Structural and Rate Studies of the Formation of Substituted Benzynes

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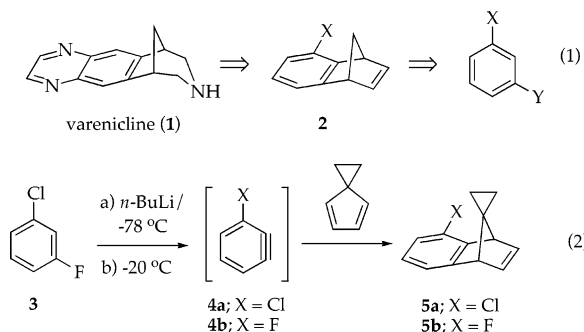Received July 22, 2007; E-mail: dbc6@cornell.edu

Abstract: The key elimination step for the formation of 3-substituted and 3,6-disubstituted benzynes from 2-haloaryllithiums displays a pronounced solvent-dependent regioselectivity. All 2-haloaryllithiums with electron withdrawing groups in the 6 position are shown by ^{6}Li and ^{13}C NMR spectroscopic studies to be monomers in THF. DFT computational studies implicate trisolvates. Rate studies reveal that LiF eliminates via monomer-based pathways requiring THF dissociation whereas LiCl eliminates via nondissociative pathways. Elimination to form 3-chloro- and 3-fluorobenzyne from 2-chloro-6-fluorophenyllithium displays a pronounced solvent-dependent regioselectivity that is traced to competing solvent-dissociative and nondissociative dissociative pathways for the elimination of LiCl and LiF, respectively.

Introduction

Benzyne has historically been a molecule of largely theoretical interest.[1] One cannot help notice, however, that the use of benzynes as reactive intermediates in synthesis has picked up markedly.[2,3] We recently reported investigations of bicyclic derivatives of general structure **2** related to varenicline (**1**), a nicotinic receptor partial agonist[4] currently marketed as an aid to smoking cessation treatment under the names Chantix and Champix (eq 1).[5] The initial syntheses of **2** relied on the generation and subsequent trapping of benzyne.[6] During the course of these studies, we discovered a pronounced solvent-dependent regioselectivity illustrated in eq 2.[6a,7] Whereas formation of benzyne from 1-chloro-3-fluorobenzene (**3**) in hydrocarbons or hydrocarbons containing low concentrations of ethereal solvents affords predominantly the product arising from elimination of LiF, the analogous reaction in neat THF solution affords a 50:1 preference for the elimination of LiCl.

We report herein structural studies of aryllithiums **6–10** and

varenicline (**1**)   **2**   (1)

3   a) *n*-BuLi/ -78 °C   b) -20 °C   **4a**; X = Cl   **4b**; X = F   **5a**; X = Cl   **5b**; X = F   (2)

solvent	selectivity (**5a:5b**)
toluene	10:1
toluene/THF	5:1
THF	1:50

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Table 1. ^{6}Li and ^{13}C Spectral Data[a]

compd	^{6}Li, δ (m, $^3J_{LiF}$)	^{13}C, δ (m, $^2J_{FC}$, $^1J_{LiC}$)
6[b]	0.81 (d, 1.2)	164.5 (dt, 130.3, 10.0)[c]
7[b]	0.49 (s)	183.4 (t, −, 11.3)
8[b]	1.20 (t, 1.4)	145.5 (tt, 127.1, 10.1)
9[d]	0.72 (s)	175.5 (t, −, 10.6)
10[d]	1.75 (d, 0.7)	154.6 (dt, 132.1, 9.6)[e]

[a] ^{6}Li NMR spectra were recorded on samples containing 0.20 M aryllithium, whereas ^{13}C NMR spectra were recorded on samples containing 0.30 M aryllithium. Coupling constants were measured after resolution enhancement. Multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet. The chemical shifts are reported relative to 0.30 M ^{6}LiCl/MeOH at −90 °C (0.0 ppm) and neat THF (25.6 and 67.6 ppm). All J values are reported in Hz. [b] Recorded at −100 °C. [c] Sample containing 0.40 M aryllithium. [d] Recorded at −110 °C. [e] Obscured by another resonance.

rate studies of their conversion to the corresponding benzyne intermediates. We show that the THF concentration-dependent regioselectivities illustrated in eq 2 derive from fundamental differences between the elimination of LiCl and LiF. Studies of the structure and reactivity of **6** were communicated previously.[7]

