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Proton Affinities and Aggregation States of Lithium Alkoxides, Phenolates, Enolates, β-Dicarbonyl Enolates, Carboxylates, and Amidates in Tetrahydrofuran

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Abstract: The proton affinities of the title compounds are represented by their heats of deprotonation, ΔH_{dep}, through reactions with lithium bis(trimethylsilyl)amide, LiHMDS, in tetrahydrofuran at 25 °C. Aggregation numbers of the parent acid and of its lithium salt at a concentration of 0.10 M were obtained by vapor-pressure osmometry at 37 °C. Lithium phenolates were also studied by conductivity at 25 °C. ΔH_{dep}s for 27 oxygen, nitrogen, and carbon acids of varied types correlate fairly well ($R = 0.95$) with their published pK_as in dimethyl sulfoxide although their degrees of aggregation in THF vary from one to over seven. In some cases, the ΔH_{dep} of an acid is strongly dependent on the concentration ratio of LiHMDS to that of the acid's lithium salt at the time of measurement. Aggregation numbers determined by VPO in this report agree with available published values obtained by previous workers using several techniques. There is no obvious relationship between the aggregation number of the lithium salt and the basicity of the corresponding anion as represented by ΔH_{dep}. This observation along with independent evidence for equilibria between monomers, dimers, tetramers, etc. for a number of compounds indicate that there are only small differences between the relative stabilities of different aggregation states. Conductance data for lithium *p*-nitrophenolate were treated by Wooster analysis, the results of which suggest equilibria between ion triplets, ion pairs, and free ions in THF. The conductance of LiHMDS in this solvent is surprisingly high, and this property was used to demonstrate an interaction between LiHMDS and lithium *o-tert*-butylphenolate.

Introduction

Many of the polar reactions encountered in organic chemistry can be viewed essentially as acid–base processes. Consequently, the relative stabilities of conjugate bases formed by deprotonating organic acids is of great value to understanding anion reactivity. Bordwell and his co-workers have determined pK_as for many protonic acids of widely varied structures and functional groups in dimethyl sulfoxide.[1] Their work provides the largest data base in organic chemistry for the quantitative comparison of structure change on reactivity. Most synthetic chemistry involving carbanions, however, utilizes organolithium compounds in solvents of low polarity where ion pairs and higher order aggregates exist as the dominant species.[2a] The relative stabilities of organolithiums under synthetic conditions are influenced by the interactions arising from aggregation and may therefore exhibit different behavior than for the potassium salts in dimethyl sulfoxide where aggregation is absent.

The importance of ion pairing to rates, equilibria, and mechanisms of organic reactions began to attract widespread attention during the 1960s due largely to the contributions of Winstein and his students.[3] Now that employment of organolithiums in tetrahydrofuran has become a popular method for stereoselective synthesis,[4] the effect that higher order aggregates have on reactivity has assumed a special urgency in physical organic chemistry. Through the use of NMR, colligative properties, kinetics, X-ray crystallography, and other methods, the structures of alkali salts under various conditions are being investigated as well as the effects of structure variation on reactivity.[5–14] The results of this

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work demonstrate or suggest different reactivities for different arrangements of organolithium species. Several review articles now address these topics.[2]

Streitwieser has determined ion-pair acidities for a variety of lithium and cesium salts in cyclohexylamine[15] and tetrahydrofuran.[16] Petrov and Shatenshtein have made acidity measurements in 1,2-dimethoxyethane of compounds whose lithium and cesium salts are also contact ion pairs.[17] Antipin and co-workers have developed an acidity scale for cryptated lithium salts in tetrahydrofuran.[18] With few exceptions, the results of these various studies suggest that acidity is rather insensitive to changes in solvent, cation, and even ion pairing. However, these cases are limited to highly delocalized systems to avoid the problems associated with higher order aggregates and to diminish ion-pair electrostatic interactions, which may be the crucial factor for deviations from dimethyl sulfoxide acidities.

Determining pK_as becomes complicated when formation of higher order aggregates occurs. Recently, Streitwieser has attempted to attack this problem by measuring equilibrium acidities over a concentration range of about $(0.6–10) \times 10^{-4}$ M.[19] The information from these experiments yields pK_as at different concentrations and an average aggregation number. Although the pK_as are concentration-dependent for higher order aggregates, approximate acidity values can be obtained since the variation does not usually exceed 1.5 pK_a units. This technique has proven successful for a few compounds, but may have limitations as a general technique for lithium enolates due to rapid addition to the parent carbonyl compound.

This report presents calorimetric enthalpies of deprotonation, ΔH_{dep}, for a wide range of organic acids. This method of study employs relatively high concentrations of lithium salts (0.05–0.10 M) and takes into consideration energetic differences arising from aggregation. Also, the complications associated with measuring equilibrium acidities as well as the need for appropriate indicators can be bypassed. However, this thermochemical method ignores entropy contributions to the free energy changes and therefore need not be correlated with pK_as. Nevertheless, it does provide energetic information on systems of differing aggregation states.

