adjacent to a high-energy glycosidic linkage. Apart from these signals, chemical shift ranges are similar to those of V-amyloses. Solution state C-1 and C-4 chemical shifts for α-cyclodextrin are closely matched if averages of solid-state shifts are taken which ignore the sites adjacent to the high-energy linkage. This suggests that α-cyclodextrin might adopt a more expanded conformation in solution compared to the solid state. The marked similarity between ^{13}C CP/MAS spectra of amorphous starches and V-type amylose complexes provides evidence for the presence of amylose/lipid inclusion complexes in starch granules.

Registry No. α-Cyclodextrin, 10016-20-3; α-cyclodextrin hydrate, 51211-51-9; β-cyclodextrin, 7585-39-9; β-cyclodextrin hydrate, 68168-23-0; α-(1→4)glucan, 9051-96-1; amylose, 9005-82-7; starch, 9005-25-8.

Structural Factors Controlling the Aggregation of Lithium Phenolates in Weakly Polar Aprotic Solvents

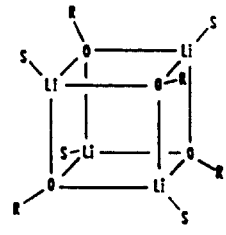
L. M. Jackman* and B. D. Smith

Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. *Received August 28, 1987*

Abstract: The structures of lithium 4-fluoro-, 4-chloro, 2- and 4-bromo-, 4-(trifluoromethyl)-, 4-methoxy-, 2-methyl-, 2-ethyl-, 2-*n*-propyl-, 2-isopropyl-, 2-*tert*-butyl-, 2-(methoxymethyl)-, 3,5-dimethyl-, 3,5-dimethyl-4-methoxy-, 4-chloro-3,5-dimethyl-, 3,5-diethyl-, and 3,5-dimethoxyphenolates in solution in weakly polar, aprotic solvents such as pyridine, tetrahydrofuran, dimethoxyethane, 1,3-dioxolane, diethyl ether, 2,6-lutidine, and triethylamine have been established by ^{13}C NMR spectroscopy. Para substituents influence the equilibrium between dimer and tetramer through their effect on the basicity of the anion. *o*-Alkyl substituents promote dimer formation through steric effects in the order of their steric bulk. The 2-methoxymethyl group stabilizes the tetramer. Dimers are favored relative to tetramers by a combination of high Lewis basicity and low steric demand of the solvent. A number of lithium phenolates in 1,3-dioxolane exist as hexamers at low temperatures. The following pairs of values for ΔH (kcal mol^{-1}) and ΔS (cal mol^{-1} K^{-1}) are found for 2 dimer ⇌ tetramer: lithium 4-bromophenolate (THF), 4.4 ± 0.5, 24 ± 2; 3,5-dimethylphenolate (pyridine), 6.6 ± 0.2, 33 ± 1; 2-isopropylphenolate (THF), 7.5 ± 0.5, 38 ± 2. For tetramer ⇌ $^2/_3$ hexamer the values for 3,5-dimethoxyphenolate (dioxolane) are −4.7 ± 0.3 and −20 ± 1.7. ^7Li quadrupole splitting constants have been determined for several dimers and tetramers.

Many important synthetic methodologies involve the reactions of organic lithium salts with electrophiles in weakly polar aprotic solvents, particularly ethers. The nucleophiles in these reactions are usually ambident anions (e.g. enolate,[1] enamide,[2] heterosubstituted allyl[3]), the corresponding lithium salts of which are contact ion pairs or ion-pair aggregates. There is evidence that such ion-pair aggregates can function as true reactants,[4-6] and it is, therefore, probable that the degree of aggregation influences reactivity and regio- and stereochemistry. An understanding of the structural factors that control the degree of aggregation together with some knowledge of the thermodynamics of aggregation equilibria are, therefore, prerequisites for any mechanistic studies of this important group of reactions.

