JOC The Journal of Organic Chemistry

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Ion Pair p*K*s of Some Amines: Extension of the Computed Lithium p*K* Scale‡

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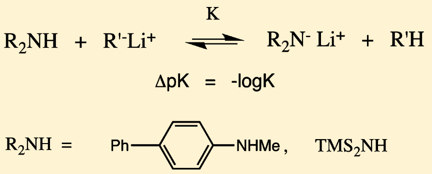
Supporting Information

ABSTRACT: The p*K* of *p*-(methylamino)biphenyl, **1**, on our Li scale, p*K*(Li) = 22.09, compared to the cesium scale, p*K*(Cs) = 28.60. For hexamethyldisilazane, HMDS, p*K*(Li) = 23.05, p*K*(Cs) = 29.26. These results are those for the monomers in THF; corrections were made for dimers present in some cases. The p*K*(Li) of these two amines fit well the previously found correlation with Hartree−Fock calculations at 6-31+g(d) using RLi coordinated with three dimethyl ethers as a computational model for RLi in THF. The results are also compared with earlier p*K*(Li)s reported from equilibria with lithium amides in which aggregation was not considered.



■ INTRODUCTION

We have recently shown how computed lithium exchange energies that include specific coordination of solvent to lithium correlate well with experimental ion pair p*K* values in THF for contact ion pair (CIP) monomeric organolithium compounds.[1] That correlation, however, contained only two amines from our own previous work and did not include the results of several other studies of organolithium p*K*s in THF in which the possible role of aggregation was not considered. In the present paper, we report experimental results for two additional amines with explicit consideration of the possible role of aggregation and extend the results to other work in the literature.

***p*-(Methylamino)biphenyl.** The method used successfully in the past for determining ion pair p*K*s and aggregation constants requires substrates having distinctive UV−vis absorptions, i.e., conjugated systems. Thus, one amine chosen for this study is *p*-(methylamino)biphenyl, **1**. *p*-Aminobiphenyl was converted to the tosylate, mp 156−7 °C (lit.[2] 160 °C) and methylated by treating a mixture of 4.69 g (14.5 mmol) and 0.58 g. (14.5 mmol) of NaOH in 100 mL of 50% aq THF with 1.27 mL (14.5 mmol) of dimethyl sulfate. The resulting precipitate was dissolved with an additional 50 mL of THF. After stirring for 24 h, 5 mL of 10% NaOH was added and the mixture was refluxed for 30 m. The cooled solution was extracted with ether. After drying, the ether was removed and the cream solid was recrystallized from 100 mL of ether and 25 mL of THF to give yellow needles, mp 127−8 °C (lit.[2] 128 °C). This tosylate was hydrolyzed by refluxing 2.23 g (6.6 mmol) with 6.6 mmol of perchloric acid and 11 g of acetic acid for 3 h. The cooled solution was neutralized with aq sodium carbonate and extracted with ether. The organic layer was washed with aq NaOH and dried over sodium sulfate, and the solvent was removed in vacuo. The product was purified by alumina column chromatography and sublimed twice using ice−water coolant to give 1.09 g (90% yield), mp 38 °C (lit.[2] 38 °C).

Acidity Measurements. The extinction coefficient of the lithium salt, **1-Li**, was determined by deprotonating a known amount with the lithium salt of 9,9,10-trimethyldihydroanthracene (PDDALi, λ_{max} 460.5 nm),[3] with the presence of excess nonequilibrating base indicating complete reaction. Three individual experiments over the formal concentration range 5.9×10^{-4} to 3.1×10^{-5} M yielded 34 spectra from which the contributions of the base were removed to yield the deconvoluted spectra having λ_{max} = 392 nm independent of concentration. A plot of absorbance versus path length times **1-Li** concentration (Figure S1, Supporting Information) yields the slope as the averaged extinction coefficient of 32 000 ± 200 cm^{-1} M^{-1}.