The present VPO experiments provide a convenient and widely applicable technique for measuring the degree of association of organolithiums at 37 °C. Conductance measurements were also performed on a few selected lithium salts as a direct electrochemical means for determining the degree of dissociation.

Experimental Section

Materials and General Procedures. Tetrahydrofuran, THF (Fisher), was used directly after distillation from sodium benzophenone ketyl. Lithium bis(trimethylsilyl)amide, LiHMDS (Aldrich), was sublimed in vacuo at 80 °C and transferred under argon to a Vacuum Atmospheres HE-43-2 dry box equipped with a VAC HE-493 purification system. LiHMDS is available commercially as a 1.0 M solution in THF (Aldrich), and appropriate dilutions of this stock solution were also used. Routine ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-300 NMR spectrometer at room temperature.

Purification of Acids. All of the parent compounds used in this study were available from Aldrich. Liquids were distilled from phosphorus pentoxide (Fisher) either under an argon atmosphere or under reduced pressure. Solids were either sublimed in vacuo or recrystallized from a suitable solvent and then placed under vacuum for 24 h. Purified compounds were then transferred under argon to a dry box for subsequent use. Purity was checked by ^{1}H and ^{13}C NMR spectroscopy in $CDCl_3$.

Product Studies of the Deprotonation Reaction. In order to ensure that LiHMDS would deprotonate each acid cleanly and that the resulting lithium salt would be both stable to rearrangement and soluble in THF, the deprotonation reaction was tested on a large enough scale to examine the products. A 0.10 M solution of LiHMDS in THF was prepared and 1 equiv of the acid was added and stirred for 5 min with careful checks for complete solubility. At this point, a suitable electrophile such as TMSCl, AcCl, or MeI was added and the reaction mixture was worked up as described by Heathcock.[20] The isolated product was then analyzed by ^{1}H and ^{13}C NMR in $CDCl_3$. In the case of carboxylates and β-dicarbonyl enolates, no electrophile was added. The solvent and HMDS were removed from the reaction mixture and the resulting solid was prepared for ^{1}H and ^{13}C NMR spectrometry in DMSO-d_6 and compared to its parent. All deprotonation products used in this study gave spectra consistent with their expected structures, and visual observation showed each lithium salt to be soluble in THF when generated this way. NMR data are provided as supplemental information.

Calorimetry. All ΔH_{dep}s were determined at 25 °C with a Tronac Model 1250 solution calorimeter operated in the 450 isoperibol mode. Solutions of LiHMDS (0.05–0.10 M) in THF were prepared either by dissolving an appropriate amount of sublimed LiHMDS in THF or by diluting the commercially available stock solution of LiHMDS in THF. This solution was transferred via a gas-tight syringe to an argon-purged Dewar calorimeter vessel. A known concentration of acid in THF was prepared and the motor-driven buret was used to introduce a precise amount into the base solution at a constant rate. Clean, linear thermograms indicated that the exothermic reactions were complete and virtually instantaneous at 25 °C. Each ΔH_{dep} presented here is the average of at least five calorimetric measurements on each of three independently prepared solutions. The heats of reaction were calculated from strip-chart thermograms by the standard method.[21] Variation of the source of LiHMDS in no case affected the magnitude of ΔH_{dep}.

Vapor-Pressure Osmometry. Aggregation numbers were all determined on a Wescor 5500-XR vapor-pressure osmometer operating at 37 °C in a dry box. A known molality of LiHMDS in THF was prepared from the sublimed solid and a certain mass was placed in a vial. One equivalent of acid was syringed into this vial from prepared solutions containing known molarities of acid in THF. This was done in such a manner as to make the resulting solution 0.10 M in lithium salt. Calibration curves of scale reading versus concentration were obtained with use of fluorene (Aldrich), biphenyl (Aldrich), and benzophenone (Aldrich) as nonelectrolyte standards. A linear least squares analysis generated correlation coefficients of at least 0.9900 for the systems reported here. A small correction factor for the hexamethyldisilizane byproduct of deprotonation was determined by preparing different concentrations of one of the above standard nonelectrolytes with 0.10 M amine and observing its deviation from the standardization curve. Each VPO datum was generated by making three independent solutions of each lithium salt and measuring each solution two to three times.

