which had been cooled to approximately −50 °C. When the THF solution became saturated with acetylene, the bulb was submerged in liquid N_2 to condense any residual acetylene. Once all the acetylene was condensed and the solution frozen solid, the bulb was sealed from the line and enclosed in a 500-mL steel bomb. The bomb was submerged in a 90 °C oil bath for 15 h and shaken periodically. The bomb was then cooled in an ice bath and opened. The materials in the bomb were removed and dissolved in about 300 mL of diethyl ether. The solution was dried with magnesium sulfate and gravity filtered. The ether was evaporated under a stream of dry nitrogen. The remaining dark liquid was then vacuum distilled at 30 Torr. A yellow liquid was collected over the temperature range 40–50 °C. Mass spectral analysis is consistent with perdeuteriated [8]annulene (93% isotopic purity) mixed with heptadeuteriated [8]annulene (7% isotopic purity).

Instrumentation. The EPR spectra were recorded at 27 °C on an IBM (Bruker) ER-200D spectrometer equipped with an IBM variable-temperature unit. The 300-MHz NMR spectra of these samples were recorded on a Varian (Gemini) 300-MHz NMR spectrometer. Mass spectral data were collected using a Hewlett-Packard Model 5970 spectrometer connected with a 5790A gas chromatograph. All ^{13}C NMR spectra were recorded at 27 °C with a Varian (Gemini) 300-MHz wide-band spectrometer.

Reductions. Portions of [6]–[8], [6]–[8]-d_7, or [6]-d_5–[8] were placed into separate capillary tubes which were in turn sealed. The tubes containing the substrates were placed into glass apparatuses. After evacuation of an entire apparatus, a freshly distilled alkali-metal mirror was deposited and the portion of the apparatus from which it came was subsequently sealed from the apparatus. Dry THF (with 10% THF-d_8 for NMR lock) or HMPA was then distilled from a storage bulb containing NaK_2, directly into the apparatus. The entire apparatus was then sealed from the vacuum system. The apparatus was then shaken to break the tube containing the substrate and expose the solution to the metal mirror. Samples of the resulting anion-radical or dianion solutions were then poured into side tubes, which were then sealed from the apparatuses and submitted to analysis. NMR samples of the dianions were not sealed from the apparatus until complete reduction to the dianion was indicated by the absence of an EPR signal.

Reaction 5. The reduction of a mixture of C_8H_8 and C_8D_8 with 1 mol of potassium metal/mol of total [8]annulene in THF yields a solution that contains mostly neutral and dianionic materials. Due to the very large equilibrium constant for disproportionation (ca. 10^9),[12] there is very little anion radical present in solution. Thus, any separation of the anionic materials from the neutral materials is in net effect a separation of the dianionic and neutral materials. Further, the ratio of isotopic isomers in the two phases (α) is controlled by the equilibrium constant for reaction 5. A mixture of 2.40 mmol of C_8H_8 and 6.66 mmol of C_8D_8 was reduced by about 7 mmol of potassium metal at room temperature in THF. The solvent and neutral [8]annulenes were removed under reduced pressure (phase 1), and the remaining solid dianion salt was reoxidized with iodine (i.e., $I_2 + K^+_2C_8H_8^{2-} \rightarrow C_8H_8 + 2K^+I^-$) and labeled phase 2. The [8]annulenes from both phases were distilled under vacuum and submitted to NMR and mass spectral analysis, which are consistent with an equilibrium constant of 0.92 at 205 K. The details of this experiment and the confirmation of the equilibrium constant via the techniques discussed in ref 7a will appear in a future communication.

Acknowledgment. We thank the National Science Foundation (Grant CHE-9011801) and the donors of the Petroleum Research fund, administered by the American Chemical Society, for support of this work. We also thank the reviewers for some very helpful comments and suggestions. We also thank NSF for a grant allowing the purchase of the 300-MHz NMR spectrometer.

Registry No. [6]-[8]$^{\bullet-}$, 53318-48-2; [6]-[8]-$d_5^{\bullet-}$, 53318-49-3; [6]-[8]-$d_7^{\bullet-}$, 137516-36-0; [6]-[8], 50277-25-3; [6]-[8]-d_5^{2-}, 137516-38-2; [6]-[8]-d_7^{2-}, 137516-37-1; deuterium, 7782-39-0.

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Solvation of Aggregates of Lithium Phenolates by Hexamethylphosphoric Triamide. HMPA Causes Both Aggregation and Deaggregation

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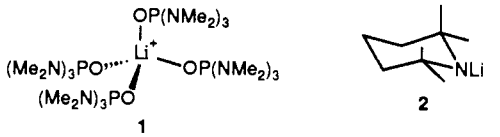
Abstract: The tetramer of lithium 3,5-dimethylphenolate in diethyl ether undergoes sequential solvation by HMPA and is fully converted to the HMPA tetrasolvate by 1 equiv of the cosolvent. Addition of 8 equiv of HMPA does not cause dissociation of the tetramer. Addition of HMPA to lithium *p*-bromo- and *p*-(trifluoromethyl)phenolates in THF results in conversion of their dimers to tetramers and, at high cosolvent ratios, monomers. Two equivalents of HMPA in either THF or diethyl ether converts dimeric lithium 2,6-dimethylphenolate to the monomer. ^{13}C, ^7Li, and ^{31}P chemical shifts for the various HMPA solvates are reported. The ^7Li quadrupole splitting constant for tetrameric lithium 3,5-dimethylphenolate HMPA tetrasolvate is 35 kHz. Lithium *p*-bromophenolate in THF at −120 °C forms a small quantity of a trimer together with the dimer and tetramer.

Hexamethylphosphoric triamide (HMPA)[1,2] and *N,N'*-dimethyl-*N,N'*-propyleneurea[2] are known to catalyze the reactions of lithium salts of carbon acids with electrophiles and often, if the anion is ambident, to result in dramatically altered regiochemistry.[3] The usual protocol calls for the addition of 4 equiv of the cosolvent to solutions of the salts in solvents such as diethyl ether, THF, etc., the idea being that this will lead to the formation of the tetrasolvated lithium cation, e.g. **1**, and an essentially free



1 **2**

anion in place of a contact ion pair or an aggregate thereof. Direct evidence that this does occur in the case of certain organolithium

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compounds has recently been reported by Reich,[4] who previously had characterized the species **1** by the multiplicities (^{7}Li–^{31}P spin–spin coupling) of its ^{7}Li and ^{31}P magnetic resonances, under conditions (−100 °C) for which exchange of HMPA is slow on the NMR time scale.[5] We have also shown that the addition of HMPA to dimeric $LiN(C_6H_5)CH(CH_3)_2$ in Et_2O causes dissociation first to the monomer and then, with ~4 equiv of the cosolvent, to the "triple ion species" $[(RR'N)_2Li]^-\cdot$**1**.[6] Collum and co-workers[7] have demonstrated that dimeric lithium diisopropylamide (LDA) in tetrahydrofuran (THF) forms the HMPA mono- and disolvates but does not give monomeric species even in the presence of 5 equiv of the cosolvent. They have further shown that lithium 2,2,6,6-tetramethylpiperidide (**2**), which coexists as a monomer and dimer in THF at −115 °C, affords a variety of HMPA solvated species including two triple ions, but without substantial change in its degree of aggregation.

In this present study, we examine the effect of HMPA on lithium phenolates, which are good models for lithium enolates, and which can exist as tetramers as well as dimers. We find that addition of HMPA does not necessarily lead to lower aggregates or solvent separated ion pairs and, in some cases, actually induces *increased aggregation.*

Experimental Section

Materials. Solvents were purified and dried as previously described.[8,9] Hexamethylphosphoric triamide was kept over calcium hydride for 24 h. It was then vacuum distilled and stored over a molecular sieve (Aldrich 13X, 8–12 mesh) in a serum capped bottle which had been flushed with dry nitrogen. 4-Bromo- and 3,5- and 2,6-dimethylphenols were purified by recrystallization from hexane immediately prior to use. 4-(Trifluoromethyl)phenol was vacuum distilled prior to use.