The p*K*(Li) was determined using the general double-indicator technique described previously.[4−6] A known amount of **1** was deprotonated with PDDALi, and 9-methylfluorene (9-MeFl) was added as an indicator. Equilibration was allowed to occur over 15 m, and spectra were obtained by successive dilutions with THF. This experiment was repeated to give six series totaling 26 spectra covering a formal concentration range of **1-Li** of 5.4×10^{-4} to 3.0×10^{-5} M. Each spectrum was computationally deconvoluted to give the spectra of the two lithium salts, 9-MeFlLi and **1-Li**. The concentration of 9-MeFlLi was corrected for dissociation to free ions,[5,6] and stoichiometry gives the corrected acidity equilibrium constant, K_{corr}, eq 1, where the curly brackets[6] indicate the formal concentration.

$$K_{corr} = \frac{\{\mathbf{1\text{-}Li}\}[\text{9-MeFl}]}{[\mathbf{1}][\text{9-MeFl}]} \qquad (1)$$

The results are detailed in Table S1 (Supporting Information) and give an average p*K*(Li) of 22.09 ± 0.04 on our p*K*(Li) scale.[7] The constancy of this p*K* with concentration indicates that **1-Li** is monomeric; more exactly the amount of

Received: November 1, 2011
Published: December 25, 2011

dimer present is too small to be detected, and therefore $K_{1,2} < 10^2$ M^{-1}. This result agrees with the value of $K_{1,2}$ = ca. 70 M^{-1} found for the lithium salt of *N*-methylaniline in THF at 17 °C by Jackman and Scarmoutzos.[8] For $K_{1,2}$ = 100 M^{-1}, at a nominal concentration of 0.01 M, the concentrations of monomer and dimer are equal, but 2/3 of the amide units are present in the dimer. At a nominal concentration of 10^{-4} M, typical of UV–vis spectroscopy, the amide is almost all monomer, whereas at 10^{-1} – 1 M, typical of NMR or preparative methods, the compound is present mostly as dimer.

The extinction coefficient of **1-Cs** was determined by deprotonating a known quantity of **1** with cumylcesium[9] in the presence of a nonequilibrating indicator of higher acidity, the spectral appearance of whose anion signifies full conversion of **1** to **1-Cs**. Over the formal concentration range studied (6.3×10^{-4} to 5.4×10^{-5} M) a spectral shift was noted for the deconvoluted **1-Cs** (λ_{max} 403–407.5 nm), indicating the presence of more than one component, although the range was too small to distinguish a clear isosbestic point. The extinction coefficient found at λ_{max} is 31200 ± 200 (Figure S2 and Table S2, Supporting Information). The spectral data for the first two runs (mj010 and mj030) were subjected to singular value decomposition (SVD) analysis.[10] Assuming a monomer–dimer (M-D) equilibrium, the first two vectors gave the M-D spectra in Figure 1. Results from the two runs show good consistency. These spectra were used to determine the M and D concentrations and the equilibrium constant for dimerization (eq 2), $K_{1,2}$ = 987 ± 46 (Table S2, Supporting Information).

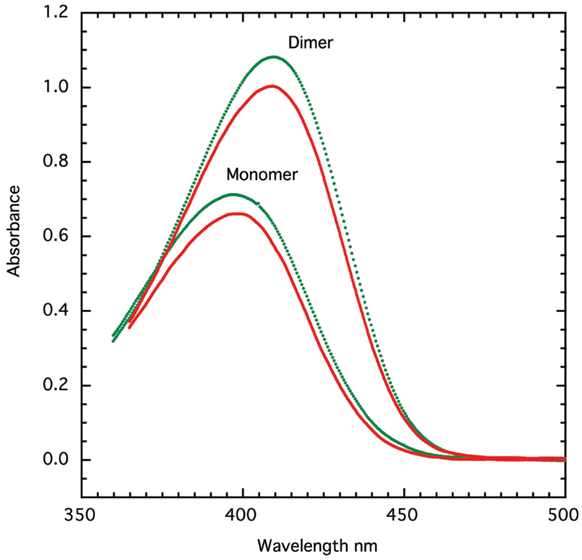


Figure 1. Monomer and dimer spectra of **1-Cs** derived from SVD analysis of runs mj010 (green, λ_{max} 399 and 410 nm) and mj030 (red, λ_{max} 397 and 409 nm.

