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Reactivity of Individual Organolithium Aggregates: A RINMR Study of *n*-Butyllithium and 2-Methoxy-6-(methoxymethyl)phenyllithium

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The high sensitivity of organolithium rates and selectivities to solvation is often attributed to variation in aggregate concentrations. Although lower aggregates appear to be more reactive in most cases, the relative reactivity of aggregates has rarely been determined[1a,2,3,4a] since kinetic studies are normally performed under Curtin−Hammett conditions, where contributions to the rate by different aggregates are inferred from nonidealized reaction orders in the organolithium reagent. More is known about N- and O-lithiated species such as amides and enolates.[5,6a]

We have developed a rapid injection NMR (RINMR) apparatus which operates at low enough temperatures that reaction rates faster than the rate of interconversion of aggregates can be measured. Our apparatus has injection syringes mounted above the spectrometer, making room for mechanical stirring of the NMR sample, so that efficient (<1 s) mixing can be achieved at any temperature in the liquid range of the solvent. All actions (lowering and raising of the stirrer paddle, injection of one or two substrates) are controlled manually or by the pulse program of the spectrometer.[7]

The temperature jump that occurs when the warm reactant is injected into the cold sample can be measured in real time using our ^{13}C chemical shift thermometer.[4b] Nearly constant temperatures are achieved by raising the temperature setting the appropriate amount (typically 5−6 degrees) 10 s before an injection.[7] At starting temperatures below −135 °C, freezing (in mixtures of Me_2O and THF) becomes problematic; therefore, the fastest process we can study has a $\Delta G^{\ddagger} = 8.6$ kcal/mol at −130 °C ($t_{1/2} = 2.7$ s). We report here on the individual aggregate reactivity of *n*-butyllithium dimers and tetramers (interconversion barrier of 10.3 kcal/mol[1b,8a,b]) and the tetramer and monomer/dimer of 2-methoxy-6-(methoxymethyl)phenyllithium (**5**, barrier of 11.7 kcal/mol). The reactivity of *n*-BuLi aggregates has been previously studied using a RINMR apparatus of a different design.[1a,c,d]

Figure 1 shows selected ^{7}Li NMR spectra from a RINMR experiment of the deprotonation of (trimethylsilyl)acetylene (**1a**) by the dimer and tetramer of *n*-BuLi. Under standard conditions (1:3 THF/Me_2O at −129 ± 1 °C), the *n*-BuLi dimer signal disappears during the 1 s mixing period ($k^2_{\text{D}-\mathbf{1a}} > 20$ M^{-1} s^{-1}). An intermediate species, identified as the mixed dimer **3a**,[7,8c] forms and then decays in a second-order process ($k^2_{\text{MD}-\mathbf{1a}} = 2.6$ M^{-1} s^{-1}). The final product is the acetylide homodimer **4a**.[5d,8c,d,10,11] The *n*-BuLi tetramer does not react with **1a** but must first dissociate to the dimer since its rate of disappearance is independent of acetylene concentration ($k^1_{\text{T}} = 1.9 \times 10^{-4}$ s^{-1}, $k^2_{\text{T}-\mathbf{1a}} < 5 \times 10^{-4}$ M^{-1} s^{-1}).[9] We can calculate $k^2_{\text{D}-\mathbf{1a}}/k^2_{\text{T}-\mathbf{1a}} > 40\,000$ as a conservative lower limit since it includes neither the actual rate of the tetramer nor that of the dimer.

To measure the actual rate ratio, we examined more reactive acetylenes to find one sufficiently acidic to react directly with the *n*-BuLi tetramer. (Triphenylsilyl)acetylene (**1b**) was unreactive, but for (phenylthio)acetylene (**1c**), reaction with the tetramer could be detected. At low concentrations, the tetramer disappearance was marginally faster than reactions with **1a** and **1b**, where dissociation is the sole pathway. Increasing the concentration of **1c** confirmed that the reaction was approaching first-order dependence on the acetylene ($k^2_{\text{T}-\mathbf{1c}} = 1.3 \times 10^{-3}$ M^{-1} s^{-1}). The reaction with (*p*-tolylsulfonyl)acetylene (**1d**) was also briefly studied; it reacted with the *n*-BuLi tetramer too fast to measure ($k^2_{\text{T}-\mathbf{1d}} \geq 50$ M^{-1} s^{-1}, at least 40 000 times as reactive as **1c**).

