carbamate 1d in 0.70 M THF/hexane solution at −40 °C reveal the absorbance of uncoordinated 1d at 1736 cm−1 along with an absorbance at 1714 cm−1, consistent with LDA—carbamate complex 5d. Uncoordinated carbamate 1d is the sole observable form in ≥3.0 M THF. By contrast,


complexation of 1d is quantitative using LDA in poorly coordinating t-BuOMe (≤ 4.0 M) or n-BuOMe (< 2.5 M). [6Li]LDA and [6Li, 15N]LDA of 5d afford 6Li and 15N resonances and couplings consistent with the assigned structure (Table 1).

Arenes bearing electron-withdrawing MeO and F meta substituents undergo rapid and quantitative ortholithiation with excess LDA in THF at -78 °C to afford mixed dimers (6) and low concentrations of aryllithiums (2). Lower THF concentrations promote mixed dimers to the exclusion of the aryllithium monomer. Mixed dimers display a highly characteristic 6Li doublet and a 15N quintet at -90 °C. The 6Li resonance of 6g resolves into two resonances (1:1) at < -125 °C, consistent with chelation by the carbamate.

It proved difficult to characterize aryllithiums 2 because of low percent conversion in the ortholithiation, high reactivity toward Fries rearrangement in the absence of excess LDA, and limited solubility in several instances. Only aryl carbamates 1g and 1h, bearing electron-withdrawing meta substituents, were quantitatively metalated with 1.0 equiv of LDA to give homoaggregated aryllithium (2g and 2h, respectively). The absence of 15N coupling in the 6Li resonance confirms the absence of an LDA fragment. Unfortunately, limited solubility rendered 13C NMR spectroscopy impractical; precedent suggests that such aryllithiums are monomeric.

Fries rearrangement of mixed dimers (6) in the presence of excess LDA affords LDA–lithium phenolate mixed dimers (7). For example, mixed dimer 7a prepared from [6Li, 15N]LDA displays a single 6Li resonance as a doublet. Inequivalent 6Li resonances arising from chelation in 7a are not observed; however, site–site exchange is often fast on NMR time scales even at < -120 °C.

Homoaggregated phenolate 8 can be generated using equimolar mixtures of carbamate and LDA and by forcing the metalation to proceed beyond the formation of a mixed dimer. Unfortunately, a combination of profound insolubilities of 8 as a class and the absence of Li–X coupling precluded detailed characterization in solution. A crystal structure of 8g (Figure 1) shows a dimer in analogy with other structurally similar phenolates.

Rate Studies: Ortholithiation. The ortholithiation was studied according to eq 3. Pseudo-first-order conditions were established by maintaining the concentration of the carbamate 1a at ≤ 0.004 M LDA, and THF concentrations were maintained at high, yet adjustable, levels, using hexane as the cosolvent. The loss of 1a monitored using in situ IR spectroscopy follows a clean first-order behavior. The resulting pseudo-first-order rate constants (kobsd) are independent of the initial concentration of 1a, confirming a first-order dependence. Under these conditions, there is no measurable buildup of an ortholithiated form, indicating a rate-limiting ortholithiation followed by a rapid Fries rearrangement. A significant isotope effect (kF/k0 = 16) is found by comparing the independently measured rate constants for the elimination of 1a and 1a-d5. Added diisopropylamine has no effect on the rates, confirming that the ortholithiations rather than the Fries rearrangements are rate limiting.

Plots of kobsd versus LDA concentration and kobsd versus THF concentration (Figures 2 and 3) reveal half-order and zeroth-order dependencies, respectively. Overall, the reaction orders and the kinetic isotope effect are consistent with the idealized rate law in eq 4,

\[
-\frac{d[1a]}{dt} = k'[{1a}][LDA]^{1/2}[THF]^{0}\]  

the mechanism described generically in eqs 5 and 6.