$$K_{1,2} = \frac{[\text{dimer}]}{[\text{monomer}]^2} \tag{2}$$

Acidity measurements were made with two indicators, 9-phenylxanthene (9-PX, λ_{max} 491 nm (17600 cm^{-1} M^{-1}), p*K*(Cs) 28.73)[11] and 9-phenylthioxanthene (9-PSX, λ_{max} 445 nm (11 700 cm^{-1} M^{-1}), p*K*(Cs) 27.88).[12] A known amount of a mixture of amine and indicator was partially deprotonated by successive additions of cumylcesium in THF, and the spectra were recorded. The contribution of the cesium salt of the indicator was determined by the spectra in a high wavelength region where **1-Cs** has no absorbance. This component was subtracted from the total spectrum to give the spectrum of **1-Cs**. These deconvoluted spectra showed λ_{max} varying over the range 406–413 nm. From the spectra and stoichiometry, the concentrations of all four components were determined and give the K_{obs} at each point (Table S3, Supporting Information). Plots of {**1-Cs**}/K_{obs} give straight lines indicative of monomer–dimer equilibria. The intercept and slope give K_0 and the dimerization constant, $K_{1,2}$, for each experiment (eq 3).[10,13] K_0 together with the p*K* of the indicator gives the p*K*(Cs) of **1**. The indicator 9-PX gives p*K*(Cs) = 28.58, K_d = 1260. Three experiments with 9-PSX give p*K*(Cs) = 28.63, 28.61, 28.61 and K_d = 897, 881, and 1039 (Figures S3–S6, Supporting Information). These values are in agreement with the SVD results. We take the average values as p*K*(Cs) = 28.60 ± 0.02, K_d = 1010 ± 100.

$$K_{obs} = K_0 + 2K_dK_0{}^2\{R^-Cs^+\}/K_{obs} \tag{3}$$

HMDS. The second amine in this study is hexamethyldisilazane (HMDS), an important amine in synthetic chemistry whose lithium salt (LiHMDS) has been extensively studied with respect to solvation, aggregation, and mixed aggregation.[14−18] Its p*K*(Li), however, has not been carefully measured. In this work, both the lithium and cesium (CsHMDS) salts were studied. These salts have no usable UV spectra and their p*K*s were determined by the single indicator technique.[3,19]

Three indicators were used with triply sublimed LiHMDS:[20] 2,3-benzofluorene (2,3-BF, p*K*(Li) 22.95, λ_{max} 430 nm (25500 cm^{-1} M^{-1}), 9-isopropylidenefulvene (IPF p*K*(Li) 22.33, λ_{max} 379 nm (27700 cm^{-1} M^{-1}), and 9-methylfluorene (9-MeFl p*K*(Li) 22.46, λ_{max} 387 nm (16200 cm^{-1} M^{-1}).[7] To a known amount of LiHMDS in THF was added a known amount of indicator solution, and the mixture was allowed to come to equilibrium. From the indicator absorbance at equilibrium, the equilibrium constant could be calculated. THF was added to dilute the mixture which was then allowed to reach the new equilibrium. Such dilutions were repeated to give a series of about six measurements in each experiment. Unfortunately, equilibration was so slow (about 8–10 h for 2,3-BF, 45–48 h for IPF and >50 h for 9-MeFl) that adventitious quenching occurred. With 2,3-BF the absorbance reached a maximum after 8–10 h and then decreased linearly for 10–35 h until it reached a plateau. Extrapolation of the linear decrease to zero time showed quenching of about 1% for the absorbance maximum of 2,3-BF and about 6–7% after 35–40 h. Since IPF and 9-MeFl required these long periods to reach equilibrium, the observed absorbances were corrected for these quenching factors. Nevertheless, the results for 9-MeFl differed so greatly from the other two indicators that its experiments were discarded. The results with 2,3-BF and IPF are detailed in Table S4 (Supporting Information) and Figure 2. Each individual experiment shows a variation of less than 0.1 p*K* units. The relative constancy of p*K* with concentration indicates that LiHMDS is monomeric in these solutions. Kimura and Brown[14] have reported the monomer–dimer equilibrium constants for LiHMDS in THF at low temperatures. Extrapolating their results to room temperature indicates that at our concentrations (~10^{-3} M), less than 1% of the LiHMDS is present as the dimer, an amount too small for us to observe.

