analogue.[29] Indeed, with purified samples we found the $(M - H)^-$ ion to be about 10 times larger than the $(M - SO_3 - H)^-$ ion, a ratio similar to that of the two phosphotyrosine peptides for the analogous loss of HPO_3. However, the phosphotyrosine peptides showed much more abundant molecular ions in the positive ion mode relative to the loss of phosphate than either CCK-8 or caerulein showed relative to loss of SO_3 or SO_4.

Thus, it appears from this preliminary study that phosphotyrosine-containing peptides are intermediate between the facile fragmentation of peptides containing sulfated tyrosines in the positive ion mode and the low abundance of similar fragments when phosphate is attached to serine (and probably threonine as well). While this is in agreement with one's expectations based on chemical stabilities in solution, it will require further analyses on a more diverse class of peptides before any conclusive statements can be made about the relative ease of fragmentation of these types of peptides during mass spectrometric analysis. Nonetheless, the mass spectrometric studies suggest that the differences in fragmentation among phosphotyrosine, phosphoserine, and sulfated tyrosine-containing peptides should be of considerable analytical use and could serve as a basis for their mass spectrometric identification, particularly when both positive and negative ion LSIMS spectra are available. In more general terms, we would also expect other related ionization techniques such as fast atom bombardment or plasma desorption to be well suited for the identification and characterization of phosphorylated (and sulfated) peptides, thus increasing the applicability of the methods described in this paper.

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(29) The purity of caerulein and CCK-8 was at least 99% as judged by HPLC and LSIMS analysis. No impurities were detected for the HPLC purified phosphotyrosine peptides after the purification by HPLC.

Structures of the Lithium Salts of Aromatic Secondary Amines in Weakly Polar Aprotic Solvents[1]

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Abstract: Lithium indolide (lithioindoline) in THF is shown, by vapor pressure barometry, to be a dimer, and its temperature-dependent, concentration-independent ^{13}C chemical shifts are interpreted in terms of the equilibrium $Li_2A_2(THF)_2 \rightleftharpoons Li_2A_2(THF)_4$ (A = amide anion). Lithium 1,2,3,4-tetrahydroquinolide exhibits the same behavior. Lithium 2-methylindolide, 2-methyl-1,2,3,4-tetrahydroquinolide, and *N*-methyl-, *N*-*n*-butyl-, and *N*-isopropylanilides form the monomer $LiA(THF)_3$ as well as the two dimers. Monomer–dimer exchange is slow on the ^{13}C NMR time scale at low (<−80 °C) temperatures. Lithium *N*-(2-methoxyethyl)anilide forms only $Li_2A_2(THF)_2$. Lithium *N*-*tert*-butylanilide exists as $LiA(THF)_2$ and $LiA(THF)_3$ depending on temperature. All the above salts form only $Li_2A_2(Et_2O)_2$ in diethyl ether. Both the indolide and *N*-*tert*-butylanilide salts exhibit slow *E*–*Z* isomerism on the ^{13}C NMR time scale at −110 °C. ^6Li, ^{15}N spin–spin couplings of 3.8 and 7.5 Hz are observed for $Li_2(PhNCH_3)_2(Et_2O)_2$ and $Li(PhNPr^i)(THF)_3$, respectively, in the corresponding solutions below −80 °C. Rotation of the phenyl group in *N*-methyl-, *N*-*n*-butyl-, *N*-(2-methoxyethyl)-, and *N*-isopropyl- but not *N*-*tert*-butylanilides is slow on the ^{13}C NMR time scale below −50 °C. Rotation of the *tert*-butyl group in $LiA(THF)_3$ (A = *N*-*tert*-butylanilide) is comparable with the ^{13}C NMR time scale at −100 °C.

Lithium enamides (1-azaallyllithium and its derivatives) are frequently employed in synthesis as alternatives to enolate ions since the low acidities of the corresponding imines usually preclude proton transfer between reagents and products, thus eliminating further reaction (e.g., dialkylation) with the electrophilic reagent.[2] Enamide anions, like enolate ions, are ambident and do, in fact, undergo reactions at both their C and N termini.[3] There is now abundant evidence that lithium enolates exist as aggregates[4] in weakly polar aprotic solvents and that aggregation plays an important role in determining the regioselectivities of their reactions with electrophiles.[5] It is, therefore, important to know if lithium enamides also form aggregates which similarly control their regiochemistry. In addition, strong interactions between anions and the lithium cation are evidently implicated in asymmetric syntheses which utilize the anions derived from chiral imines,[6] hydrazones,[7] oxazolines,[8] and imino ethers.[9] As part of a survey of the solution

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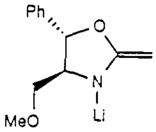
structures of reagents of this general class we have examined a series of lithium salts of aromatic secondary amines in weakly polar aprotic solvents, the expectation being that these compounds will parallel the behavior of lithium enamides in the same way as lithium phenolates exhibit much the same solution behavior as lithium enolates.[10]

X-ray structures are available for a number of lithium salts of secondary amines. These structures include a monocyclic tetramer,[11] cyclic trimers,[12,13] as well as a number of dimeric[11,13-15] and monomeric[16] species. Two points are of interest. First, no *cubic* tetrameric structures have been observed for secondary lithium amides and, secondly, even in the case of the lithium derivative of the relatively unhindered secondary amine, dibenzylamine, each lithium in the dimer is only monosolvated by diethyl ether or hexamethylphosphoric triamide.[14] In addition, the monolithium salt of the *primary* amine, 2,4,6-tri-*tert*-butylaniline, which crystallizes as a monomer from tetramethylethylenediamine (TMEDA), also has a lithium atom which is formally only tricoordinate.[17] $Ph_2C{=}NLi{\cdot}$pyridine, in which steric effects in the vicinity of the N–Li bond are greatly reduced, does, however, exist as a cubic tetramer.[18] Evidently, steric factors are important in controlling the degree of association and solvation.

