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A Relative Organolithium Stability Scale Derived from Tin−Lithium Exchange Equilibria. Substituent Effects on the Stability of α-Oxy- and α-Aminoorganolithium Compounds

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Received January 9, 2002

Abstract: Quantitative thermodynamic stability scales of organolithium compounds can be derived from measurements of tin−lithium exchange equilibria. A ΔG_{eq} scale of α-oxy- and α-aminoorganolithium compounds was established, and quantitative stabilization effects of *O*-alkyl, *O*-alkoxyalkyl, *O*-carbamoyl, *N*-carbamoyl, and *O*-carbonyl groups of the α-carbanion are presented. It has been found that an α-oxycarbanion is far better stabilized by a carbonyl group as the *O*-substituent than by an alkyl or alkoxyalkyl group, while the anion-stabilizing effects of the different *O*-carbonyl substituents are comparable. An *N*-carbamoyl group was found to have a somewhat higher stabilizing effect than its *O*-carbamoyl counterpart. NMR data are presented that show that benzylic *N*- or *O*-substituted carbanions have highly planarized structures where the negative charge is highly delocalized. The stability data obtained from the tin−lithium exchanges can be easily converted into “effective p*K*” data that are useful for predicting the acid−base behavior of this type of organolithium species.

Introduction

α-Heteroatom-substituted organometallic compounds have gained considerable synthetic status due to their broad utility. α-Oxy- and α-aminoorganolithium reagents, in particular, have been the focus of much attention, especially by the groups of Hoppe and Beak, among others, and a great deal of knowledge has accumulated about their modes of generation, their configurational stabilities, and the effect of substituents on their ease of formation and their reactivity,[1] but despite all of the attention devoted to these systems, there remain unanswered some fundamental questions about this type of reagents. For instance, it was established very early that both oxygen and nitrogen atoms considerably increase the stability of an α-carbanion,[1c,2] and yet no data on the quantitative, or even qualitative, influence of the heteroatom substituents on their carbanion-stabilizing effects have been reported, despite the obvious synthetic importance of the results derived from such a study. This situation is just an instance of a more general, unresolved problem, that of the development of a method to quantitatively compare the stability of structurally related, synthetically useful, highly basic organometallics.

One potential approach to solve this problem could be the measurement of the p*K* of the corresponding carbanions,[3] since the basicity of an anion is strongly correlated with its thermodynamic stability, but the determination of the p*K* of the more basic, highly functionalized, most synthetically useful carbanions is still problematic, despite the fact that Streitwieser has provided data for several types of aromatic, heteroaromatic, and benzylic systems.[4] The measurement of the equilibrium acidities of hydrocarbon acids under synthetically significant conditions (approximately 0.1 M ethereal solutions at low temperatures) is very difficult because proton-transfer equilibration with bases of known p*K* (the usual way to determine equilibrium acidities)[3−5] take place very slowly in this environment, allowing decomposition reactions of the involved carbanions to become competitive.[4c] An additional inconvenience of the use of acidity measurements to quantify the stability of organometallic compounds is that ion pairing and aggregation effects have no reflection on the p*K* data, since they refer only to solvent-separated, nonaggregated species.

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[1] α-Alkoxyorganolithiums: (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (b) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (c) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842 and references therein. α-Acyloxyorganolithiums: (d) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282 and references therein. (e) Heimbach, D. K.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synlett* **2000**, 950. α-Aminoorganolithiums: (f) Pippel, D. J.; Weisenburger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919. (g) Gross, K. M. B.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315 and references therein. (h) Iula, D. M.; Gawley, R. E. *J. Org. Chem.* **2000**, *65*, 6196 and references therein.

[2] Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471.

[3] (a) Stratakis, M.; Wang, P. G.; Streitwieser, A. *J. Org. Chem.* **1996**, *61*, 3145 and references therein. (b) Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632 and references therein. (c) For an account of the earlier results see: Cram, D. J. *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965.