6 **7** **8** **9** **10**
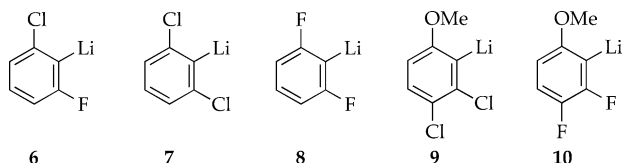
Results

Structures of Haloaryllithiums. Haloaryllithiums [^{6}Li]**6**–**10** used for NMR spectroscopic analysis were prepared by treatment of their arene precursors in THF at −196 °C with recrystallized [^{6}Li]*n*-BuLi in pentane.[8] ^{13}C NMR spectra recorded at −100 °C contain a single resonance displaying ^{6}Li–^{13}C coupling of the ^{6}Li-bearing carbon consistent with aryllithium monomers. The C-1 resonances of [^{6}Li]**6**, [^{6}Li]**8**, and [^{6}Li]**10** also display two-bond ^{13}C–^{19}F coupling ($^2J_{F-C} \approx$ 130–140 Hz).[9,10] Thus, the ^{13}C NMR spectra of [^{6}Li]**6** and [^{6}Li]**10** display a doublet of triplets, and the spectrum of [^{6}Li]**8** displays a triplet of triplets (Table 1, Figure 1A). The ^{6}Li NMR spectra reveal a doublet for [^{6}Li]**6** and [^{6}Li]**10** and a triplet for [^{6}Li]**8**. All show nearly identical ^{6}Li–^{19}F coupling constants ($^3J_{Li-F} \approx 1$ Hz, Figure 1B). We did not ascertain the solvation numbers of the aryllithiums spectroscopically, but DFT calculations (below) and analogy with crystal structures[11] provide support for trisolvated monomers.[12] We presume that the exclusive formation of monomer stems from a combination of
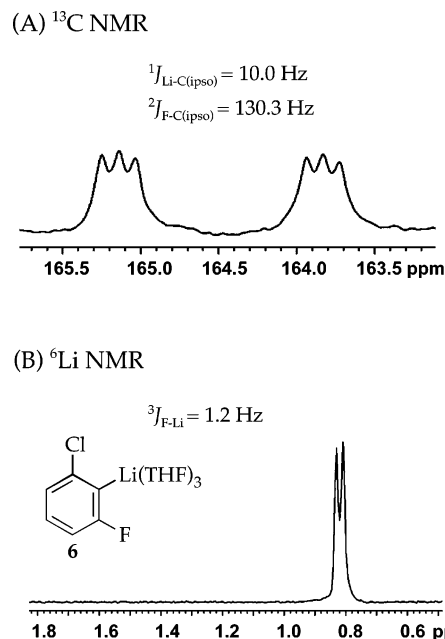
(6) (i) Synthesis via formation of 3-halobenzyne: (a) Coe, J. W.; Wirtz, M. C.; Bashore, C. G.; Candler, J. *Org. Lett.* **2004**, *6*, 1589. (ii) For alternative routes, see: (b) Brooks, P. R.; Caron, S.; Coe, J. W.; Ng, K. K.; Singer, R. A.; Vazquez, E.; Vetelino, M. G.; Watson, Jr. H. H.; Whritenour, D. C.; Wirtz, M. C. *Synthesis* **2004**, 1755. (c) Singer, R. A.; McKinley, J. D.; Barbe, G.; Farlow, R. A. *Org. Lett.* **2004**, *6*, 2357.

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(9) Spin quantum numbers: ^{6}Li has $I = 1$; ^{19}F has $I = \frac{1}{2}$.

(10) (i) Similar $^2J_{F-C}$ values have been observed for related 2-fluorophenyllithiums: (a) Singh, K. J.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 13753. (b) Menzel, K.; Fisher, E. L.; DiMichele, L.; Frantz, D. E.; Nelson, T. D.; Kress, M. H. *J. Org. Chem.* **2006**, *71*, 2188. (ii) $^2J_{C-F}$ values have been correlated with π-bond orders and total electronic charge at the ^{13}C atom: (c) Doddrell, D.; Jordan, D.; Riggs, N. V. *J. Chem. Soc., Chem. Commun.* **1972**, 1158. (d) Doddrell, D.; Barfield, M.; Adcock, W.; Aurangzeb, M.; Jordan, D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 402.

(A) ^{13}C NMR

$^1J_{Li-C(ipso)} = 10.0$ Hz

$^2J_{F-C(ipso)} = 130.3$ Hz

(B) ^{6}Li NMR

$^3J_{F-Li} = 1.2$ Hz

Figure 1. (A) ^{13}C NMR spectrum of 0.40 M [^{6}Li]3-chloro-6-fluorophenyllithium (**6**) in neat THF at −100 °C, and (B) ^{6}Li NMR spectrum of 0.20 M [^{6}Li]-(**6**) in THF (10.3 M) with toluene cosolvent at −100 °C.

Table 2. Approximate Relative Rate Constants (k_{rel}) for Benzyne Formation from Aryllithiums **6**–**10** in THF Corrected to −35 °C

ArLi	1.0 M THF	9.0 M THF
6[a]	25	15
7[a]	35	−
8[a]	7	1
9[b]	115	−
10[c]	140	10

[a] Measured at −25 °C. [b] Measured at −50 °C. [c] Measured at −35 °C.

inductive stabilization of the charge and modest (less consequential) steric inhibition of aggregation.[13]

Solvent-Dependent Relative Rate Constants. Relative rate constants for the elimination of lithium halide from aryllithiums **6**–**10** were measured using protocols described below and are listed in Table 2. The values should be viewed qualitatively in that adjustments to −35 °C were calculated assuming a 2-fold change in rate with each 10 °C change.

Kinetics of Benzyne Formation. Aryllithiums **6**–**10** used for rate studies were generated in situ by treatment of the corresponding haloarenes at ≤-25 °C with freshly recrystallized[8] commercial *n*-BuLi. Ortholithiations to form **6**–**8** were essentially instantaneous. The halogens at the 4-position of aryllithiums **9** and **10** were required to accelerate the ortholithiation relative to the benzyne formation so as to avoid *n*-Bu-

(11) (a) X-ray of monomeric 2,3,4,5-tetrafluorophenyllithium: Kottke, T.; Sung, K.; Lagow, R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1517. (b) For a related monomer, see: Bosold, F.; Zulauf, P.; Marsch, M.; Harms, K.; Lohrenz, J.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1455. (c) 2,3,5,6-Tetrafluorophenyllithium exists as a monomer in THF: Stratakis, M.; Wang, P. G.; Streitwieser, A. *J. Org. Chem.* **1996**, *61*, 3145.

(12) (a) Schlosser, M. In *Organometallics in Synthesis: A Manual,* 2nd ed.; Schlosser, M., Ed.; John Wiley & Sons: Chichester, 2002; Chapter 1. (b) Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. Ö.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201. (c) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *22*, 1624.

