

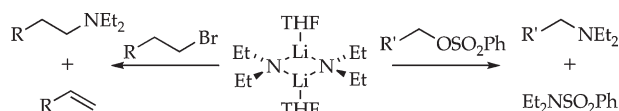
Reaction of Lithium Diethylamide with an Alkyl Bromide and Alkyl Benzenesulfonate: Origins of Alkylation, Elimination, and Sulfonation

Lekha Gupta, Antonio Ramírez, and David B. Collum*

Department of Chemistry and Chemical Biology Baker Laboratory, Cornell University Ithaca, New York 14853-1301, United States

dbc6@cornell.edu

Received July 30, 2010

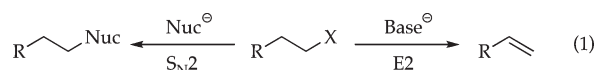


A combination of NMR, kinetic, and computational methods are used to examine reactions of lithium diethylamide in tetrahydrofuran (THF) with *n*-dodecyl bromide and *n*-octyl benzenesulfonate. The alkyl bromide undergoes competitive S_N2 substitution and E2 elimination in proportions independent of all concentrations except for a minor medium effect. Rate studies show that both reactions occur via trisolvated-monomer-based transition structures. The alkyl benzenesulfonate undergoes competitive S_N2 substitution (minor) and N-sulfonation (major) with N-sulfonation promoted at low THF concentrations. The S_N2 substitution is shown to proceed via a disolvated monomer suggested computationally to involve a cyclic transition structure. The dominant N-sulfonation follows a disolvated-dimer-based transition structure suggested computationally to be a bicyclo[3.1.1] form. The differing THF and lithium diethylamide orders for the two reactions explain the observed concentration-dependent chemoselectivities.

Introduction

Many may remember being confounded by the substitution-elimination dichotomy presented in our first course on organic chemistry (eq 1).¹ It was difficult to grasp why a given electrophile-nucleophile-solvent combination causes the prevalence of substitution over elimination (or vice versa), despite support from an enormous body of empirical observations. In our opinion, the confusion stems from the incomplete picture of how solvation and aggregation influence nucleophilicity and basicity. The nomenclature based on “ion pairing” prevalent in the older literature is too inflexible to describe underlying aggregation effects. Similarly, using terms such as “polarity” to explain solvent-dependent reactivities and selectivities is inadequate to describe inherently molecular solvation events. Amid the few studies designed to untangle the coordination chemistry

underlying substitutions and eliminations,² the efforts of Streitwieser and co-workers are prominent.³



Understanding the S_N2–E2 dichotomy is more than an aging academic problem. One is struck, for example, by the profound importance of C–N bond formation in pharmaceutical syntheses and the role played by S_N2 substitutions.⁴ Given the scope of the applications and their scales,⁵ even incremental improvements in simple N-alkylations of mono- and dialkylamines could prove significant.

We describe herein reactions of lithium diethylamide (Et₂NLi) in tetrahydrofuran (THF) with an *n*-alkyl bromide (eq 2) and an *n*-alkyl sulfonate (eq 3). The competing

(1) (a) Smith, M.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; Wiley-Interscience: New York, 2007; Chapters 10,17. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 5th ed.; Springer: New York, 2007; Chapters 4.5. (c) Saunders, W. H., Jr.; Cockerill, A. F. *Mechanisms of Elimination Reactions*; John Wiley & Sons: New York, 1973; Vol. II, pp 60–68. (d) Baciocchi, E. In *The Chemistry of Halides, Pseudo Halides and Azides, Supplement D*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, U.K., 1983.

(2) (a) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; VCH: Weinheim, 2003; Chapter 5. (b) Hiraoka, M. *Crown Compounds: Their Characteristics and Application*; Elsevier: Amsterdam, 1982. (c) Atwood, J. L., Steed, J. W., Eds. *Encyclopedia of Supramolecular Chemistry*; CRC Press: Boca Raton, FL, 2004; pp 940–949.

(3) (a) Wang, D. Z.; Streitwieser, A. *J. Org. Chem.* **2003**, *68*, 8936. (b) Harder, S.; Streitwieser, A.; Petty, J. T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1995**, *117*, 3253. (c) Streitwieser, A.; Choy, G. S. C.; Abu-Hasanayn, F. *J. Am. Chem. Soc.* **1997**, *119*, 5013. (d) Streitwieser, A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 8288–8290. See also ref 19. (e) Streitwieser, A.; Jayasree, E. G. *J. Org. Chem.* **2007**, *72*, 1785.

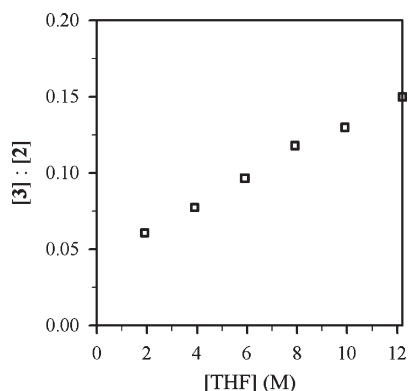


FIGURE 1. Plot of [3]:[2] vs [THF] in toluene cosolvent for the reaction of 0.004 M 1-bromododecane (**1**) with Et₂NLi (0.10 M) at 0 °C.

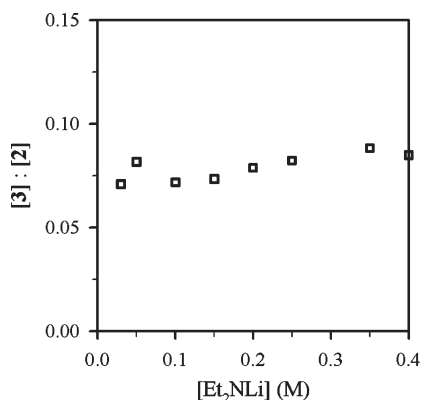
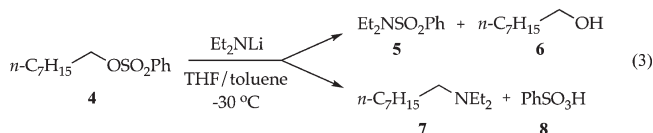
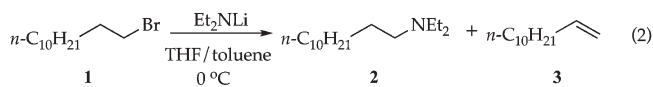


FIGURE 2. Plot of [3]:[2] vs [Et₂NLi] in THF (3.9 M) and toluene cosolvent for the reaction of 0.004 M 1-bromododecane (**1**) with Et₂NLi at 0 °C.