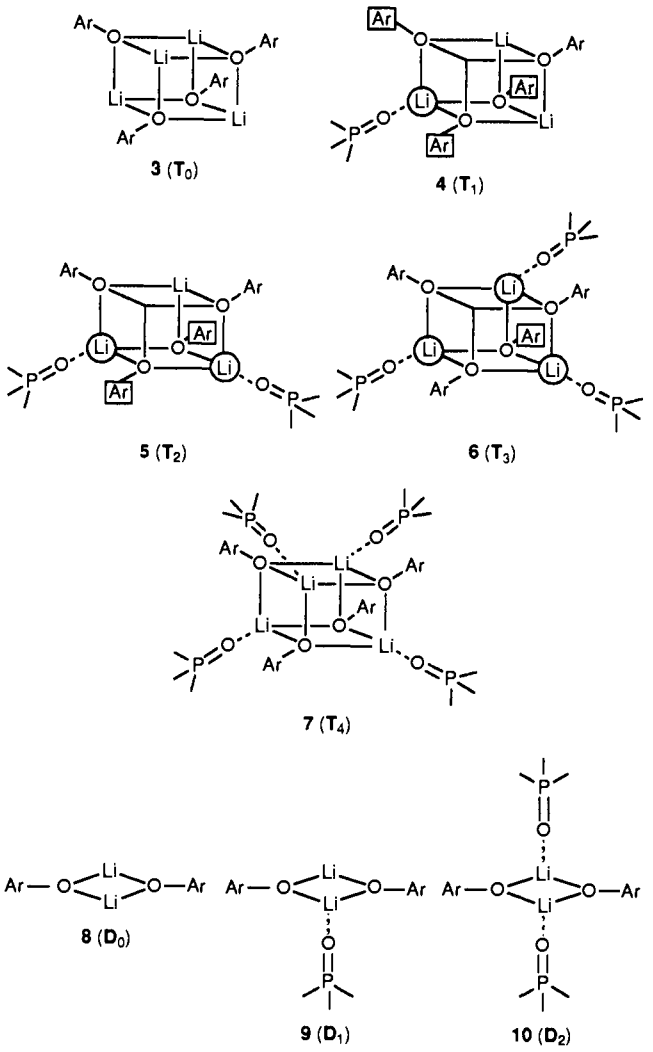
Sample Preparation. Three vacuum line methods for preparing moisture and air free, sealed 5-mm NMR samples of lithium phenolates have been previously described.[8] In method A, the phenol in diethyl ether is titrated with butyllithium in hexane. In method B, methanolic lithium methoxide is used in the titration. The resulting salt was then pumped to dryness and heated under high vacuum at 80 °C for 48 h, to remove the methanol and water. Method C is the same as method A except provision is made for repeated recrystallization of the salt in a sealed apparatus. In the present experiments, introduction of HMPA was achieved by back-filling the vacuum apparatus with dry N_2, opening a port on the side of reaction flask, syringing in the appropriate amount of HMPA through a serum cap, and resealing the port. As it was difficult to introduce accurately known quantities of HMPA, its final concentrations were obtained by integration of the ^{13}C spectra.

Lithium 3,5-dimethylphenolate samples were prepared by method A. Those of lithium 4-bromophenolate were prepared by all three techniques which gave essentially identical results. The samples of lithium 4-(trifluoromethyl)phenolate were prepared by method A but, since the dry salt readily undergoes both thermal and photochemical decomposition, it was necessary to avoid its exposure to light and not to allow it to warm to above 0 °C. Its solutions in the THF appear to be stable for at least a month at ambient temperatures.

NMR Spectroscopy. Spectra were obtained using Bruker AM-300, WM-360, or AM-500 spectrometers. ^{13}C chemical shifts were referenced to internal C_6D_{12} (δ 26.40) or THF (δ 26.50). ^{7}Li (or ^{6}Li) was referenced through *internal* ^{13}C references to ^{7}Li (or ^{6}Li) (δ 0.000) in LiCl (0.30 M) in methanol-*O*-*d* at 23 °C by a previously described technique.[8] In a similar manner, the ^{31}P chemical shifts were referenced to triphenylphosphine (δ −4.81 relative to 85% H_3PO_4) in $CDCl_3$ at 23 °C.

Accurate integration of the C(1) and C(4) ^{13}C resonances of lithium 4-bromophenolate in THF at −120 °C were required for determining the dimer/trimer/tetramer equilibrium constants. These spectra were acquired at 125 mHz. Comparison of a normal broadband decoupled spectrum with that obtained with the decoupler gated off during the relaxation delay indicated that the nuclear Overhauser enhancement for these nonprotonated carbons is negligible, presumably because relaxation by the chemical shift anisotropy mechanism dominates at 11.7 T.

Chart I



Results

In the following presentation, we are concerned with tetrameric (**3–7**) and dimeric (**8–10**) species which for easy reference we will symbolize as $\mathbf{T}_n$ and $\mathbf{D}_n$ (n = number of attached HMPA molecules), respectively. It is assumed that, in the case of the tetramer, lithium sites without HMPA are solvated by the principal solvent. The lithium and carbon nuclei in $\mathbf{T}_1$, $\mathbf{T}_2$, and $\mathbf{T}_3$ exhibit nonequivalence as indicated in the structures **4**, **5**, and **6**, respectively. Unless otherwise stated the samples were observed at −115 to −120 °C. Somewhat above −110 °C chemical exchange is sufficiently rapid to average the ^{7}Li–^{31}P splittings.

Lithium 3,5-Dimethylphenolate/HMPA. This salt exists exclusively as its tetrasolvated tetramer in diethyl ether at −60 °C[9] and, since both its ^{13}C and ^{7}Li chemical shifts are unchanged at −120 °C, we conclude that it also has this structure at the lower temperature. Figure 1 shows the ^{7}Li, ^{31}P, and ^{13}C (of HMPA) magnetic resonance spectra at −120 °C resulting from the addition of increasing amounts of HMPA, and chemical shift and coupling constant data are given in Table I. The ^{7}Li spectra are especially informative since the resonances of those lithium nuclei with attached HMPA appear as doublets and progressive HMPA solvation of the tetramer with increasing cosolvent concentration can be readily traced. An analogous set of resonances (1:1:1:1 quartets resulting from coupling with ^{7}Li ($I = {}^3/_2$) is observed in the ^{31}P spectra. The corresponding ^{13}C spectra, particularly the C(4) resonances, are also in accord with the tetrameric structures. Progressive solvation of the lithium cations by the Lewis base should increase the π-electron densities at the ortho

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Table I. Chemical Shift and Coupling Constant Data for HMPA Solvates of Substituted Lithium Phenolates (0.2 M) at −120 °C[h]

	δ C(1)					δ C(4)				
compd solvent	3,5-Me_2 Et_2O	3,5-Me_2 THF	*p*-Br THF	*p*-CF_3 THF	2,6-Me_2 Et_2O	3,5-Me_2 Et_2O	3,5-Me_2 THF	*p*-Br THF	*p*-CF_3 THF	2,6-Me_2 Et_2O
T_0	**167.80**	**167.83**	**167.04**			**116.70**	**116.26**	**105.53**		
T_1	*−0.24*	*−0.83*	*−1.21*			*0.15*	*0.27*	*0.01*		115.00
a	*−0.83*	*−0.77*	*−0.45*			*0.77*	*0.68*	*0.35*		~115.0
T_2	*−1.21*	*−1.17*	*−0.70*			*0.94*	*0.97*	*0.66*		114.45
b	*−1.62*	*−1.57*	*−1.00*			*1.65*	*1.40*	*1.12*		113.7
T_3	*−1.98*	*−1.87*	*−1.36*	172.48		*1.94*	*1.86*	*1.49*	114.29	114.1
c	*−2.33*	*−2.08*	*−1.63*	172.82	165.34	*2.42*	*2.37*	*1.98*		113.4
T_4	*−2.77*	*−2.72*	*−2.07*	173.20	168.32	*2.87*	*2.65*	*2.50*	113.58	113.36
D_0			**169.16**	**173.50**				**102.03**	**112.09**	
D_1				*−0.49*					*0.87*	
D_2			*−0.89*	*−1.03*				*0.77*	*1.86*	
M			170.67	174.80	168.34			99.39	109.3	110.03