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Table 3. Summary of Rate Studies for the Elimination of Lithium Halide from Aryllithiums **6**−**10**

ArLi	temp (°C)	ArLi[a] order	THF order
6	−25	1.05 ± 0.04^{b}	$-1.12 \pm 0.09, 0$
7	−25	0.98 ± 0.04^{b}	0
8	−25	1.06 ± 0.07^{b}	-0.98 ± 0.07
9	−50	1.1 ± 0.1^{c}	0
10	−35	1.00 ± 0.09^{c}	-1.10 ± 0.06

[a] Values derived from the best fit of initial rates.[15] [b] [THF] = 6.8 M. [c] [THF] = 5.0 M.
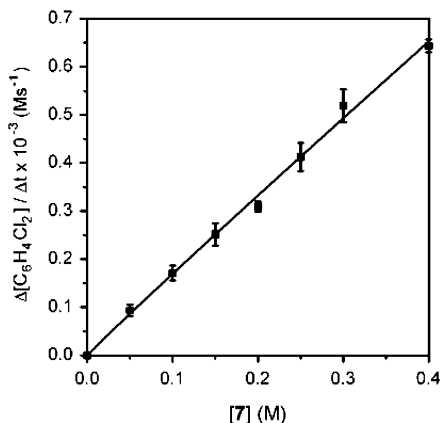
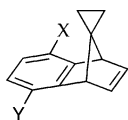***Figure 2.*** Plot of the initial slope $\Delta[C_6H_4Cl_2]/\Delta t$ vs initial [**7**] in THF (0.3 M) and toluene cosolvent for the elimination of LiCl from **7** at −25 °C. The curve depicts the result of an unweighted least-squares fit to $\Delta[C_6H_4\text{-}Cl_2]/\Delta t = k[\mathbf{7}]^n$ ($k = (1.6 \pm 0.1) \times 10^{-3}$, $n = 0.97 \pm 0.04$).

containing byproducts.[6a] Aryllithiums **9** and **10** also required a slight excess of starting arene to ensure the metalation was complete prior to the onset of benzyne formation.[14]

The rates of benzyne formation were determined by the method of initial rates[15] using an aqueous quench and subsequent GC analysis of the haloarenes relative to an *n*-octane or *n*-decane internal standard.[16] The reaction temperatures were chosen to obtain convenient time scales ($t_{1/2}$ = 45−300 min in 2.0 M THF). The resulting benzynes were trapped with excess spiro-[2.4]hepta-4,6-diene[17] as the corresponding cycloadducts **5a**−**d**. In the absence of diene, the benzynes reacted with the aryllithiums, affording spurious rate data and complex product mixtures containing biphenyls. Representative data are plotted in Figures 2−5. The rate studies are summarized in Table 3. Additional graphical and tabular data are included in Supporting Information.

5a; X = Cl, Y = H
5b; X = F, Y = H
5c; X = OMe, Y = Cl
5d; X = OMe, Y = F

Reaction Orders in ArLi. The values of k_{obsd} are independent of the initial concentrations of aryllithiums **7**−**10**, consistent with a first-order dependence.[18] Alternatively, plots of the initial

(14) Rates of benzyne formation from aryllithiums **9** and **10** showed inverse dependencies at low arene concentrations due to incomplete metalation at low temperatures.
(15) The initial rates ($\Delta[\text{arene}]/\Delta t$) were converted to their corresponding observed first-order rate constants (k_{obsd}, see Supporting Information).
(16) (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.
(17) Hart, H.; Lai, C.; Chukuemeka, G.; Shamouilian, S. *Tetrahedron* **1987**, *43*, 5203.
(18) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*, 2nd ed.; McGraw-Hill: New York, 1995.
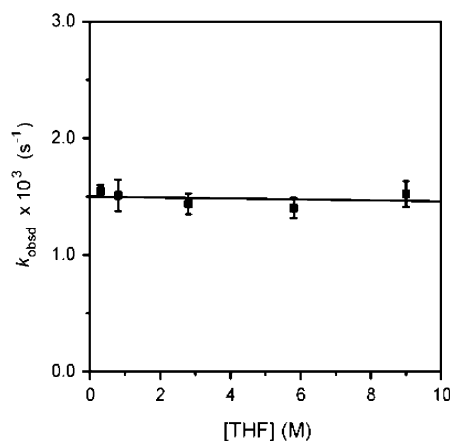
Figure 3. Plot of k_{obsd} vs [THF] in toluene cosolvent for the elimination of LiCl from **7** at −25 °C. The curve depicts the result of an unweighted least-squares fit to $k_{obsd} = k[\text{THF}] + k'$ ($k = (-4 \pm 9) \times 10^{-6}$, $k' = (1.5 \pm 0.1) \times 10^{-3}$).
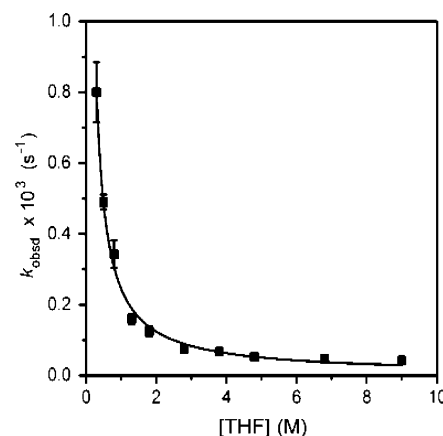

Figure 4. Plot of k_{obsd} vs [THF] in toluene cosolvent for the elimination of LiF from **8** at −25 °C. The curve depicts the result of an unweighted least-squares fit to $k_{obsd} = k[\text{THF}]^n + k'$ ($k = 2.4 \pm 0.2) \times 10^{-4}$, $n = -1.0 \pm 0.1$, $k' = (0.1 \pm 2.0) \times 10^{-5}$).

slopes versus initial aryllithium concentrations are all nearly linear; Figure 2 is representative. In conjunction with the assignments of aryllithiums **7**−**10** as monomers, the rates are consistent with monomer-based eliminations.[19] In the case of the mixed halogenated derivative **6**, contributions of the two pathways could be separated (as described in detail below) and shown to follow first order behaviors. In addition, the independence of the product ratio (**5a**:**5b**) on both the percent conversion and the initial concentration of ArLi confirm that the competitive pathways proceed via transition structures of equivalent (monomeric) aggregation states.