N-substitution, elimination, and N-sulfonation (O-desulfonation) pathways are traced to specific solvation and aggregation events.⁶



Results

Concentration-Dependent Selectivities. Using protocols and conditions described below, the selectivities of N-alkylation, elimination, and N-sulfonation versus Et₂NLi and THF

(4) (i) For a survey of chemical syntheses within the process chemistry R&D departments of GlaxoSmithKline, AstraZeneca and Pfizer, see: (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (b) Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Process Res. Dev.* **2005**, *9*, 253. (ii) For examples of N-alkylation of lithium dialkylamides, see: (c) Smith, J. K.; Bergbreiter, D. E.; Newcomb, M. J. *Org. Chem.* **1985**, *50*, 4549. (d) Sard, H.; Duffley, R. P.; Razdan, R. K. *Synth. Commun.* **1983**, *13*, 813. (iii) For representative reactions of lithium dialkylamides with sulfonates, see: (e) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700. (f) Andersen, K. K.; Gowda, G.; Jewell, L.; McGraw, P.; Phillips, B. T. *J. Org. Chem.* **1982**, *47*, 1884.

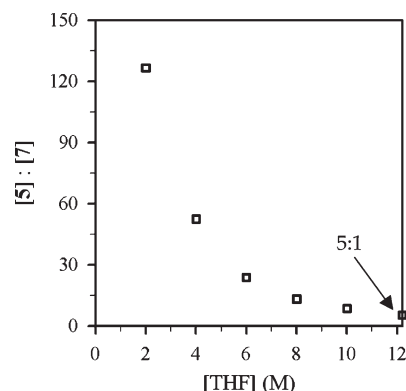


FIGURE 3. Plot of [5]:[7] vs [THF] in toluene cosolvent for the reaction of 0.004 M 1-octyl benzenesulfonate (**4**) with Et₂NLi (0.10 M) at −30 °C.

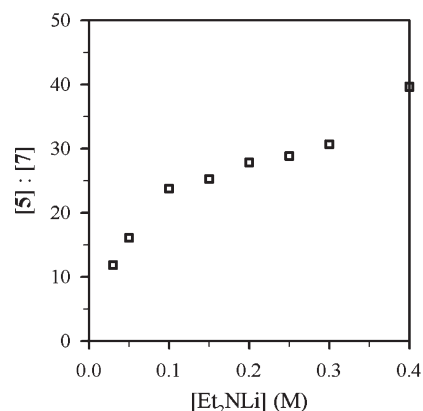
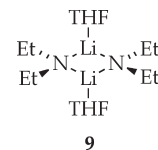


FIGURE 4. Plot of [5]:[7] vs [Et₂NLi] in THF (6.0 M) and toluene cosolvent for the reaction of 0.004 M 1-octyl benzenesulfonate (**4**) with Et₂NLi at −30 °C.

concentrations were measured and are depicted graphically in Figures 1–4. The notable feature is that *n*-alkyl bromide **1** affords ratios of **2** and **3** displaying a minor THF dependence (Figures 1 and 2), whereas the relative proportions of N-sulfonation (**5**) and N-alkylation (**7**) show both a dependence on the Et₂NLi concentration and a striking THF concentration dependence (Figures 3 and 4). The product ratios allow us to deconvolute the mechanistic contributions to each pathway.

Structure of Lithium Diethylamide. Previous ⁶Li and ¹⁵N NMR spectroscopic investigations have shown that [⁶Li,¹⁵N]-Et₂NLi is a dimer in THF (**9**).⁷ Computational studies suggest that dimer **9** is disolvated (see Supporting Information). At low THF concentrations (< 2.0 M), minor amounts of 3- and 4-rung ladders are observed.^{7,8}



General Protocols. Pseudo-first-order rate constants (*k*_{obsd}) were determined using excess Et₂NLi (0.030–0.40 M) and

(5) Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green, S. P.; Marziano, I.; Sherlock, J.-P.; White, W. *Chem. Rev.* **2006**, *106*, 3002.

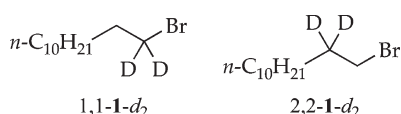
TABLE 1. Summary of Rate Studies for the Et₂NLi-Mediated Reactions (eqs 2 and 3)

entry	substrate	product(s)	THF order	Et ₂ NLi order	k _H /k _D ^d	k _H /k _D ^e
1	1	2+3	2.0 ± 0.1 ^a	0.54 ± 0.03 ^b	1.1 ± 0.1	1.22 ± 0.05
2		2	2.0 ± 0.1 ^a	0.52 ± 0.03 ^b	1.1 ± 0.1	1.12 ± 0.05
3		3	2.5 ± 0.1 ^a	0.57 ± 0.03 ^b	1.1 ± 0.1	3.02 ± 0.04
4	4	5+7	0 ^a	0.98 ± 0.05 ^c		
5		5	0 ^a	0.99 ± 0.04 ^c		
6		7	1.29 ± 0.05 ^a	0.59 ± 0.04 ^c		

^a[Et₂NLi] = 0.10 M. ^b[THF] = 3.9 M in toluene cosolvent. ^c[THF] = 6.0 M in toluene cosolvent. ^dMeasured using 1 and 1,1-*d*₂. ^eMeasured using 1 and 2,2-*d*₂.

limiting substrate concentrations (0.004 M). THF was restricted to > 2.0 M to avoid the larger aggregates observed at low THF concentrations.^{7,8} The disappearance of the substrate (1 or 4), and the formation of products were monitored relative to an internal *n*-decane standard using gas chromatographic (GC) analysis of quenched aliquots; they displayed clean first-order decays. Measured values of *k*_{obsd} are independent of the initial concentrations of the substrate (±10%), consistent with first-order dependencies on the substrates. The product ratios allow *k*_{obsd} to be partitioned into the rate constants for the parallel pathways as described below. Results from the rate studies are summarized in Table 1. Additional data are archived in Supporting Information.

N-Alkylation and Elimination of 1-Bromododecane. Reaction of Et₂NLi with 1-bromododecane (1) in THF/toluene yields *N,N*-diethyldodecylamine (2)⁹ and 1-dodecene (3) as shown in eq 2 and Figure 5. *n*-Dodecane that resulted from reduction¹⁰ was also detected, but the concentrations were erratic and very low (<2%).¹¹ Plots of *k*_{obsd} versus THF concentration (Figure 6) and *k*_{obsd} versus Et₂NLi concentration (Figure 7) furnish orders of 2.0 ± 0.1 and 0.54 ± 0.03, respectively. Replacing toluene cosolvent with 2,2,4,4-tetra-methyltetrahydrofuran revealed no measurable cosolvent dependence, arguing against long-range medium effects as the source of second-order THF dependence.^{6b,12}