The main driving force for aggregation in weakly polar solvents is, of course, the maximization of electrostatic interactions between cations and anions. Aggregation, however, will generally occur at the expense of solvation of the ions, which, for weakly polar *donor* solvents, will principally involve the lithium cation. The overall process may, therefore, be viewed as a competition between anions and solvent for the available coordination sites (usually three or four) around the lithium cation and will thus reflect their Lewis basicities. In addition to considerations of intrinsic basicity, steric factors involving solvent and anion will be important. It might also be supposed that the number of lone pairs on the donor atoms of the anion could effect aggregation since in the cubic tetramer **1**, for example, a total of three lone pairs can be directed



1

toward three cations. This does not appear to be a dominant factor, however, since alkyllithium compounds often have the structure **1** in ether solvents.[7] Finally, solvation, which is associated with the loss of translational freedom of small molecules, is a process with a substantial negative entropy change so that increased solvation at the expense of aggregation will be favored by lower temperatures.

We present here a study of lithium phenolates undertaken in order to provide insight into the various factors affecting aggregation. Phenolates are ideal for this purpose in that a series of compounds having a wide range of electronic and steric effects

(1) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737.
(2) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; p 1. Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517.
(3) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. Hoppe, D. *Ibid.* **1984**, *23*, 932.
(4) Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494. Jackman, L. M.; Dunne, T. S. *Ibid.* **1985**, *107*, 2805.
(5) Seebach, D. Proceedings of The Robert A. Welch Foundation Conferences on Chemical Research, Houston, TX, 1984.
(6) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805.
(7) (a) West, P.; Waack, R. *J. Am. Chem. Soc.* **1967**, *89*, 4395. (b) Brown, T. C. *Pure Appl. Chem.* **1970**, *23*, 447. Seebach, D.; Hassig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308. (c) Bauer, W.; Seebach, D. *Ibid.* **1984**, *67*, 1972. (d) Heinzer, J.; Oth, J. F. M.; Seebach, D. *Ibid.* **1985**, *68*, 1848.

0002-7863/88/1510-3829$01.50/0

is readily obtainable and because it has been shown[8] that degrees of aggregation can be inferred from the chemical shifts of the para carbon atoms. Furthermore, lithium phenolates are good models for enolates since the ligand atoms (oxygen) are the same and can be expected to have similar Lewis basicities. In addition to delineating the important factors controlling aggregation, we have obtained thermodynamic parameters for four systems and have made a survey of the relative solvating power of seven weakly polar solvents.

Experimental Section

Materials. Solvents were purified as previously described.[8] All but three phenols were obtained from Aldrich Chemical Co. and were purified by recrystallization, distillation, or sublimation immediately prior to use. 2-(Methoxymethyl)phenol was prepared by heating 2-hydroxybenzyl alcohol with methanol in a sealed tube.[9] 3,5-Dimethyl-4-methoxyphenol was obtained in four steps from 4-bromo-2,6-dimethylphenol,[10] and 3,5-diethylphenol was prepared by heating 4-ethylphenol in the presence of aluminum chloride.[11] The anisoles were prepared by methylating the appropriate phenols[8] and their ^{13}C NMR spectra obtained under the same conditions as the phenolates. *n*-Butyllithium (1.6 M) was obtained from Aldrich Chemical Co. and assayed by the usual methods.

Sample Preparation. The preparations were carried out with the previously described vacuum-line techniques for filling NMR tubes.[8,12] The following three procedures were used to prepare the lithium 4-bromophenolate solutions in dioxolane. Method A was used to prepare all other lithium phenolate samples.

Method A. The reaction vessel was attached to the vacuum manifold and evacuated overnight. The system was back-filled with dry nitrogen, opened, and charged with a solution (10 mL) of 4-bromophenol (0.346 g, 2 mmol) in dry hexane/ether (9:1) with a few crystals of 1,10-phenanthroline. The solution was then frozen under a strong nitrogen flow and the filling port sealed by glass blowing. The solution was degassed by three freeze–pump–thaw cycles. The flask was then cooled in an ice bath with a magnetic stirrer and the system back-filled with nitrogen gas. The port was opened, and *n*-butyllithium (1.63 M, 1.24 mL) was added dropwise by syringe until the reddish end point persisted. A few drops of dilute 4-bromophenol solution was added to back-titrate, and then the port was sealed. The solvent was removed under vacuum, and the residue was pumped overnight. The salt was washed once with 1,3-dioxolane (degassed and stored over calcium hydride), achieved by transferring the solvent on and off under vacuum. Finally, degassed 1,3-dioxolane (3.8 mL) and C_6D_{12} lock standard (0.2 mL) were transferred from calcium hydride, and the flask was removed from the manifold. The phenolate solution was then drained through a sintered frit into the NMR tube, which was then frozen and sealed.