Few studies have been directed toward determining the structures of secondary lithamides in solution. Kimura and Brown[19] showed by ^{1}H, ^{7}Li NMR and isopiestic and cryoscopic molecular weight determinations that lithium bis(trimethylsilyl)amide is dimeric in benzene and an equilibrium mixture of monomer and dimer in diethyl ether and tetrahydrofuran (THF). Hogen-Esch and Jenkins[20] have studied α-lithio-2-ethylpyridine, which formally contains the enamide moiety. Conductivity measurements show it to be an ion pair. Since, in THF, there is little difference between its ^{13}C chemical shifts and those of the corresponding sodium and potassium salts, it is likely that it is monomeric. It exists in solution as *E* and *Z* isomers indicating a planar structure with a high barrier to rotation about C(2)–C(α) (a high barrier is also present in α-lithio-2-picoline[21]). These systems are, therefore, probably π-type ion pairs with structures similar to the triethylenediamine solvate of benzyllithium[22] and to the diethyl ether solvate of α-lithio-α-trimethylsilyl-2-picoline and the TMEDA solvate of α-lithio-α,α'-bis(trimethylsilyl)-2-picoline.[23] Bauer and Seebach[24] have determined, cryoscopically, the degrees of aggregation of several secondary lithium amides in THF at −108 °C. They showed that lithium diisopropylamide is a mixture of a dimer and monomer, while the lithio derivative, **1**, of Meyers'[8] oxazoline is a dimer with one THF per lithium. Of particular interest in the present context is Schollkopf's reagent, **2**,[9b] a lithium dienamide which, at 0.1 M, was found to be a 5:1 mixture of monomer and dimer even though it crystallizes as a trisolvated dimer.[25] Read, Barr, Mulvey, and Snaith[18b] have examined solvated and unsolvated lithium imides (RR′C:NLi) and lithium dibenzyl- and dicyclohexylamines in the nonpolar solvent benzene. On the basis of cryoscopic measurements and ^{7}Li and ^{1}H NMR studies, they concluded that the degree of association found in the solid state can change on dissolution in benzene.



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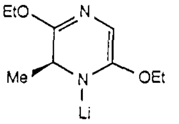

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For mechanistic studies, information concerning aggregate structures and equilibria will often be required over a wide range of conditions. The most useful criterion for lithium ambident anion salts in weakly polar, aprotic solvents is probably provided by ^{13}C chemical shift data of a *remote carbon atom*(*s*) which shares the π-negative charge. This is illustrated by earlier studies of lithium phenolates.[10] Characteristic ^{13}C chemical shifts have also been observed for enolates[26] and for phenyllithium.[27] Data are usually obtainable over wide ranges of temperatures and concentrations in a variety of such solvents. Before the ^{13}C chemical shift criterion can be applied to a particular class of anions, however, bench mark values for the various possible aggregate structures are needed. It is, therefore, necessary to make limited use of alternative, absolute methods for establishing aggregate structure, methods which generally are more time consuming and only applicable over a narrow range of conditions. One such method, which allows an unambiguous determination of aggregate structure, is the ^{6}Li/^{7}Li and ^{1}H/^{2}H isotope replacement technique for the determination of a definitive number of internuclear distances from spin–lattice relaxation rates. This procedure has been successfully applied to phenyllithium in solution.[27] The method, is, however, not always readily implemented. A more general approach is the use of colligative methods for determination of the degree of association, *n*.[28] The structures do not, however, necessarily follow from a knowledge of *n*. For example, a tetramer could be monocyclic or cubic, and a monomer could be either a π- or σ-type ion pair. Such data, however, can often be combined with ^{6}Li/^{13}C[34] or ^{6}Li/^{15}N spin–spin multiplicities to arrive at un-

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equivocal structures, although the latter, alone, do not permit a distinction between dimers and *monocyclic* trimers, tetramers, or higher oligomers. In the present study, $^6Li/^{15}N$ multiplicities, *n* (determined barometrically), and ^{13}C chemical shifts have been used to study the solution structures of lithium amides.

The degree of solvation of aggregates is also germane to any mechanistic study. Direct determination of the degree of solvation of lithium in aggregates is, in principle, available from spin–lattice relaxation data for solute and solvent nuclei, but in practice, a number of assumptions must be made. This approach has been applied to one carefully designed system (lithium phenolate in pyridine) and then only with limited success.[10] The observation of a biphasic temperature dependence of chemical shifts which is *independent of concentration* may be taken as evidence of an equilibrium between differently solvated species having the same degree of aggregation, particularly if the equilibrium involves a substantial (80–160 $J{\cdot}mol^{-1}{\cdot}deg^{-1}$) entropy change. This has been demonstrated for lithioisobutyrophenone in dioxolane and THF.[4a] Similar studies have now been carried out with lithium enamides. These experiments do not, of course, establish the absolute degrees of solvation although plausible values can be suggested. In the following paper, we show that ^7Li nuclear quadrupole coupling constants can provide additional evidence regarding the degree of solvation.

We now report the application of the above principles to the study of the solution structures of lithium salts of aromatic secondary amines in weakly polar aprotic solvents.

Experimental Section

Materials. Diethyl ether and tetrahydrofuran were refluxed over sodium benzophenone ketyl and distilled immediately prior to use. Triethylamine, *N,N,N′,N′*-tetramethylethylenediamine, and benzene were fractionally distilled from freshly ground calcium hydride under nitrogen. Hexamethylphosphoric triamide and all amines were vacuum distilled from freshly ground calcium hydride and stored under a nitrogen atmosphere. *N*-Methylaniline, *N*-isopropylaniline, indoline, tetrahydroquinoline, and 2-methyltetrahydroquinoline were purchased from Aldrich. *N-tert*-Butylaniline was prepared by the method of Hickinbottom.[35] 2-Methylindoline was prepared by trimethylamine–borane reduction of the corresponding indole by the method of Berger.[36] *N*-Methylaniline-^{15}N and *N*-isopropylaniline-^{15}N were prepared from 50% enriched ^{15}N-labeled aniline by literature methods.[37] *N-n*-Butylaniline and *N*-methoxyethylaniline were prepared from aniline and the corresponding alkyl bromide by the same method.[37] *n*-Butyllithium, 1.6 M in hexane, was obtained from Aldrich and assayed by the usual methods. Lithium-6 isotopomeric salts were generated with *n*-propyllithium-6. The *n*-propyllithium-6 was prepared from dried, degassed *n*-propyl bromide and lithium-6 metal (obtained from Oak Ridge National Laboratory) by literature methods[38] with the following modification: an equivalent amount of alkyl bromide was used and the ether solution was never allowed to rise above 10 °C. The propyllithium-6 was purified by bulb-to-bulb distillation under high vacuum ($\sim 3 \times 10^{-3}$ torr); the receiving flash was sealed by torch and removed from the vacuum manifold. The contents of the flask was transferred, in a glove box, into a septum-capped bottle containing dried, degassed hexane. The propyllithium solution in hexane was removed from the glove box and assayed by the usual methods. All glassware, syringes, and needles were oven-dried and cooled in a desiccator.