Reaction Orders in THF. The dependencies of the decay of **7**−**10** on THF concentration (in toluene) show two distinct behaviors. Plots of k_{obsd} versus THF concentration for the decomposition of dichloro derivatives **7** and **9** show THF-concentration-independent rates (rate $\propto$ [THF]^0, Figure 3) consistent with a mechanism requiring neither association nor dissociation of THF. In contrast, plots of k_{obsd} versus THF concentration for the decomposition of difluoro derivatives **8** and **10** follow inverse-first-order THF concentration dependencies (Figure 4). Eliminations of **8** and **10** may also have
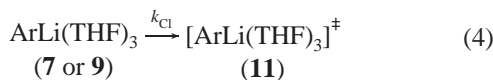
(19) A single report indicates that the elimination of LiCl from 2-chloro-3-dimethylamino-6-phenylsulfonylphenyllithium is a first-order process: Zieger, H. E.; Wittig, G. *J. Org. Chem.* **1962**, *27*, 3270.

contributions from a zeroth-order dependency evidenced by small, but nonzero, values of k_{obsd} in the high THF concentration limit (rate $\propto C_1/[THF] + C_2[THF]^0$).
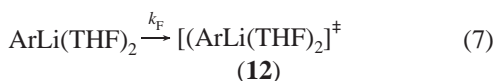
A plot of k_{obsd} versus THF concentration for the decomposition of the mixed halogenated aryllithium **6** is shown in Figure 5. k_{obsd} is a composite rate constant described as $k_{obsd} = k_{LiF} + k_{LiCl}$, such that k_{LiF} and k_{LiCl} correspond to the rate constants for the elimination of LiF and LiCl, respectively. The product ratio, **5a/5b**, provides k_{LiF}/k_{LiCl}. Consequently, k_{LiF} and k_{LiCl} can be monitored independently (Figure 5). It is evident that the competitive elimination of LiF and LiCl from **6** is a composite of the zeroth-order and inverse-order pathways observed for **7** and **8**, respectively.

Overall Rate Laws. The structural and rate studies combine to provide the idealized[20] rate laws and mechanisms described by eqs 3−12. The rate data are consistent with generic transition structures **11**−**13**. The solvation numbers of aryllithiums **6**−**10** and, by inference from the rate laws, transition structures **11**−**13** are based on DFT computations described below.
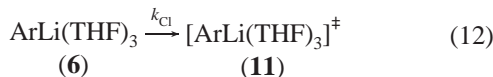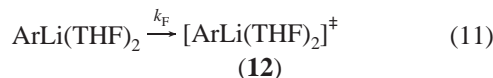
Elimination of 7 and 9:

$$-d[ArLi]/dt = k_{Cl}[ArLi][THF]^0 \qquad (3)$$

$$\underset{(\textbf{7 or 9})}{ArLi(THF)_3} \xrightarrow{k_{Cl}} \underset{(\textbf{11})}{[ArLi(THF)_3]^\ddagger} \qquad (4)$$

Elimination of 8 and 10:

$$-d[ArLi]/dt = k_F K_{eq}[ArLi][THF]^{-1} + k_F'[ArLi][THF]^0 \quad (5)$$

$$\underset{(\textbf{8 or 10})}{ArLi(THF)_3} \underset{}{\overset{K_{eq}}{\rightleftharpoons}} ArLi(THF)_2 + THF \qquad (6)$$

$$\underset{}{ArLi(THF)_2} \xrightarrow{k_F} \underset{(\textbf{12})}{[(ArLi(THF)_2]^\ddagger} \qquad (7)$$

$$\underset{(\textbf{8 or 10})}{ArLi(THF)_3} \xrightarrow{k_F'} \underset{(\textbf{13})}{[(ArLi(THF)_3]^\ddagger} \qquad (8)$$

Elimination of 6:

$$-d[ArLi]/dt = k_F K_{eq}[ArLi][THF]^{-1} + k_{Cl}[ArLi][THF]^0 \quad (9)$$

$$\underset{(\textbf{6})}{ArLi(THF)_3} \overset{K_{eq}}{\rightleftharpoons} ArLi(THF)_2 + THF \qquad (10)$$

$$\underset{(\textbf{6})}{ArLi(THF)_2} \xrightarrow{k_F} \underset{(\textbf{12})}{[ArLi(THF)_2]^\ddagger} \qquad (11)$$

$$\underset{(\textbf{6})}{ArLi(THF)_3} \xrightarrow{k_{Cl}} \underset{(\textbf{11})}{[ArLi(THF)_3]^\ddagger} \qquad (12)$$

DFT Calculations. All calculations were performed with Gaussian 03[21] using the hybrid density functional theory B3LYP method[22] and 6-31G(d) basis set for geometry optimizations.

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

(21) Frisch, M. J.; et al. *Gaussian 03*, revision B.04; Gaussian, Inc.: Pittsburgh, PA, 2003.