Conductance. All conductivity measurements were performed by utilizing a Beckman RC18-A conductivity bridge with the oscilloscope operating at 1 kHz. The conductivity cell utilized three concentric open-ended cylindrical electrodes in which the innermost and outermost cylinders were connected by a platinum bridge. These two cylinders together made up one electrode and the central cylinder alone was the other. The electrodes were made of platinum separated by a distance of 2 mm. The cell was operated under an argon atmosphere and was maintained at 25 °C by means of a constant-temperature water bath. The cell constant was determined by the method of Jones and Bradshaw[22] and was found to be 7.30×10^{-3} cm^{-1}. The solutions used for the conductivity measurements were prepared by adding 1 equiv of dissolved acid in THF to a THF solution containing LiHMDS such that the resulting solution contained 0.10 M lithium salt and 0.10 M HMDS. The source

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Table I. ΔH_{dep} (LiHMDS/THF), pK_as (DMSO), and Aggregation Numbers (VPO)

no.	compound	pK_a (DMSO)	ΔH_{dep} (kcal/mol)[b]	aggregation no. (0.10 M)	
				parent acid	lithium salt[b]
1	*p*-nitrobenzoic acid	8.98	−32.9 ± 0.4		precipitates
2	*p*-chlorobenzoic acid	10.20	−31.3 ± 0.1		precipitates
3	benzoic acid	11.03	−30.9 ± 0.1		precipitates
4	dibenzoylmethane	13.36	−28.9 ± 0.1	1.0	1.4 ± 0.1
5	dipivaloylmethane	15.43	−26.3 ± 0.1		1.5 ± 0.1
6	diethyl phenylmalonate	16.28	−25.9 ± 0.3		1.0 ± 0.1
7	diethyl malonate	16.37	−25.7 ± 0.2	1.1	1.2 ± 0.2
8	diethyl methylmalonate		−23.7 ± 0.2	1.2	1.2 ± 0.1
9	diethyl isopropylidenemalonate		−21.2 ± 0.1		1.0 ± 0.1
10	*p*-nitrophenol	10.78	−29.2 ± 0.4		2.3 ± 0.3
11	*p*-cyanophenol	13.19	−27.3 ± 0.3		2.2 ± 0.1
12	*p*-carbomethoxyphenol	14.32	−26.8 ± 0.3		precipitates
13	*p*-chlorophenol	16.75	−25.1 ± 0.7		3.7 ± 0.4
14	phenol	18.05	−23.5 ± 0.4	1.0	4.0 ± 0.6
15	*p*-*tert*-butylphenol	19.03	−22.9 ± 0.5		3.9 ± 0.2
16	*p*-methoxyphenol	19.12	−22.7 ± 0.4		4.8 ± 0.7
17	*o*-*tert*-butylphenol	19.03	−22.2 ± 0.5[a]		2.1 ± 0.1
18	2,2,2-trifluoroethanol	23.54	−20.3 ± 0.2		4.4 ± 0.2
19	benzyl alcohol		−17.8 ± 0.5	1.1	3.5 ± 0.3
20	benzhydrol		−17.1 ± 0.1		2.8 ± 0.1
21	*n*-butyl alcohol		−15.7 ± 0.6		5.1 ± 0.3
22	isopropyl alcohol	30.25	−15.4 ± 0.3[a]		4.7 ± 1.0
23	neopentyl alcohol		−13.9 ± 0.4[a]		5.4 ± 0.3
24	*tert*-butyl alcohol	32.20	−12.1 ± 0.5[a]		4.8 ± 0.2
25	*p*-bromoacetanilide	20.31	−17.2 ± 0.2		4.0 ± 0.2
26	*p*-methylacetanilide	21.75	−14.9 ± 0.1		5.5 ± 0.1
27	acetanilide	21.46	−15.5 ± 0.2		7.1 ± 0.6
28	*p*-nitroacetophenone		−18.5 ± 0.1		2.4 ± 0.1
29	acetophenone	24.72	−16.4 ± 0.1		3.8 ± 0.5
30	cyclohexanone	26.25	−15.8 ± 0.2		3.4 ± 0.6
31	cyclopentanone	25.83	−15.1 ± 0.2		5.6 ± 0.7
32	*p*-methoxyacetophenone	25.66	−14.5 ± 0.5		3.3 ± 0.2
33	*o*-methoxyacetophenone	25.66	−14.3 ± 0.1	0.92	3.3 ± 0.4
34	pinacolone	27.66	−12.7 ± 0.6[a]		4.0 ± 0.6

[a] Indicates that ΔH_{dep} varies with the ratio of LiHMDS to deprotonated lithium salt. [b] ± Values are reported at the 95% confidence level.

of LiHMDS, purified by sublimation or dilution of a commercially available solution, proved to be unimportant. The added conductance of 0.10 M HMDS in solution was determined to be negligible by measuring a blank sample containing only HMDS. Each datum presented is the average of at least three independent measurements. Lithium *p*-nitrophenoxide for the Wooster analysis was isolated as a pure solid by the method described below and then redissolved in THF.