Method B. The reaction flask was back-filled with nitrogen and charged with a solution of 4-bromophenol (0.346 g, 2 mmol) in dry methanol (10 mL). The solution was cooled in an ice bath, and a lithium methoxide (2.86 mL, 0.70 M) solution in methanol was added with a syringe. The solvent was removed and the remaining white salt heated (80 °C) under vacuum for 48 h. The sample was then washed with 1,3-dioxolane (10 mL) before being taken up in 1,3-dioxolane (3.8 mL) and C_6D_{12} (0.2 mL). The low-temperature ^{13}C NMR spectrum was identical with that obtained for the sample prepared by method A.

Method C. A lithium 4-bromophenolate sample (8 mmol) was prepared by titrating the phenol in ether/hexane with butyllithium according to method A. The resulting salt, however, was then recrystallized[13] three times under vacuum from ether/toluene (1:3, 10 mL). The recrystallized salt was washed with 1,3-dioxolane and then taken up in 1,3-dioxolane (5.0 mL) and C_6D_{12} (0.3 mL). The final solution was completely clear and colorless. The sample remaining in the recrystallization apparatus was recovered and titrated to determine the concentration of the sealed sample (0.66 M). The ^{13}C NMR spectra were identical with those of the other samples prepared by methods A and B.

NMR Spectroscopy. NMR spectra were obtained with Bruker WP-200 and Bruker WH-360 instruments. ^{13}C chemical shifts are reported relative to internal C_6D_{12} (26.40 ppm) or THF (26.50 ppm). For the thermodynamic determinations where precise sample temperatures were needed, a calibrated methanol sample was used; otherwise, absolute temperatures were not determined, but the nominal values are known to be accurate within ±2 °C.

The ^7Li and ^{13}C relaxation times were carried out with a 10-mm broad-band probe, and the inversion–recovery method was employed. Proton decoupling was accomplished by the Waltz sequence, and the decoupler was kept on during ^7Li observation to avoid possible changes in temperature. The two sets of relaxation times were obtained back to back without altering the temperature setting. The relaxation times were calculated by the three-parameter nonlinear least-squares program. At least three separate determinations of each relaxation time were made.

The low-temperature equilibrium constants for dimer/tetramer exchange of the 0.42 M 4-bromophenolate solution in THF were obtained from direct integration of the respective C(2) bands in the proton-decoupled ^{13}C NMR (90.56 MHz). The equilibrium constants for dimer/tetramer exchange in the 0.50 M 2-isopropylphenolate solution in THF were obtained by integrating the C(4) bands in the ^{13}C NMR. The equilibrium constants for the tetramer/hexamer exchange for the various 3,5-dimethoxyphenolate solutions in dioxolane were measured from the integrations of the respective C(2) signals in the ^{13}C NMR. A 90° pulse width and relaxation delay $>5T_1$ were used, and all spectra were obtained with high S/N. The equilibrium constants for dimer/tetramer exchange for the 0.20 M 3,5-dimethylphenolate solution in pyridine were obtained by simulating the observed line shapes for the exchanging methyl proton resonances in the 360-MHz ^1H NMR. The observed spectra were treated as an unequally populated two-site exchange problem, in which both population and rate of exchange are a function of temperature. The spectra were simulated by DNMR3, which requires as input the chemical shifts of exchanging sites at the limit of slow exchange, the relative population, T_2^*, and the rate constant. The thermodynamic quantities were extracted by the nonlinear least-squares method.