(22) For related B3LYP computations of aryllithiums, see: (a) Wiberg, K. B.; Sklenak, S.; Bailey, W. F. *J. Org. Chem.* **2000**, *65*, 2014. (b) Kremer, T.; Junge, M.; Schleyer, P. v. R. *Organometallics* **1996**, *15*, 3345. See also ref 10a.
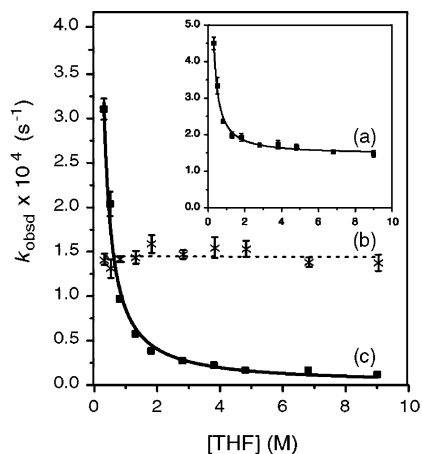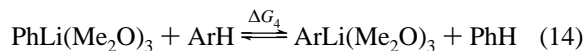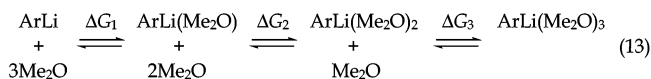

Figure 5. (a) Plot of k_{obsd} vs [THF] in toluene cosolvent for the elimination of LiCl and LiF from **6** (0.20 M) at −25 °C. The curve depicts the result of an unweighted least-squares fit to $k_{obsd} = k[THF]^n + k'$ ($k = (8 \pm 1) \times 10^{-5}$, $n = (-1.1 \pm 0.1)$, $k' = (1.5 \pm 0.1) \times 10^{-4}$). (b) Plot of k_{LiCl} vs [THF]. The curve depicts the result of an unweighted least-squares fit to $k_{LiCl} = k[THF] + k'$ ($k = (1 \pm 9) \times 10^{-7}$, $k' = (1.4 \pm 0.1) \times 10^{-4}$). (c) Plot of k_{LiF} vs [THF]. The curve depicts the result of an unweighted least-squares fit to $k_{LiF} = k[THF]^n + k'$ ($k = (8 \pm 1) \times 10^{-5}$, $n = -1.1 \pm 0.1$, $k' = (1 \pm 8) \times 10^{-6}$).
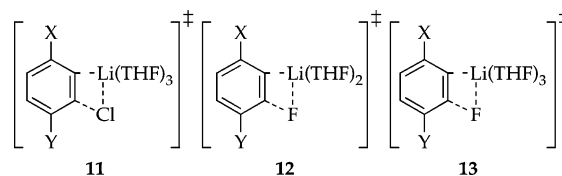
Vibrational frequencies calculated at the same level characterized these stationary points as minima. Me$_2$O was used as a model for THF. Fully optimized structures were obtained for aryllithiums **6**−**10**. Structures with idealized C(2)−C(1)−Li angles were examined in addition to those containing Li−halogen and Li−OMe interactions detected during the computational studies of aryllithiums with low solvation numbers.[23] Selected geometric characteristics of the calculated structures are archived in Supporting Information.

Calculated ArLi Structures. Serial solvation of monomeric aryllithiums **6**−**10** was investigated as summarized in eq 13 and Table 4. PhLi is included for comparison.[24] The relative free energies as defined by eq 14 are also listed in Table 4.

$$\underset{3Me_2O}{ArLi} \overset{\Delta G_1}{\rightleftharpoons} \underset{2Me_2O}{ArLi(Me_2O)} \overset{\Delta G_2}{\rightleftharpoons} \underset{Me_2O}{ArLi(Me_2O)_2} \overset{\Delta G_3}{\rightleftharpoons} ArLi(Me_2O)_3 \quad (13)$$

$$PhLi(Me_2O)_3 + ArH \overset{\Delta G_4}{\rightleftharpoons} ArLi(Me_2O)_3 + PhH \quad (14)$$

The optimized aryllithiums **6**−**10** routinely display Li−C(1) and Li−O bond distances that increase with increasing solvation

(23) (a) Li-F contacts have been found with *ab initio* calculations and associated to the formation of benzyne: Streitwieser, A. Abu-Hasanayn, F.; Neuhaus, A.; Brown, F. *J. Org. Chem.* **1996**, *61*, 3151. (b) DFT computations indicate that Li-F interactions are stronger than Li-Cl contacts and control structure and solvation of carbenoid precursors: Pratt, L. M.; Ramachandran, B.; Xidos, J. D.; Cramer, C. J.; Truhlar, D. G. *J. Org. Chem.* **2002**, *67*, 7607. (c) For a discussion on anti-MeO-Li interactions, see: Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191.

(24) (i) In THF, PhLi is a mixture of monomer and dimer.[12b] For a recent DFT calculation of PhLi(Me$_2$O)$_3$, see: (a) Krasovsky, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159. (ii) For computational discussions of lithiated benzenes, see: (b) Bachrach, S. M.; Chamberlin, A. C. *J. Org. Chem.* **2004**, *69*, 2111. (c) Kwon, O.; Sevin, F.; McKee, M. L. *J. Phys. Chem. A* **2001**, *105*, 913.

Table 4. Calculated Free Energies (ΔG, kcal/mol) of Aryllithiums **6**–**10** Solvated by Me_2O (eqs 13 and 14)

| ArLi[a]	ΔG_1	ΔG_2	ΔG_3	ΔG_4
PhLi	−14.0	−4.3	+3.1	0.0
6	−13.2	−4.3	+3.8	−19.8
7	−13.1	−4.9	+5.3	−16.4
8	−14.3	−2.9	+2.5	−21.4
9	−12.2	−3.1	+5.3	−15.3
10	−13.0	−2.9	+4.5	−17.9

[a] ArLi refers to unsolvated analogues of aryllithiums **6**–**10** and phenyllithium.

number. Attempts to locate minima corresponding to tetrasolvates resulted in desolvation. Trisolvation of aryllithiums **7**, **9**, and **10** substituted by ortho Cl or MeO groups is less favored (∼2 kcal/mol) than trisolvation of PhLi and aryllithiums **6** and **8**, which are ortho substituted by sterically undemanding H and F atoms.[25] Although the free energies of the third solvation step (ΔG_3) are positive, this is not unusual[10a,26] because DFT computations on microsolvated models tend to overestimate steric effects.[27] The discussion focuses on the trisolvated forms.[28]