Sample Preparation. Method I. The apparatus shown in Figure 1A was attached to the vacuum manifold via hemispherical O-ring joint A and evacuated overnight. The system was back-filled with dry nitrogen, and the port on side arm B was opened; under a strong nitrogen flow, diethyl ether and a 10–15% excess of amine were syringed into the flask. The flask, C, was frozen with liquid nitrogen and side arm B was glass-sealed by torch. The solution was degassed by three freeze–pump–thaw cycles. The flask was then cooled in an ice bath with magnetic stirring, the system back-filled with nitrogen gas, and side arm B reopened; under a nitrogen flow, *n*-butyllithium solution was slowly syringed into the stirred amine solution. The flask was then frozen; side arm B was sealed, and evacuated. The solution was thawed and stirred in an ice bath for ~0.5 h. The solvent was then removed by vacuum transfer. The degassed NMR solvent and lock standard (~10% C_6D_{12}), stored over calcium hydride, was then vacuum transferred into flask C (if the NMR solvent was not diethyl ether, the salt was first "washed" with the appropriate solvent which was then removed), and the flask frozen, sealed, and removed from the manifold at the constriction A. The contents of the flask was drained through sintered frit D into the NMR tube, E. The constriction at the NMR tube was washed by solvent condensation with a cold swab to prevent charring and the tube was frozen, sealed, and removed.

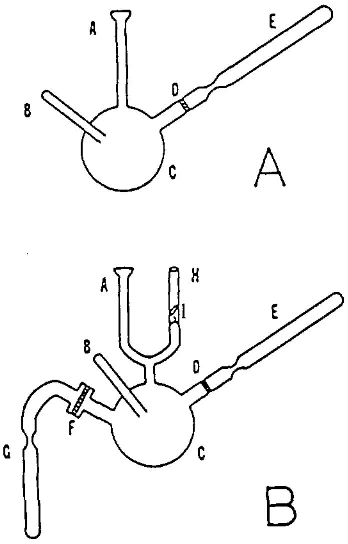

Figure 1. Apparatus for preparing samples of lithium amides for NMR studies.

Table I. Apparent Degree of Association (*n*) of Lithium Indolide in Tetrahydrofuran at 17 °C

concn (M)	*n*	concn (M)	*n*
0.093	1.8	0.198	1.9
0.112	1.8	0.489	1.9
0.156	1.9		

Method II (Amine Free Salts). The lithium salts were generated as in method I but using the apparatus shown in Figure 1B. Purification of the salt was accomplished by vacuum-line recrystallization or precipitation from diethyl ether/toluene or THF/toluene as follows. A storage bulb containing the degassed solvent system (over CaH_2) was vacuum transferred into reaction flask C. The salt was recrystallized or precipitated by slow evaporation of the solvent while cooling. The reaction apparatus was then sealed and removed from the manifold at constriction A. The supernatant was decanted through coarse porosity frit F, into tube G. An aliquot of solvent was condensed back into flask C from tube G, by cooling with liquid nitrogen; the salt was washed with solvent and decanted through frit F. The constriction in tube G was washed by solvent condensation with a cold swab and the contents of the tube frozen. The tube was sealed and removed from the apparatus. Tube G was opened and the contents quenched with H_2O and titrated to determine the amount of salt remaining in flask C. The apparatus was glass blown onto the vacuum line at break-seal tube H, containing a glass-enclosed metal bar I. The tube was evacuated and the glass seal broken with the metal bar. The preparation was completed as described in method I.

Barometry. The apparatus and procedure have been previously described in detail.[10] The system was calibrated with THF and benzil as solvent and solute, respectively. The lithium salt of indoline was prepared in THF by *n*-butyllithium titration using the tosylhydrazone of 1,3-diphenylpropanone as an indicator in an ice/NaCl/H_2O bath as described in the above reference. The lithium salt of *N*-methylaniline was prepared by method II. The temperature was maintained at 17.0 ± 0.1 °C.

NMR Spectroscopy. High-field ^{13}C spectra were obtained using a Bruker WM360 spectrometer. Variable-temperature spectra are uncalibrated. ^{13}C chemical shifts are reported in ppm relative to internal

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Table II. ^{13}C Chemical Shifts for Lithium Amides

compound	solvent	concn (M)	temp (°C)	C(1)	C(2/6)[a]	C(3/5)	C(4)
6 (R = CH_3)	Et_2O	0.54	26	162.6	112.1	130.4	111.2
			−100	162.6	115.4	131.2	110.3
					109.0	129.2	
	Et_2O/HMPT[b]	1.5	26	163.7	112.3	128.1	103.1
	C_6D_6/TMEDA[c]	0.4	26	163.7	115.8	131.1	109.3
					108.8	*d*	
	THF	0.16	26	163.9	112.9	129.2	108.4
			−60	163.7	119.4	129.8	108.0
					107.2	127.3	
6 (R = *n*-Bu)	THF	0.31	26	162.5	112.7	129.7	108.1
	e		−100	162.2	117.1	129.6	103.8
					106.5	127.9	
				163.2	119.9	*f*	107.7
					109.1	*f*	
6 (R = Pr^i)	Et_3N	0.33	26	160.4	114.1	130.5	111.3
	Et_2O	0.28	26	160.7	113.0	130.6	110.7
			−100	160.0	113.7	131.8	110.4
					111.3	130.4	
	THF	0.11	26	161.6	112.7	129.5	106.1
			−100	161.1	116.7	129.7	103.6
					107.0	128.1	
6 (R = Bu^t)	THF	0.31	26	161.1	115.6	128.8	104.6
			−110	160.8	119.1	128.5	103.1
					112.2	128.1	
	Et_2O	0.56	26	159.6	118.3	129.9	111.0
	g		−110	159.6	117.9	130.3	110.8
				159.1	117.7	130.0	110.7
6 (R = $CH_3OCH_2CH_2$)	THF	0.31	26		113.4	129.3	110.3
			−100	161.9	119.2	129.7	107.9
					108.7	128.6	

compound	solvent	concn (M)	temp (°C)	C(3)	C(4)	C(5)	C(6)	C(1)	C(2)
7 (R = H; *n* = 1)	THF	0.73	26	123.3	108.1	127.5	106.7	167.8	131.4
			−100	123.1	107.5	127.3	107.1	168.1	
	Et_2O	0.33	26	124.3	110.8	128.2	104.4	166.2	
	h		−120	124.1	109.7	128.1	105.1	166.7	131.9
				123.9	109.6	*i*	106.8	167.1	131.8
7 (R = CH_3; *n* = 1)	THF	0.45	26	123.9	108.6	128.0	104.3	166.1	130.7
	j		−95	123.6	108.1	127.5	107.9	165.8	129.8
				122.7	103.2	128.0	103.0	166.6	*k*

compound	solvent	concn (M)	temp (°C)	C(3)	C(4)	C(5)	C(6)	C(1)	C(2)
7 (R = H; *n* = 2)	THF	1.0	26	120.4	109.0	127.1	114.7	158.9	130.1
			−60	119.0	107.5	125.7	118.1	160.0	129.6
7 (R = CH_3; *n* = 2)	THF	0.27	26	119.4	107.6	127.3	114.0	158.6	129.7
	l		−60	116.7	103.0	126.7	114.6	158.9	128.9

[a] In cases where both signals are separately observed, the down field resonance is assigned to the carbon *syn* to the Li, on the basis (ref 40) that it is more strongly coupled to ^{15}N in the *N*-methyl- and *N*-isopropylanilides. [b] 4 equiv of HMPT. [c] 1 equiv TMEDA. [d] Obscured by C_6D_6. [e] Monomer:dimer = 2.8:1. [f] Obscured by monomer resonance. [g] Relative intensities of 110.8:110.7 ppm = 1.3:1 at 0.31 M 110.8:110.7 ppm = 1.3:1. [h] Relative intensities of 124.1:123.9 ppm = 1:2.2, at 0.17 M 124.1:123.9 ppm = 1:2.1. [i] Unresolved. [j] Monomer:dimer = 1:1.4, at 0.22 M monomer:dimer = 1.3:1. [k] Obscured by dimer resonance. [l] Evidence of dimer formation.