(16) For other examples of spectroscopically observable LDA–substrate complexes, see: Sun, X.; Collum, D. B. J. Am. Chem. Soc. 2000, 122, 2452. Also, see ref 18b.
(20) In contrast to some recently characterized ortho fluoro aryllithium monomers, the 6Li resonance of 2g shows no detectable 6Li–F coupling.
Analogous rate studies for the metalation of 1d in 2.5 M n-BuOMe/hexane (eq 7) reveal a markedly different result. Under these conditions the observable starting material is monocomplexed dimer 5d. Plots of \( k_{\text{obsd}} \) versus [n-BuOMe] concentration (Figure 4) and \( k_{\text{obsd}} \) versus LDA concentration (Figure 5) afford the idealized rate law in eq 8, consistent with the mechanism depicted generically in eq 9 and with open dimer-based transition structure 10.\(^{25}\) Of course, the marked changes in the concentration dependencies are, in part, a consequence of the starting form being an LDA–arene complex.\(^{26}\) Nonetheless, the emergence of dimer-based reactivity

\[ \text{1/2} (i-\text{Pr}_2\text{NLi})_2(\text{THF})_2 \rightleftharpoons (i-\text{Pr}_2\text{NLi})(\text{THF}) \tag{5} \]

\[ (i-\text{Pr}_2\text{NLi})(\text{THF}) + 1\text{a} \rightleftharpoons [(i-\text{Pr}_2\text{NLi})(\text{THF})(1\text{a})]_2 \tag{6} \]

\[ \frac{-d[1\text{d}]}{dt} = k'[5\text{d}][\text{LDA}]^n[n-\text{BuOMe}]^m \tag{8} \]

\[ [(i-\text{Pr}_2\text{NLi})_2(n-\text{BuOMe})(1\text{d})] \rightleftharpoons (5\text{d}) \]

\[ [(i-\text{Pr}_2\text{NLi})_2(n-\text{BuOMe})(1\text{d})]^2 \tag{10} \]
represents a fundamental change in mechanism affiliated with a change to a poorly coordinating solvent.27

Rate Studies: Fries Rearrangement. Fluorinated carbamate 1g offered the best view of the anionic Fries rearrangement (eq 10).28 We generated mixed aggregate 6g as a 0.004 M solution in THF at −40 °C by adding 1g to an excess of LDA. (The fluoro substituent ensured quantitative metalation at −78 °C.) The loss of 6g and the formation of 7g follow clean first-order behavior. The resulting values of k_{obsd} are independent of the initial concentration of 6g, confirming the first-order dependence. The decays also follow first-order dependencies, as shown by their least-squares fits to the nonlinear Noyes equation.29 A plot of k_{obsd} versus LDA concentration (Figure 6) reveals two mechanisms: (1) an inverse half-order dependence on LDA concentration consistent with a mechanism requiring mixed aggregate dissociation30 and (2) a zeroth-order dependence consistent with a mixed dimer-based rearrange-

Figure 6. Plot of k_{obsd} versus [LDA] in 9.8 M THF/hexane for the Fries rearrangement of 1g (0.004 M) at −40 °C. The curve depicts an unweighted least-squares fit to k_{obsd} = k[LDA]^{b} + k^′ [k = (1.7 ± 0.3) × 10^{-2}, k^′ = (1.9 ± 0.7) × 10^{-4}, n = -0.48 ± 0.04].

Figure 7. Plot of k_{obsd} versus [THF] in hexane cosolvent for the Fries rearrangement of 1g (0.004 M) by LDA (0.098 M) at −40 °C. The curve depicts an unweighted least-squares fit to k_{obsd} = k[THF]^{c} [k = (3.6 ± 0.4) × 10^{-5}, n = 1.08 ± 0.05].

Figure 8. Plot of k_{obsd} versus [THF] in hexane cosolvent for the Fries rearrangement of 1g (0.004 M) by LDA (0.42 M) at −40 °C. The curve depicts an unweighted least-squares fit to k_{obsd} = k[THF]^{c} [k = (1.2 ± 0.2) × 10^{-3}, n = 1.75 ± 0.07].

(28) Carbamate 1d forms a complex with LDA (5d). Subsequent ortholithiation of 5d with LDA in t-ButOMe at −55 °C is first order in LDA with a significant nonzero intercept. The nonzero intercept is consistent with a pathway which is zero order in LDA as described for the ortholithiation of 5d by LDA/t-ButOMe. LDA dependence, however, implicates a role of LDA that is quite unusual and as discussed in a forthcoming manuscript.
(30) Related inverse half-order dependencies on LDA concentration were observed in the context of ester enolization by LDA–lithium enolate mixed dimers.19b
(31) Fitting the data to y = a[THF] affords a = (1.2 ± 0.2) × 10^{-3}, n = 1.75 ± 0.07. Alternatively, fits to y = a[THF] + c to account for a small but possible nonzero intercept affords a = (7.0 ± 3.0) × 10^{-6}, n = 1.96 ± 0.17, and c = (4.1 ± 2.7) × 10^{-5}. A last perspective is provided by a fit to y = a[THF] + b[THF]^{2}, affording a = (2.7 ± 1.0) × 10^{-2}, b = (1.4 ± 1.9) × 10^{-3}, n = 2.5 ± 0.5.
(i-Pr₂NLi)(ArLi)(THF) + THF →