Results and Discussion

^7Li Quadrupole Splitting Constants. This quantity (QSC) is given in the following equation, which also shows how it can be evaluated from ^7Li and ^{13}C spin–lattice relaxation times, T_1^q and T_1^{dd}, respectively.

$$\mathrm{QSC} = (1 + \eta^2/3)^{1/2}(e^2Qq_{zz}/h) = 70.0(T_1^{dd}/T_1^q)^{1/2}\ (\mathrm{kHz})$$

Q is the ^7Li electric quadrupole moment. The quantity q_{zz} is the principal electric field gradient at the lithium nucleus and $\eta = (q_{xx} - q_{yy})/q_{zz}$ is its asymmetry parameter. The various assumptions in applying this equation have been considered in an earlier paper.[14] In general, T_1^{dd} must refer to a singly protonated ^{13}C nucleus and must reflect the reorientation of q_{zz} due to rotational diffusion of the molecule. This will usually be the case for T_1^{dd} of an unsubstituted C(4) of a lithium phenolate.

Values of QSC are used in some of the structural arguments presented below. Empirical relations between QSC and the degrees of aggregation and of solvation of lithium salts in weakly polar aprotic solvents have been established, and these are in reasonable agreement with predictions of relative magnitudes of q_{zz} based on single point charge models.[14]

4-Substituted Lithium Phenolates. ^{13}C chemical shift data for a series of 4-substituted phenolates and 3,5-dimethylphenolates are presented in Table I. The 3,5-dimethyl analogues were included because the salts have better solubilities than the corresponding phenolates. Of the two solvents employed, pyridine is the stronger donor (see Table X) and will, therefore, favor dimer formation. As we have pointed out previously,[8] the difference, $\Delta\delta_{c(4)}$, between the chemical shift of the para carbon in the salt and that in the corresponding anisole is a convenient parameter for characterizing the degree of aggregation since it responds mainly to the π-charge density at that position. $\Delta\delta_{c(3)}$ is affected very little by aggregation, and $\Delta\delta$ for C(1) and C(2) respond to both charge densities and proximity effects, which makes their interpretation more difficult.

For tetramers in pyridine, $\Delta\delta_{c(4)}$ lies in the range 4.2–6.1 compared to 8.5–10.6 for the dimers. It is clear that there is a significant electronic effect controlling the dimer/tetramer equilibrium. Thus, CH_3O and F substitutions result in tetramer formation at room temperature while lithium 4-bromophenolate

(8) Jackman, L. M.; Debrosse, C. W. *J. Am. Chem. Soc.* **1983**, *105*, 4177.
(9) DeJonge, J.; Bibo, B. H. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 1448.
(10) Bruice, T. C.; Kharasch, N.; Winzler, R. J. *J. Org. Chem.* **1953**, *18*, 83.
(11) Baddeley, G. *J. Chem. Soc.* **1943**, 527.
(12) Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954.
(13) Jackman, L. M.; Scarmoutzos, L. M. *J. Am. Chem. Soc.* **1987**, *109*, 5348.
(14) Jackman, L. M.; Scarmoutzos, L. M.; Debrosse, C. W. *J. Am. Chem. Soc.* **1987**, *109*, 5355.

Table I. ^{13}C Chemical Shifts for 4-Substituted Lithium Phenolates and 3,5-Dimethylphenolates