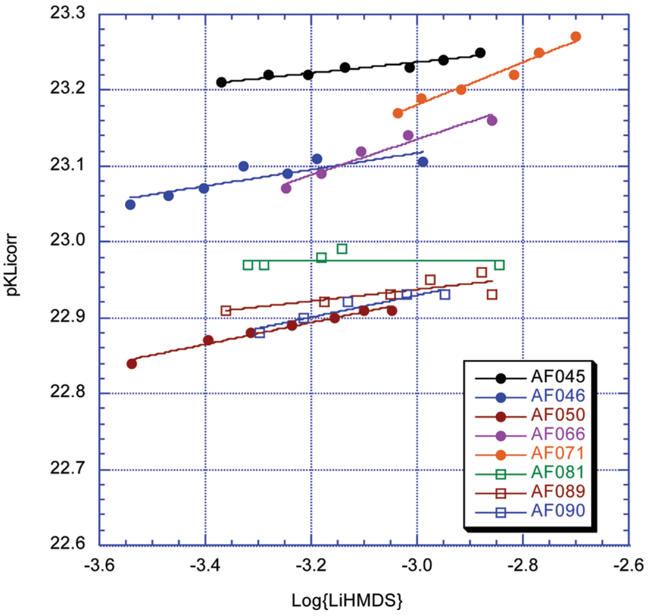


Figure 2. Equilibration experiments of LiHMDS with two indicators, 2,3-BF (circles) and IPF (squares). The variations found with respect to concentration are a measure of experimental error. If aggregation were significant, the lines would have opposite slope.

The p*K*(Li) found for HMDS is 23.05 ± 0.13 (Table S4, Supporting Information).

For CsHMDS two indicators were used, 9-PX and 9-phenyl-10,10-dimethyldihydroanthracene (PDDA, p*K*(Cs) = 28.11).[11] The results are summarized in Table S5 (Supporting Information). Note that the RCs equilibria are rapid and quenching is not a problem. The p*K* results are independent of concentration indicative of a monomer at these concentrations. The average p*K*(Cs) from four experiments is 29.26 ± 0.09.

■ RESULTS AND DISCUSSION

The p*K*(Li) and p*K*(Cs) determined in the present work are summarized in Table 1 and compared to the two amines from our previous studies. As expected, the Li CIP are tighter than the corresponding Cs CIP and lead to lower effective p*K* values. The two sets of p*K*s are linearly related as shown in Figure 3. Such correlations are not uncommon; for example, the Cs and Li p*K*s of enolates are also linearly related.[6] The present case, however, is an instructive example of a *false* correlation. The slope of almost unity is determined primarily by the extreme point of carbazole. We would expect a slope similar to the N-M bond ratios[6] and, indeed, the three points other than carbazole give a steeper slope. Our study of the cesium and lithium salts of carbazole showed that for the cesium salt π-bonding of Cs^+ to the ring is competitive with σ-bonding to nitrogen.[21] We would not expect, therefore, that cesium carbazide would fit a correlation given by normal cesium amides. The apparently excellent correlation in Figure 3 is deceptive and would not be expected to apply generally to other amines.