[4] p*K* of polyhalogenated benzenes: (a) Reference 3a. (b) Streitwieser, A.; Abu-Hasanyan, F.; Neuhaus, A.; Brown, F. *J. Org. Chem.* **1996**, *61*, 3151. p*K* of benzylsilanes: (c) Streitwieser, A.; Xie, L.; Wang, P.; Bachrach, S. M. *J. Org. Chem.* **1993**, *58*, 1778. p*K* of benzyl and fluorenyl hydrocarbons: (d) Streitwieser, A.; Ciula, J. C.; Krom, J. A.; Thiele, G. *J. Org. Chem.* **1991**, *56*, 1074. (e) Kaufman, M. J.; Gronert, S.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 2829 and references therein.

[5] For other important methods of measuring p*K* values see: (a) Jaun, B.; Schwarz, J.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 5741 and references therein. (b) Arnett, E. M.; Venkatasubramaniam, K. G. *Tetrahedron Lett.* **1981**, 987.

10.1021/ja025552r CCC: $22.00

A more promising alternative is based on the pioneering work of the groups of Applequist and Dessy, who established that halogen−Li and Hg−Mg interchange equilibria could be used to measure the relative stabilities of simple alkyl-, alkenyl-, and aryllithium reagents,[6] although the extension of these methods to determine the stabilities of more complex organometallics, especially of α-heterosubstituted carbanions, is thwarted by the instability or unavailability of the halogenated or mercuriated precursors. A far more convenient option can be traced to the work of Macdonald and McGarvey, who used the Sn−Li exchange reaction (eq 1 in Figure 1) to establish a *qualitative* scale of the thermodynamic stabilities of several α-alkoxycarbanions. As for the halogen−Li and Hg−Mg exchanges, the position of the equilibrium depends on the difference of the stabilities of the carbanions involved, the exchange favoring the pairing of the most stable carbanion with the more electropositive (Li or Mg) cation.[1c,7] We sought to extend this Sn−Li exchange methodology to provide *quantitative* data on the stabilities of α-oxy- and α-aminocarbanions, since the Sn-containing precursors of these organometallics are readily available and the Sn−Li exchanges can be run under conditions where most of the synthetically useful organolithium compounds are stable. The first key issues that we wished to address are (1) to what extent (if any) a carbonyloxy group is more stabilizing than an alkoxy (or alkoxyalkyl) group and (2) the effect of the heteroatom attached to the carbanionic center (O vs N) on the stability of the corresponding α-heterosubstituted carbanions.

Fraser and co-workers have determined the "aggregate acidities" of a number of benzylic, aromatic, and heteroaromatic compounds by abstraction of their most acidic hydrogens with lithiated bases of known p*K* under synthetically significant conditions (in THF at low temperatures).[8] Their data can be straightforwardly converted to free energy differences between the corresponding organolithium compounds, thus providing a set of reference compounds which can be used to establish quantitative relative stability scales of, in principle, any type of carbanions.

Results and Discussion

The organolithium compounds (and their stannane precursors) selected for this study are shown in Figure 1 along with the reference compounds used.

The benzylic organolithiums **2**, **4**, and **6** were chosen since their stabilities were estimated to be well within the limits of the Fraser scale. The reference compounds **7**−**9** were chosen post facto. The reference 0.0 kcal/mol level was arbitrarily assigned to the most stable reference compound used.[8] The ΔG_{eq} values shown for the reference compounds were calculated by us from the original p*K* data provided by Fraser.[8]