	δ ^{7}Li[d]					δ ^{31}P[e]				
compd solvent	3,5-Me_2 Et_2O	3,5-Me_2 THF	*p*-Br THF	*p*-CF_3 THF	2,6-Me_2 Et_2O	3,5-Me_2 Et_2O	3,5-Me_2 THF	*p*-Br THF	*p*-CF_3 THF	2,6-Me_2 Et_2O
T_0	**0.545**	**0.678**	**0.657**			**(24.66)**[f]				
T_1	*0.014*	*0.066*	*0.061*		1.264	*0.01*	*0.02*	*0.86*	*0.03*	1.24
g	*−0.319*	*−0.187*	*−0.466*		0.743					
T_2	*0.071*	*0.134*	*0.098*		1.503	*0.17*	*0.33*	*0.02*		1.51
g	*−0.303*	*−0.140*	*−0.341*		0.783					
T_3	*0.079*	*0.241*	*0.237*	0.522	2.057	*0.13*	*0.15*	*0.43*		1.49
g	*−0.199*	*−0.082*	*−0.233*	0.842	0.789					
T_4	*−0.122*	*−0.019*	*−0.107*	0.756	0.837	*0.11*	*0.07*	*0.22*	*0.43*	1.18
D_0			**0.755**	**0.760**						
D_1				*0.000*						
g				*0.128*					0.97	
D_2				*0.128*					0.68	

	J(Li–P), Hz					δ ^{13}C(HMPA)				
compd solvent	3,5-Me_2 Et_2O	3,5-Me_2 THF	*p*-Br THF	*p*-CF_3 THF	2,6-Me_2 Et_2O	3,5-Me_2 Et_2O	3,5-Me_2 THF	*p*-Br THF	*p*-CF_3 THF	2,6-Me_2 Et_2O
T_0						**(37.30)**[f]				
T_1	12.1	10.8	11.4		13.8	*0.07*		*0.2*		
T_2	11.2	10.6	10.3		12.8	*0.23*		*0.2*		
T_3	11.0	10.8	10.5		12.7	*0.38*		*0.2*		
T_4	10.6	10.7	10.0	10.8	11.4	*0.43*		*0.2*	*0.05*	
D_1				9.1					*0.44*	
D_2				9.1					*0.53*	

[a–c] For phenolates attached to 1, 2, and 3 HMPA solvated lithium ions, respectively. [d,e] Referenced to the resonance frequencies of ^{7}Li in 0.3 M LiCl in methanol-*O*-*d* and ^{31}P of 85% H_3PO_4, respectively, at 23 °C using a previously described technique.[7] [f] Free HMPA. [g] The HMPA solvated Li. [h] $\mathbf{T}_n$, $\mathbf{D}_n$, and **M** refer to tetramer, dimer, and monomer, respectively, and ***n*** to the number of HMPA molecules. Italicized values of δ's are [δ(**0**) − δ(***n***)] or, for HMPA, [δ(free) − δ(bound)], δ(**0**) and δ(free) being shown in boldface.

and para positions of the aromatic ring resulting in upfield shifts of resonances of C(4) which are uninfluenced by proximity effects. It is further expected that the greater the number of attached HMPA-solvated lithium cations the greater will be the magnitude of the shift. This is born out by the data in Table I. Furthermore, the species T_1, T_2, and T_3 each have nonequivalent phenolate residues which give rise to well-resolved pairs of C(4) resonances with expected intensity ratios (upfield:downfield) of 3:1, 2:2, and 1:3, respectively. The C(1) resonances exhibit similar behavior, but now the intensity ratios are reversed, i.e., solvation of lithium by HMPA results in deshielding of the ipso carbon nucleus of the attached phenolate ion.

The bound HMPA in each of the $\mathbf{T}_n$ species gives rise to distinct ^{13}C resonances (Figure 1c). No free HMPA is observed until more than 1 equiv of the cosolvent has been added, indicating that, as expected, diethyl ether is too poor a cation-solvating solvent to compete with the much stronger and sterically unencumbered Lewis base.

Only the $\mathbf{T}_4$ species exists in the presence of 8 equiv of the cosolvent. This is best seen in the ^{7}Li spectrum (Figure 1a). We conclude that *lithium 3,5-dimethylphenolate is not dissociated by HMPA* under these conditions. Furthermore, the exchange of bound and free HMPA remains slow on the NMR time scale even in the presence of a large excess of the latter.

Confirmation of the $\mathbf{T}_4$ structure has been provided by the determination of its ^{7}Li quadrupole splitting constant (QSC), a parameter which we have previously shown can often provide information regarding the state of solvation of lithium.[10] The value of QSC obtained from the ^{7}Li and ^{13}C (para position) spin–lattice relaxation times (0.62 and 0.153 s, respectively, at −114 °C) is 35 kHz. Values <70 kHz are highly characteristic of tetrasolvated cubic tetramers.[10] The QSC's for lithium 3,5-dimethylphenolate in diethyl ether and dioxolane are 57 (−57 °C)[9] and 51 (−51 °C),[9] respectively, and ~39 (30–90 °C)[10] for lithium phenolate in pyridine. The trend in QSC for the tetrasolvated tetramers roughly parallels the Lewis basicities of the solvents toward BF_3, the enthalpies (kJ mol^{-1} at 298.15 K) for complex formation being 68.6 (dioxolane),[11] 78.7 (diethyl ether),[12] 128.1 (pyridine),[12] and 117.5 (HMPA).[12] This is expected, because an increase in the strength of the bonding of the solvent will make its crystal field contribution more nearly equal to those of the three phenolate oxygen anions, which in turn will result in a more nearly tetrahedral distribution of negative charge and a smaller field gradient at the lithium nucleus.

Similar results are obtained with THF as the solvent (Table I). With a large excess (~4 equiv) of HMPA, however, some (~15%) solvent-separated monomer is formed in addition to the fully HMPA-solvated tetramer and possibly some monomeric contact ion pair. Evidence for the solvent-separated monomer

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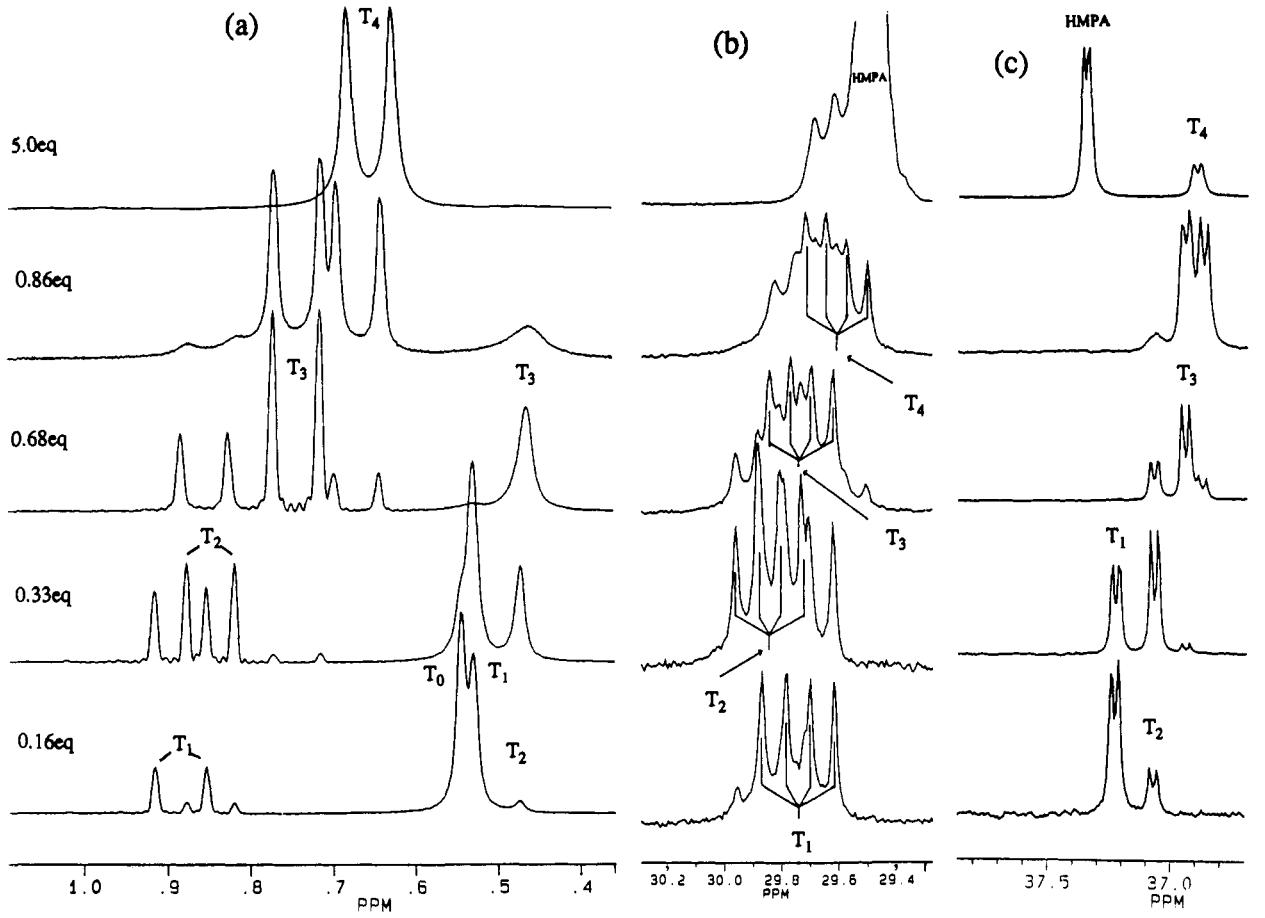