Isolation of Lithium *p*-Nitrophenoxide. LiHMDS (1.10 equiv of 1.0 M in hexanes (Aldrich)) was syringed into a stirred slurry of *p*-nitrophenol in pentane under an argon atmosphere. Bright yellow crystals fell to the bottom of the flask. The top blanket of solvent was syringed off and fresh pentane was added. This washing procedure was repeated five times. After the last removal of solvent by syringe, the flask was placed under vacuum for 24 h. The purity of the phenoxide was confirmed by ^{1}H and ^{13}C NMR analyses in DMSO-d_6.

Results

Enthalpies of Deprotonation. The enthalpies of reaction between the title compounds and LiHMDS in THF at 25 °C are presented in Table I along with the corresponding pK_as determined in Me_2SO[1] by Bordwell's group. In most cases, the heat of reaction did not vary by more than experimental error over the series of sequential injections of the acid into the basic solution although the concentration ratios of formed lithium salt to LiHMDS varied from 0.03 to over 3.

Figure 1, however, shows the interesting deprotonation behavior of pinacolone. Each incremental addition of the ketone to the calorimeter consumed only about 5–10% of the available base in the reaction vessel. As shown, the enthalpy of deprotonation for the first titration, that which consumed the first 10% of the base, was much less exothermic than that for the fifth addition, for example, at the point where there was roughly a 60:40 ratio of remaining LiHMDS to lithiopinacolonate formed from the deprotonation. Each data point on Figure 1 was calculated by summing the heat released from all additions up to that point and dividing this value by the total number of moles of acid delivered to the reaction vessel. As an example, if it took five titrations to consume 62% of the available base in the reaction vessel, the value for ΔH_{dep} at 62% was obtained by summing the heat released from all five individual titrations and dividing by the total number of moles delivered in those five runs. The reported value for this reaction (−12.7 kcal/mol) was then obtained by extrapolating the curve to 100% reaction. This is the best estimate of the value that would have been obtained if it had been possible to introduce exactly 1 equiv of pinacolone into a THF solution of LiHMDS at 25 °C. The errors in these cases were estimated by visually assessing the limits of deviation from the curve.

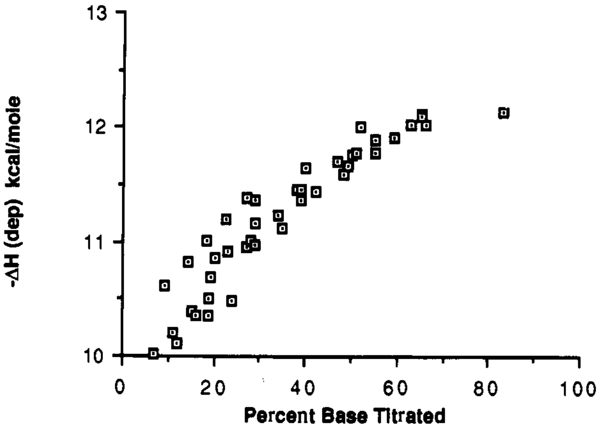

Figure 1. Enthalpies of deprotonation of pinacolone as a function of percent base consumed.

Variation of the enthalpy of reaction as a function of the amount of added acid was not exhibited by all compounds, however. Figure 2 compares the deprotonations of *p*-*tert*-butylphenol and *o*-*tert*-butylphenol. Clearly, ΔH_{dep} for *o*-*tert*-butylphenol is dependent on the relative ratios of LiHMDS to lithium phenoxide, whereas *p*-*tert*-butylphenol is not. Only pinacolone, *tert*-butyl

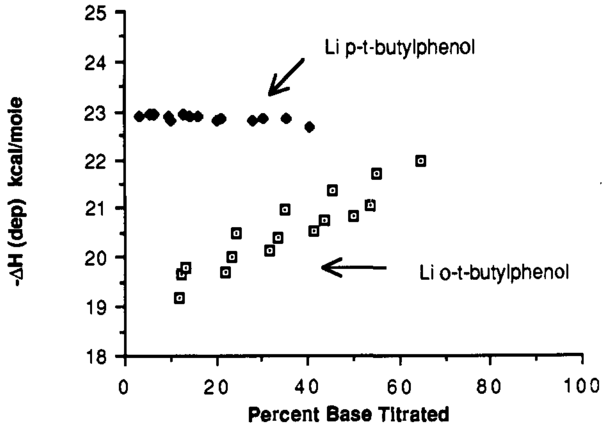

Figure 2. Enthalpies of deprotonation for *o*- and *p*-*tert*-butylphenols as a function of percent base consumed.