$$R^1SnR^3_3 + R^2Li \rightleftharpoons R^1Li + R^2SnR^3_3 \qquad (1)$$

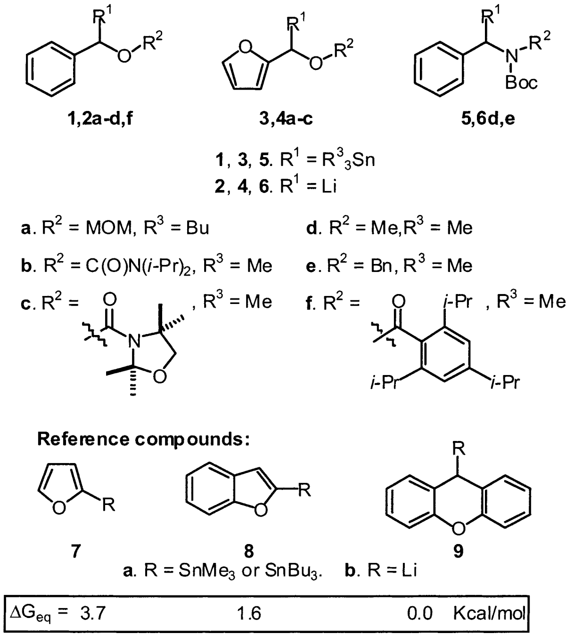

Figure 1. Organolithium compounds studied and their precursors. ΔG_{eq} values relative to that of **9b**.

To set up the tin−lithium exchange equilibria, equimolar amounts of stannanes **1**, **3**, and **5** and organolithium reagents **7b**−**9b** (obtained from the corresponding stannanes **7a**−**9a** and 100 mol % *n*-BuLi or PhLi) were mixed and kept at the appropriate temperature for 1−24 h.[9] The equilibrium concentrations were measured after low-temperature protonation of the reactions and analysis of the resulting mixtures of hydrocarbons and stannanes by NMR and/or GC.[1c,10] That a true equilibrium had been reached was established by performing the reverse reaction in each case. The results obtained are shown in Figure 2. The ΔG_{eq} data are reported as a single number when the same K_{eq} was obtained from the forward and reverse reactions, and as an interval when different, but proximate, values were obtained from the forward and reverse reactions. The conditions for each particular reaction were optimized regarding carbanion stability, the rate of the Sn−Li exchange, and minimization of side reactions.

The Sn−Li exchanges were usually performed at concentrations of 0.08−0.1 M, but the same K_{eq} values were obtained when selected reactions were run at concentrations as high as 0.2 M or as low as 0.02 M, which indicates that the species involved in the equilibria maintain the same degree of association throughout the range of concentrations studied.

Analysis of the data shown in Figure 2 uncovered some interesting facts regarding the data obtained in THF: (1) An α-oxycarbanion is far better stabilized by a carbonyl group as the *O*-substituent than by an alkyl or alkoxyalkyl group ($\Delta\Delta G_{eq}$ is approximately 3 kcal/mol; compare entries 1 and 2 with entries 3−5 and entry 6 with entries 7 and 8). This rather large

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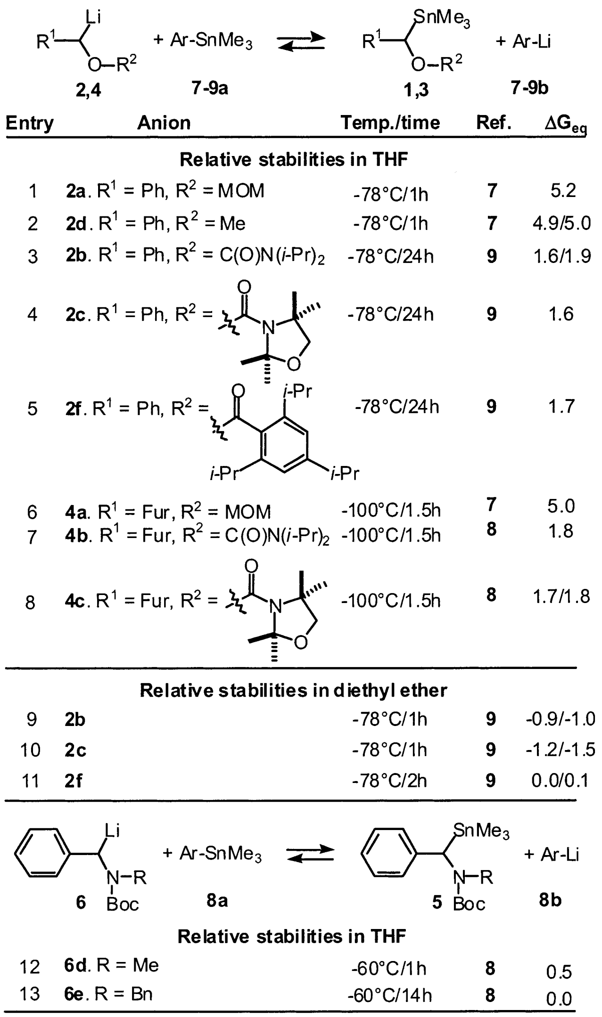
[6] (a) Applequist, D. E.; O'Brien, D. F. *J. Am. Chem. Soc.* **1963**, *85*, 743. (b) Dessy, R. E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chivers, T. *J. Am. Chem. Soc.* **1966**, *88*, 460. (c) Salinger, R. M.; Dessy, R. E. *Tetrahedron Lett.* **1963**, 729.