C_6D_{12} = 26.40 or THF = 26.50 ppm. ^{15}N spectra were obtained on a Bruker WP200 spectrometer and are referenced to external [^{15}N]-methylaniline (52.80 ppm).[39]

Results and Discussion

Lithium Indolide (Lithioindoline, 7, R = H; *n* = 1). The determination of the degree of association of the salt in THF by vapor pressure barometry establishes it as a dimer at 17 °C in the concentration range 0.1–0.5 M (Table I). We have also measured the ^{13}C chemical shifts for this system as a function of temperature. The shifts for all carbon atoms are essentially constant in the range −100 to −40 °C. Above −40 °C, however, significant temperature dependencies of chemical shifts are observed. In particular, the shielding of C(4) and C(6) exhibit marked decreases and increases, respectively (Table II), and $\Delta\delta(=\delta_{C(4)} - \delta_{C(6)})$ is therefore a sensitive parameter with which to examine the changes which occur with increasing temperature (Figure 2). The chemical shift of C(4), which is well removed from the site of ion pairing, will only respond to changes in π-charge density. The observed in-

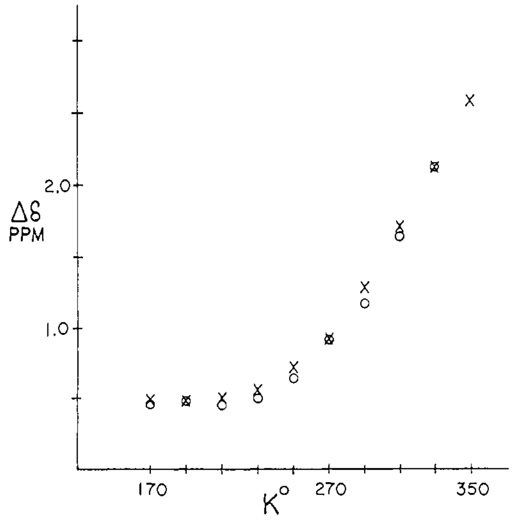

Figure 2. The temperature dependence of the difference (Δδ) in chemical shifts between C(4) and C(6) of 0.16 (O) and 0.75 M (X) lithium indolide in tetrahydrofuran.

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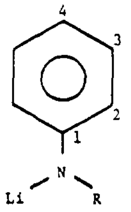
(39) Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*, 1st ed.; Wiley: New York, 1979; p 57.

(40) Reference 39, pp 125.

crease with increasing temperature, therefore, corresponds to decreased charge density at C(4) and, presumably, to increased localization of the anion charge on nitrogen. This phenomenon cannot, however, be ascribed to changes in the degree of association since it is independent of concentration (Figure 2). We, therefore, conclude that the solvation of the dimer is decreasing at the higher temperatures in accordance with the following equilibria (A ≡ anion, S ≡ solvent), since solvation of lithium will be exothermic.

$$\underset{3}{[\mathrm{A(LiS_2)}]_2} \rightleftharpoons \underset{5}{[\mathrm{A(LiS_2)A(LiS)}]} \rightleftharpoons \underset{4}{[\mathrm{A(LiS)}]_2}$$

We make the assumption that at very low temperatures the species **3**, in which the lithium atoms have obtained a formal coordination number of 4, prevails. Since at 80 °C (the boiling point of the solvent) the chemical shifts are still strongly temperature dependent, the limiting chemical shifts for **4** cannot be determined for S = THF.



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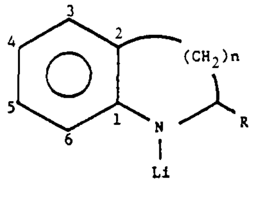
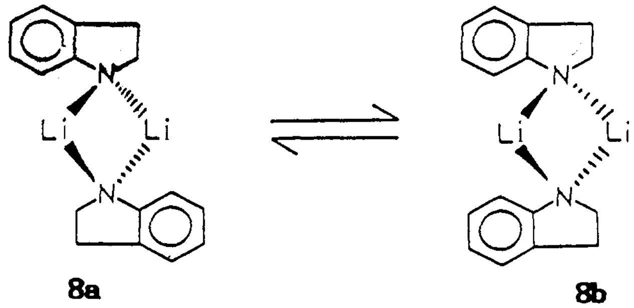


7

We have also examined the ^{13}C spectrum of this salt in diethyl ether as a function of concentration and temperature (Table II). $\delta_{C(4)}$ exhibits only a weak, linear dependency on temperature (78 × 10^{-4} ppm/°C)[41] and its value, 110.8 ppm, at room temperature corresponds to a lower charge density than found for the species **3** (S = THF) at low temperatures in THF. We, therefore, assign the structure as **4** (S = Et$_2$O).

At low temperature (∼−100 °C) the ^{13}C spectrum of the species in ether exhibits dynamic NMR behavior and, at −120 °C two unequally populated species are observed. The relative concentrations of these two species are the same for 0.33 and 0.17 M solutions, and they differ mainly in the chemical shifts of C(6) and C(1), the shifts of C(4) being almost identical. These observations exclude differences in aggregation or solvation for the two species, and we, therefore, postulate that they are *E* and *Z* isomers (**8**) for which stereomutation is slow on the ^{13}C NMR time scale at −120 °C. No evidence for such stereoisomerism is observed for the species in THF down to −100 °C. This could be due to the existence of only one geometric isomer or, more likely, to a more rapid isomerization of the THF solvate. It has been reported[15] that the diisopropylamine solvate of the lithium salt of *N*-(1-cyclohexenyl)aniline in toluene at −54 °C exhibits a similar phenomenon and that this too is a manifestation of *E*/*Z* isomerism.