Table 1. p*K*s of Amines Determined in THF

amine	p*K* Li	p*K* Cs
diphenylamine[10]	19.05	24.20
carbazole[21]	13.48	19.24
p-(methylamino)biphenyl, **1**	22.09	28.60
HMDS	23.05	29.26

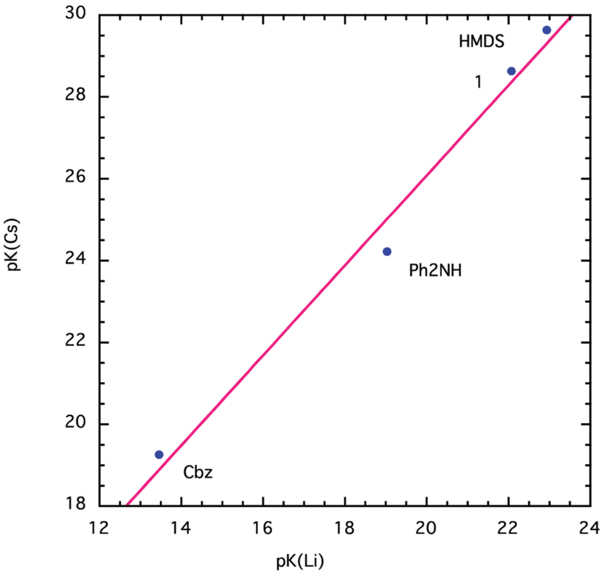


Figure 3. Correlation of p*K*(Cs) and p*K*(Li) for four amines. The regression line is 4.08 ± 1.83 + (1.000 ± 0.093)*x*; R^2 = 0.986. This correlation is not expected to be general for other cesium amides as discussed in the text.

Ab Initio Modeling. We next inquire as to how well these new lithium p*K* data fit the previously established correlation of a variety of p*K*(Li) results (fluorinated benzenes, dithianes, carboxamides, ketones, etc.) with ab initio computations.[1] That correlation was based on eq 4, an isodesmic-type equation with solvation considered by explicit coordination of solvent with lithium. THF was modeled by dimethyl ether (E).

$$\mathrm{RH + PhLi{\cdot}3E \overset{\Delta \mathit{E}}{=} RLi{\cdot}3E + PhH} \qquad (4)$$

The theory used was the Hartree−Fock energy plus the zero point energy (ZPE) with the 6-31+g(d) basis set. Note that this was the best of several other theory levels tested.[1] The regression correlation of 23 p*K*s of lithium contact ion pairs of fluorinated benzenes, carboxamides, sulfur compounds, ketones, and two amines is given by eq 5.

$$pK(\mathrm{Li}) = 39.88 \pm 0.62 + (0.654 \pm 0.019)\Delta E$$
$$R^2 = 0.983 \qquad (5)$$

The new computation results are summarized in Table 2 with full details in the Supporting Information. With the two new amine p*K*s established in the present work, the correlation becomes that shown in Figure 4. The new points are the two blue circles indicated. The new points clearly fit well such that no significant change in the regression correlation is required.

Extension to Other Amines. There are relatively few publications concerned with the effective p*K*s of organolithium compounds in THF despite the widespread use of these reagents. Moreover, most of these few papers date to the 1980s, a period when there was less concern with the complications introduced by aggregation. Moreover, much of this work was done by NMR methods at relatively high concentrations in which aggregation would be exacerbated. With our present ability to compute such p*K*s with a precision of better than ±1 p*K* unit, we are now in a position to reevaluate some of this literature. For example, in 1986, Ahlbrecht and Schneider[22]