Figure 1. NMR spectra of lithium 3,5-dimethylphenolate (0.2 M) in diethyl ether containing varying amounts of HMPA at −120 °C: (a) 140.0-mHz ^{7}Li spectra; (b) 145.8-mHz ^{31}P spectra (referenced to 0.3 M Ph_3P in $CDCl_3$); (c) 90.56-mHz ^{13}C spectra (HMPA resonances).

is the presence in the ^{7}Li spectrum of a quintet at δ −0.330, characteristic of **1**.[4] THF also competes more successfully with HMPA than diethyl ether. With ~1.5 equiv of HMPA in THF some 40% of the phenolate is still present as T_3, the remainder being the T_4 species. Thus, signals for T_3, T_4, and free HMPA are observed in the ^{31}P spectrum.

Lithium 4-Bromophenolate. We have shown[9] that this compound coexists as a dimer and tetramer in a 0.2 M solution in THF at −60 °C. We now find that, at −120 °C, three species are observable in the ^{13}C spectrum (Figure 2). Two of the species have C(1) and C(4) chemical shifts which characterize them as the dimer (δ 169.3 and 102.0; cf. 169.5 and 102.3, respectively, at −60 °C) and the tetramer (δ 167.0 and 105.5; cf. 167.0 and 1.06, respectively, at −60 °C). The third species, which in the concentration range 0.2–0.75 M is present in minor amounts (<5%), is independent of the method of sample preparation and purification (see Experimental Section). It is characterized by the chemical shifts of C(1) and C(4) (δ 168.8 and 103.3, respectively; **Tri** in Figure 2) and that of ^{7}Li (δ 0.716) which are intermediate between the corresponding values for the dimer and tetramer. The carbon resonances (at 75 mHz) begin to broaden at about ~80 °C and are no longer observable at −60 °C by which temperature the dimer and tetramer resonances are also becoming broadened by exchange. This behavior suggests that the third species is also an aggregate. Since its carbon chemical shifts, particularly that of C(4), resemble more closely those of the dimer than of the tetramer, we believe that it is the monocyclic trimer **11**. This structure is supported by the observed dependence of

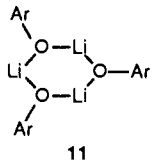

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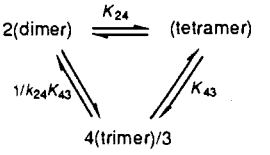
Table II. The Effect of Concentration of Lithium 4-Bromophenolate on the Fractions of Dimer, Trimer, and Tetramer Present in THF at −100 °C

	dimer		trimer		tetramer	
concn, M	obs	calc[a]	obs	calc[a]	obs	calc[a]
0.750	0.64	0.64	0.041	0.041	0.32	0.32
0.624	0.67	0.67	0.044	0.039	0.28	0.29
0.559	0.69	0.69	0.047	0.038	0.27	0.27
0.419	0.75	0.73	0.031	0.037	0.22	0.23
0.140	0.86	0.86	0.026	0.027	0.11	0.11

[a] See text.

Scheme I



$$K_{24} = x_4/(x_2 - 2x_4)^2 \quad (1)$$

$$K_{43} = (x_3)^{4/3}/(x_4 - 3x_3/4) \quad (2)$$

$$K_{32} = (x_2)^2/(x_3 - 2x_2/3)^{4/3} \quad (3)$$

the relative proportions of the three coexisting species on the total lithium phenolate concentration (Table II). The equilibrium system is shown in Scheme I. If the equilibrium constants K_{24} and K_{43} are known, the concentration of dimer (x_2), trimer (x_3), and tetramer (x_4) can be obtained by repeatedly solving eqs 1–3, beginning with x_2 = [phenolate]/2, until the x_n's converge to a desired limit (10^{-5} M required 4–5 iterations). K_{24} and K_{43} can then be varied to find the best fit with the observed values of x_n. The values of K_{24} = 1.03 M^{-1} and K_{43} = 0.038 $M^{1/3}$ are obtained from the data in Table II, and the good agreement between the

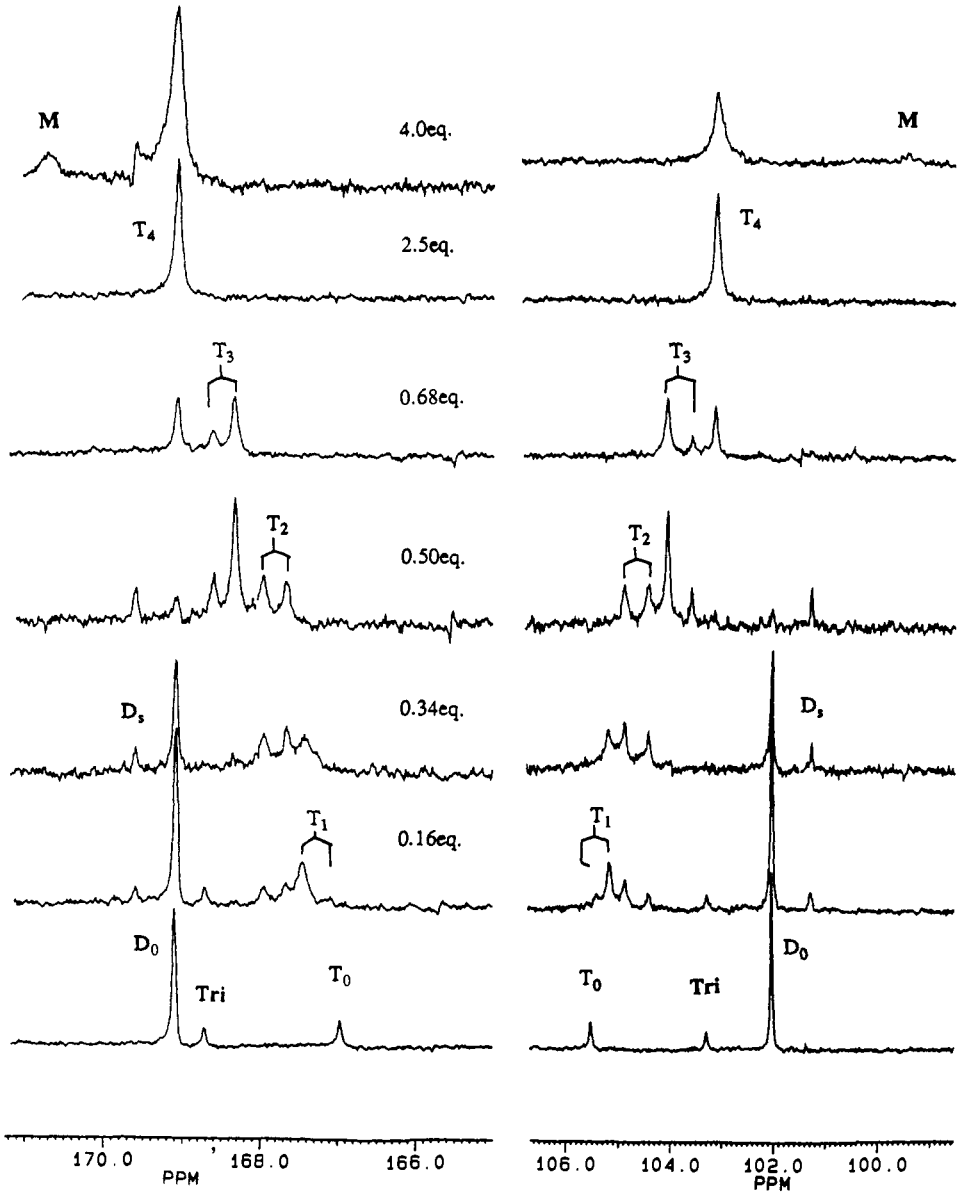
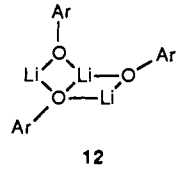