\[
6g \\
[(i-Pr₂NLi)(ArLi)(THF)]^+ \text{(14)}
\]

and transition structures 11 and 12. The solvation number assigned to 6g is based on DFT calculations (below). Thus, the solvation number of 11 and 12 should be viewed as tentative.

**Computational Studies: General.** We addressed several lingering issues using density functional theory calculations [B3LYP method and the 6-31G(d) basis set]. Corrections for entropy afforded the energy denoted as \( \Delta G^\ddagger \) (activation energy). Me₂NLi and Me₂O were used as models for LDA and THF, respectively. Ranges of initial geometries were sampled for all reactant and transition structures. Legitimate saddle points were shown by the existence of single imaginary frequencies. Intrinsic reaction coordinate analyses verified that transition structures corresponded to desired transformations. To make comparisons with experiment as direct as possible, we focused on carbamate 1a for the monomer-based ortholithiations, carbamate 1d for the dimer-based ortholithiations, and carbamate 1g for the Fries rearrangement.

**Computational Studies: Ortholithiation.** Disolvated dimer 13 is the reference state for the values of \( \Delta G^\ddagger \) for the monomer-based ortholithiation (eq 15). The monosolvated monomer-based transition structure 14a for the metalation of carbamate 1a was implicated by the rate studies. Computations show a strong penchant for coordination by the carbonyl group; a variety of uncomplexed carbonyl orientations converge on 14a. The N–H–C angle of 14a is nearly 180°, consistent with a preference for linear proton transfer. The influence of electron-withdrawing groups probed using fluorinated carbamate 1g revealed transition structure 14g with a 5 kcal/mol reduction in \( \Delta G^\ddagger \) when compared with the unsubstituted case. The influence of fluorine in facilitating the metalation via 14g is probably inductive. By comparison, the ortholithiation via fluoro-directed analogue 15 is only slightly less favorable than that via 14g. Similar effects have been noted previously. Conversely, comparing the \( \Delta G^\ddagger \) for 15 with the analogous \( \Delta G^\ddagger \) for the directed metalation of fluorobenzene shows that the noncoordinating carbamate group facilitates the ortholithiation by approximately 3 kcal/mol.

We briefly examined the dimer-based metalations shown to occur from an observable complex in weakly coordinating solvents (eq 16).

\[
1 + (\text{Me}_2\text{NLi})_2(\text{Me}_2\text{O})_2 \xrightarrow{\Delta G^\ddagger} \text{[(Me}_2\text{NLi})_2(\text{Me}_2\text{O})(1)]^+ + \text{Me}_2\text{O} \text{ (16)}
\]

Although we use uncomplexed dimer 13 as the reference state (rather than a lithium amide dimer—arene complex as observed experimentally), substitution of 1 for an Me₂O ligand on dimer 13 is endothermic by < 1.0 kcal/mol. Transition structures for dimer-based ortholithiations of the unsubstituted and methoxy-substituted carbamates are illustrated as 17 and 18. The open-dimer motif has been implicated computationally on many occasions. The most intriguing observation is that the methoxy moiety offers little stabilization when compared with the unsubstituted carbamate. According to the calculations, a methoxy moiety does not facilitate the carbamate metalation. This lack of activation by an ancillary (noncoordinating) meta methoxy moiety has been noted previously.