Table 2. Computation Results at HF 6-31+G* for Amines and Coordinated Lithium Amides[a]

amine	RH, E+ZPE, au	RLi.3E, E+ZPE, au	Δ*E*, eq 4 kcal mol^{-1}	p*K*(Li), exptl	p*K*(Li), eq 5
1	−554.080958	−1022.979887	−28.092	22.1	21.55
HMDS	−870.430163	−1339.322225	−29.877	23.1	24.37
dimethylamine	−134.143025	−603.018469	−14.236	29.7^{b}	31.19
methylethylamine	−173.150914	−642.022981	−13.912	30.9^{b}	32.58
methylisopropylamine	−212.156645	−681.025226	−10.830	31.7^{b}	34.01
methyl-*tert*-butylamine	−251.160375	−720.030576	−12.614	32.4^{b}	33.35
diisopropylamine	−290.168822	−759.033998	−6.834	34.4^{b}	35.41
morpholine	−285.859436	−754.737285	−16.078	28.8^{b}	30.21
piperidine	−250.022586	−718.896682	−13.809	30.7^{b}	31.75
2,6-dimethylpiperidine	−328.040082	−796.906875	−8.563	33.6^{b}	34.75
2,2,6,6-tetramethylpiperidine	−406.040599	-874.905474^{c}	−11.258	37.9^{b}	35.53
dicyclohexylamine	−521.917079	−990.782134	−12.524	34.7^{b}	35.46
isopropyl-*tert*-butylamine	−329.170680	-798.036867^{c}	−12.094	36.3^{b}	34.99

[a] Only the first two p*K*(Li) values were determined in the present work. [b] Reference 22. [c] Optimization of RLi.3E gave a structure with one long Li−O bond (4.9 Å). This amide probably has no more than two coordinated ethers.

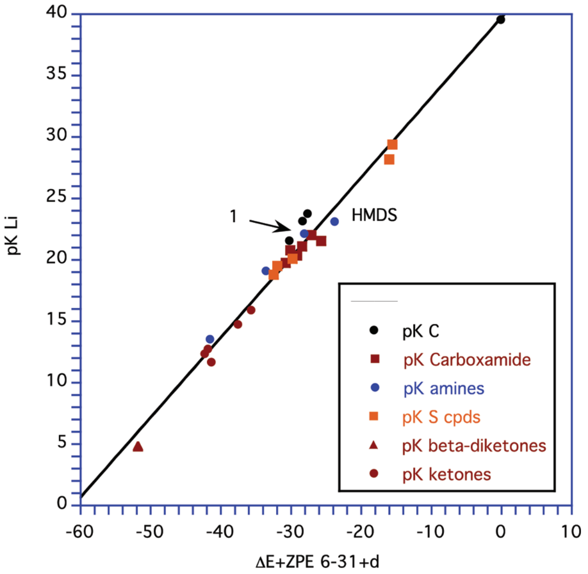


Figure 4. Plot of experimental p*K*(Li) for various monomeric RLi vs the HF energy for eq 4. This figure adds the two amines of the present study to the correlation reported previously in ref 1. The regression line shown excludes tetralones. The line shown is p*K*(Li) = 39.76 ± 0.61 + (0.651 ± 0.019)*x*; R^2 = 0.981. This correlation differs insignificantly from eq 5.

measured a number of p*K*(Li) values for amines. They used an NMR method at concentrations of 0.4 M with a scale based on our value for the p*K* of the *cesium salt* of diphenylmethane. This reference choice is probably satisfactory. The relative p*K*s of solvent separated ion pair (SSIP) lithium salts are similar to those of the CIP cesium salts,[7] and diphenylmethyllithium is known to be a mixture of comparable amounts of CIP and SSIP in THF at room temperature.[23] Thus, the p*K*(Li) that would be an appropriate reference is probably numerically similar to the corresponding p*K*(Cs). A closer comparison is with triphenylmethane, Ph_3CH. Ahlbrecht and Schneider derived p*K* = 30.4 for the lithium salt which they compared to the p*K*(Cs) = 31.0 that we had reported in 1983.[24] Later,[25] we were able to obtain a direct measurement of p*K*(Li) = 31.0 for Ph_3CH on the present scale, a value sufficiently close to theirs.