8a **8b**

Lithium 2-Methylindolide (7, R = CH$_3$; *n* = 1). At −95 °C in THF, this compound exists as two species which exchange slowly on the ^{13}C NMR time scale (Figure 3a). These species are well characterized by their $\delta_{C(4)}$ values (Table II). One species, which predominates at high concentration, has $\delta_{C(4)}$ 108.1 ppm and is assigned as the dimeric species **3** (S = THF) because of the close correspondence of this value to that of lithium indolide under similar conditions. The second species ($\delta_{C(4)}$ 103.2 ppm), which is the major one at low concentrations, must, therefore, be a monomeric ion pair, presumably ALiS$_3$.

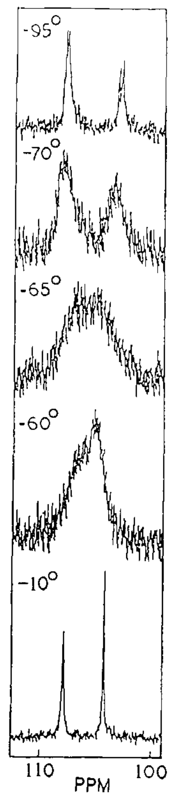


Figure 3. The C(4) and C(6) region of the 90.52-MHz ^{13}C spectrum of lithium 2-methylindolide in tetrahydrofuran at (a) −95, (b) −70, (c) −65, (d) −60, and (e) −10 °C.

In the temperature range −70 to −60 °C, the rates of exchange between these two aggregates become comparable with the ^{13}C NMR time scale and coalescence of the pairs of signals for C(4) and C(6) is observed (Figure 3b–d). Attempts to analyze these spectra in order to extract thermodynamic and kinetic parameters proved difficult. Whereas the broadened spectra below coalescence could be simulated reasonably well in terms of the low-temperature chemical shifts ($\Delta G^{\ddagger}_{208} \sim 38$ kcal mol^{-1}), spectra obtained at higher temperatures could not. It is evident from a comparison of Figure 3, parts a and d, that the chemical shift of C(4) in the dimer is temperature sensitive in the same way observed for lithium indolide in THF. The conversion of **3** to **4**, however, occurs at lower temperatures in the case of the 2-methyl analogue and, for example, a 0.45 M solution at 23 °C has $\delta_{C(4)}$ 110.6, which is close to the value expected for species **4**.

Lithium *N*-Methylanilide. Since a meta alkyl substituent has almost no effect on the ^{13}C chemical shift of a benzenoid carbon atom,[43] it is expected that, for a given type of aggregate, the chemical shifts of C(4) in *N*-alkylanilides and indolides will be the same. The value of $\delta_{C(4)}$ for lithium *N*-methylanilide in diethyl ether (Table II) is, therefore, indicative of species **4** (S = Et$_2$O). That this species is a dimer is consistent with the observation that the ^{15}N resonance of the ^{6}Li,^{15}N isotopomer is resolvable at −100 °C into a 1:2:3:2:1 pentuplet (*J* = 3.8 Hz) (Figure 4a) indicating that each nitrogen atom is attached to two lithium atoms. The insensitivity (71 × 10^{-4} ppm/°C) of $\delta_{C(4)}$ with temperature suggests that species **4** predominates even at low temperatures. With this salt, and most of the other *N*-alkylanilides discussed below, the

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[41] Monotonic changes in $\delta(^{13}\mathrm{C})$ with temperature of the order of 10–80 × 10^{-4} ppm/°C are common and are not necessarily indicative of equilibria between two or more species.[42]

[42] Lambert, J. B.; Vagenas, A. R.; Somani, S. *J. Am. Chem. Soc.* **1981**, *103*, 6398. Maple, S. R.; Allerhand, A. *J. Magn. Reson.* **1986**, *66*, 168.

[43] Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; Wiley: New York, 1980; pp 111.

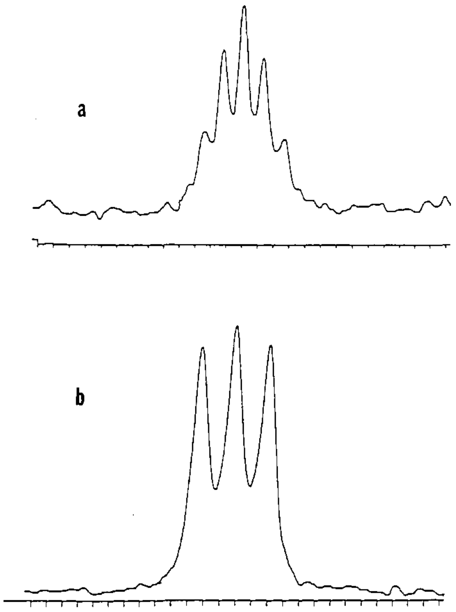

Figure 4. The ^{15}N resonance at 20.3 MHz of (a) lithium [$^{15}N_1$]-*N*-methylanilide in diethyl ether at −100 °C and (b) lithium [$^{15}N_1$]-*N*-isopropylanilide in tetrahydrofuran at −80 °C.

Table III. Apparent Degree of Association (*n*) of Lithium *N*-Methylanilide in Tetrahydrofuran at 17 °C

concn (M)	*n*	concn (M)	*n*
0.053	1.5	0.110	1.6
0.062	1.5	0.149	1.7
0.078	1.5	0.183	1.8
0.093	1.6		

rate of rotation of the phenyl group about the C–N bond becomes comparable with the ^{13}C NMR time scale below room temperature so that, at low temperatures, two sets of resonances are observed for C(2) and C(3). We have not yet studied these rate processes because their rates are of the same order as exchange of the organic moiety between salt and free amine. Scrupulously pure samples will, therefore, be required in order to avoid catalysis of rotation through the intermediacy of free amine.

The system in THF is more complex. The results of vapor pressure barometric measurements (Table III) indicate that, in the concentration range 0.05–0.18 M at 17 °C, both dimer and monomer coexist with K_{eq} (17 °C) ~ 70 M^{-1} for 2 monomer ⇌ dimer. Because of poor solubility, it was not possible to reach temperatures below which interaggregate exchange was slow enough to observe $^6Li,^{15}N$ splittings or the ^{13}C resonances of the individual components. At −60 °C, however, there is broadening and a shift to higher field (Table II) of the C(4) resonance, suggesting the presence of significant concentrations of monomer.

It proved possible to prepare a 1:1 solvate of the salt with *N,N,N′,N′*-tetramethylethylenediamine which is soluble in benzene. In this solvent $\delta_{C(4)}$ is 109.3 ppm which is close to the values for species **3** in the indolide series. In another experiment, 4 equiv of hexamethylphosphoric triamide (HMPT) was added to an Et$_2$O solution of lithium *N*-methylanilide. The resulting species has $\delta_{C(4)}$ 103.1 ppm which, in turn, is close to the value found for monomeric lithium 2-methylindolide, suggesting it is the contact ion pair ALiS$_3$ (S = HMPT).