Table II. Data for Wooster Analysis

no.	[Li–OAr]^a × 10^4	Λ^2[Li–OAr] × 10^7	no.	[Li–OAr]^a × 10^4	Λ^2[Li–OAr] × 10^7
1	1.15	6.64	6	6.47	25.98
2	2.33	11.65	7	7.37	28.21
3	3.43	13.34	8	8.27	31.73
4	4.47	17.94	9	9.12	35.32
5	5.50	20.85	10	9.75	37.51

^{a} [Li–OAr] = molarity of lithium *p*-nitrophenoxide.

alcohol, *o*-*tert*-butylphenol, and to a lesser extent, neopentyl alcohol and isopropyl alcohol exhibited this type of concentration dependence.

Vapor-Pressure Osmometry. Aggregation numbers for the parent compounds and their lithium salts at a concentration of 0.10 M in THF at 37 °C are given in Table I. All parent acids were monomeric. Also, lithium β-dicarbonyl enolates were essentially monomeric with some dimer present in a few cases. Lithium phenolates varied between dimers and tetramers, depending on the basicities of the anions as well as steric considerations. Other lithium salts gave aggregation numbers of about 4. Some lithium alkoxides and amidates yielded higher aggregation numbers, indicating that even hexamers may be present in these systems.

The three lithium carboxylates and lithium *p*-carbomethoxyphenolate precipitated from solution during the VPO measurement. All four of these lithium salts were completely soluble when the solutions were made up for the VPO experiments and were soluble when the product studies were performed. Apparently, the sudden warming and cooling process that occurs during the experiment is enough of a shock to begin the crystallization process.

Conductance. Results of the conductivity experiments with lithium *p*-nitrophenolate solutions are presented in Table II. This salt gave high enough conductances to give a meaningful Wooster analysis,[23] which is useful for determining dissociation constants as well as suggesting the existence of triple ions. Attempts were made with other lithium phenolates, but the conductances were too low at appropriate concentrations for Wooster analysis. In the limit of weak electrolytes, the original Arrhenius equation holds, $\alpha = \Lambda/\Lambda_0$, where Λ is the measured equivalent conductance and Λ_0 is the equivalent conductance at infinite dilution. A value of 107 $\text{ohm}^{-1}\ \text{cm}^2\ \text{mol}^{-1}$ has been determined by Gilkerson for the ionic mobility of lithium picrate in THF[24] and this value was used for all lithium phenolates in this study, on the basis of the assumption that the phenolates are similar enough in structure to not alter this property significantly. An iterative method developed by Marshall and Grunwald[25] was employed to obtain values for α, which were corrected for electrophoretic and relaxation effects.

Table III. α and pK_d Determinations from Conductance

no.	substituted lithium phenoxide (0.10 M)	α × 10^6	pK_d
1	*p*-nitro	1010	6.99 ± 0.02
2	*p*-cyano	302	8.04 ± 0.10
3	*p*-chloro	86.5	9.13 ± 0.01
4	unsubstituted	26.4	10.16 ± 0.20
5	*p*-methoxy	9.24	11.07 ± 0.06
6	*p*-*tert*-butyl	10.9	10.87 ± 0.21
7	*o*-*tert*-butyl	27.1	10.13 ± 0.07

Table IV. Conductance of Mixed Systems

no.	species in THF solution at 25 °C	conductivity × 10^6	% difference
1	LiHMDS (0.050 M) + HMDS (0.050 M) (reference solution)	7.2 $\text{ohm}^{-1}\ \text{cm}^{-1}$	reference
2	LiHMDS (0.050 M) + HMDS (0.050 M) + lithium *o*-*tert*-butylphenoxide (0.050 M)	3.1 $\text{ohm}^{-1}\ \text{cm}^{-1}$	57%
3	LiHMDS (0.050 M) + HMDS (0.050 M) + lithium salt of dibenzoylmethane (0.050 M)	7.2 $\text{ohm}^{-1}\ \text{cm}^{-1}$	0%

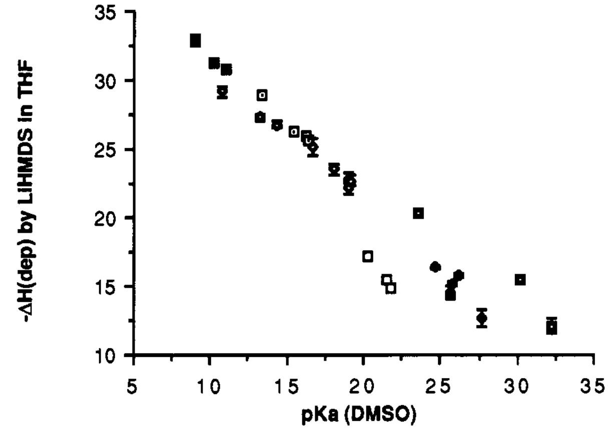

Figure 3. Enthalpies of deprotonation by LiHMDS in THF at 25 °C in THF vs pK_as in DMSO, reported by Bordwell: ⊡, β-dicarbonyls; ◆, ketones; ▣, alcohols; ◇, phenols; ■, carboxylic acids; and □, acetanilides.