**Computational Studies: Fries Rearrangement.** Fries rearrangement starting with mixed dimer 6g appeared to proceed via both a dissociative (monomer-based) pathway and a non-dissociative (mixed dimer-based) pathway (11 and 12, respectively). Modeling the reaction using mixed dimer 19 reveals that the most favorable monomer-based pathway (via disolvate 20; eq 17) and the most favorable mixed dimer-based pathway (via disolvate 21; eq 18)
Anionic Fries Rearrangement of Aryl Carbamates

\[ 19 + 2\text{Me}_2\text{O} \rightleftharpoons [\text{ArLi}](\text{Me}_2\text{O})_2] + \frac{1}{2} \text{13} \]  \hspace{2cm} (17)

\[ 19 + \text{Me}_2\text{O} \rightleftharpoons [\text{ArLi}](\text{Me}_2\text{NLi})(\text{Me}_2\text{O})_2] \]  \hspace{2cm} (18)

have comparable activation energies. Interestingly, 21 shows evidence of both N–Li and O–Li (η²) coordination to lithium.34

\[ \Delta G^\ddagger = 32.9 \text{ kcal/mol} \]  \hspace{2cm} (20)

\[ \Delta G^\ddagger = 32.5 \text{ kcal/mol} \]  \hspace{2cm} (21)

Discussion

Summary. The tandem ortholithiation–Fries rearrangement depicted generically in eq 1 was studied at several levels. Qualitative IR spectroscopic studies revealed that the meta substituents on the arene ring and the alkyl groups on the carbamoyl moiety influence metalation and rearrangement rates. Electron-withdrawing meta substituents accelerate the lithiation, allow it to proceed to full conversion, and retard the subsequent Fries rearrangement—all consistent with a stabilized aryllithium. The alkyl substituents on the carbamate group have little influence on the ortholithiation but show marked effects on the Fries rearrangement; large alkyl groups retard the rearrangement.

NMR spectroscopic studies revealed an assortment of species summarized in Scheme 1. Judicious choices of substrate and reaction conditions were required to document the different structural forms. Poorly coordinating solvents, for example, promote LDA–arene complex 5. Aryl carbamates bearing electron-withdrawing meta substituents (MeO or F) and only 1.0 equiv of LDA are required to form aryllithium 2 as the predominant species. Metalation of aryl carbamates with excess LDA affords mixed dimer 6 as the major species. Fries rearrangement in the presence of excess LDA affords 7, whereas the analogous rearrangement in the absence of excess LDA affords 8. Although dimer 4 and mixed aggregates 5–7 are rigorously characterized, limited solubility rendered the assignment of 2 incomplete and dependent on analogy with other aryllithiums. Profoundly low solubility of 8 and the absence of Li–X coupling rendered NMR spectroscopy useless; X-ray crystallography showed a dimer (Figure 1), as noted for related derivatives.21

Detailed rate studies of the ortholithiation of 1a reveal that the metalation proceeds via monosolvated monomer-based transition structure 9. Metalation in a poorly coordinating solvent \((n\text{-BuOMe})\) starting from an LDA dimer–arene complex analogous to 5 proceeds via monosolvated dimer-based transition structure 10. The Fries rearrangement of mixed dimer 6, a rare example of a carefully delineated mixed aggregate-based reaction, proceeds via both dissociative and nondissociative pathways via transition structures 11 and 12 (respectively).

Computational studies using Me₂NLi and Me₂O as models for LDA and THF, respectively, provide support to the proposed transition structures described above; these studies also offer experimentally elusive structural and energetic details. The most stable monomer-based transition structure for the metalation of carbamate 1a is monosolvate 14a consistent with experiment. Acceleration by fluorne is confirmed and is consistent with strong inductive effects. Moreover, the versatility of fluoro groups as ortho directors is ortho-directed lithiation is competitive (cf., 14g and 15). By contrast, an ancillary methoxy moiety offers little or no cooperative assistance to a carbamate-directed ortholithiation. The computational studies also provided insights into the Fries rearrangements. Both aryllithium monomer- and mixed-dimer-based rearrangements appear viable, as found experimentally.

On the Role of Mixed Aggregates. Mixed aggregation introduces a complexity whose prevalence and importance is easily underestimated.35 Odd solvent effects or demands for excess organolithium reagents are easily dismissed as mysteries of science, but they have firm structural and mechanistic origins that can be elucidated with some effort. We have noticed, for example, that Snieckus and co-workers, the most avid users of Fries rearrangements, use excess LDA with great success.2,7 Underneath this success lie interesting phenomena. Using only 1.0 equiv of LDA causes the metalation to stall owing to the buildup of mixed aggregates and affiliated autoinhibition.18a,b Conversely, the Fries rearrangement is faster in the absence of LDA. Thus, in this two-step sequence, excess LDA promotes the first step and retards the second. Although this conflict is not fatal—the reaction works quite well overall—it illustrates the complexities of such two-step protocols.