Lithium *N*-*n*-Butylanilide. This salt is sufficiently soluble in THF to permit low-temperature studies. At −100 °C, it exists as two species characterized by values for $\delta_{C(4)}$ of 103.8 and 107.7 ppm. The former is clearly a monomer, presumably the trisolvated species ALiS$_3$, and the latter, in view of the close agreement between its value for $\delta_{C(4)}$ and that (107.5 ppm) for $\delta_{C(4)}$ of lithium indolide under the same conditions, must be the species **3** (S = THF).

Lithium *N*-Isopropylanilide. The chemical shift of C(4) for the salt in diethyl ether indicates that it exists as species **4** (S = Et$_2$O) over the entire accessible temperature range. Because of poor solubility, it was not possible to reach temperatures low enough to resolve $^6Li,^{15}N$ splittings. At −90 °C, however, the ^{15}N chemical shift was found to be in good agreement with that observed for the analogous *N*-methylanilide system (Table IV). Species **4** also prevails in triethylamine at room temperature.

Table IV. ^{15}N NMR Parameters of Lithium [$^{15}N_1$]-*N*-Methyl- and [$^{15}N_1$]-*N*-Isopropylanilides

	PhNLiCH$_3$	PhNLiCH(CH$_3$)$_2$	
solvent	Et$_2$O	Et$_2$O	THF
concn (M)	0.54	0.28	0.11
temp, °C	−80	−90	−80
$\delta(^{15}N)$, ppm	90.7	127.0	152.5
$\Delta\delta^a$	37.9	40.4	65.9
$J(^6Li,^{15}N)$, Hz	3.8	*b*	7.5

[a] $\Delta\delta = \delta(^{15}N)_{salt} - \delta(^{15}N)_{amine}$. [b] Salt crystallized out of solution.

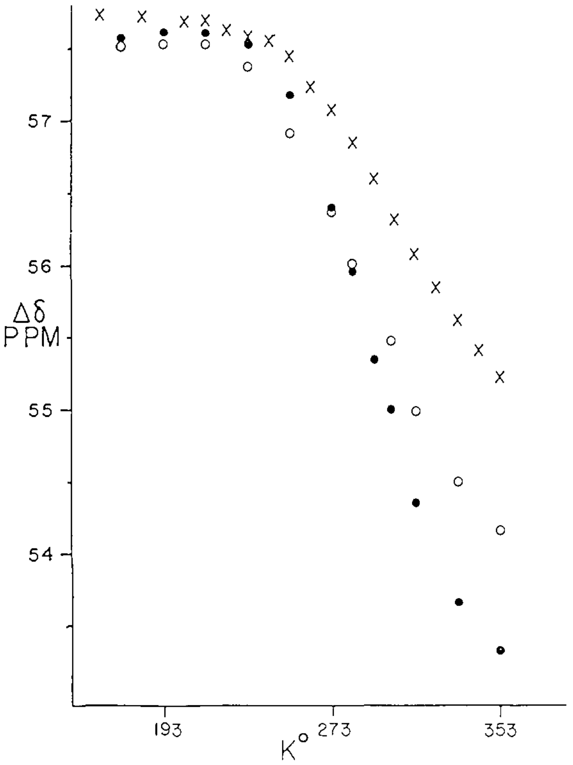

Figure 5. The temperature dependence of $\Delta\delta = (\delta_{C(1)} - \delta_{C(4)})$ for 0.11 M (○) and 0.89 M (●) lithium *N*-isopropylanilide and 0.31 M (×) lithium *N*-*tert*-butylanilide in tetrahydrofuran.

The solubility of the salt in THF at low temperatures was better, and at −80 °C the ^{15}N resonance was observed as a 1:1:1 triplet (Figure 4b; Table IV). The species is exclusively a monomer ALiS$_3$. As the temperature is raised, no evidence of dynamic behavior affecting the C(4) resonance is observed [dynamic behavior associated with phenyl rotation is observed for C(2) and C(3)]. There is, however, a progressive shift of the C(4) signal to lower fields, and the magnitudes of the chemical shift changes are concentration dependent as is best seen from plots of ($\delta_{C(1)} - \delta_{C(4)}$) vs. temperature (Figure 5). At 80 °C, values of $\delta_{(4)}$ for 0.11 and 0.89 M solutions are 107.4 and 108.2 ppm, respectively, indicating that some monomer is present at this temperature, at least in 0.11 M solution. It is not feasible to analyze further the data presented in Figure 5 because they result from the coexistence of **3**, **4**, ALiS$_3$, and possibly ALiS$_2$.

It is of interest to note that $J(^6Li,^{15}N)$ for the monomeric species is twice as large as that for the dimeric form **4** (S = Et$_2$O) of lithium *N*-methylanilide (Table IV).

Lithium *N*-*tert*-Butylanilide. As with the other systems described above, this salt in diethyl ether exists as dimer **4** (S = Et$_2$O) characterized by $\delta_{(4)}$ ~111 ppm, which shows little variation (7 × 10^{-4} ppm/°C) over the temperature range −100 to 26 °C. At

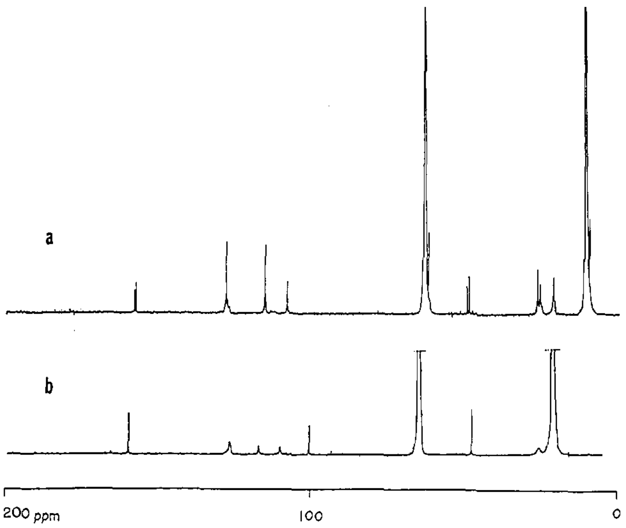

Figure 6. The 90.52-MHz ^{13}C spectrum of lithium *N-tert*-butylanilide: (a) 0.56 M in diethyl ether at −110 °C, (b) 0.31 M in tetrahydrofuran at −110 °C.