Table III gives the results of the values obtained for α and the calculated pK_ds of the lithium phenoxides at a concentration of 0.10 M.

Despite the high basicity of LiHMDS, it is twice as conducting as even lithium *p*-nitrophenoxide in THF at 0.10 M. Table IV shows that when a solution is made that contains the same amount of LiHMDS as the reference solution and also 1 equiv of lithium *o*-*tert*-butylphenolate, the conductance is reduced by 57%. In contrast, if the added compound is the lithium salt of dibenzoylmethane, no change in conductivity is observed.

Discussion

Two facts stand out from the data presented in Table I where the various acids are arranged in order of decreasingly exothermic ΔH_{dep}s from the LiHMDS/THF system. First, the most acidic compounds in terms of their pK_as in DMSO give the most exothermic ΔH_{dep}s although, as Figure 3 makes clear, the standard free energies of ionization in DMSO are by no means correlated perfectly with the ΔH_{dep} values in THF. Some years ago we demonstrated a surprisingly good correlation ($R = 0.99$) between Bordwell's pK_a values for ionization of a wide variety of acids in DMSO and the corresponding heats of deprotonation in that solvent.[26] However, it is quite a different matter to find a good correlation between pK_as measured in DMSO and ΔH_{dep}s obtained with LiHMDS in THF, considering the different degrees of aggregation in the two systems.

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[23] Wooster, C. B. *J. Am. Chem. Soc.* **1937**, *59*, 377.

[24] Gilkerson, W. R.; Jackson, M. D. *J. Am. Chem. Soc.* **1979**, *101*, 4096.

[25] Marshall, H. P.; Grunwald, E. *J. Chem. Phys.* **1953**, *21*(12), 2143.

[26] (a) Arnett, E. M.; Small, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 808. (b) Arnett, E. M.; Venkatasubramaniam, K. G. *J. Org. Chem.* **1983**, *48*, 1569.

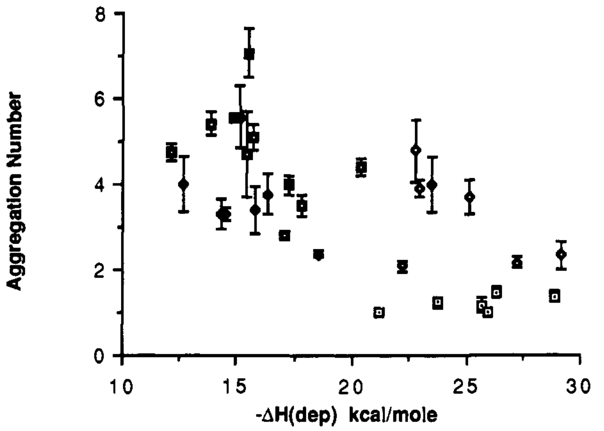


Figure 4. Aggregation numbers determined by VPO for all lithium salts studied vs enthalpies of deprotonation by LiHMDS in THF: ▣, β-dicarbonyls; ◆, ketones; □, alcohols; ◇, phenols; and ■, acetanilides.

Second, as is clear under the column for aggregation numbers, the products from deprotonation by this lithium base in THF cover a wide range of states of aggregation at 0.10 M, from essentially monomeric ion pairs for diethyl isopropylidenemalonate to acetanilide, which appears to be forming mostly hexamers. What is so remarkable then about Figure 3 is that free energies or enthalpies of ionization for the formation of mostly dissociated potassium salts in DMSO should correlate as well as they do with heats of deprotonation in THF where a variety of organolithium monomers, dimers, tetramers, and hexamers are formed by the deprotonation process.

The important conclusion that must be drawn from the correlations between thermodynamic properties of the production of ions and ion pairs in DMSO and of a variety of aggregates in THF is that in this ether solvent there must be very little difference between the heats of formation of the different types of aggregated lithium salts in Table I. Support for this claim lies in the number of nonintegral values for the aggregation numbers, suggesting that many of them are simply averaged for equilibrium mixtures of two or more aggregation states of nearly equal populations. If this is true, they must be of almost equal stability in terms of free energy. Further evidence may be cited from a recent study of the aggregates produced by deprotonation with LiHMDS/THF of a series of β-substituted 1-phenylpropanols whose lithium alkoxides showed a variety of aggregation states by VPO and also by freezing point depression.[27]

Figure 4, which compares the aggregation numbers for the organolithiums versus ΔH_{dep} for the parent acids in Table I, provides further evidence for the remarkably small difference in heats of formation for the various types of aggregates. Clearly, there is no particular correlation between the affinities of the various ions for protons, as represented by ΔH_{dep}s, and the corresponding driving forces for aggregation with lithium ions. The most dramatic comparison is between *o*- and *p*-*tert*-butylphenols whose pK_as in DMSO are identical and whose ΔH_{dep}s in THF are within experimental error. However, the aggregation number of the para-substituted salt is close to that for a tetramer, whereas the ortho compound is dimeric. One can only conclude that the difference in the heats of formation for the two types of aggregates is within the experimental error of about 0.5 kcal/mol. Brown[12c] and Jackman[5c] have both observed equilibria between aggregation states for LiHMDS and lithium *p*-bromophenoxide in THF and found the enthalpies for interconversion by the method of van't Hoff to be less than 5 kcal/mol.