On the Role of “Precomplexes”. The notion that Lewis basic functionalities on a substrate can interact with a metal in the rate limiting transition structures to facilitate organometallic reactions, the complex-induced proximity effect (CIPE), is widely accepted.36 Mechanistic discussions of a heteroatom-directed ortholithiation, for example, are dominated by concerns about the role of substituent-lithium interactions in fostering ortholithiation.2,36 Indeed, the computational support for a distinct carboxyl–lithium interaction in the rate-limiting transition structures such as 9 and 10 is convincing. There is, however, a tendency to ascribe importance to transiently formed complexes preceding the rate-limiting step. Such “precomplexes” are often construed as critical to preorganizing the species undergoing reaction. To invoke such an interpretation of the CIPE is to ascribe a path dependence that is invalid.37 Any


number of transiently formed species can precede the rate limiting step; none is kinetically relevant.

What are the consequences of observable LDA–arene complex 5? Was it not the formation of 5 and an affiliated preorganization that diverted the metalation from a monomer- to a dimer-based pathway? In a word, no. The relative efficacies of the monomer- and dimer-based metalations are described by eq 19. The solvent-dependent change in mechanism—the solvent-dependent relative preferences for 9 versus 10—derives from the energetic cost of solvent dissociation, a cost that is relatively low for weakly coordinating solvents. Observable complexation to form 5 also depends on the cost of solvent dissociation. Thus, observable complexation and a preference for dimer-based metalation share a common “lurking” variable, solvent dissociation, but there is no direct causal relationship between complexation and dimer-based reaction.

Conclusions

As mechanistic organic chemists, we are enamored with the elegance of the structural and mechanistic complexity accompanying the tandem ortholithiation–Fries rearrangement. The dual role of LDA–ArLi mixed aggregates as inhibitors of both the ortholithiation and the Fries rearrangement offers an unusually clear and rare view into mixed aggregation effects. We are reminded that simplistic mechanistic models to explain product distributions are quite likely to be wrong. The picture of relentless complexity, however, may frustrate those looking for prompt, simple answers. In our opinion, the principles emerging from detailed organolithium mechanistic studies are very rational, even enlightening, but neither punctuality nor simplicity is guaranteed.

So are these results merely curiosities? Synthetic chemists have done a remarkable job empirically tuning complex organolithium reactions to render them widely useful. The anionic Fries rearrangement has been very dependable without accompanying structural mechanistic insights. That is not to say, however, that empirical methods are necessarily optimized. Reactions that may have stalled inexplicably, for example, appear to have been achieved by simply adding excess base or the Fries rearrangement on the THF concentration suggests that strongly coordinating solvents should promote the Fries rearrangement. The extent to which the ortholithiation and the subsequent Fries rearrangement are fundamentally different processes suggests one should view them as such.

Experimental Section

Reagents and Solvents. THF, hexane, and pentane were distilled from blue or purple solutions containing sodium benzophenone ketyl. Crystalline LDA was prepared from n-BuLi. Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques. Solutions of n-BuLi and LDA were titrated using a literature method. Substrates were prepared by literature procedures.

NMR Spectroscopic Analyses. All NMR tubes were prepared using stock solutions and sealed under a partial vacuum. Standard 1H, 13C, and 15N NMR spectra were recorded on a 500 MHz spectrometer at 76.73, 125.79, and 50.66 MHz (respectively). The 1H, 13C, and 15N resonances are referenced to 0.3 M [1H]LiCl/MeOH at −90 °C (0.0 ppm), CH2=O resonances of THF at −90 °C (67.57 ppm), and neat Me4N+ at −90 °C (25.7 ppm), respectively.

IR Spectroscopic Analyses. 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 8 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. Following evacuation under a full vacuum and flushing with argon, the T-joint was capped by a septum for injections and an argon line. After recording a background spectrum, a carbamate (I) was added to the LDA/THF mixture at −78 °C from a dilute stock solution (100 μL, 0.404 M) with stirring. IR spectra were recorded over the course of the reaction. To account for mixing and temperature equilibration, spectra recorded in the first 1.5 min were discarded. All reactions were monitored to >5 half-lives.

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Supporting Information Available: NMR spectra, rate and computational data, experimental protocols, and complete ref 32. This material is available free of charge via the Internet at http://pubs.acs.org.

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