substituents					δ				
3,5	4	solvent	concn, M	temp, °C	C(1)	C(2)	C(3)	C(4)	$-\Delta\delta_{C(4)}$[a]
H	H	pyridine	0.5	26	169.0	120.6	130.2	114.3	7.0
CH_3	H	pyridine	0.17	26	169.5	118.7	138.7	114.5	8.6
CH_3	H	pyridine	0.17	−40	171.5	119.0	139.0	114.6	8.5
					169.1	118.7	139.0	117.0	6.1
H	Br	pyridine	0.17	26	170.4	122.4	132.9	103.0	10.6
H	Cl	pyridine	0.15	26	170.0	121.5	130.1	115.9	9.9
CH_3	Cl	pyridine	0.50	75	167.5	120.9	136.7	119.2	7.7
CH_3	Cl	pyridine	0.50	−40[b]	169.7	120.9	136.7	117.1	9.8
CH_3	Cl	pyridine	0.13	75	168.1	120.9	136.7	118.5	8.4
CH_3	Cl	pyridine	0.13	−40[b]	169.7	120.9	136.7	117.1	9.8
H	F	pyridine	0.17	26	165.8	119.9	116.1	153.1	4.2
H	OCH_3	pyridine	0.15	26	163.7	120.3	116.3	150.1	4.9
CH_3	OCH_3	pyridine	0.52	85	164.7	120.2	130.9	147.4	4.3
CH_3	OCH_3	pyridine	0.52	−40	164.8	120.2	131.1	147.2	4.5
CH_3	H	THF	0.24	26	168.3	118.2	138.4	116.5	6.5
CH_3	H	THF	0.24	−70	168.1	118.1	138.3	116.4	6.6
H	CF_3	THF	0.46	50	172.8	119.8	127.6	115.2	8.4
H	CF_3	THF	0.46	−70	173.5	119.4	127.4	112.7	10.9
H	CF_3	THF	0.23	50	173.1	119.7	127.5	115.4	8.2
H	CF_3	THF	0.23	−70	173.5	119.4	127.4	112.6	11.0
H	Br	THF	0.42	26	167.9	121.8	132.7	105.8	7.7
H	Br	THF	0.42	−60	167.0	122.0	132.7	106.0	7.5
					169.5	121.4	132.3	102.3	11.2
H	OCH_3	THF	0.15	50	162.6	119.7	115.6	150.6	4.4
H	OCH_3	THF	0.15	−55	162.2	119.6	115.7	150.0	5.0

[a] $\Delta\delta_{C(4)} = \delta_{C(4)}(\text{salt}) - \delta_{C(4)}(\text{anisole})$. [b] Very broad signal.

Table II. ^{13}C Chemical Shifts for 2-Alkyl-Substituted Lithium Phenolates (0.5 M) in THF

		$\delta_{^{13}C}$						
substituent	temp, °C	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	$-\Delta\delta_{C(4)}$,[a] ppm
CH_3	−70	166.4	127.1	131.0	114.8	127.7	119.3	6.3
CH_2CH_3	−60	165.8	132.5	127.6	115.0	127.3	119.3	7.2
		168.2	132.5	128.2	111.9	127.3	119.3	10.4
$CH_2CH_2CH_3$	−60	165.8	130.9	129.3	114.9	127.3	119.3	6.3
		168.2	131.2	128.2	111.8	127.3	119.5	9.4
$CH(CH_3)_2$	−60	164.4	137.6	126.8	115.5	126.5	120.2	6.0
		167.3	137.1	126.8	112.3	125.3	119.6	9.2
$C(CH_3)_3$	−70	169.5	137.3	126.2	112.0	127.0	122.3	9.0

[a] See footnote *a*, Table I.

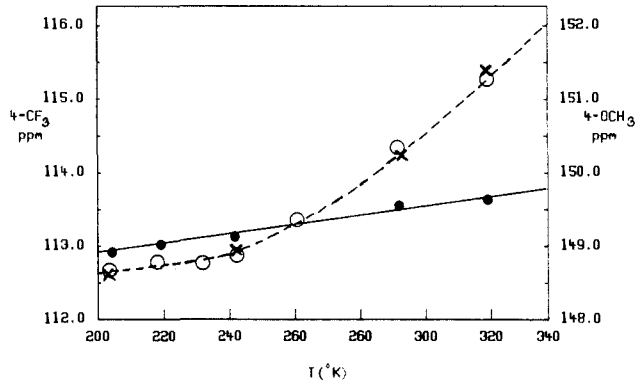


Figure 1. Temperature dependences of $\delta_{C(4)}$ for 4-substituted lithium phenolates in THF. 4-CF_3: O, 0.46 M; ×, 0.23 M. 4-CH_3O: ●, 0.15 M.