- (6) (a) DePue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5518. (b) DePue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524. (7) (a) Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **1999**, *121*, 10198. For recent computational studies of Et₂NLi aggregation and solvation states, see: (b) Pratt, L. M. *THEOCHEM* **2007**, *811*, 191. (8) (a) Gardiner, M. G.; Raston, C. L. *Inorg. Chem.* **1996**, *35*, 4162. (b) Gardiner, M. G.; Raston, C. L. *Inorg. Chem.* **1996**, *35*, 4047. (c) Gardiner, M. G.; Raston, C. L. *Inorg. Chem.* **1995**, *34*, 4206. (d) Boche, G.; Langlotz, I.; Marsch, M.; Harms, K.; Nudelman, N. E. S. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1205. (e) Barr, D.; Clegg, W.; Hodgson, S. M.; Lamming, G. R.; Mulvey, R. E.; Scott, A. J.; Snaith, R.; Wright, D. S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1241. (f) Armstrong, D. R.; Barr, D.; Clegg, W.; Hodgson, S. M.; Mulvey, R. E.; Reed, D.; Snaith, R.; Wright, D. S. *J. Am. Chem. Soc.* **1989**, *111*, 4719. (9) Ceruti, M.; Balliano, G.; Viola, F.; Cattel, L.; Gerst, N.; Shuber, F. *Eur. J. Med. Chem.* **1987**, *22*, 199. (10) (a) Majewski, M.; Gleave, D. M. *J. Organomet. Chem.* **1994**, *470*, 1. (b) Newcomb, M.; Reeder, R. A. *J. Org. Chem.* **1980**, *45*, 1489. (c) Newcomb, M.; Burchill, M. T. *J. Am. Chem. Soc.* **1984**, *106*, 8276. (d) Newcomb, M.; Burchill, M. T. *J. Am. Chem. Soc.* **1984**, *106*, 2450. (11) We do note, however, that the highest levels of *n*-dodecane loosely correlated with higher THF concentrations. (12) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772.

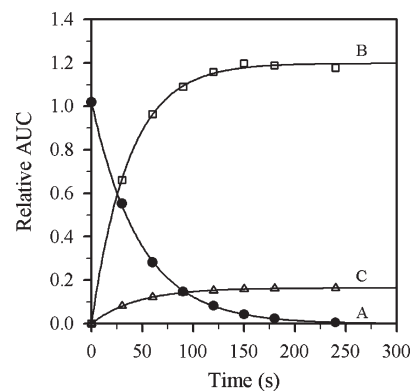


FIGURE 5. Representative plot of the time-dependent decay of 1 (curve A) and formation of 2 (curve B) and 3 (curve C) relative to an *n*-decane internal standard (relative area under the curve, AUC) for sequentially quenched samples of a reaction mixture containing Et₂NLi (0.10 M), THF (9.90 M), 1 (0.004 M), and toluene cosolvent at 0 °C. The curves depict least-squares fit to: (A) $y = ae^{-bx}$ ($a = 1.022 \pm 0.005$, $b = k_{\text{obsd}} = (2.11 \pm 0.02) \times 10^{-2}$); (B) $y = \{a(1 - e^{-bx})\}$ ($a = 1.199 \pm 0.006$, $b = k_{\text{alk}} = (2.71 \pm 0.06) \times 10^{-2}$); (C) $y = \{a(1 - e^{-bx})\}$ ($a = (1.648 \pm 0.003) \times 10^{-1}$, $b = k_{\text{elim}} = (2.25 \pm 0.02) \times 10^{-2}$).

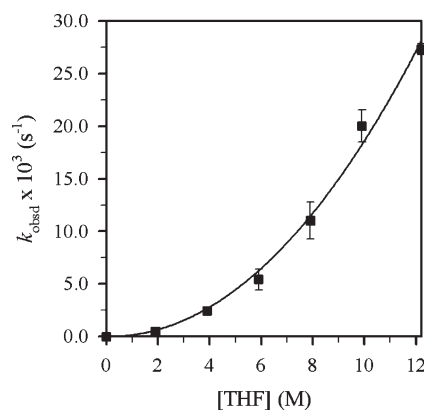


FIGURE 6. Plot of *k*_{obsd} vs [THF] in toluene cosolvent for the reaction of 1 (0.004 M) with Et₂NLi (0.10 M) at 0 °C. The curve depicts an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{THF}]^n$ ($k = (1.6 \pm 0.4) \times 10^{-4}$, $n = 2.0 \pm 0.1$).

To separate contributions from the two pathways one simply notes that $k_{\text{obsd}} = k_{\text{alk}} + k_{\text{elim}}$ and $[2]/[3] = k_{\text{alk}}/k_{\text{elim}}$ such that k_{alk} and k_{elim} correspond to the pseudo-first-order rate constants for N-alkylation and elimination, respectively. The task was simple because the product ratios were nearly independent of all concentrations (see Figures 1 and 2); the rate laws for substitution and elimination are identical. (A slight preference for the formation of 3 at elevated THF concentrations is reflected by the slightly higher order; Table 1, entry 3.)

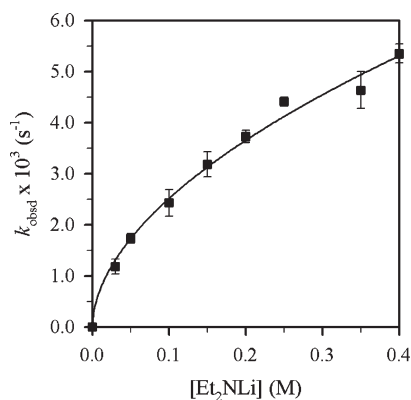
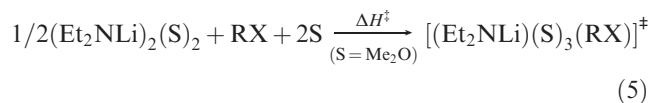


FIGURE 7. Plot of k_{obsd} vs $[\text{Et}_2\text{NLi}]$ in THF (3.9 M) and toluene cosolvent for the reaction of **1** (0.004 M) with Et_2NLi at 0 °C. The curve depicts an unweighted least-squares fit to $k_{\text{obsd}} = k[\text{Et}_2\text{NLi}]^n$ ($k = (8.7 \pm 0.4) \times 10^{-3}$, $n = 0.54 \pm 0.03$).

Thus, the idealized rate law¹³ is described by eq 4. The product ratios are sensitive to isotopic substitution. The measured isotope effects using 1,1- d_2 and 2,2- d_2 (Table 1) are consistent with an $\text{S}_{\text{N}}2$ substitution¹⁴ and E2 elimination.¹⁵ GC-MS analyses also confirmed β - rather than α -eliminations.¹⁶ The stereochemistries of N-alkylation and elimination were *not* addressed experimentally.¹⁷

$$-d[\mathbf{1}]/dt = (k_{\text{alk}} + k_{\text{elim}})[\text{Et}_2\text{NLi}]^{1/2}[\text{THF}]^2[\mathbf{1}] \quad (4)$$

A variety of seemingly plausible transition structures for substitution and elimination are shown in Chart 1. Density functional theory (DFT) calculations using the SVP basis set for Br and 6-31G(d) for the rest of the atoms¹⁸ afforded enthalpies of activation (ΔH^\ddagger , kcal/mol) that include thermal corrections at 298.15 K. 1-Bromododecane, Et_2NLi , and THF were modeled using EtBr, Me_2NLi and Me_2O , respectively, to restrict the number of conformers. Calculated activation free energies were ridiculously high even with MP2/6-31G*/B3LYP/6-31G(d) single-point calculations. Enthalpies of activation are reported according to eq 5. Although absolute energies are not terribly informative, the relative values and calculated geometries are.