It has been known for some time that complex aggregates involving different organolithium compounds may exist in a crystal structure.[9e,f] We believe that the peculiar behavior demonstrated in Figure 1, where the observed ΔH_{dep} value varies as a function of the amount of LiHMDS remaining in solution, is the result of the formation of a mixed aggregate between lithium pinacolonate and LiHMDS. As more pinacolone is added, the mixed aggregate formed initially eventually becomes the reactive base and forms the homonuclear aggregate product containing only lithium pinacolonate. Scheme I illustrates the reactions we believe to be occurring at different ratios of LiHMDS to lithium pinacolonate. When this ratio is high, reaction A dominates and when this ratio is low, reaction B becomes important. These two reactions, or perhaps more if more than one type of mixed aggregate forms, would occur to different degrees as the ratio of LiHMDS to lithium pinacolonate changes. Correspondingly, the other compounds that showed similar behavior interact with LiHMDS in an analogous manner. Those compounds that did not show this type of behavior may still be forming mixed aggregates and coincidentally giving similar ΔH_{dep}s at any point during the addition of acid.

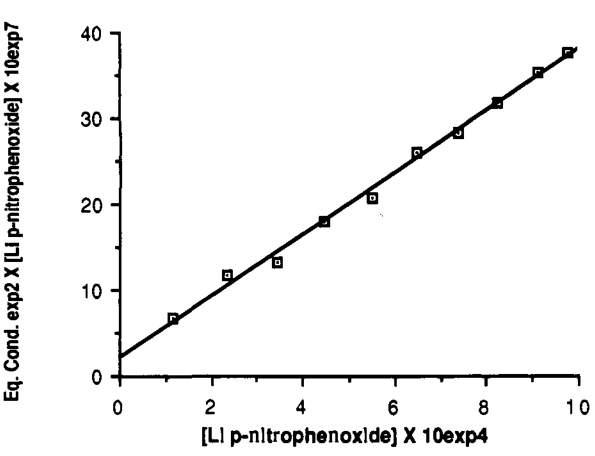
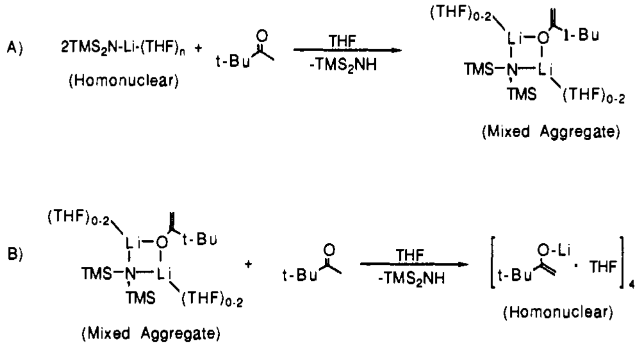


Figure 5. Wooster plot for *p*-nitrophenoxide in THF, $y = 2.1392 + 3.5909x$, $R = 1.00$.

Scheme I



Finally, Bartmess and Thomas[28] have compared many of these ΔH_{dep}s with their gas-phase acidities. With the exception of HMDS, whose gas-phase acidity is anomalously high, 21 of the compounds yield a rough linear correlation of ΔH_{dep} (THF) versus ΔH_{acid} (gas), with a slope of 2.3 and $R = 0.89$. Obviously, the proportionality of the two sets of data implies that differential structural effects on solvation, ion pairing, and aggregation cancel to a considerable extent as the anions are transferred from the gas phase to solution and paired with lithium cations. The usual attenuation factor on going from the gas phase to solution is found.

Colligative Properties. VPO, cryoscopy, and ebulliometry are valuable tools for determining the higher states of aggregation, but are of less value for detecting conducting species such as free ions or ion triplets. Since monomeric lithium chelates or free enolate ions have frequently been considered as reactive intermediates for the aldol and related reactions of lithium enolates in nonpolar media, we have examined the conductance of several lithium phenolates in THF at 25 °C. Not surprisingly, the lithium phenoxides are very weak electrolytes under these conditions. The

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(27) Arnett, E. M.; Nichols, M. A.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 7059.