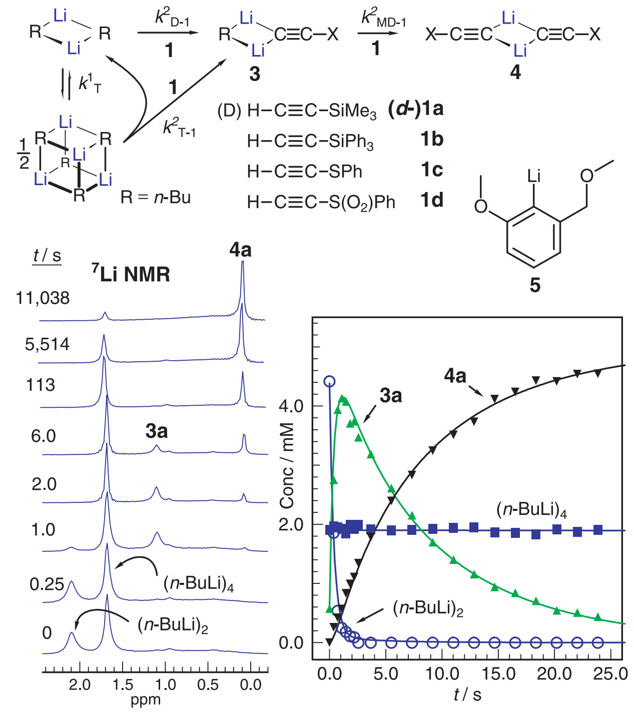

Figure 1. Selected spectra, concentration versus time plot, and kinetic scheme derived from a RINMR experiment of **1a** (0.20 mL in THF/ether, 2 equiv) injected into 4 mL of *n*-BuLi (0.026 M) in 1:3 THF/Me_2O at −135 °C. The lines are simulations using the kinetic scheme shown.

With a rate constant for the *n*-BuLi tetramer reacting with **1c** in hand, we needed to estimate the rate constant for the dimer. The rate of reaction of deuterated (trimethylsilyl)acetylene (***d*-1a**) with the *n*-BuLi dimer was readily measurable and first order in acetylene ($k^2_{\text{D}-d\text{-}\mathbf{1a}} = 2.1$ M^{-1} s^{-1}). A deuterium isotope effect of 38 ± 10 was measured by injection of *n*-BuLi into a mixture of **1a** and ***d*-1a** (this is an average of the isotope effects for deprotonation by *n*-BuLi dimer and by **3a**). We were also able to measure by RINMR the isotope effect for reaction of **3a** with **1a** and ***d*-1a** ($k^2_{\text{MD}-\mathbf{1a}}/k^2_{\text{MD}-d\text{-}\mathbf{1a}} = 65$). From these values, we can calculate $k^2_{\text{D}-\mathbf{1a}} = 52k^2_{\text{D}-d\text{-}\mathbf{1a}} = 110$ M^{-1} s^{-1}.

Competition experiments were then performed between **1a**, **1b**, and **1c** in reactions with *n*-BuLi, giving relative rates of 1:63:3800. Thus $k^2_{\text{D}-\mathbf{1c}} = 3800k^2_{\text{D}-\mathbf{1a}} = 4.2 \times 10^5$ M^{-1} s^{-1}. To circumvent the mixing problems in competition experiments involving very fast reactions,[12] *n*-BuLi in hexane was injected as its unreactive tetrameric form into a solution of two acetylenes at −129 °C in THF/Me_2O, where its slow dissociation to dimers ensures homogeneity throughout the reaction. Comparison of $k^2_{\text{D}-\mathbf{1c}}$ and $k^2_{\text{T}-\mathbf{1c}}$

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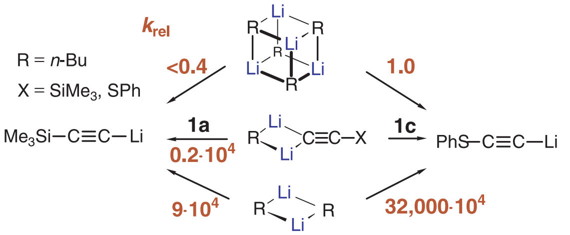

Figure 2. Summary of relative rates for reaction of *n*-BuLi aggregates with acetylenes.

shows that *n-BuLi dimer is 3.2 × 10^8 times as reactive as the tetramer* toward **1c**! This value is 5 orders of magnitude larger than any previous estimates of organolithium aggregate relative reactivity, which, with two exceptions,[1a,4a] were made under Curtin−Hammett conditions and hence had limited dynamic range.

The importance of understanding mixed aggregate reactivity and formation is highlighted by their ubiquity in asymmetric organolithium-mediated reactions,[6b,13] as well as the potential for reaction products to be incorporated into the parent aggregate.[6c,d] Still, quantitative information is scarce.[5a] We note that the acetylide ligand in **3a** has a rate-retarding effect on the reactivity of the remaining butyl fragment ($k^2_{\mathrm{D-}\mathbf{1a}}/k^2_{\mathrm{MD-}\mathbf{1a}} = 42$), which is consistent with the weaker coordinating ability of an acetylide anion; the butyl fragment will thus coordinate more tightly to lithium (see Figure 2 for a rate summary). This contrasts with the higher reactivity found for *n*-BuLi/alkoxide mixed tetramers[1a] and an enolate/amide mixed dimer[5b] compared to that of the homoaggregates.