[7] Reich et al. have used this method to establish that the equilibrium ratio of PhLi and TolLi is 65:35, although no relative stability data were derived. See ref 14 in Reich, H. J.; Borst, J. P.; Coplien, M. B.; Phillips, N. H. *J. Am. Chem. Soc.* **1992**, *114*, 6577.

[8] (a) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790. (b) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Chem. Soc., Chem. Commun.* **1983**, 620. (c) Fraser, R. R.; Mansour, T. S. *J. Organomet. Chem.* **1986**, *310*, C60. (d) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232. (e) Fraser, R. R.; Mansour, T. S.; Savard, S. *Can. J. Chem.* **1985**, *63*, 3505.

[9] The presence of 100 mol % n-BuSnR$^3_3$ or PhSnR$^3_3$, which proceeds from the generation of the initial alkyl- or aryllithium species, should not influence the equilibrium position.

[10] This analysis allowed us to establish whether the equilibrium had been reached and to check for signs of decomposition or other competing reactions.



Entry	Anion	Temp./time	Ref.	ΔG_{eq}
	Relative stabilities in THF			
1	**2a**. R^1 = Ph, R^2 = MOM	-78°C/1h	**7**	5.2
2	**2d**. R^1 = Ph, R^2 = Me	-78°C/1h	**7**	4.9/5.0
3	**2b**. R^1 = Ph, R^2 = $C(O)N(i\text{-}Pr)_2$	-78°C/24h	**9**	1.6/1.9
4	**2c**. R^1 = Ph, R^2 =	-78°C/24h	**9**	1.6
5	**2f**. R^1 = Ph, R^2 =	-78°C/24h	**9**	1.7
6	**4a**. R^1 = Fur, R^2 = MOM	-100°C/1.5h	**7**	5.0
7	**4b**. R^1 = Fur, R^2 = $C(O)N(i\text{-}Pr)_2$	-100°C/1.5h	**8**	1.8
8	**4c**. R^1 = Fur, R^2 =	-100°C/1.5h	**8**	1.7/1.8
	Relative stabilities in diethyl ether			
9	**2b**	-78°C/1h	**9**	-0.9/-1.0
10	**2c**	-78°C/1h	**9**	-1.2/-1.5
11	**2f**	-78°C/2h	**9**	0.0/0.1
	Relative stabilities in THF			
12	**6d**. R = Me	-60°C/1h	**8**	0.5
13	**6e**. R = Bn	-60°C/14h	**8**	0.0

Figure 2. Relative stability data of anions **2**, **4**, and **6**. ΔG_{eq} values in kilocalories per mole relative to that of **9b** in each solvent.