The results of the DFT computations (B3LYP/6-31G(d)) are illustrated in Chart 2. Optimization of type **I** structures resulted in legitimate transition structure **10** displaying an N–Li interaction and a highly bent N–C–Br bond angle (155°).¹⁹

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

(14) (a) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science, 2006; Chapter 11. (b) Fang, Y.-R.; Westaway, K. C. *Can. J. Chem.* **1991**, *69*, 1017. (c) Westaway, K. C.; Lai, Z.-G. *Can. J. Chem.* **1989**, *67*, 345.

(15) (a) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 4081. (b) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5573.

(16) Dehydrobrominations of 2,2- d_2 -dodecane afforded exclusively 1- d_1 -dodecene, whereas dehydrobrominations of 1,1- d_2 -dodecane yielded 1- d_2 -dodecene.

(17) (a) Bock, P. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 2826. (b) Whitesides, G. M.; Fischer, W. F., Jr.; San Filippo, J., Jr.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.

CHART 1

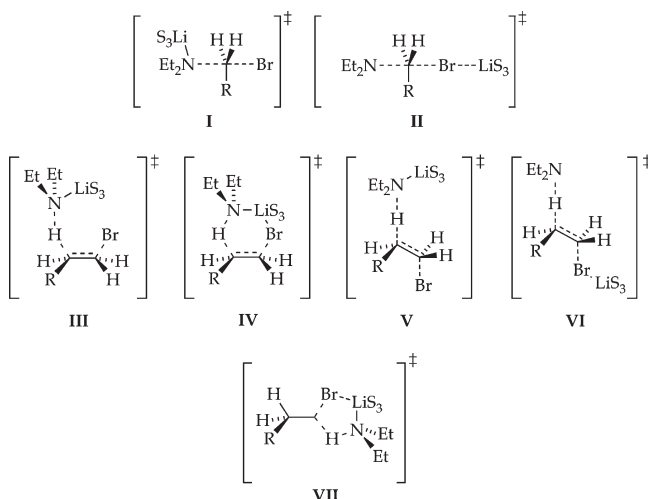
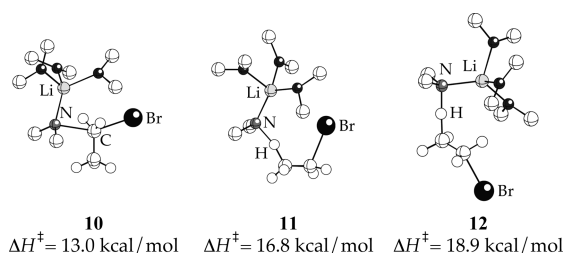


CHART 2



In contrast, we failed to locate structures akin to **II**.²⁰ Optimizations of β -eliminations **III**–**VI** afforded only **11** and **12** (types **III** and **V**), both containing N–Li contacts. No structures of type **IV** or **VI** displaying Br–Li contacts could be found.²¹

(18) All calculations were executed using *Gaussian 03*, revision B.04; Gaussian, Inc.: Pittsburgh, PA, 2003. See Supporting Information for the full list of authors. The combination of the Ahlrichs all-electron SVP basis set for second-row atoms and 6-31G* for the rest is denoted as 631A and has been previously applied to mechanistic studies on organolithium-mediated reactions: Nakamura, E.; Yamanaka, M.; Yoshikai, N.; Mori, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1935. Mori, J.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2000**, *122*, 7294 and references therein.

(19) Recent theoretical studies on $\text{S}_{\text{N}}2$ reactions involving lithium-containing species: (i) No solvent: (a) Ren, Y.; Gai, J.-G.; Xiong, Y.; Lee, K.-H.; Chu, S.-Y. *J. Phys. Chem. A* **2007**, *111*, 6615. (b) Streitwieser, A.; Jayasree, E. G.; Leung, S. S.-H.; Choy, G. S.-C. *J. Org. Chem.* **2005**, *70*, 8486. (c) Pratt, L. M.; Nguyen, N. V.; Ramachandran, B. *J. Org. Chem.* **2005**, *70*, 4279. (d) Pomelli, C. S.; Bianucci, A. M.; Crotti, P.; Favero, L. *J. Org. Chem.* **2004**, *69*, 150. (e) Ren, Y.; Chu, S. Y. *J. Comput. Chem.* **2004**, *25*, 461. (f) Xiong, Y.; Zhu, H.; Ren, Y. *J. Mol. Struct.* **2003**, *664*–*665*, 279. (g) Leung, S. S.-H.; Streitwieser, A. *J. Comput. Chem.* **1998**, *19*, 1325. (ii) Dielectric solvation models: (h) Streitwieser, A.; Jayasree, E. G.; Hasanayn, F.; Leung, S. S.-H. *J. Org. Chem.* **2008**, *73*, 9426. (i) Ren, Y.; Li, M.; Wong, N.-B.; Chu, S.-Y. *J. Mol. Model.* **2006**, *12*, 182. (j) Ren, Y.; Chu, S. Y. *J. Phys. Chem. A* **2004**, *108*, 7079. (k) Zhu, H.; Ren, Y.; Ren, J. *J. Mol. Struct.* **2004**, *686*, 65. (iii) Microsolvation models: (l) Streitwieser, A.; Jayasree, E. G. *J. Org. Chem.* **2007**, *72*, 1785. (m) Ando, K. *J. Org. Chem.* **2006**, *71*, 1837. (n) Ando, K. *J. Am. Chem. Soc.* **2005**, *127*, 3964. See also reference 20a.

(20) RBr–Li interactions do not appear to be stabilizing: (a) Zuend, S. J.; Ramirez, A.; Lobkovsky, E.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 5939. (b) Ikuta, Y.; Tomoda, S. *Org. Lett.* **2004**, *6*, 189.

(21) For additional examples showing that Br leaving groups do not require metal assistance during the alkylation of lithium-based nucleophiles, see: (a) Zuend, S. J.; Ramirez, A.; Lobkovsky, E.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 5939. (b) Ikuta, Y.; Tomoda, S. *Org. Lett.* **2004**, *6*, 189. (c) For a general discussion of lithium-assisted departure of the leaving group, see: Reich, H. J.; Sanders, A. W.; Fiedler, A. T.; Bevan, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 13386.