exists exclusively as the dimer. The 4-chlorophenolates are mixtures at room temperature, with the dimer being the major component. The 4-unsubstituted salts are also mixtures.[8]

In the less powerful donor solvent, THF, the equilibria are moved toward tetramers. Thus, lithium 3,5-dimethylphenolate is a tetramer and the 4-bromophenolate a mixture of dimer and tetramer. Lithium 4-(trifluoromethyl)phenolate appears to be a dimer. The chemical shift of C(4), however, exhibits a marked nonlinear dependence on temperature (Figure 1), although these shifts are independent of concentration. This behavior is interpreted as arising from conversion of the fully isolated dimer, $Li_2A_2S_4$, to the disolvated species, $Li_2A_2S_2$. Analogous behavior has been observed for dimeric lithium arylamides in THF.[13] In contrast, the analogous plot for lithium 4-methoxyphenolate is linear with a normal[15] slope of 5.8×10^{-3} ppm/°C, and it is, of course, a tetramer throughout the temperature range.

The general trend is clear. Increasing electron withdrawal by a para substituent favors dimer formation. In other words, the less basic phenolate ions compete less favorably with solvents for the lithium cation. The total spread in the pK_b (48% aqueous ethanol) values of the anions of the salts in Table I is only 2.0[16]

Table III. Dimer to Tetramer Ratios (D:T) for Lithium 2-Alkylphenolates (0.5 M) in THF at −60 °C

substituent	D:T	substituent	D:T
CH_3	0:100	$CH(CH_3)_2$	40:60
CH_2CH_3	6:94	$C(CH_3)_3$	100:0
$CH_2CH_2CH_3$	38:62		

Table IV. Spin–Lattice Relaxation Times for ^{13}C and ^7Li and ^7Li Quadrupole Splitting Constants for Lithium 2-Methyl- and 2-*tert*-Butylphenolates (0.5 M) in THF at 30 °C

	T_1, s	
nucleus	2-CH_3	2-$C(CH_3)_3$
C(4)	0.680	0.962
^7Li	0.947	0.230
QSC, kHz	59.3	143.2

(15) Lambert, J. B.; Vagenas, A. R.; Somani, S. *J. Am. Chem. Soc.* **1981**, *103*, 6398.

Table V. ^{13}C Chemical Shifts for Lithium 2-(Methoxymethyl)- and 2-(Trifluoromethyl)phenolates (0.45 and 0.48 M, Respectively) in THF

	2-methoxymethyl		2-trifluoromethyl	
nucleus	−70 °C	+26 °C	−90 °C	+26 °C
C(1)	168.2	168.1	169.2	169.0
C(2)	125.9	125.8	118.0	118.3
C(3)	130.8	130.8	126.9	127.1
C(4)	113.6	113.9	111.1	111.6
C(5)	131.3	131.3	133.5	133.5
C(6)	120.4	120.5	123.0	123.0
C_α	74.6[a]	74.6[a]	128.0	128.0

[a] $\delta_{OCH_3} = 57.0$.

Table VI. ^{13}C Spin–Lattice Relaxation Times and ^7Li Quadrupole Splitting Constants for Lithium 2-*n*-Propyl-, 2-(Methoxymethyl)-, and 2-(Trifluoromethyl)phenolates (0.51, 0.45, and 0.48 M, Respectively) in THF

	T_1, s				
	2-*n*-propyl:	2-methoxymethyl			2-CF_3:
nucleus	−40 °C	−60 °C	−40 °C	+30 °C	+30 °C
C(3)	*a*	0.143	0.220	0.725	
C(4)	0.253[b]	0.142	0.205	0.642	1.12
C(5)	0.321[b]	0.149	0.211	0.711	1.51
C(6)	*a*	0.140	0.233	0.709	1.40
^7Li	0.238[b]		0.191	0.475	0.361
QSC,[c] kHz	72.2		72.5	81.6	123.3

[a] Peaks unresolved. [b] Assigned to tetramer. [c] Based on T_1 for C(4).

units, and yet, this is enough to produce a change from predominantly dimer to tetramer in THF.