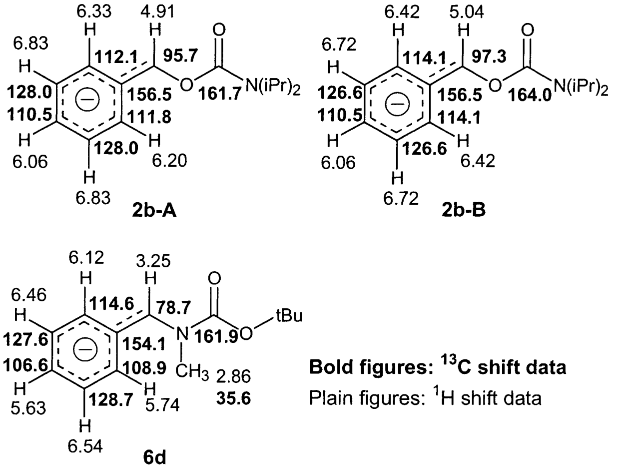


Figure 3. ^{1}H and ^{13}C chemical shift data of anions **2** and **6** in THF (0.1−0.4 M solutions). Chemical shifts are almost identical in THF and Et_2O.

difference can provide an explanation for the observation that α-*carbamoyloxy*alkyltrimethylstannanes undergo tin−lithium exchange more cleanly than the analogous α-*alkoxy*alkyltrimethylstannanes, presumably due to the formation of a more stable α-oxyorganolithium species in the former case.[11] (2) *Ester* and *carbamate* substituents impart approximately the same degree of stabilization to the α-carbanion (compare entries 3−5). This result should provide some impetus to the design of more synthetically useful *ester* activating groups for the preparation of this type of α-heterosubstituted carbanions, since they might be more easily removed from the final products than the *carbamate* groups. (3) *O*-Substituted carbanions do not appear to be sensitive to the electron-rich-ness of the aryl substituent (compare entry 1 with entry 6, entry 3 with entry 7, and entry 4 with entry 8). (4) The stabilizing effect of a carbamate group is slightly larger when it is attached to the carbanionic center through its nitrogen atom rather than through the oxygen (compare entries 3 and 4 with entries 12 and 13), a surprising result that might imply that the carbamate group acts as an electron-withdrawing group *as a whole*, regardless of the atom which binds it to the carbon bearing the negative charge, the electronegativity of the heteroatom directly attached to the carbanionic center playing only a minor stabilizing role. A negatively charged carbanionic center should also experience a greater repulsion with the *two* lone pairs of an attached oxygen than with the only lone pair of a nitrogen, an effect that can also contribute to the observed result.

We have measured the relative stabilities of selected substrates in diethyl ether to check for solvent effects on the stabilization of these benzylic anions by *O*-acyl groups (entries 9−11). The stabilities of *O-carbamoyl*carbanions **2b**,**c** and *O-acyl*carbanion **2f** were drastically altered when the solvent was changed from THF to ether. Thus, **2b**,**c**,**f** are equally stable in THF, while ester **2f** is clearly approximately 1 kcal/mol less stable than its carbamate counterparts in diethyl ether. It is interesting to note that the Sn−Li exchanges of *O-acyl*stannanes **1b,c,f** occurred much faster in ether than in the more polar THF, a trend that is opposite to what has been reported for *O-alkoxyalkyl*stannanes.[1c]

To rule out the possibility that the somewhat surprising stability trends recorded in Figure 2 were due to differences in the aggregation states, or to other subtle structural dissimilarities of the implicated organolithium compounds, we proceeded to obtain NMR spectra of carbanions **2b** and **6d** in THF and diethyl ether at low temperature. Boche et al. have provided ^{6}Li−^{13}C coupling data that strongly suggest that *O*-carbamoyl*alkyl*lithium compounds are monomeric contact ion pairs in THF at low temperature, which are the structures prevalent in the solid state as well,[12] but the ^{1}H and ^{13}C shift data that we have obtained for **2b** and **6d** (Figure 3) are strongly suggestive of highly planarized, almost definitely monomeric structure, in which the negative charge is largely delocalized toward the aromatic rings. The fact that the spectra did not undergo any noticeable modifications when the concentrations were varied in the 0.1−0.4 M range or when the solvent was changed from THF to diethyl ether are also suggestive that **2b** and **6d** are monomeric in both solvents. The large upfield shifts of the *ortho* and *para* aromatic hydrogen and carbon atoms and the low chemical shifts

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(11) Chong, J. M.; Nielsen, N. *Tetrahedron Lett.* **1998**, *39*, 9617.