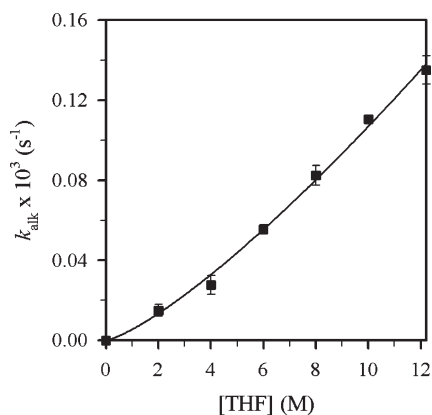


FIGURE 8. Plot of k_{alk} vs [THF] in toluene cosolvent for the N-alkylation of **4** (0.004 M) with Et_2NLi (0.10 M) at -30°C . The curve depicts an unweighted least-squares fit to $k_{\text{alk}} = k[\text{THF}]^n$ ($k = (5.5 \pm 0.7) \times 10^{-6}$, $n = 1.29 \pm 0.05$).

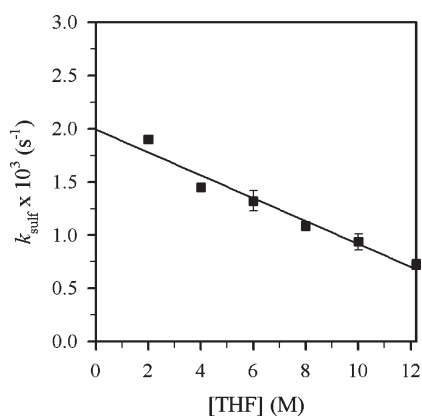


FIGURE 9. Plot of k_{sulf} vs [THF] in toluene cosolvent for the N-sulfonation of **4** (0.004 M) with Et_2NLi (0.10 M) at -30°C . The curve depicts an unweighted least-squares fit to $k_{\text{sulf}} = c[\text{THF}] + k'$ ($c = (-1.07 \pm 0.08) \times 10^{-4}$, $k' = (1.99 \pm 0.06) \times 10^{-3}$).

Efforts to find structure **VII** corresponding to a hypothetical (unobserved) α -elimination failed, possibly because the trisolvation implicated by the rate studies precludes a Br–Li interaction.²² The relative enthalpies of transition structures **10**, **11** and **12** indicate that the nucleophilic substitution (**10**) is enthalpically favored.

N-Alkylation and N-Sulfonation of *n*-Octyl benzenesulfonate. The reaction of 1-octyl benzenesulfonate (**4**) with 0.10 M Et_2NLi in THF/toluene mixtures at -30°C affords products derived from N-sulfonation (**5** and **6**) and N-alkylation (**7** and **8**) to the exclusion of 1-octene expected from elimination (eq 3). Figure 3 shows the THF dependence on the ratio of substitution and elimination (**5/7**). In contrast to the reaction of 1-bromododecane, the selectivity is highly sensitive to the proportion of THF. By monitoring the **5/7** ratio (vide supra), k_{obsd} can be deconvoluted to give the rate constants for the N-sulfonation (k_{sulf}) and N-alkylation (k_{alk}).

(22) (i) Basic nucleophiles tend to generate Nuc-H α complexes upon unrestricted geometry optimizations (a) Yi, R.; Basch, H.; Hoz, S. *J. Org. Chem.* **2002**, *67*, 5891. (b) Buhl, M.; Schaefer, H. F. *J. Am. Chem. Soc.* **1993**, *115*, 9143. (ii) Nu-CR₃-X angle restriction to collinearity is a common technique to circumvent this limitation in the study of S_N2 reactions: (c) Hoz, S.; Basch, H.; Wolk, J. L.; Hoz, T.; Rozental, E. *J. Am. Chem. Soc.* **1999**, *121*, 7724.

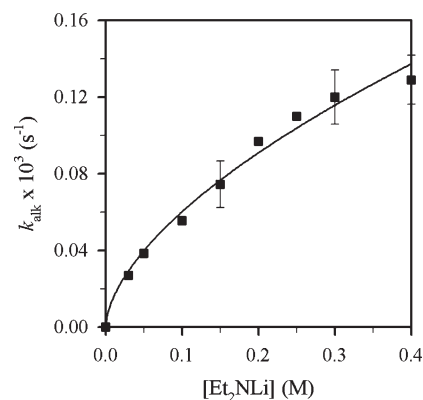


FIGURE 10. Plot of k_{alk} vs $[\text{Et}_2\text{NLi}]$ in THF (6.0 M) and toluene cosolvent for the N-alkylation of **4** (0.004 M) with Et_2NLi at -30°C . The curve depicts an unweighted least-squares fit to $k_{\text{alk}} = k[\text{Et}_2\text{NLi}]^n$ ($k = (2.4 \pm 0.1) \times 10^{-4}$, $n = 0.59 \pm 0.04$).

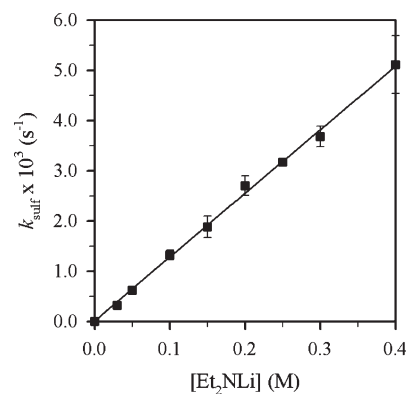
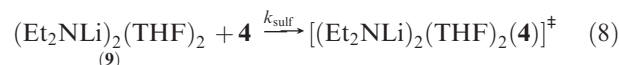
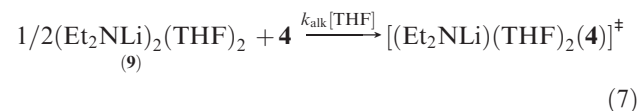


FIGURE 11. Plot of k_{sulf} vs $[\text{Et}_2\text{NLi}]$ in THF (6.0 M) and toluene cosolvent for the N-sulfonation of **4** (0.004 M) with Et_2NLi at -30°C . The curve depicts an unweighted least-squares fit to $k_{\text{sulf}} = k[\text{Et}_2\text{NLi}]^n$ ($k = (1.26 \pm 0.07) \times 10^{-2}$, $n = 0.99 \pm 0.04$).