Figure 2. 90-mHz ^{13}C spectra of lithium *p*-bromophenolate (0.2 M) in THF at −115 °C with varying amounts of HMPA. Ipso carbon atoms, 166–170 ppm. Para carbon atoms 100–106 ppm.

observed and predicted relative concentrations is evidence for the trimer. Degrees of aggregation <2 and >4 for the third species cannot be accommodated by the data.

The assignment of the monocyclic structure (**11**) to the trimer is equivocal. The bicyclic structure (**12**) can also be considered,



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provided there is rapid exchange between the three bridging possibilities even at −120 °C. In fact, the significant downfield shift of C(4) relative to that for the dimer is consistent with the expected weighted average (1:2) of the shifts for a phenolate in the bridge (tetramer-like) and outer (dimer-like) positions in **12**.

Lithium 4-Bromophenolate/HMPA in THF. The effect of the addition of HMPA is illustrated in Figure 2 in which the species produced are characterized by the ^{13}C chemical shifts of their C(1) and (4) resonances. The principle effect of increasing amounts of HMPA is the *conversion of the dimer and the small amount of trimer to HMPA-solvated tetramer* so that ~0.9 equiv completely converts the phenolate to a mixture of the tetramers T_3 and T_4. With 2.5 equiv of the cosolvent the sole species present is T_4. In the presence of 4 equiv of the cosolvent T_4 still predominates but is accompanied by a new species which we believe to be a monomer. Other data used to characterize these various species are included in Table I.

There are resonances (designated D_s in Figure 2) which are consistent with the formation of a small amount of an HMPA-solvated dimer at the lower cosolvent ratios. The corresponding ^7Li resonances cannot be identified because of strong, overlapping signals in the same region. It is therefore not possible to establish how many HMPA molecules are presence in this species. The evidence for the formation of monomeric species is somewhat tenuous being based on the downfield shift of 2.6 ppm, relative to the monomer, for C(4). A similar difference (2.9 ppm) has been found between the dimer and monomer of lithium 2,4,6-tribromophenolate in THF without HMPA.[12] The ^7Li spectrum of the sample with 4 equiv of HMPA is uniformative because of overlap with the strong tetramer resonance. A trace of the solvent-separated lithium ion (**1**) is observable at δ −0.330, but the nature of its counterion is unknown.

Lithium *p*-(Trifluoromethyl)phenolate/HMPA in THF. In the absence of the cosolvent, this salt in THF in the temperature range −120 to −60 °C exists exclusively as the dimer which is charac-

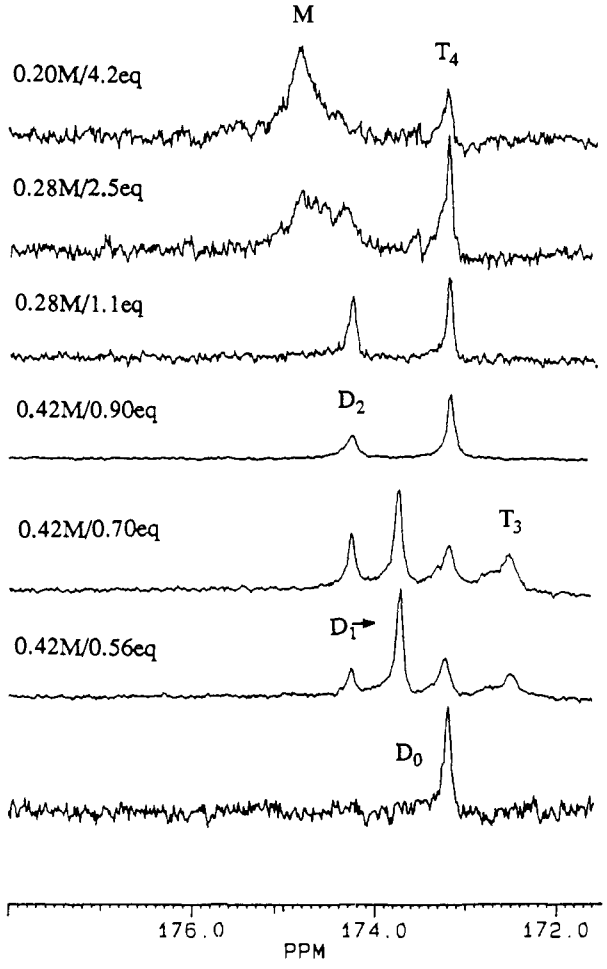


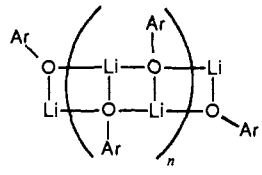
Figure 3. 90-mHz ^{13}C spectra of the ipso carbon atom of lithium *p*-(trifluoromethyl)phenolate in THF at −120 °C with varying amounts of HMPA.

terized by its C(1) and C(4) chemical shifts[8] (Table I; Figure 3). Addition of increasing amounts of HMPA initially results in the formation of dimers and tetramers which are partially solvated by HMPA. Because the C(4) resonances of these species are quartets due to splitting by ^{19}F nuclei of the CF_3 group, these changes are best observed through the C(1) signals (Figure 3). The situation is most clear when ~1 equiv of HMPA is present since only two species are observed. These are assigned the $\mathbf{D}_2$ and $\mathbf{T}_4$ structures, and the relative intensities of their C(1) signals exhibit the expected concentration dependence. These assignments are confirmed by the corresponding ^7Li spectra (Figure 4) which consist of two major resonances, both doublets. The higher field doublet corresponds to $J(^7Li,^{31}P)$ = 10.8 Hz which is in the range found for the other tetrameric species. The other doublet has a significantly smaller splitting (9.0 Hz) which we believe must be characteristic of dimers.

When smaller amounts (0.56 and 0.7 equiv) of cosolvent are present, both dimers and tetramers with intermediate degrees of HMPA solvation are observed. The spectral assignments for the $\mathbf{D}_1$ species are based on the following considerations. Both the C(1) and C(4) resonances have chemical shifts intermediate between those of the $\mathbf{D}_0$ and $\mathbf{D}_2$ species (Table I; Figure 3). The ^7Li spectra are more complicated since the signals of the Li nuclei with and without attached HMPA coincide with those of the $\mathbf{D}_2$ and $\mathbf{D}_0$ species, respectively. Comparison of Figures 2 and 4 reveals that the intensities of the singlet near δ 0.76 in the ^7Li spectra parallel those at δ 173.9 assigned to C(1) of $\mathbf{D}_1$ in the ^{13}C spectra and that this signal is still present when the amount of $\mathbf{D}_0$ species is negligible (0.7 equiv of HMPA). That the doublets arising from the $\mathbf{D}_1$ and $\mathbf{D}_2$ species are coincident, even in 194-mHz spectra, follows from the corresponding ^{31}P spectra (Figure 5) in which *two* 1:1:1:1 quartets with $J(^7Li,^{31}P)$ = 9.0 Hz are completely resolved. In addition to the dimers, both $\mathbf{T}_3$ and $\mathbf{T}_4$ species are present at the lower cosolvent concentrations and give rise to characteristic ^{13}C and ^7Li resonances.