(12) (a) Boche, G.; Bosold, F.; Lohrenz, J. C. W.; Opel, A.; Zulauf, P. *Chem. Ber.* **1993**, *126*, 1873. (b) Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887. (c) Pippel, D. J.; Weisenburger, G. A.; Wilson, S. R.; Beak, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2522. (d) Marsch, M.; Harms, K.; Zschage, O.; Hoppe, D.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 0, 321.

(13) (a) Vanermen, G.; Toppet, S.; Van Beylen, M.; Geerlings, P. *J. Chem. Soc., Perkin Trans. 2* **1986**, 699. (b) Vanermen, G.; Toppet, S.; Van Beylen, M.; Geerlings, P. *J. Chem. Soc., Perkin Trans. 2* **1986**, 707. (c) Fraenkel, G.; Russell, J. G.; Chen, Y.-H. *J. Am. Chem. Soc.* **1973**, *95*, 3208. (d) Sandel, V. R.; Freedman, H. H. *J. Am. Chem. Soc.* **1963**, *85*, 2328.

displayed by the benzylic hydrogens and carbons in both anions are clearly indicative of this type of structure.[13,14] Apparently, only one species was present in solution for the case of *N*-substituted anion **6d**, while two species (1:1 ratio) were detected in solutions of the *O*-substituted organolithium compound **2b**. The precise nature of the difference between these two species could not be ascertained from our data, but it is clear that both of them show the same degree of charge delocalization into the phenyl ring. The appearance of hindered rotation around the exocyclic C−C bond in two of the observed species also lends credence to the planar, highly delocalized structures.[13c]

The solvent effect on the relative stabilities of carbamoylcarbanions **2b**,**c** and acylcarbanion **2f** is probably originated by differences in their aggregation behaviors. The NMR data presented above clearly suggest that the carbamate anions have the same type of structure in both solvents, and thus no difference in their *relative* stabilities is to be expected when the solvent is changed from THF to Et_2O. A change in their *absolute* stabilities can be explained taking into account that the aggregation state of the *reference* xanthenyllithium **9b** changes with the solvent (probably a greater proportion of contact ion pair monomer is present in ether), as indicated by its different UV absorptions in THF and ether (λ_{max}(in THF) = 475 nm, λ_{max}(in Et_2O) = 412 nm, −30 °C). This localization of the charge of the xanthenyl anion **9b** in Et_2O should have as a consequence its *relative* destabilization with respect to the carbamoylcarbanions **2b**,**c** in this solvent (compare entries 3 and 4 with entries 9 and 10, Figure 2). The fact that acyl anion **2f** is destabilized *relative* to the carbamoyl anions **2b**,**c** when the solvent is changed from THF to Et_2O can likewise be explained by solvent-induced changes in the aggregation state of **2f**.

The thermodynamic data shown in Figure 2, taken together with the structural picture derived from our NMR studies, point to the fact that the stabilization imparted by a carbonyloxy group in “dipole-stabilized” carbanions is at least partly derived from an electron-withdrawing effect, and not only from the traditionally accepted effect of the chelation of the Li atom bound to the carbanionic center with the carbonyl oxygen,[15] a conclusion that should be helpful in the design of new, synthetically useful “dipole-stabilizing” groups.