Plots of k_{alk} and k_{sulf} versus THF concentration (Figures 8 and 9) reveal first- and zeroth-order dependencies, respectively. The linear and slightly inverse THF concentration dependence observed for k_{sulf} is consistent with secondary shell (medium) effects accompanying the increasing THF concentration.^{6b,12} Figures 10 and 11 illustrate the dependence of k_{alk} and k_{sulf} on the Et_2NLi concentration (0.03–0.40 M) in 6.0 M THF. The fractional order ($k_{\text{alk}} \propto [\text{Et}_2\text{NLi}]^{0.59 \pm 0.04}$) and first order ($k_{\text{sulf}} \propto [\text{Et}_2\text{NLi}]^{0.99 \pm 0.04}$) are consistent with monomer- and dimer-based pathways, respectively. The data support the idealized rate law in eq 6 and the generic mechanisms in eqs 7 and 8.

$$-\text{d}[\mathbf{4}]/\text{d}t = k_{\text{alk}}[\text{Et}_2\text{NLi}]^{1/2}[\text{THF}]^1[\mathbf{4}] + k_{\text{sulf}}[\text{Et}_2\text{NLi}]^1[\text{THF}]^0[\mathbf{4}] \quad (6)$$



Rate data indicate that N-alkylation occurs via disolvated Et_2NLi monomer, possibly with a minor contribution from

CHART 3

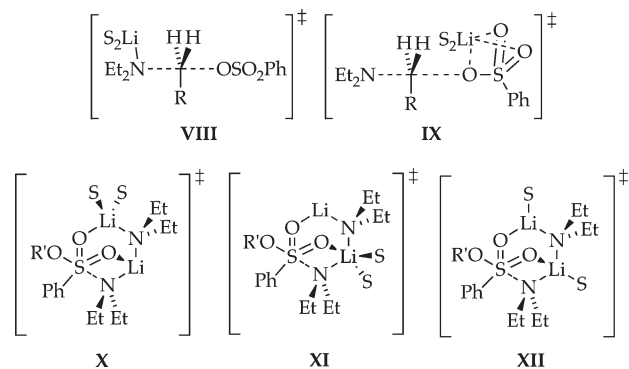
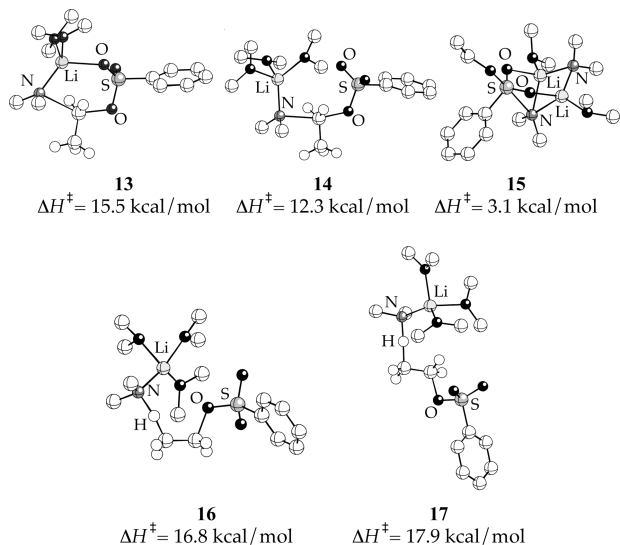


CHART 4



trisolvated monomer, whereas N-sulfonation takes place via disolvated Et₂NLi dimer. The generic transition structures in Chart 3 seem plausible, yet a much smaller subset proved computationally viable (Chart 4). Attempts to optimize parent geometries VIII and IX for the nucleophilic substitution (using PhSO₂OEt as a model) converged on hybrid isomer 13, which displays a 6-membered ring and a tetra-coordinate lithium²³ that interacts with the sulfonyl leaving group.²⁴ Transition structure 13 corresponds to a 6-*endotet* closure, which is considered to be geometrically implausible in many settings.²⁵ Transition structure 14, a trisolvated analog of 13, lacks an S=O–Li contact.

Searches for disolvated-dimer-based transition structures for N-sulfonation afforded only structure 15 (type XII), solvated

at the external and internal Li atoms. Optimization of proximally solvated forms (types X and XI) led to desolvation.^{26,27} Transition structure 15 displays a bicyclo[3.1.1] ring system with coordination of each S=O moiety to one lithium atom of the Me₂NLi dimer. The sulfur atom adopts trigonal bipyramidal hybridization with the attacking nitrogen and the leaving RO group in apical positions. IRC calculations support a stepwise addition–elimination.²⁸ The computations qualitatively support a preference for N-sulfonation over N-alkylation.

Cursory searches of hypothetical (unobserved) monomer-based β-eliminations afford 16 and 17. Activation enthalpies suggest that eliminations will not compete with alkylation and sulfonation.

Discussion

We introduced this paper with the assertion that nucleophilic substitutions and eliminations can be confounding because of a limited understanding of how aggregation and solvation—two inherently molecular phenomena—influence the mechanisms. A combination of kinetic and computational methods was used to study reactions of Et₂NLi in THF with *n*-alkyl bromide 1 and *n*-alkyl benzenesulfonate 4 (eqs 2 and 3). The resulting mechanistic scenario summarized in Scheme 1 is discussed in the context of several long-standing issues.

S_N2–E2 Dichotomy. We intended to study the mechanistic basis underlying competing substitutions and eliminations. Such an analysis of sulfonate 4 was precluded by its failure to undergo detectable elimination, which is somewhat surprising given the pronounced Brønsted basicity of Et₂NLi.²⁹ Focusing on *n*-alkyl bromide 1, we found that both substitution and elimination proceed via isomeric trisolvated-monomer-based pathways. One of the most obvious and practical consequences is that concentration changes provide no means of controlling selectivity (Figures 1 and 2). The drifting selectivity with increasing THF concentration shown in Figure 1 derives from secondary shell solvation effects; *vide infra*.

S_N2 Substitutions: RBr versus ROSO₂Ph. Inspection of transition structure 18 (or the structurally simpler computed analog 10) reveals pronounced steric interactions between

(23) Schlosser, M. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; 2nd ed.; John Wiley & Sons: Chichester, 2002; Chapter 1.

(24) (i) For reports on R₂SO₂–Li complexation, see: (a) Linnert, M.; Bruhn, C.; Wagner, C.; Steinborn, D. *J. Organomet. Chem.* **2006**, *689*, 2358. (b) Rhodes, C. P.; Frech, R. *Macromolecules* **2001**, *34*, 2660. (c) Pregel, M. J.; Dunn, E. J.; Buncel, E. *J. Am. Chem. Soc.* **1991**, *113*, 3545. (d) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1980**, *45*, 4536. (ii) The nucleophilic substitutions of arylsulfonates with lithium halides occur with inversion of configuration: Braddock, D. C.; Pouwer, R. H.; Burton, J. W.; Broadwith, P. *J. Org. Chem.* **2009**, *74*, 6042.

(25) (a) Beak, P. *Acc. Chem. Res.* **1992**, *25*, 215. (b) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (c) Baldwin, J. E. *Further Perspectives in Organic Chemistry: A Ciba Foundation Symposium*; Elsevier: Amsterdam, 1978, 736. (d) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476.