Increasing the number of equivalents in HMPA to 2.5 leads to formation of appreciable amounts of the monomer, and at 4.2 equiv this becomes the major species. The monomer is largely a contact ion pair which gives rise to a broad ^7Li resonance at δ 0.637. In addition, there is a weak quintet at −0.330 corresponding to **1** which may be due to the solvent-separated monomer. The C(1) and C(4) resonances of the monomer contact ion pair are at δ 174.8 and 99.4, respectively.

Lithium 2,6-Dimethylphenolate/HMPA. In diethyl ether at −120 °C and in the absence of HMPA, this salt appears to exist as a complex mixture of aggregates. The C(4) resonances are at δ 115.5, 114.6, 114.5, 114.3, and 112.9 and they coalesce, due to fast exchange, when the temperature is raised to near −60 °C. The chemical shifts of the first four are consistent with the phenolates attached to three lithium cations and could arise from hexamers, tetramers, and/or the internal residues of ladder oligomers (**13**). The remaining resonance could be associated with a dimer or the terminal residues of **13**. The relatively high coalescence temperature argues against these species being related only by different degrees of solvation or that some of the species arise from different conformations of the aryl groups.



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The addition of increasing amounts of HMPA to the phenolate in ether appears to produce the series of HMPA-solvated tetramers ($\mathbf{T}_n$) (Table I). Certainly, the C(1) and C(4) chemical shifts and the large values of $J(^7Li,^{31}P)$ are consistent with this view. The ^7Li chemical shifts show a different trend in that the unsolvated lithium atoms are now at lower field than those with attached HMPA. The total spread of the ^7Li shifts in Table I is, however, less than 1 ppm, and the conformationally dependent contributions of the long-range shielding of the aryl groups probably dominates these observed differences. With higher proportions of cosolvent, dissociation to monomeric species occurs so that with 1.1 equiv of HMPA the phenolate consists of a ~1:1 mixture of the monomer and $\mathbf{T}_4$. By the time 2.1 equiv have been added only the monomer [δ 168.3 and 110.0 for C(1) and C(2), respectively], almost completely as the contact ion pair, is present. Further addition of HMPA causes conversion of the contact ion pair to the solvent-separated species. A 0.4 M solution of phenolate with 8 equiv of the cosolvent at −120 °C has about 10% of the lithium present as the tetrasolvated ion **1**; the major species is the contact ion pair [$\delta(^7Li)$ 0.67].

Lithium 2,6-dimethylphenolate is dimeric in THF[13] and dioxolane.[13,14] With both solvents, however, the spectra at −120 °C of a series of samples containing incremental additions of HMPA exhibit no resonances which can be assigned to tetrameric species. Instead, conversion of the dimer to the monomeric contact ion pair is observed, and with 2 equiv of HMPA the latter is the only apparent species [δ $^{13}C(4)$ 110.03, 110.75, 110.05 and δ ^7Li, 0.670, 0.607, 0.833 in THF, dioxolane, Et_2O, respectively], apart from a trace of the solvent-separated lithium cation **1**. Addition of further amounts of HMPA to the THF system causes substantial increases in the proportion of **1** which in the presence of 8 equiv of cosolvent accounts for about 35% of the total lithium. The solvent-separated anion has C(1) and C(2) resonances at δ 168.4 and 106.2, respectively.

Discussion

A summary of the effects of the addition of HMPA to lithium phenolates is provided in Table III. The most surprising result is, of course, the HMPA-induced conversion of the dimers of *p*-bromo- and *p*-(trifluoromethyl)phenolates to the tetramers ($\mathbf{T}_4$).

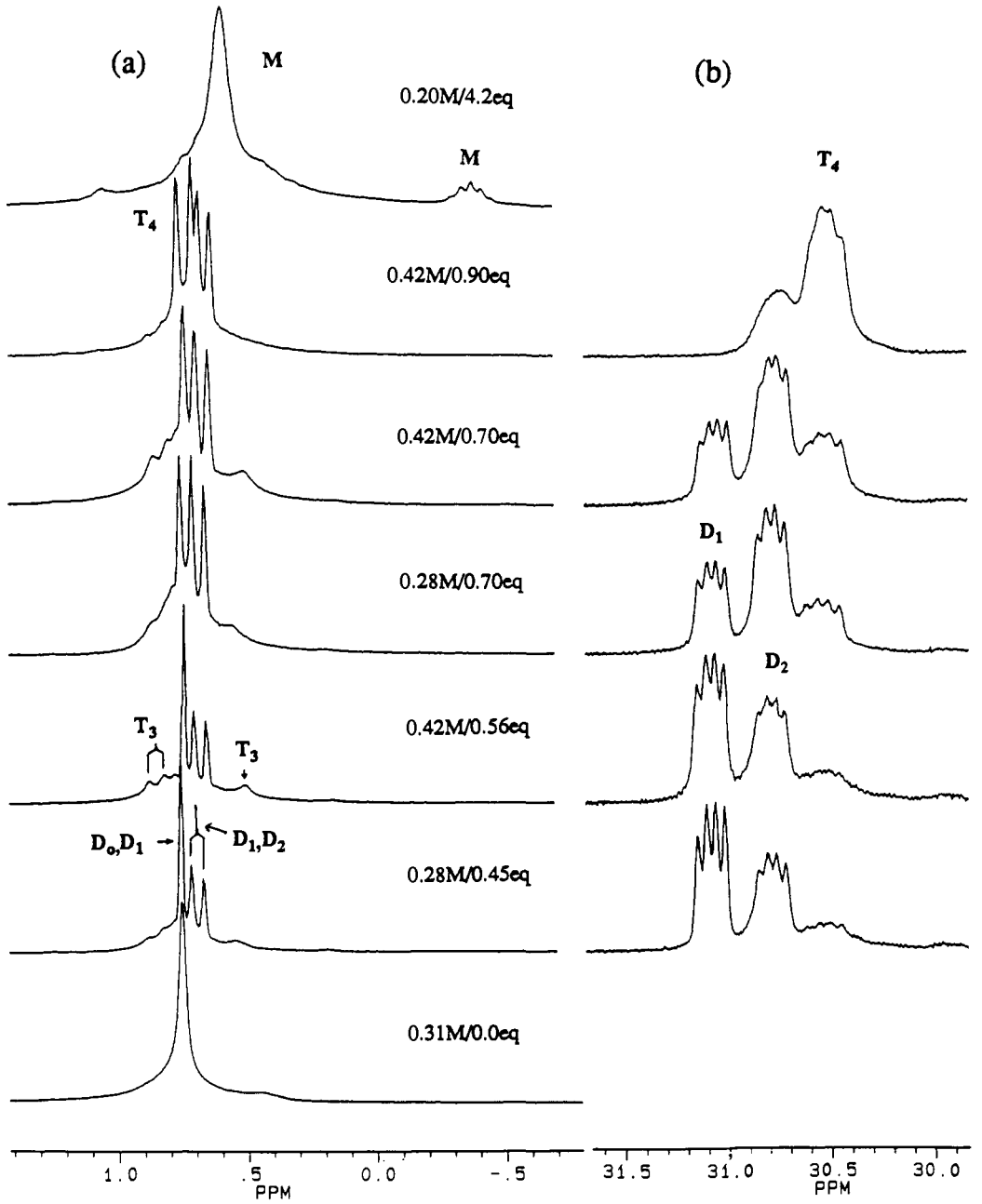

Figure 4. NMR spectra of lithium *p*-(trifluoromethyl)phenolate in THF at −120 °C with varying amounts of HMPA: (a) 194-mHz ^{7}Li spectra; (b) 202.4-mHz ^{31}P spectra (referenced to 0.3 M Ph_3P in $CDCl_3$).