−110 °C, the spectrum corresponds to two unequally populated species. Because the populations are concentration independent and in view of the close similarity of the chemical shifts of the two sets of peaks, particularly those of C(4), we conclude that the species are *E* and *Z* isomers of **4** (S = Et_2O) analogous to those (**8**) of lithium indolide in ether. Such isomerism is not observed for the other lithium anilides at the same temperature and field strength. One other interesting feature of this species is that rotation of the phenyl ring remains fast on the NMR time scale even at −110 °C (Figure 6a). This is presumably a result of steric destabilization of the ground state due to the presence of the *tert*-butyl group.

Lithium *N-tert*-butylanilide exists as the monomer $ALiS_3$ in THF at −110 °C. The chemical shift difference $\delta_{C(1)} - \delta_{C(4)}$, shows a biphasic temperature dependence (Figure 5). The limiting high-temperature value (ca. 105.5 ppm) is, however, significantly lower than the values 107.7 and 111 ppm expected for species **3** and **4**, respectively. We conclude that the species at the high-temperature limit is the disolvated monomer, $ALiS_2$. This assignment receives strong support from studies of ^7Li nuclear quadrupole coupling constants presented in a subsequent paper.[44] Rotation of the phenyl ring is also rapid in this solvent, although two rotamers are observable at −110 °C (Figure 6b). Another interesting feature of the spectrum is the broad signal of the methyl carbons. Evidently the rate of rotation of the *tert*-butyl group is of the order of the ^{13}C NMR time scale at this temperature which is consistent with its proximity to the bulky trisolvated lithium cation.

Lithium *N*-(2-Methoxyethyl)anilide. This compound exists as only a dimer in THF at −100 °C. This is in contrast to the isosteric *N-n*-butyl analogue which is an approximately 3:1 mixture of the monomer ($ALiS_3$) and the dimer **3** (S = THF) under the same conditions. The C(4) chemical shift (107.9 ppm) corresponds to species **3**, but one of the solvent molecules on each lithium cation is presumably replaced by the side arm, a process which evidently stabilizes the dimer with respect to the monomer.

Lithium 1,2,3,4-Tetrahydro- and 2-Methyl-1,2,3,4-tetrahydroquinolides. Data for these two salts in THF are included in Table II. It is seen that they behave in a manner very similar to that of the indolides.

Structures of Lithium Arylamide Ion Pairs. The above results, while defining degrees of aggregation and solvation, provide little information regarding molecular geometries and electronic structure. $LiNH_2$ and its oligomers have been the subject of intensive study by Schleyer and his collaborators,[45] using ab initio methods. Their findings, even though solvation was not included, show that the dimer is a planar Li_2N_2 array with the four hydrogens in a plane perpendicular to it. Since the calculated geometries are in good agreement with the X-ray structures of $[Li(NR_2)\cdot Et_2O]_2$ for both R = $(CH_3)_3Si$[11] and $PhCH_2$,[12] including the observed acute Li–N–Li angle (~75°), it is reasonable to conclude that both **3** and **4** have similar geometries. The calculated energy of the totally planar structure for $(LiNH_2)_2$ is some 120 kJ higher than the perpendicular geometry corresponding to a barrier for the interconversion of the type **8a** ⇌ **8b**. The actual barrier for **8** is certainly much less than this, and the process probably involves a solvent mediated ring opening.

The picture which appears to emerge from the theoretical studies[45] of $(LiNH_2)_n$, and also of organolithium compounds, is that the Li–X bonding is largely ionic with perhaps some small contribution associated with multicenter covalent character in the cases of aggregates. It is, therefore, of interest to consider the magnitudes of $^6Li,^{15}N$ spin–spin couplings in the light of this conclusion. For the monomer $LiA(THF)_3$ derived from isopropylaniline, the observed value of 7.5 Hz is very nearly equal to the value of 7.6 Hz obtained by multiplying $^1J(^{13}C,^{15}N)$ for *N*-methylaniline[46] by $\gamma(^6Li)/\gamma(^{13}C)$, although less than 12.8 Hz, derived from $^1J(^1H,^{15}N)$ in the same compound. The smaller value (3.8 Hz) for the dimeric species **4** is consistent with the larger calculated bond lengths and, presumably, increased ionic character of the Li–N bonds in $(LiNH_2)_2$ compared with those in the monomer (1.94 and 1.75,[45] respectively, at the 6-31G* level).[47] The fact remains, however, that the couplings in both the monomer and dimer are similar to that found for covalent bonds. The important question, therefore, remains as to what extent the magnitudes of one-bond couplings between first-row (or hydrogen) elements reflects the covalent character of the bond.

Recently, Dietrich, Mahdi, and Knorr[48] have obtained the X-ray structure of the ether solvate of lithium *N*-(3,3-dimethylbut-1-en-2-yl)anilide $[PhNLiC(Bu^t):CH_2]$. It has the dimer structure **4**. An interesting structural feature in the solid state is the participation of the aromatic system in an apparent π-bonding of lithium across the 1 and 2 positions of the phenyl ring, although the essentially σ character of the Li_2A_2 framework is maintained. This type of bonding, however, is not observed in the solid-state structure of lithium (1-cyclohexenyl)anilide which also is an $Li_2A_2S_2$ system (S = diisopropylamine).[15] A π-type interaction is presumably possible in the systems to which we have assigned the structures **4**, **5**, and $LiAS_2$. If this is the case, however, the cation would appear to interact much more strongly with the nitrogen than with the carbon terminus of the "π-allyl" system, since no $^6Li,^{13}C$ coupling is observed. Furthermore, the absence of observable restricted rotation of the phenyl group in **4** when A is the *N-tert*-butylanilide ion, even at −110 °C, suggests that, at least in this system, the π-interaction is energetically unimportant.

Conclusions

The lithium amides studied here are seen to form a variety of aggregates which conform to the equilibria:

$$\underset{\mathbf{9}}{LiAS_3} \rightleftharpoons \underset{\mathbf{10}}{LiAS_2} \rightleftharpoons \underset{\mathbf{3}}{Li_2A_2S_4} \rightleftharpoons \underset{\mathbf{5}}{[Li_2A_2S_3]} \rightleftharpoons \underset{\mathbf{4}}{Li_2A_2S_2}$$

We presently have no direct evidence for the mixed solvate **5**, since, at temperatures at which it is likely to occur, all species will exchange rapidly on the NMR time scale, but the known crystallographic structure **2** is evidence for the possibility of its ex-

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[44] Jackman, L. M.; Scarmoutzos, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.*, following paper in this issue.

[45] Sapse, A.-M.; Kaufmann, E.; Schleyer, P. v. R.; Gleiter, R. *Inorg. Chem.* **1984**, *23*, 1569. Sapse, A.-M.; Raghavachari, K.; Schleyer, P. v. R.; Kaufmann, E. *J. Am. Chem. Soc.* **1985**, *107*, 6483.