We have performed a similar analysis on 2-methoxy-6-(methoxymethyl)phenyllithium (**5**), unique since three coexisting aggregates are present: monomer, dimer, and tetramer in a 1.0:0.4: 0.3 ratio at 0.04 M in 3:2 THF/ether at −130 °C. The lithium signals of the monomer and dimer coalesce at −132 °C ($\Delta G^{\ddagger}_{-132°\mathrm{C}}$ ca. 7.2 kcal/mol), whereas the tetramer signal coalesces with the other two at −29 °C ($\Delta G^{\ddagger}_{-29°\mathrm{C}}$ ca. 11.7 kcal/mol).[7] Thus, the monomer/dimer reactions will be under Curtin−Hammett conditions, but those of the tetramer can be easily measured relative to the monomer/dimer pair. The tetramer of **5** is unreactive in the deprotonation of the highly reactive **1d** ($k^1_{\mathrm{T}} = 2.2 \times 10^{-5}$ s^{-1}, $k^2_{\mathrm{T-}\mathbf{1d}} < 6 \times 10^{-5}$ M^{-1} s^{-1} at −127 °C). Even with the much less reactive **1a**, the coalesced monomer/dimer signal of **5** disappears too quickly to measure, but the reaction with ***d*-1a** is measurable ($k^2_{\mathrm{M-}\boldsymbol{d}\mathrm{-}\mathbf{1a}} = 0.6$ M^{-1} s^{-1}, assuming the monomer is the reactive species). Thus $k^2_{\mathrm{M-}\mathbf{1a}} = 67$ M^{-1} s^{-1} using the measured isotope effect of 66. Competition experiments such as those for *n*-BuLi show that the monomer of **5** reacts 2900 times as fast with **1c** as with **1a**. The extrapolation from **1c** to **1d** cannot be made precisely, but we know that **1d** is at least 40 000 times as reactive as **1c** toward the *n*-BuLi tetramer. If we assume that the monomer of **5** has a similar **1d** to **1c** rate ratio (other relative rates are very similar for *n*-BuLi dimer and **5M**), then we can estimate $k^2_{\mathrm{M-}\mathbf{1d}} = 40\,000 \times 2900 \times k^2_{\mathrm{M-}\mathbf{1a}} = 5 \times 10^9$ M^{-1} s^{-1}. Comparison of $k^2_{\mathrm{M-}\mathbf{1d}}$ and $k^2_{\mathrm{T-}\mathbf{1d}}$ shows that *the monomer of **5** is at least 10^{14} times as reactive as the tetramer.*

Such large rate effects are not necessarily general since basic substrates could coordinate to lithium and gain access to the relatively inaccessible anion of the higher aggregates.[5c,8e] McGarrity, Ogle, Brich, and Loosli studied the reaction of *n*-BuLi aggregates with benzaldehyde at −85 °C.[1a] While we confirmed their observation that the tetramer reacts directly with benzaldehyde ($k^2_{\mathrm{T}} = 7.6 \times 10^{-3}$ M^{-1} s^{-1}), we find that the dimer reacts faster than mixing ($k^2_{\mathrm{D}} > 32$ M^{-1} s^{-1}), with an estimated $k^2_{\mathrm{D}}/k^2_{\mathrm{T}}$ of >4200. Thus, the added dynamic range provided by our RINMR setup makes it immediately clear that the dimer/tetramer rate ratio is much larger than the factor of 10 they reported. For the less reactive *p*-diethylaminobenzaldehyde, where the *n*-BuLi dimer still reacts on the time scale of mixing, the tetramer is unreactive (zero order in aldehyde). This allowed a relative rate estimate of *at least* 20 000. The tetramer was also unreactive with a variety of other substrates, including benzoyl chloride, 3-methoxyacetophenone, 3-methoxy-*N*,*N*-dimethylbenzamide, acetone, and methyl benzoate. The rate-limiting step when *n*-BuLi in hexane is added to a THF solution of such substrates is dissociation of the tetramer to dimer.

In conclusion, we have demonstrated the utility of a newly developed RINMR apparatus by showing that the differences in reactivity between the higher and lower aggregates of *n*-BuLi and of the ArLi reagent **5** are enormously larger than previous estimates. This has particular significance for rationales of regio-, stereo-, and chemoselectivities of organolithium reactions which invoke competition between aggregation states. The RINMR apparatus opens up exciting possibilities for directly determining aggregate and mixed aggregate contributions to organometallic reactions.

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Supporting Information Available: Detailed description of the RINMR apparatus and its use, sample spectra, kinetic runs, and characterization of **3**, **4**, **5**, and the reaction and quenching products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) We measure $\Delta G^{\ddagger}_{-135°\mathrm{C}} = 10.3$ kcal/mol for the *n*-BuLi tetramer dissociation in 3:1 Me$_2$O/THF. Barriers of $\Delta G^{\ddagger}_{-135°\mathrm{C}} = 10.8$[1b] and 8.1 kcal/mol[8b] can be calculated for tetramer−dimer interchange from DNMR activation parameters measured in pure THF.

(10) Lithium acetylide products were characterized by ^{13}C NMR spectroscopy: **4a**, **4b**, and **4c** are dimeric in 1:3 THF/Me$_2$O,[5c,d] and **4d** is monomeric, with a 1:1:1:1 quartet for the C−Li carbon from coupling to one ^{7}Li.[8a] This is the first reported characterization by NMR of a monomeric lithium acetylide.[5d,14]

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