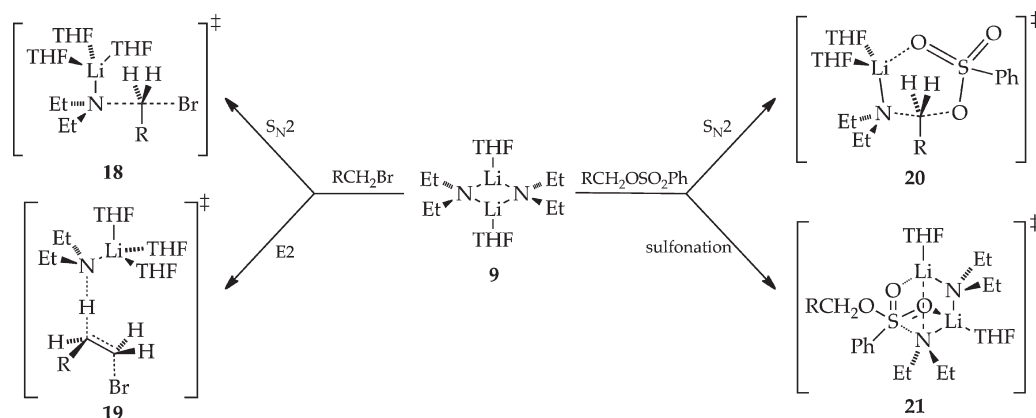
(26) (a) Fressigné, C.; Lautrette, A.; Maddaluno, J. *J. Org. Chem.* **2005**, *70*, 7816. (b) Pomelli, C. S.; Bianucci, A. M.; Crotti, P.; Favero, L. *J. Org. Chem.* **2004**, *69*, 150. (c) Gillies, M. B.; Tønder, J. E.; Tanner, D.; Norrby, P. *J. Org. Chem.* **2002**, *67*, 7378. (d) Fressigné, C.; Maddaluno, J.; Marquez, A.; Giessner-Pretre, C. *J. Org. Chem.* **2000**, *65*, 8899.

(27) (a) Ramirez, A.; Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 10326. (b) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 2166. Searches for structures disolvated at the external Li led to severe transannular interactions involving the solvent and the S=O–Li bridge.

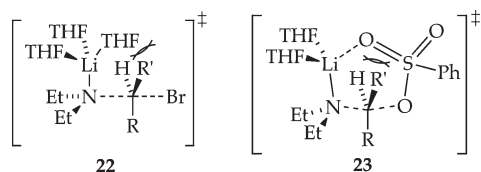
(28) For discussions of S_N2 mechanism versus that with a discrete tetrahedral intermediate, see: (a) Erdik, E.; Eroglu, F. *Cent. Eur. J. Chem.* **2008**, *6*, 237. (b) Fox, J. M.; Dmitrenko, O.; Liao, L.; Bach, R. D. *J. Org. Chem.* **2004**, *69*, 7317. (c) Weiner, H.; Sneen, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 292. (d) Chang, F. C. *Tetrahedron Lett.* **1964**, *6*, 305.

(29) (i) For studies on the acidity of Et₂NH in THF, see: (a) Furlong, J. J. P.; Lewkowicz, E. S.; Nudelman, N. S. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1461. (ii) For selective substitutions of sulfonates with organolithiums, see: (b) Nelson, T. D.; Rosen, J. D.; Smitrovich, J. H.; Payack, J.; Craig, B.; Matty, L.; Huffman, M. A.; McNamara, J. *Org. Lett.* **2005**, *7*, 55. (c) Kusumoto, T.; Ichikawa, S.; Asaka, K.; Sato, K.-I.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 1071. (iii) For a recent discussion on β-eliminations of benzenesulfonates, see: (d) Mohrig, J. R.; Alberg, D. G.; Cartwright, C. H.; Pflum, M. K. H.; Aldrich, J. S.; Anderson, J. K.; Anderson, S. R.; Fimmen, R. L.; Snover, A. K. *Org. Biomol. Chem.* **2008**, *6*, 1641.

SCHEME 1



the $\text{CH}_2\text{-Br}$ moiety and the THF ligands. Now imagine an analogous substitution of a secondary alkyl bromide via transition structure **22**. The vast literature suggests that it would be markedly slower (possibly orders of magnitude) due to destabilizing $\text{Et}_2\text{N-RBr}$ contacts. It appears, however, that solvent–substrate interactions are pronounced and that focusing on $\text{Et}_2\text{N-RBr}$ interactions may be misleading. The literature also suggests that highly ionizing conditions can markedly promote the $\text{S}_{\text{N}}2$ substitution,^{21c,30} which would logically stem from both the increasing charge on the nucleophile as well as dissociation of the lithium cation and, with it, the solvent–substrate contacts. This scenario is very unlikely to occur, however, for Et_2NLi even under highly ionizing conditions. The conclusion is a recurring theme: steric demands of solvation are an important determinant of aggregate structure and reactivity.³¹



Comparing the mechanism for $\text{S}_{\text{N}}2$ substitutions of *n*-alkyl bromide **1** and benzenesulfonate **4** reveals that the sulfonate ester undergoes substitution via a disolvated rather than a trisolvated monomer. Computational studies show that transition structure **20** (Scheme 1), in which a THF ligand has been replaced by chelation of the sulfonate, is quite plausible with a 25° distortion of the N-C-O angle from the optimal 180° , a distortion comparable to that observed for the alkyl bromide.³² Those who use Baldwin's ring closure rules categorically may find transition structure **20** disquieting. Let us return to the hypothetical displacements

(30) (a) Humeres, E.; Nunes, R. J.; Machado, V. G.; Gasques, M. D. G.; Machado, C. *J. Org. Chem.* **2001**, *66*, 1163. (b) Westaway, K. C.; Lai, Z. *Can. J. Chem.* **1988**, *66*, 1263. (c) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988; Chapter 7. (d) Arnett, E. M.; Maroldo, S. G.; Schriver, G. W.; Schilling, S. L.; Troughton, E. B. *J. Am. Chem. Soc.* **1985**, *107*, 2091. (e) Doolittle, R. E. *Org. Prep. Proceed. Int.* **1980**, *12*, 1. (f) Parker, A. J.; Mayer, U.; Schmid, R.; Gutmann, V. *J. Org. Chem.* **1978**, *43*, 1843. (g) Sam, D. J.; Simmons, H. E. *J. Am. Chem. Soc.* **1974**, *96*, 2252.

(31) Collum, D. B.; McNeil, A. J.; Ramirez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3002.

(32) For challenges to the reputed linear trajectory of ideal $\text{S}_{\text{N}}2$ reactions, see: Sato, M.; Yamataka, H.; Komeiji, Y.; Mochizuki, Y.; Ishikawa, T.; Nakano, T. *J. Am. Chem. Soc.* **2008**, *130*, 2396 and references cited therein.

and consider the displacement of a secondary alkyl sulfonate ester. The additional alkyl moiety (R') in cyclic transition structure **23** would likely render the reaction untenable because of acute interactions between the sulfonyl moiety and the alkyl group of the sulfonate ester. The reaction would be forced to proceed through a noncyclic form, which is suggested by the rate studies to be less viable. The interactions *within the sulfonate ester moiety* are quite prominent whereas those with the Et_2N moiety almost seem to be of secondary importance. Although this description is certainly an oversimplification, most conventional discussions of $\text{S}_{\text{N}}2$ displacements of sulfonate esters do not consider interactions between the sulfonyl moiety and the alkyl substituents as potentially dominant.³³

$\text{S}_{\text{N}}2$ Substitution versus N-Sulfonation. The reaction of Et_2NLi with sulfonate **4** in THF affords products of substitution and N-sulfonation. The name N-sulfonation, however, is a lithium amide-centric view. It would be equally valid to call it O-desulfonation. Such desulfonations are consequential side reactions during displacements of tosylates and related sulfonate esters.³⁴ In contrast to the substitution-elimination selectivity observed for *n*-alkyl bromide **1**, the alkylation-sulfonation selectivity is sensitive to both THF and Et_2NLi concentrations (Figures 3 and 4). The dominant sulfonation (120:1) becomes less so (<5:1) at low Et_2NLi and high THF concentrations. The concentration dependencies derive from differential solvation and aggregation numbers in transition structures **20** and **21**. The sulfonation appears to benefit from multidentate contacts with lithium as well as from conservation of the Et_2NLi dimer structure. IRC calculations revealed a two-step (addition–elimination) mechanism.