(28) Bartmess, J. E.; Thomas, D. A. Personal Communication.

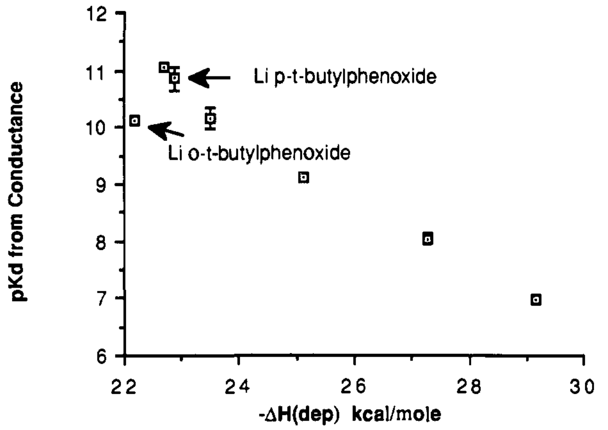

Figure 6. Plot of pK_ds obtained from conductance vs enthalpies of deprotonation by LiHMDS in THF.

data were examined by the method of Marshall and Grunwald for dissociation of ion pairs to free ions and by that of Wooster, which assumes equilibria between free ions, ion pairs, and ion triplets. Figure 5 presents a Wooster plot of Λ^2 versus concentration for lithium *p*-nitrophenoxide. The good linearity implies that all three species were present in equilibrium. The intercept is equal to $K_d\Lambda^2$, where K_d is the equilibrium constant between ion pairs and free ions. By using Gilkerson's[24] value of 107 ohm^{-1} cm^2 mol^{-1} for Λ, the value for K_d is found to be 1.87×10^{-11}, surely a very low concentration of free ions even for this salt, which should be one of the most dissociated in Table I.[29] Wooster plots were also tried for the lithium *p*-chloro- and *p*-cyanophenolates. Although good straight lines were obtained, their negative intercepts vitiated any attempts at meaningful analysis.

Lithium phenoxides in THF are very weak electrolytes and it is therefore reasonable to assume that $\alpha = \Lambda/\Lambda_0$. Also, the corrected value of α found by using the Marshall and Grunwald treatment was not much different from our initial approximation. It may be shown that $K_d = \alpha^2C/(1 - \alpha)$, and Table III contains the corrected values of α at 0.10 M and calculated K_ds. Figure 6 presents a plot of K_d versus ΔH_{dep}, where all lithium phenoxides are 0.10 M. This indicates that the basicity of the anion plays an important role in the dissociation of the lithium ion pair. Especially interesting is the fact that dimeric lithium *o-tert*-butylphenoxide gives almost the same number of free ions as its para tetrameric counterpart. In this case, the factors that control equilibria between higher aggregates are not effective in controlling the dissociation to free ions. It would be unwise to draw any conclusions from this single observation.

Evidence for mixed aggregate formation between LiHMDS and lithium *o-tert*-butylphenoxide is found in Table IV, which shows that when 1 equiv of lithium *o-tert*-butylphenoxide is added to a solution of LiHMDS plus HMDS, the conductance is reduced from 7.2×10^{-6} to 3.1×10^{-6} ohm^{-1} cm^{-1}, a 57% reduction. A logical explanation for this behavior is that the two lithium salts form a mixed aggregate, which does not dissociate as readily as pure LiHMDS. In contrast, the addition of 1 equiv of lithium dibenzoylmethide has no effect on the conductance of the reference solution of LiHMDS plus HMDS. This information is inconclusive concerning whether or not interaction occurs between lithium dibenzoylmethide and LiHMDS.

Conclusions

(1) Reasonably good correlation between ΔH_{dep} (THF) and pK_a (DMSO) values (R = 0.95) suggests that there is little difference between the heats of formation of different aggregation states for these organolithium compounds.

(2) In some cases, ΔH_{dep} changes during the incremental addition of acid to the reaction vessel. We propose that this is due to the formation of mixed aggregates between LiHMDS and the lithium salt formed from the deprotonation reaction.

(3) Aggregation numbers determined in THF by vapor-phase osmometry vary from one to over seven, depending on the steric bulk, proton affinity, and type of acidic group of the parent organolithium under study.

(4) Conductivities of substituted lithium phenoxides give dissociation constants that correlate well with their proton affinities (R = 0.97), but not with aggregation numbers (R = 0.70). Conductivity also demonstrates an interaction between LiHMDS and lithium *o-tert*-butylphenoxide.

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Supplementary Material Available: Listings of ^{1}H and ^{13}C NMR data for product studies done on β-dicarbonyl compounds, phenols, carboxylic acids, and acetanilides and on ketone and alcohol deprotonations (12 pages). Ordering information is given on any current masthead page.

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[29] Kaufman, M. J.; Gronert, S.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 2829.