2-Alkyl-Substituted Lithium Phenolates. Our earlier studies[8] suggest that steric effects are important in controlling the degree of aggregation of lithium phenolates, and this is now confirmed for the series of ortho substituents, CH_3, CH_3CH_2, $CH(CH_3)_2$, and $C(CH_3)_3$. ^{13}C chemical shift data for the aromatic carbon atoms are presented in Table II, and the ratios of dimer to tetramer at −60 °C are given in Table III. Clearly, these results confirm the important role of steric hindrance in controlling the degree of aggregation.

We have also determined the values of ^7Li QSC for the 2-methyl- and 2-*tert*-butylphenolates. The relaxation times from which the QSC's are calculated are given in Table IV. The value for the 2-methyl analogue is as expected for the tetrasolvated tetramer while that for the 2-*tert*-butyl salt shows it to be the tetrasolvated dimer.

Chelating Substituents. In a study of the aggregation of lithium N-substituted anilides, we noted that the *N*-methoxyethyl group stabilized the dimer relative to the monomer.[13] It is of interest to establish whether similar substitution in the phenolate systems will stabilize tetramers relative to dimers. Lithium 2-(methoxymethyl)phenolate is an appropriate compound for this purpose.

The ^{13}C spectra of the 2-methoxymethyl salt in THF exhibit only one set of resonances, the chemical shifts (Table V) of which, at −70 and +26 °C, show little variation. The values of $\Delta\delta_{c(4)}$ at the two temperatures are 7.6 and 7.3 ppm, respectively, and are characteristic of a tetramer. We have also determined QSC's (Table VI) at −40 and +30 °C, and these too are indicative of a tetramer. The values are very similar to that observed for tetrameric lithium 2-*n*-propylphenolate, both being some 10 kHz larger than for the 2-methyl analogue but considerably lower than expected[14] for a dimer (120–150 kHz).

The ^{13}C relaxation times (Table VI) for the proton-bearing, aromatic carbon atoms at −60 °C show that the phenolate is locked in one conformation on the rotational diffusion time scale. At higher temperatures, T_1 for C(4) becomes appreciably shorter than for C(3), C(5), and C(6), indicating that some fast libration of the aryl ring is occurring. This motion is most likely a conformation exchange in the chelate ring resulting in the flipping of the aromatic ring between two orientations.[18]

Since lithium 2-*n*-propylphenolate coexists as a dimer and tetramer in THF at −60 °C, it follows that the 2-methoxymethyl substituent does indeed stabilize the tetramer and that, in general, chelating substituents may favor higher states of aggregation.

It has been suggested[19] that chelation involving the trifluoromethyl group is responsible for high enantioselectivity in the hydroxylation of certain lithium enolates and ester enolates by Vedejs' reagent (MoO_5–pyridine–HMPT).[20] Accordingly, we have examined the effect of the 2-trifluoromethyl group on aggregation. The values of $\Delta\delta_{c(4)}$ for 0.48 M solution of lithium 2-(trifluoromethyl)phenolate in THF at −90 and +26 °C are −11.6 and −11.1 ppm, respectively, indicating that the salt is a dimer in this temperature range. The value of QSC (Table VI) confirms this conclusion. Since the isosteric analogue, lithium 2-methylphenolate, is a tetramer under comparable conditions, we conclude the chelation effect, if any, of the trifluoromethyl substituent is insufficient to offset its electronic effect on the basicity of the anion, which favors the dimer.

Thermodynamics of Dimer/Tetramer Equilibria. Three systems, 4-bromophenolate in THF, 3,5-dimethylphenolate in pyridine, and 2-isopropylphenolate in THF, consist of coexisting dimers and tetramers below temperatures at which the rate of interaggregate exchange is comparable with the ^{13}C time scale at 90 MHz. Thus, it was possible, using line shape analysis and/or direct integration, to determine the dimer/tetramer pseudoequilibrium constants[21] as functions of temperature. These data, together with the thermodynamic parameters calculated by the method of nonlinear least squares, are presented in Table VII. They may be compared with $\Delta H = 2.1 \pm 1.1$ kcal mol^{-1} and $\Delta S = 19 \pm 4$ cal mol^{-1} K^{-1} reported by Heinzer, Oth, and Seebach[7d] for the dimer/tetramer equilibrium of *n*-butyllithium in THF.