Dichloroaryllithium **7** shows significant distortion by Li−Cl interactions (**14**) but only in the chemically unrealistic unsolvated and monosolvated forms; the higher solvates show no Li−Cl interaction. By contrast, the difluoro derivative **8** shows significant distortion and possibly affiliated stabilization attributable to a Li−F interaction even in the di- and trisolvated forms (**15**). The mixed halogenated derivative **6** is a composite of **7** and **8** and converges to structure **16** displaying a Li−F interaction regardless of starting geometry.
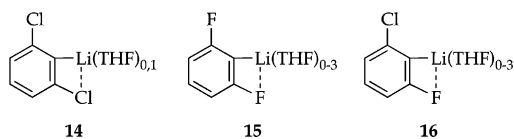
Haloanisole-derived aryllithiums **9** and **10** afforded optimized structures with the methoxy oriented either syn or anti relative to lithium (see below).[23c] The most stable trisolvates are *anti*-**9** and *anti*-**10**, in which the lone pairs on oxygen are directed toward the lithium, but neither display Li−OMe contacts. Trisolvated *anti*-**9** does not show a Li−Cl interaction, whereas the analogous *anti*-**10** trisolvate displays a Li−F contact that is stabilizing when compared with the trisolvated *anti*-**10** without Li-heteroatom interactions (∼0.5 kcal/mol).[23a] At lower solvation numbers, the syn-oriented isomers of the lower solvates of fluoroanisole **10** show a distinct Li−F contact and are more stable than the anti isomers (∼2.5 kcal/mol), even though the anti forms display potentially stabilizing Li−OMe contacts. By
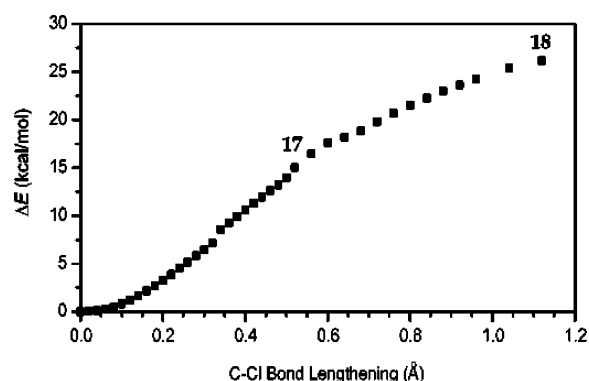
Figure 6. Potential energy (ΔE, kcal/mol) as a function of C−Cl bond lengthening (Å) relative to fully optimized **7**-$(Me_2O)_3$.

contrast, the lower solvates of chloro analogue **9** prefer the anti-oriented isomer with Li−OMe contacts.

syn-**9**; X = Cl   *anti*-**9**; X = Cl
syn-**10**; X = F   *anti*-**10**; X = F
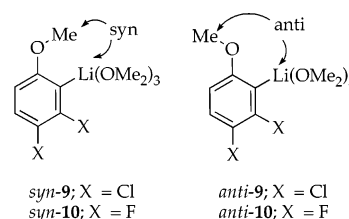
Evaluation of the Reaction Pathways. We examined the reaction coordinates for the decomposition of aryllithiums **6**–**10** using DFT computations. Exhaustive unconstrained searches failed to converge.[29] In short, weak benzyne-lithium halide bonding affords a flat potential energy surface with many floppy structures displaying significant geometrical variations separated by trivial differences in stability. The alternative protocol of gradually lengthening the C(2)-halide bond and optimizing all remaining parameters—the so-called relaxed-scan approximation—affords *potential energy* profiles that are generated from nonstationary points.[30] With caution and the hope that it may be instructive, we offer a representative relaxed scan (Figure 6). Lengthening of the C(2)−halide bond is accompanied by simultaneous lengthening of the Li−C(1) distance and contraction of both Li−halide and C(1)−C(2) distance for all solvation numbers represented emblematically by structures **17** and **18**. Arene and C(1)−C(2)−Li-halogen substructures are located in almost co-incident planes. In all cases, the structures defining the limits of benzyne-lithium halide dissociation display residual C(2)−halide contacts (∼2.5 Å) along with clear Li−C(1) disconnection (≥3.0 Å) suggestive of a E1cb-type mechanism.[31,32] In general, the affiliated energies approach 20−35

14

15

16

(25) For a discussion of the ortho-substituent effect on reducing solvent access to halophenylcesiums, see: Streitwieser, A. Abu-Hasanyan, F.; Neuhaus, A.; Brown, F. *J. Org. Chem.* **1996**, *61*, 3151.

(26) Recent example of a small positive ΔG for the third solvation of an organolithium monomer calculated using DFT: Pratt, L. M.; Mu, R.; Jones, D. R. *J. Org. Chem.* **2005**, *70*, 101.

(27) (i) Examples of a large positive ΔG for the third solvation of an organolithium monomer calculated using DFT: (a) Zuend, S. J.; Ramirez, A.; Lobkovsky, E.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 13753. (b) Mogali, S.; Darville, K.; Pratt, L. M. *J. Org. Chem.* **2001**, *66*, 2368. (ii) For a discussion on the limitations of DFT microsolvation models in organolithium chemistry, see: (c) Pratt, L. M.; Mogali, S.; Glinton, K. *J. Org. Chem.* **2003**, *68*, 6484.

(28) Serial solvation of aryllithiums reveals negative enthalpies up to trisolvation (in kcal/mol): ΔH_3(**6**) = −8.0, ΔH_3(**7**) = −7.6, ΔH_3(**8**) = −8.7, ΔH_3(**9**) = −6.5, ΔH_3(**10**) = −7.6, ΔH_3(PhLi) = −9.3.

(29) Carlqvist, P.; Östmark, H.; Brinck, T. *J. Org. Chem.* **2004**, *69*, 3222.