Primary Shell versus Secondary Shell Solvation. Both N-alkylation and β -elimination of 1-bromododecane show approximate second-order THF dependencies, which we attribute to monomer-based pathways in THF/toluene mixtures. The THF order for the elimination pathway is actually 2.5 ± 0.1

(33) (a) Bentley, T. W.; Bowen, C. T.; Morten, D. H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5466. (b) Bentley, T. W.; Bowen, C. T.; Parker, W.; Watt, C. I. F. *J. Am. Chem. Soc.* **1979**, *101*, 2486. (c) Bentley, T. W.; Bowen, C. T. *J. Chem. Soc., Perkin Trans. 2* **1978**, 557. (d) Mori, A.; Nagayama, M.; Mandai, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1669.

(34) Studies on nucleophilic displacements at sulfonate sulfur: (a) Holterman, H. A. J.; Engberts, B. F. N. *J. Org. Chem.* **1977**, *42*, 2792. (b) Van de Langkruis, G. B.; Engberts, J. B. F. N. *J. Org. Chem.* **1984**, *49*, 4152. (c) Mori, A.; Nagayama, M.; Mandai, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1669. (d) Weiner, H.; Snee, R. A. *Tetrahedron Lett.* **1963**, 1309.

(Table 1, entry 3). One consequence is that the selectivity shows a preference for elimination at elevated THF concentrations (Figure 1). By using 2,2,5,5-tetramethyltetrahydrofuran, a cosolvent with a polarity akin to that of THF but no capacity to coordinate competitively to lithium, the THF order for the β -elimination drops to 2.1 ± 0.1 .³⁵ Thus, there is a medium effect of marginal practical consequence. The N-sulfonation using sulfonate **4** shows an analogous medium effect, except that a slight rate reduction occurs at elevated THF concentrations. Similar secondary shell effects contributing to solvent-dependent rates have been documented previously.^{6,36} Moreover, they are known to cause both modest accelerations and decelerations, depending on the specific reaction. Although it may be tempting to focus on how and why the medium influences reaction rates, we find that the medium effects are surprisingly minor given that lithium amides are often viewed as highly polar species. The chemistry of lithium amides in particular, and probably organolithium reagents in general, is dominated by ligands in the primary coordination shell.

Conclusion

Reaction of Et_2NLi with an *n*-alkyl bromide reveals competing $\text{S}_{\text{N}}2$ substitution and E2 elimination via trisolvated lithium amide monomers in both instances. Within this sliver of the enormous field of substitution and elimination, the relative reaction rates and, consequently, the chemoselectivity are insensitive to solvent and lithium amide concentrations. Analogous reaction of Et_2NLi with an *n*-alkyl arylsulfonate affords low levels of substitution and substantial N-sulfonation to the exclusion of elimination. Because the N-alkylation proceeds via disolvated monomers and the N-sulfonation via disolvated dimers, the selectivity is controllable by adjusting concentrations, although the N-sulfonation remains dominant under all conditions. Whereas primary shell solvation is of profound importance, secondary-shell solvation (medium effects) has marginally detectable influence on rates and selectivities. We are reminded that to understand organolithium reaction mechanism is to understand

(35) The dielectric constants of substituted THFs are only slightly lower than THFs. Harada, Y.; Salomon, M.; Petrucci, S. *J. Phys. Chem.* **1985**, *89*, 2006. Carvajal, C.; Tolle, K. J.; Smid, J.; Szwarc, M. *J. Am. Chem. Soc.* **1965**, *87*, 5548.

(36) Related secondary shell effects: (a) Ma, Y.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 14818. (b) Ma, Y.; Ramirez, A.; Singh, K. J.; Keresztes, I.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 15399. (c) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 7300.

the coordination chemistry of lithium, not vague notions of polarity and ionicity.

Experimental Section

Reagents and Solvents. THF and toluene were distilled from blue or purple solutions containing sodium benzophenone ketyl. The toluene still contained 1% tetraglyme to dissolve the ketyl. $[\text{}^6\text{Li}]\text{Et}_2\text{NLi}$ and $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\text{Et}_2\text{NLi}$ were prepared as insoluble white solids by metalating Et_2NH and $[\text{}^{15}\text{N}]\text{Et}_2\text{NH}$ (respectively) with $[\text{}^6\text{Li}]\textit{n}$ -BuLi in pentane.³⁷ Recrystallization from hexane/diethyl ether as the etherate and subsequent evacuation afforded solvent-free Et_2NLi .⁷ Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques. Solutions of *n*-BuLi and Et_2NLi were titrated for active base using a literature method.³⁸

Kinetics. For a kinetic run corresponding to a single rate constant, a stock solution of Et_2NLi (0.03–0.4 M) in a THF-toluene solution was prepared. A series of oven-dried, nitrogen-flushed 5 mL serum vials (10 per rate constant) fitted with stir bars were charged with the Et_2NLi stock solution and brought to the desired temperature (± 0.2 °C) using a constant-temperature bath fitted with a thermometer. The substrate (**1** or **4**) was added as a 0.08 M stock solution in hexane containing decane (0.08 M) as a GC standard. The vessels were periodically quenched with 1:1 H_2O -THF at intervals chosen to ensure an adequate sampling of each of the first three half-lives. The quenched aliquots were extracted into Et_2O and the extracts analyzed using GC. The reactions were monitored by following the decrease of substrates **1** or **4** and the formation of products **2** and **3** or **5** and **7** (eqs 2 and 3) relative to the internal decane standard. Following the formation of the corresponding products afforded equivalent rate constants within $\pm 10\%$. Rate constants were determined using nonlinear least-squares fits. The reported errors correspond to one standard deviation. The observed rate constants were shown to be reproducible within $\pm 10\%$.

Acknowledgment. We thank the National Institutes of Health (GM39764) for direct support of this work.

Supporting Information Available: NMR, rate, and computational data, experimental protocols, and complete list of authors for ref 18. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(37) (a) Rennels, R. A.; Maliakal, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 421. (b) Kottke, T.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 580.

(38) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.