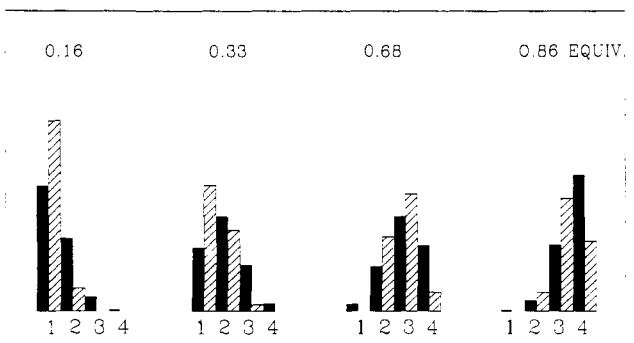

Figure 5. Relative proportions of the T_n species formed by lithium 3,5-dimethylphenolate (0.2 M) with varying amounts of HMPA in diethyl ether at −120 °C. The filled bars correspond to the statistical distributions.

Before we discuss the possible explanations of this result it will be useful if we draw some qualitative conclusions regarding the relative ease of the steps in the sequential solvation of tetramers and dimers by HMPA.

For lithium 3,5-dimethylphenolate in diethyl ether, HMPA competes very strongly with the solvent for the cation sites and, in fact, free cosolvent is only observed after **1** equiv has been added. The distributions of the T_n species corresponding to different proportions (<1) of added HMPA have been estimated by integration of the ^{7}Li spectra (Figure 1) and are compared in Figure 3 with the statistical distributions calculated assuming that the ease of HMPA solvation of a given lithium site is not influenced by the nature of the solvation of the other three sites. It is seen that the populations of the more heavily HMPA-solvated species consistently lag behind the statistically predicted values although the effect is not a large one. That the presence of HMPA on one lithium ion affects the remaining lithium ions and their attached phenolate ions is also clearly indicated by the increased electron densities at the para positions of the latter resulting in significant upfield ^{13}C chemical shifts (Table I).

The progressive solvation of a dimer by HMPA is best observed for lithium *p*-(trifluoromethyl)phenolate in THF. Because of the

Table III. Summary of Species Formed by the Addition of HMPA to Solutions of Lithium Phenolates at ~−120 °C

phenolate	solvent	equiv of HMPA (E)	species
3,5-dimethyl	Et_2O	0	$\mathbf{T}_0$
		$0 < E < 1$	$\mathbf{T}_1$, $\mathbf{T}_2$, $\mathbf{T}_3$, $\mathbf{T}_4$
		$1 < E < 8$	$\mathbf{T}_4$
	THF	0	$\mathbf{T}_0$
		$0 < E < 1$	$\mathbf{T}_1$, $\mathbf{T}_2$, $\mathbf{T}_3$, $\mathbf{T}_4$
		2	$\mathbf{T}_3$, $\mathbf{T}_4$
		9	$\mathbf{T}_4$, $\mathbf{M}$
p-bromo	THF	0	$\mathbf{D}_0$, $\mathbf{T}_0$
		$0 < E < 0.7$	$\mathbf{D}_2$,[a] $\mathbf{T}_1$, $\mathbf{T}_2$, $\mathbf{T}_3$, $\mathbf{T}_4$
		0.85	$\mathbf{T}_3$, $\mathbf{T}_4$
		~2	$\mathbf{T}_4$
		~4	$\mathbf{T}_4$, $\mathbf{M}$
p-(trifluoromethyl)	THF	0	$\mathbf{D}_0$
		$0 < E < 1$	$\mathbf{D}_1$, $\mathbf{D}_2$, $\mathbf{T}_3$, $\mathbf{T}_4$
		~2	$\mathbf{D}_2$, $\mathbf{T}_4$
		~4	$\mathbf{T}_4$, $\mathbf{M}$
2,6-dimethyl	Et_2O	0	[b]
		$0 < E < 0.8$	$\mathbf{T}_1$, $\mathbf{T}_2$, $\mathbf{T}_3$, $\mathbf{T}_4$
		~1	$\mathbf{T}_4$, $\mathbf{M}$
		~2	$\mathbf{M}$
	THF	$0 < E < 2$	$\mathbf{D}_0$, $\mathbf{M}$
		~2	$\mathbf{M}$
	dioxolane	$0 < E < 2$	$\mathbf{D}_0$, $\mathbf{M}$
		~2	$\mathbf{M}$

[a] Species could be $\mathbf{D}_1$. [b] Complex mixture of aggregates. See Results section.

concomitant formation of $\mathbf{T}_n$ species and the resulting overlaps which exist in the ^{7}Li, ^{13}C, and ^{31}P spectra, it is not possible to make a quantitative assessment of the relative ease of forming the $\mathbf{D}_1$ and $\mathbf{D}_2$ species although it appears that it is more difficult to add the second molecule of cosolvent. What is clear, however, is that formation of $\mathbf{D}_3$ and $\mathbf{D}_4$ does not occur. This finding is consistent with the observations of Collum and his co-workers,[7] who found that lithium diisopropylamide in THF adds no more than one HMPA/Li even in the presence of 5 equiv of cosolvent. They did observe that the lithamide **2** affords a very small amount of $\mathbf{D}_4$ but only with 2 equiv of HMPA. With the phenolate system, $\mathbf{D}_3$ and $\mathbf{D}_4$ are evidently unstable with respect to monomeric species with two or more HMPA/Li. Unfortunately, solvent exchange for the monomeric contact ion pair is too fast to allow the experimental determination of the actual number of attached HMPA molecules in these species.

We now turn to a consideration of the HMPA-induced conversion of dimer to tetramer which is observed for *p*-bromo- and *p*-(trifluoromethyl)phenolates in THF. The free energy for the dimer–tetramer equilibrium (eq 4) for a given phenolate (P) in

$$2Li_2P_2(solv)_4 \rightleftharpoons Li_4P_4(solv)_4 + 4solv \qquad (4)$$

various solvents (S) and can be roughly broken down into components which are solvent dependent and those which are independent of S. The latter includes the enthalpy (ΔH_{agg}) for converting dimer to tetramer in the absence of solvent and most of the entropy change for (4). The solvent-dependent component can be further divided into bonding and steric terms. The former consists essentially of the electrostatic interaction between the negative terminus of the solvent dipole and the effective positive charge of the lithium cation. We expect the effective cation charge to be higher in the dimer since the cation is attached to two, rather than three, anions. Therefore, the change in the bonding term ($\Delta\Delta H_{el}$) accompanying replacement of one S (=THF) in the aggregates by the much stronger Lewis base HMPA will probably make an *endothermic* contribution to (4). In considering the steric term we note that the introduction of one or two ortho substituents into the phenolate moiety destablizes the tetramer relative to the dimers indicating a more stringent steric demand in the structure of the former.[8,14] Solvation of the lithium cations in the two species should be subject to similar, relative constraints, i.e. steric hindrance to solvation will be more severe for tetramers than for dimers. The steric requirement of HMPA, with its monosubstituted oxygen atom, must be substantially less than that of THF. Thus, replacing one S (=THF) by the less sterically demanding HMPA will make an *exothermic* contribution ($\Delta\Delta H_{st}$) to the dimer–tetramer equilibrium 4. We conclude that, for the systems under consideration here, the steric term is the more important and, since it is evidently difficult to add a third or fourth HMPA to the dimer, conversion of dimers to HMPA-solvated tetramers occurs.

We now summarize the observations for the various systems investigated in terms of the foregoing discussion.

Lithium 3,5-Dimethylphenolate in Diethyl Ether. With a relatively basic phenolate in such a poor cation solvating solvent the situation is dominated by the electrostatic advantage (ΔH_{agg}) of associating ion pairs as cubic tetramers rather than dimers or monomers. Addition of HMPA therefore sequentially solvates the tetramer. Because of the low dielectric constant of the solvent (ϵ 4.3), dissociation to dipolar monomers $\mathbf{M}_2$, or $\mathbf{M}_3$, or to solvent-separated ion pairs $\mathbf{M}_4$ is not observed.