Although it must be pointed out that the Sn−Li exchange equilibria cannot be used to derive true p*K* values since it is not clear that all the involved carbanions are present as solvent-separated ion pairs, it would be very useful, from the synthetic point of view, to test whether the “apparent p*K*” values that can be easily obtained from our data (by combining eqs 1 and 2, Figures 1 and 4) have any bearing on the acid−base behavior of parent hydrocarbons.

$$\boxed{pKa\,(R^1Li) - pKa\,(R^2Li) = -\log\frac{[R^1Li]}{[R^1SnR^3{}_3]} + \log\frac{[R^2Li]}{[R^2SnR^3{}_3]}} \quad (2)$$

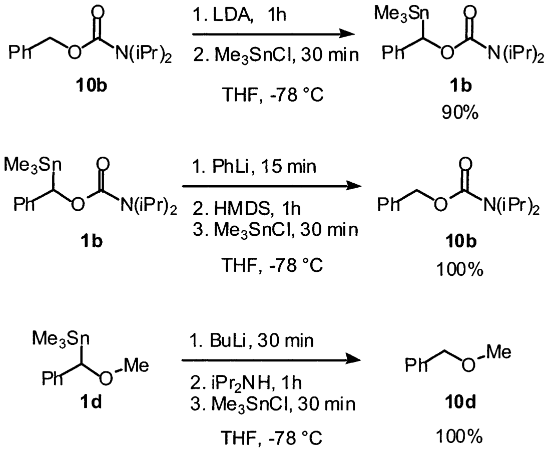

Figure 4. Protonation−deprotonation experiments of **10b** and anions **2b**,**d** with secondary amines/amides.

By using eq 2 (Figure 4) and the “aggregate p*K*” data reported by Fraser,[8] a p*K* value of 33.2−33.4 can be derived for carbamate **10b** from our $\Delta\Delta G_{eq}$ data (Figure 2), which means that the benzylic hydrogens of **10b** should be abstractable by LDA, since a p*K* of 35.7 has been reported for diisopropylamine, and that carbanion **2b** should be basic enough to deprotonate HMDS (p*K* = 29.5).[16] In fact, when **10b** was reacted with 150 mol % LDA in THF at −78 °C and the resulting solution was quenched with Me_3SnCl, the corresponding stannyl carbamate **1b** was obtained in 90% yield. On the other hand, when a solution of organolithium compound **2b**, generated from **1b** and PhLi, was treated with 100 mol % HMDS prior to quenching with Me_3SnCl, no stannylation took place. As further proof that the apparent p*K* values are useful to predict the acid−base behavior of carbanions **2**, **4**, and **6**, we tested the ability of diisopropylamine to protonate anion **2d** (apparent p*K* = 37.3). Thus, **2d** was prepared by reaction of stannyl ether **1d** with 100 mol % *n*-BuLi, and then reacted first with diisopropylamine and then with Me_3SnCl; only protonated material (**10d**) was recovered from this reaction. These protonation tests were run alongside control reactions where no amine was added before quenching with Me_3SnCl. From these control reactions the corresponding stannylated products **1b**,**d** were isolated in excellent yields. It is thus apparent that the use of this Sn−Li exchange methodology can not only provide valuable quantitative information about the stabilities of closely related organolithium compounds, but also supply effective p*K* data that can be used to predict the acid−base behavior of these carbanions as well. In view of this fact the following list with the effective p*K* data of compounds **2**, **4**, and **6** in THF is provided (compound/p*K*): **2a**/37.3, **2d**/36.9−37.0, **2b**/33.2−33.5, **2c**/33.2, **2f**/33.3, **4a**/37.2, **4b**/33.4−33.5, **4c**/33.3−33.4, **6d**/32.1, **6e**/31.5.

We believe that the methodology presented herein will have wide application for the study of stability−structure relationships of highly functionalized organolithium reagents, as well as for the derivation of approximate acidity data that should be of value in the planning of syntheses involving carbanion reagents.

Acknowledgment. Financial support from the CICYT (Spain; Grant SAF99-0127 and a fellowship to P.G.) and the Xunta de Galicia (Grant PGIDT00PXI20909PR) is gratefully acknowledged. This paper is dedicated to Prof. Rafael Suau.

Supporting Information Available: Complete experimental procedures and spectroscopic and analytical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) ^1H and ^{13}C chemical shift assignments were obtained from homonuclear and heteronuclear two-dimensional experiments.

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(16) Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442.