[46] Axenrod, T. In *Nitrogen NMR*; Witanowski, M., Webb, G. A., Eds.; Plenum Press: New York, 1973; p 278.

[47] Whiteside, R. A.; Frisch, M. J.; Benkley, J. S.; Defrees, D. J.; Schlegel, H. B.; Raghawachari, K.; Pople, J. A. *Carnegie Mellon Quantum Chemistry Archive*, 2nd ed.; Carnegie Mellon: Pittsburgh, 1981.

[48] Dietrich, H.; Mahdi, W.; Knorr, R. *J. Am. Chem. Soc.* **1986**, *108*, 2462.

Table V. Solution Structures of the Lithium Enamides **7** and **6**

anion (A)	structure	solvent (S)
6 (R = CH_3)	$ALiS_3$	HMPT/Et_2O; THF[a]
	$A_2Li_2S_2$	Et_2O
	$A_2Li_2S_4$	THF; TMEDA/C_6H_6
6 (R = *n*-Bu)	$ALiS_3$	THF
	$A_2Li_2S_4$	THF
6 (R = Pr^i)	$ALiS_3$	THF
	$A_2Li_2S_2$	Et_2O; Et_3N; THF[b]
	$A_2Li_2S_4$	THF[b]
6 (R = Bu^t)	$ALiS_2$	THF
	$ALiS_3$	THF
	$A_2Li_2S_2$	Et_2O
6 (R = $CH_3OCH_2CH_2$)	$A_2Li_2S_4$	THF
7 (R = H; *n* = 1)	$A_2Li_2S_2$	Et_2O; THF[a]
	$A_2Li_2S_4$	THF
7 (R = CH_3; *n* = 1)	$ALiS_3$	THF
	$A_2Li_2S_2$	THF[a]
	$A_2Li_2S_4$	THF
7 (R = H; *n* = 2)	$A_2Li_2S_2$	THF[a]
	$A_2Li_2S_4$	THF
7 (R = CH_3; *n* = 2)	$ALiS_3$	THF
	$A_2Li_2S_2$	THF[a]
	$A_2Li_2S_4$	THF

[a] Complete conversion to this species was not attained at the temperatures studied. [b] At certain temperatures, coexistence of $A_2Li_2S_2$, $A_2Li_2S_4$, $ALiS_3$, and, possibly, $ALiS_2$ is observed (see Figure 5).

istence. Indeed, it is conceivable that the limiting species to which we have assigned structure **4** could, in fact, be **5**. It is also not possible to say whether **10** is necessarily intermediate between **9** and **3**. It is possible that conditions exist in which lithium *N*-isopropylanilide in THF coexists as all five species, but **10** has really only been characterized in the case of the *tert*-butyl analogue. Table V summarizes the structures observed for the various systems investigated.

It is clear that, in the present series of compounds, steric factors play a dominant role in determining their degree of aggregation. This is well illustrated by the *N*-alkylanilide series in which the state of aggregation in THF at <−50 °C decreases from mainly dimer for methyl, through a mixture of monomer and dimer for *n*-butyl, to exclusively monomers for isopropyl and *tert*-butyl. A minimum degree of steric hindrance is evidently provided by pinning back the *N*-alkyl substituent by ring formation as in **7** (R = H, *n* = 1 or 2). The effect of "internal" solvation by an appropriate substituent, such as the 2-methoxyethyl group, is significant. The stabilization of a rather rigid dimer species of type **3** may well play an important role in effecting the high enantioselectivities of reagents such as **1** and **2**.

The role of the solvent is also striking in that the entire series of salts studied here exist exclusively as the dimers **4** (S = Et_2O) in diethyl ether even at temperatures as low as −120 °C. In contrast, for example, lithium indolide in THF is not completely converted from **3** to **4** even at 80 °C. The donicity of diethyl ether, as measured by its heat of complexation with boron trifluoride in methylene chloride,[49] is somewhat less than that of THF ($\Delta H°_{BF_3}$ = −78.77 and −85.36 kJ·mol^{-1}, respectively). Steric factors must, however, play an important role in the effectiveness of the solvent in solvating the dimer since lithium *N*-isopropylanilide in the much more highly donating solvent, triethylamine ($\Delta H°_{BF_3}$ = −135.9 kJ·mol^{-1}), exists only as the dimer **4**.

We have shown that the ^{13}C chemical shifts of "para" carbons are remarkably constant for the different amine structures studied here, provided the degrees of aggregation are the same. A change to lower aggregation is associated with an upfield shift of 4–5 ppm, whereas a decrease in solvation results in a 1–2 ppm shift in the opposite direction. Virtually no change is observed between *E* and *Z* isomeric dimers. The chemical shifts of carbon atoms close to the nitrogen atom are influenced by proximity effects. This is particularly noticeable in the *N*-alkylanilides in which the shifts of the two ortho carbon atoms differ by as much as 12 ppm when the rotation of the phenyl group is slow on the NMR time scale.

The observations of multiplicities due to $^6Li,^{15}N$ one-bond spin coupling are seen to provide important structural information even though the interpretation of the magnitudes of ^1Js is not obvious.

Finally, the systems studied here exhibit a rich variety of dynamic processes which are accessible on the NMR time scale, and which include amine–amide exchange, phenyl ring rotation, interaggregate exchange, and stereomutation in dimers. It is expected that kinetic studies of these processes will throw additional light on the electronic structures and reactivities of the various types of ion pairs and their aggregates.

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Lithium Quadrupole Coupling Constants and the Structures of Organic Lithium Compounds in Solution

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Abstract: The quadrupole splitting constants (QSC), defined as $(1 + \eta^2/3)^{1/2}(e^2Qq_{zz}/h)$, for ^7Li in lithium arylamides, phenolates, and enolates and for several organolithium compounds in ether and tertiary amine solvents are determined from ^7Li and ^{13}C spin–lattice relaxation data. The effect of anisotropic rotational diffusion on the apparent values of QSC is considered. Values of QSC range from 40 to 350 kHz. Empirical correlations between QSC and the degree of aggregation and solvation of lithium are presented. Large differences between QSC for tri- and tetracoordinated lithium are noted. A crude model based on a point charge approximation for calculating the principal field gradients reproduces the qualitative features of the empirical correlations. The degrees of solvation of aggregated lithium salts are discussed.

In the preceding paper,[1] we presented evidence that lithium arylamides exist as either, or both, monomeric and dimeric contact ion pairs in solvents such as tetrahydrofuran (THF) and diethyl ether. In addition, evidence based on the temperature and concentration dependencies of ^{13}C chemical shifts suggests that the degree of solvation of these species can change with temperature, the less highly solvated species presumably being preferred at high temperatures. We had also reported similar temperature effects for tetrameric lithium isobutyrophenone in THF and dioxolane.[2]

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