Lithium 3,5-Dimethylphenolate in THF. The situation is similar to the diethyl ether system except that in the more polar solvent (ϵ 7.6) dissociation of the tetramer to monomer occurs at high (15% at 9 equiv) HMPA ratios.

Lithium 4-Bromophenolate in THF. The lower basicity of this phenolate makes ΔH_{agg} less exothermic[7] to the extent that its lithium salt now coexists as the dimer and tetramer (and trimer) under conditions for which the 3,5-dimethylphenolate is entirely a tetramer. Even though the decreased basicity of the anion is expected to make $\Delta\Delta H_{el}$ more endothermic, $\Delta\Delta H_{st}$ still dominates and complete HMPA-induced conversion of dimer (and trimer) to tetramer is observed. The subsequent dissociation to monomers occurs at lower HMPA ratios than in the 3,5-dimethyl system, presumably as a consequence of the lower basicity of the *p*-bromophenolate ion.

Lithium 4-(Trifluoromethyl)phenolate in THF. ΔH_{agg} is even less exothermic for this weakly basic phenolate and no tetramer is observed in the absence of the cosolvent. $\Delta\Delta H_{el}$ for this system has increased endothermically to the extent of being comparable with $\Delta\Delta H_{st}$, and the $\mathbf{D}_0$ species is converted to a mixture of $\mathbf{D}_2$ and $\mathbf{T}_4$. The conversion of these species to monomers occurs even more readily than with the *p*-bromo derivative so that in the presence of ~4 equiv of HMPA the monomeric contact ion pair is the dominant species.

Lithium 2,6-Dimethylphenolate in Various Solvents. Although this phenolate has a relatively high basicity, ΔH_{agg} is substantially reduced by steric factors and its lithium salt is dimeric in THF and dioxolane. In THF and dioxolane, addition of HMPA converts the dimer directly to monomeric species with no evidence for the formation of $\mathbf{T}_n$ species. There is also no evidence for intervention of the species $\mathbf{D}_1$ or $\mathbf{D}_2$. HMPA-solvated aggregates ($\mathbf{T}_n$) are only observed in diethyl ether, and even in this solvent monomeric species are formed at higher cosolvent ratios. An interesting feature of this salt is the extensive formation of monomeric solvent-separated ion pairs in THF no doubt due to the high steric demand of the anion.

It is now clear that HMPA can elicit a variety of changes in the solution structures of organic lithium compounds, including both increased and decreased[4,6] aggregation as well as triple ion formation.[6,7] The observed behavior appears to depend on both the basicity of the anion and steric factors, as well as the polarity of the mother solvent. The full understanding of the way in which this cosolvent causes changes in reactivity, regiochemistry, and stereochemistry will require identification of the true reactant in the particular process under consideration, most probably through a combined study of solution structure and reaction kinetics. In the case of lithium phenolates, and presumably enolates, there

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is a reasonable expectation that significant amounts of monomers will form in the presence of 4 equiv of HMPA, particularly with THF as the solvent, and such species must be regarded as likely candidates for the reactive species. It will, however, be interesting to establish whether HMPA enhances or decreases the reactivity of lithium 3,5-dimethylphenolate in diethyl ether since there is no evidence for the formation of dissociated species in this system.

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Proton Chemical Shift Assignments in Citrate and Trimethyl Citrate in Chiral Media

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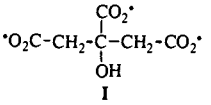
Abstract: The citrate ion gives rise to four different methylene proton chemical shifts in the presence of (*S*)-lactate and Pr^{3+}. Trimethyl citrate behaves similarly in the presence of (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. The four methylene shifts have been assigned in an absolute way by comparisons with those from the corresponding spectra of (2*R*,3*R*)-citrate-*2-d* and trimethyl (2*R*,3*R*)-citrate-*2-d*, respectively. The chemical shifts of the three methyl groups in trimethyl citrate in the presence of the anthryl shift reagent have also been assigned. Deuterium isotope effects on the proton chemical shifts of these molecules have been determined. In the absence of shift reagents these effects are mainly of the intrinsic type, but in their presence there are equilibrium perturbation contributions. The ^1H NMR line widths and chemical shifts in the citrate–lactate–$PrCl_3$ system depend strongly on the pH, spectrometer frequency, and temperature, with the best results obtained at room temperature, pH $\approx$ 3.8, and a spectrometer frequency of 200 MHz.

Introduction

Citric acid and its salts are of great importance in biochemistry and commerce. Citrate, which plays a key role in the metabolic pathway known as the Krebs, tricarboxylic acid, or citric acid cycle, has interesting stereochemical and symmetry features, despite its structural simplicity, lack of a stereogenic center, and achirality.[1-4] The inclusion of free citrate in the Krebs cycle was once considered to be impossible because experiments with isotopically labeled compounds seemed incompatible with the symmetry present in that ion.[5] However, in a classic paper in 1948, Ogston showed that the two $CH_2CO_2^-$ groups in citrate could be differentiated in theory by an enzyme, essentially because of the latter's chirality, and this molecular recognition was discussed in terms of a "three-point" complexation model.[6] Hirschmann has emphasized that this differentiation can be deduced from symmetry alone without the consideration of a specific complexation model.[7]

The two methylene groups in citrate (I) have different (diastereomeric) interactions with a chiral molecule such as the enzyme aconitase, which can selectively dehydrate citrate to aconitate with the stereospecific breaking of only one of the four C–H bonds in I. In principle, therefore, citric acid (or citrate) in any chiral



I

medium should show four different CH chemical shifts in its ^1H NMR spectrum, but conditions under which these shifts are large enough to be resolved have not been reported, to our knowledge. This problem, which forms the subject of the present work, can be approached by means of chiral solvents or chiral shift reagents[8-13] or by converting citrate into an unsymmetrical derivative.[14]

Stereochemical Nomenclature. The ^1H NMR spectrum of the methylene groups in citric acid (or citrate) in D_2O, i.e., in an achiral medium, shows a single AB quartet and thus only two chemical shifts, in agreement with the symmetry of the molecule.[15]

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(13) Bertinini, I.; Luchinat, C. *NMR of Paramagnetic Molecules in Biological Systems*; Benjamin/Cummings; Menlo Park, CA, 1986.
(14) A monomethyl citric acid ester with the methyl attached to carbon 1 should show four methylene chemical shifts. However, this type of compound is chiral, and the determination of the position of a deuterium incorporated into the molecule would require a resolution step or an asymmetric synthesis of the ester. A more elegant method of observing four chemical shifts would be to convert the OH group attached to carbon 3 in citric acid (or, more conveniently, trimethyl citrate) into an ester function with a chiral acid, e.g., with optically active *O*-methylmandelic acid: Raban, M.; Mislow, K. *Tetrahedron Lett.* **1966**, 3961.
(15) A single AB quartet, $|\delta_A - \delta_B| = 0.16$ ppm, $|^2J| = 15$ Hz, is observed for tripotassium citrate in D_2O. The geminal coupling constants in the CH_2 groups of citric acid and related compounds are undoubtedly negative (Bovey, F. A.; Jelinski, L.; Mirau, P. A. *Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; Academic Press: New York, 1988; pp 191-195), and this is assumed to be so in the rest of the present paper. The two diastereotopic protons in either of the two $CH_2CO_2^-$ groups have different chemical shifts and are coupled to one another, whereas the two enantiotopic CH_2 groups are not differentiated in water, which is an achiral medium: Villafranca, J. J.; Mildvan, A. S. *J. Biol. Chem.* **1972**, *247*, 3454. These workers, who used a 100-MHz sweep NMR spectrometer with time averaging, were the first to observe the proton NMR spectrum of enzymatically prepared citrate-*2-d* and thereby showed that the proton that exchanges in D_2O in the presence of aconitase is one of the two lesser shielded protons that give rise to the AB quartet in citrate. They measured a deuterium isotope effect of −23 ppb on the CHD proton.

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