(30) (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-Prettre, C. *J. Org. Chem.* **2000**, *65*, 8899.

(31) (a) Saunders, W. H., Jr.; Cockerill, A. F. *Mechanisms of Elimination Reactions*; John Wiley & Sons: New York, 1973; Vol. II, pp 60−68. (b) Baciocchi, E. In *The Chemistry of Halides, Pseudo Halides and Azides, Supplement D*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, U. K., 1983.

(32) Theoretical studies of benzyne-halide ion complexes: (a) Morgon, N. H. *J. Phys. Chem.* **1995**, *99*, 17832. (b) Wong, M. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2227. (c) Linnert, H. V.; Riveros, J. M. *J. Chem. Soc., Chem. Commun.* **1993**, 48.

kcal/mol as the C(2)−halide bond significantly exceeds normal bond lengths.[33,34]

17   **18**
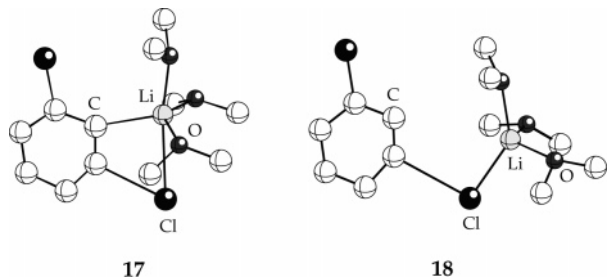
Discussion

An interest at Pfizer in the synthesis of varenicline (Champix and Chantix; **1**) and structurally related modulators of nicotinic receptors led to extensive investigations of 2-haloaryllithium eliminations, which form benzynes.[5,6] It was the pronounced solvent-dependent regioselectivity described in eq 2 that led to a Pfizer-Cornell collaboration and the results described herein.

Aryllithium Structures. Structural and computational studies afford a reasonably coherent description of the structures of 2-haloaryllithiums **6**−**10**. [6]Li and ^{13}C NMR spectroscopic studies reveal that **6**−**10** are exclusively monomeric in THF and THF/hydrocarbon mixtures. The solvation numbers were evaluated using DFT methods. Serial solvation of aryllithiums reveal negative enthalpies up to trisolvation and negative free energies for all but the third solvation. Because DFT methods often overestimate steric effects in congested systems,[27] it seems quite likely that **6**−**10** are trisolvated.

Spectroscopic studies offered indirect evidence of strong Li−F interactions in monomers **6**, **8**, and **10** in the form of unusually large two-bond [13]C−[19]F coupling.[10] The computations implicate distorted geometries (see **15** or **16**) even at the highest solvation numbers. It would seem, however, that the difluoro derivative **8** ought to display an attenuated per-fluorine [19]F−[13]C coupling because of a 50% statistical weighting;[27a,35] both fluorines in **15** cannot interact with Li concurrently. Nonetheless, **8** shows no diminished [19]F−[13]C coupling when compared with **6** and **10**.

Mechanism of Benzyne Formation. Rate studies reveal distinct patterns in the lithium halide eliminations en route to benzyne. Eliminations of LiF from **8** and **10** occur predominantly via pathways requiring dissociation of a single THF prior to the rate-limiting steps. Assignment of the aryllithium monomers as trisolvates implicates disolvated monomer-based transition structure **12**. The trisolvated transition structure **13** may also contribute to a limited extent, but the evidence is not compelling. By contrast, the LiCl eliminations from **7** and **9** require no such dissociations, suggesting that direct elimination via trisolvated monomer-based transition structure **11** is the exclusive pathway.

Regioselectivity of Benzyne Formation. The solvent-dependent regioselectivity described by eq 2 favors elimination

of LiF at low THF concentrations and elimination of LiCl at high THF concentrations (eq 15). To be more precise, it is the dependence of the LiF elimination on the THF concentration that causes regiochemical variation; the rate of LiCl elimination is independent of THF concentration. Rate studies of the competitive elimination of aryllithium **6** show that LiCl and LiF eliminate via **19** and **20**, respectively.
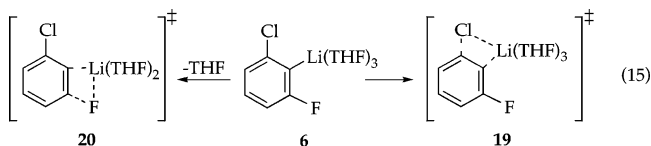
Aryllithium Reactivities. Two aspects deriving from experiment attracted our attention: (1) the solvent-dependent elimination of LiCl versus LiF and (2) the high reactivity of lithiated haloanisoles **9** and **10**. A number of literature precedents note that haloanisoles are especially reactive toward LiX elimination.[36] Comparing the calculated aryllithium energies (eq 14, Table 4) with measured relative rate constants qualitatively shows that greater stability correlates with lower reactivity (Table 2). Unfortunately, computational studies of the LiX elimination to form benzynes have been thwarted on several occasions. Brinck and co-workers studied the decomposition of 2-halophenyl carbanions (no counterion) using B3LYP and MP2 computational methods.[29] Although strong solvent effects were implicated, the computations failed to find gas-phase transition structures. We also failed to find legitimate transition structures starting from lithium counterions and the full range of solvation numbers.[37] The relaxed-scan approximation showed that stretching the Li−C(1) bond causes more extensive lengthening of the Li−Cl bond than Li−F bond, suggesting a greater E1cb (carbanion) flavor to the LiF elimination.

Conclusions

We described herein structural and mechanistic studies of 2-haloaryllithiums and their conversion to benzynes. A number of facets of this work would have been difficult to predict only a few years ago. Certainly using benzynes for the synthesis of the pharmacologically important varenicline in a pharmaceutical setting is unorthodox. Also, the rates and mechanisms of the lithium halide eliminations to form benzynes are unusual. It seems unlikely, for example, that many would have predicted that elimination of LiF could be more facile than elimination of LiCl.[38] By probing the role of solvation as a decidedly

(33) As the C(2)−halide bond was lengthened, achieving wave function convergence became more difficult, a common limitation of DFT calculations.