A more important problem is their assumption that the lithium amides are monomeric since it is now well established that lithium diisopropylamide[26] (LDA), lithium isopropylcyclohexylamide,[27] and lithium diethylamide[28] are mostly dimeric in typical THF solutions. Even the highly hindered lithium tetramethylpiperidide[29−31] is substantially dimeric in THF solution. It seems likely that all of the lithium amides measured by Ahlbrecht and Schneider are extensively or wholly aggregated and that therefore their experimental p*K*s cannot be directly compared to our theoretical values, which are applicable only to monomers.

Table 3. Computation Results at HF 6-31+G* for Some Fraser Compounds

compound	RH, E+ZPE au	RLi.3E, E+ZPE au	Δ*E*, eq 4kcal mol^{-1}	p*K*(Li), Fraser	p*K*(Li), eq 5
methyldithiane	−990.034949	−1458.903216	−8.773	$35.7^{a,b}$	34.14
thiophene	−551.224531	−1020.102244	−14.672	33.3^{c}	30.28
anisole	−344.450248	−813.311361	−4.284	39.0^{c}	37.08
thioanisole	−667.114353	−1135.980474	−7.426	38.6^{c}	35.02
dithiane	−951.028449	−1419.906442	−14.876	34.8^{a}	30.15
furan	−228.557241	−697.431381	−12.458	35.6^{d}	31.73
N-methylpyrrole	−247.728872	−716.591297	−5.107	39.5^{d}	36.54
N-methylimidazole	−263.747731	−732.6276082	−16.059	33.7^{d}	29.37
N-(dimethylamino)pyrrole	−341.701147	−810.566037	−6.654	37.0^{d}	35.53
benzofuran	−381.172526	−850.052610	−16.188	33.2^{d}	29.29
N-methylpyrazole	−263.729205	−732.602344	−11.830	$35.9^{d,e}$	32.14

[a] Reference 34. [b] Assumed reference value. [c] Reference 36. [d] Reference 38. [e] Value for *N*-(*n*-propyl)pyrazine.

A comparison is made in Table 2 between the reported experimental and computed p*K*s. Computations were made at the HF 6-31+g(d) level for the amines studied by Albrecht and Schneider[22] and the corresponding lithium amides coordinated to three dimethyl ethers for application of eqs 4 and 5. For amines such as diisopropylamine that can exist in several conformations, only the most stable conformation was used. Computational results are summarized in Table 2, and complete details are given in the Supporting Information.

The effective p*K* of an aggregated lithium salt is always *lower* than that of the monomer. In Table 2 it is shown that most of the "experimental" p*K*s determined by Ahlbrecht and Schneider are indeed lower than the computed values, but not by much. This comparison suggests that the aggregation equilibrium constants are not large—no more than a few powers of ten. The several amines whose experimental p*K*s are higher than the computed values are all highly hindered amines. It seems likely in these cases that transmetalaton is slow and equilibrium was not reached. Such behavior was recorded in some of our experimental results discussed above.

In the 1980s, Fraser et al. published a number of p*K*(Li) values for a variety of compounds in a series of generally short communications with a paucity of experimental details.[32−39] They generally used NMR measurements with 1 M solutions in THF at room temperature, but Ahlbrecht and Schneider noted[22] that in several cases where both groups examined the same compounds the results disagreed. For example, the Fraser group[32] reported a p*K*(Li) difference between diisopropylamine and tetramethylpiperidine of 1.6 compared to Ahlbrecht and Schneider's 2.6. One important difference is the choice of reference system. The Fraser group chose our cesium p*K* = 37.8 of methyldithiane in cyclohexylamine[40] as the reference. This salt is undoubtedly a CIP, and the lithium salt is expected to be a tighter ion pair corresponding to a lower p*K*. The calculated value using eq 5 is 34.14 (Table 3). One direct comparison is provided by triphenylmethane where Fraser's p*K* of 32.9 is two units higher than our 31.0 (vide supra). A further indication that Fraser's scale is about 2−3 units too high compared to our present scale is their reported value for HMDS, 25.8,[37] compared to our value of 23.1 reported in this paper. They reported p*K*(Li)s for several other amines whose probable aggregation affects limit their generality. These amides were then used to determine lithiation equilibria with other compounds whose lithium salts are probably monomeric. Because the lithium amides were used in approximately the same concentrations throughout, any aggregation effects probably largely cancel in these applications and the relative lithium acidities obtained are probably not unreasonable.

In Table 3 we compare some of the Fraser nonamine p*K*s with those calculated using the correlation in eq 5. Many of their values are within 2−4 p*K* units of the calculated p*K*s, with an average difference of 3.2, indicative that the major difference is the choice of reference. The comparison is shown more clearly in Figure 5. The result shows a respectable correlation with two outlying points (*N*-(dimethylamino)pyrrole and thiophene), but the slope of 0.76 suggests that the Fraser scale (which covers only 6 p*K* units) is somewhat compressed relative to ours, perhaps because of some systematic error stemming from use of lithium amide aggregates.

More recently, Sardina et al.[41−43] have used organotin−lithium exchange equilibria as quantitative measures of organolithium stabilization. They used Fraser's p*K*(Li) as reference and report that with one exception, "our data were coincident with those obtained from Fraser..."[42], but unfortunately no experimental data are reported to permit a quantitative evaluation of this generalization. They are primarily interested in α-oxy carbanions, and none of the compounds studied are on our p*K*(Li) scale. Thus, extension of our theoretical treatment to their results would be a separate study.

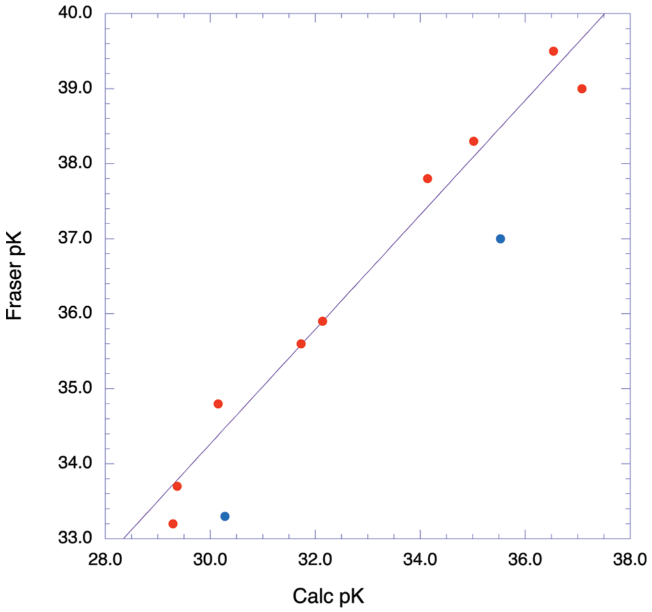


Figure 5. p*K*(Li) reported by Fraser for compounds in Table 3 compared to calculated values from eq 5. The regression line without the two outlying points (blue) is $(0.763 \pm 0.048)x + 11.37 \pm 1.57$; $R^2 = 0.973$.

CONCLUSIONS

Earlier measurements of basicities of lithium amides often have only qualitative significance because account was not taken of the now known aggregation of many such amides. Under appropriate conditions, such lithium amides can still be used in metalation equilibria to give useful information. Organolithium structures with coordinated dimethyl ethers are useful models for ab initio computations of relative stabilities in THF solutions.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables of experimental and computational results. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENTS

This work was supported in part by a Dreyfus Senior Mentor grant. We also thank Dr. Kathleen Durkin and Dr. Jamin Krinsky of the Molecular Graphics and Computational Facility (supported in part by NSF grants CHE-0233882 and CHE-0840505), College of Chemistry, UC Berkeley, for their assistance. We also thank Michael J. Ross for important experiments, Terry Singhapricha, Steven Vu, Kamesh Shah, and Julius Reyes for preliminary computations and Thorsten Müh for experimental assistance.

■ DEDICATION

[‡]Dedicated to Professor Michael Hanack on the occasion of his 80th birthday.

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