(34) Calculations of separate benzyne and XLiS₃ products result in the following ΔG values relative to the reactants (kcal/mol): ΔG(**6**$_{LiF}$) = +33.8, ΔG(**6**$_{LiCl}$) = +17.3, ΔG(**7**) = +15.1, ΔG(**8**) = +35.6, ΔG(**9**) = +8.9, ΔG(**10**) = +26.5.

(35) De la Lande, A.; Fressigné, C.; Gérard, H.; Maddaluno, J.; Parisel, O. *Chem.−Eur. J.* **2007**, *13*, 3459.

(36) (i) Reports of facile formation of benzyne from a 2-halo-6-methoxyaryl-lithiums: (a) Dabrowski, M.; Kubicka, J.; Lulinski, S.; Serwatowski, J. *Tetrahedron Lett.* **2005**, *46*, 4175. (b) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernández, Y. *Chem.−Eur. J.* **2002**, *8*, 2034. (c) Slocum, D. W.; Dietzel, P. *Tetrahedron Lett.* **1999**, *40*, 1823. (d) Iwao, M. *J. Org. Chem.* **1990**, *55*, 3622. (e) Adejare, A.; Miller, D. D. *Tetrahedron Lett.* **1984**, *25*, 5597. (ii) For the role of the ortho-substituent on the stabilization as 2-haloaryllithiums toward benzyne formation, see: (f) Mongin, F.; Rebstock, A.-S.; Trécourt, F.; Quéguiner, G.; Marsais, F. *J. Org. Chem.* **2004**, *69*, 6766. (g) Gohier, F.; Mortier, J. *J. Org. Chem.* **2003**, *68*, 2030.

(37) For analogous results of shallow potentials during the evaluation of transition structures involving C-halogen lengthening, see: (a) Xie, J.; Feng, D.; Feng, S.; Zhang, *J. Chem. Phys.* **2006**, *323*, 185. (b) Flock, M.; Marschner, C. *Chem.−Eur. J.* **2005**, *11*, 4635. (c) Gronert, S.; Kass, S. R. *J. Org. Chem.* **1997**, *62*, 7991. (d) Merrill, G. N.; Gronert, S.; Kass, S. R. *J. Phys. Chem. A* **1997**, *101*, 208.

(38) For examples of preferential elimination of F versus Cl, see: (a) Bach, R. D.; Evans, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 1374. (b) Baciocchi, E.; Ruzziconi, R. *J. Org. Chem.* **1984**, *49*, 3395. (c) Baciocchi, E.; Ruzziconi, R.; Sebastiani, G. V. *J. Am. Chem. Soc.* **1983**, *105*, 6114. (d) Baciocchi, E.; Ruzziconi, R.; Sebastiani, G. V. *J. Org. Chem.* **1982**, *47*, 3237. (e) Okuhara, K. *J. Org. Chem.* **1976**, *41*, 1487.

molecular phenomenon, we found that LiF and LiCl eliminations are distinguished by the dissociation of a THF ligand in the former. We suspect that the importance of solvent dissociation from organolithiums (rather than association) may not be widely appreciated by the community at large. One of the most pedestrian observations, the unusually large two-bond $^{13}C-^{19}F$ coupling first mentioned in the preliminary communication,[7] has found a niche. Menzel and co-workers at Merck exploited the large coupling to confirm the ortholithiation of an aryl fluoride.[10b] One never knows a priori what will pique the interest of the community.

Experimental Section

Reagents and Solvents. Arenes used to form **6−10** are commercially available. *n*-BuLi used in the rate studies was obtained from Acros and recrystallized.[8] [^{6}Li]*n*-BuLi was prepared and recrystallized as described previously.[8] THF, *n*-pentane, and toluene were distilled from sodium/benzophenone. The pentane still contained 1% tetraglyme to dissolve the ketyl. The diphenylacetic acid used to check solution titers[39] was recrystallized from methanol and sublimed at 120 °C under full vacuum. Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glove box, vacuum line, and syringe techniques.

Kinetics. For a kinetic run corresponding to a single rate constant, a relatively concentrated (2.2 M) solution of *n*-BuLi in toluene at −78 °C was prepared and titrated to determine the precise concentration. The solution was diluted to a concentration appropriate for the particular

series and titrated a second time. A series of oven-dried, argon-flushed 5 mL serum vials (8−10 per rate constant) fitted with stir bars were charged with a stock solution containing the corresponding haloarene, spiro[2.4]hepta-4,6-diene (in excess relative to the aryllithium),[17] THF/toluene, and *n*-octane (0.15 M; GC standard). The reaction vials were maintained at the indicated temperature ±0.2 °C (Table 3). The reactions were initiated by adding aliquots of *n*-BuLi in toluene, also maintained at the same temperature as the vials, to afford the desired overall ArLi concentration with a 0.2 M excess of ArH. The vessels were serially quenched with 1:1 H_2O-THF at intervals chosen to ensure an adequate sampling of the first 10% conversion. The quenched aliquots were extracted into Et_2O, and the Et_2O extracts were washed with saturated aqueous solution of NH_4Cl. The extracts were analyzed using an autoinjecting GC fitted with a 60 meter DB-5 column. The metalations were monitored by following the decrease of haloarene relative to the internal *n*-octane standard. The observed rate constants were determined by nonlinear least-squares analyses and shown to be reproducible within ±10%. Following the formation of the corresponding cycloadducts, **5a−d** afforded initial slopes that were converted to rate constants. The reported errors correspond to one standard deviation.

Supporting Information Available: NMR, rate, and computational data. Complete refs 5b and 21. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0754655

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