All three systems are characterized by quite large increases in entropy on going from dimer to tetramer, and this is, of course, qualitatively consistent with the liberation of some solvent as, for example, in the equilibrium

$$2Li_2A_2S_4 \rightleftharpoons Li_4A_4S_4 + 4S$$

The dominant entropy term is the gain of translational freedom of the solvent molecules, and the values of ΔS calculated from the translational partition functions for the various species in the equilibrium are ~65 cal mol^{-1} K^{-1} at 298 K. The smaller, observed values might be a consequence of a lower degree of solvation of the dimer, as has been tentatively suggested[22] for the analogous dimer/tetramer equilibrium for *n*-butyllithium in THF. We believe that this cannot be the case for the lithium 3,5-dimethylphenolate/pyridine system at 298 K. Our studies[14] of ^7Li quadrupole splitting constants (QSC) have shown that lithium 2,6-dimethylphenolate in pyridine at this temperature exists as the species $Li_2A_2S_4$, and this is a much more sterically hindered system than the 3,5-dimethyl system. Other possible explanations include a primary solvation of greater than 1 per lithium for the tetramer, which is unlikely, or greater ordering of solvent molecules in the higher solvent shells in the case of the tetramer. Support for the latter is provided by the observation of the roughly linear relation between ΔH and ΔS, which indicates that increased exothermicity of tetramer formation is partly compensated for

(16) Calculated from the Hammett σ and ρ values given in Tables 3-1 and 6-1, respectively, in ref 17.

(17) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley-Interscience: New York, 1975.

(18) London, R. E.; Phillipi, M. A. *J. Magn. Reson.* **1981**, *45*, 476.

(19) Morizawa, Y.; Yasuda, A.; Uchida, K. *Tetrahedron Lett.* **1986**, *27*, 1833.

(20) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(21) Since the degrees of solvation of reactants and products are not necessarily known, we adopt the practice of Heinzer, Oth, and Seebach[7d] and use the pseudoequilibrium constant defined as $K_{eq} = [T]/[D]^2$. Assuming that conversion of two molecules of dimer to one of tetramer is accompanied by the release of four molecules of solvent and that the molarity of the solvent is ≈13, the values of $\Delta H°$ and $\Delta S°$ are smaller by 0.1 kcal mol^{-1} and greater by 4–5 cal mol^{-1} K^{-1} than the respective values of ΔH and ΔS in Table VII.

(22) Kaufmann, E.; Raghavachi, K.; Reed, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 2553.

Table VII. Equilibrium Constants and Thermodynamic Parameters for 2 Dimer ⇌ Tetramer Equilibria for Three Lithium Phenolates

lithium 4-bromophenolate (0.42 M) in THF			lithium 3,5-dimethylphenolate (0.2 M) in pyridine			lithium 2-isopropylphenolate (0.5 M) in THF		
temp, K	$I(t)/I(d)^a$	K_{eq}, mol^{-1}	temp, K	$I(t)/I(d)^b$	K_{eq}, mol^{-1}	temp, K	$I(t)/I(d)^c$	K_{eq}, mol^{-1}
195	0.54	2.00	233	0.94	11.0	195	0.64	2.12
200	0.67	2.64	237	0.82	13.6	199	0.85	3.08
205	0.81	3.49	244	0.70	17.5	206	1.05	4.29
210	1.01	4.81	252	0.55	25.6	211	1.36	6.40
215	1.13	5.71	258	0.46	33.9	218	1.85	10.5
227	1.61	9.91	266	0.35	53.8	225	3.27	27.5
			274	0.29	76.6	232	4.13	42.0
						240	5.10	62.3
ΔH = 4.4 ± 0.5 kcal mol^{-1}			ΔH = 6.6 ± 0.2 kcal mol^{-1}			ΔH = 7.5 ± 0.5 kcal mol^{-1}		
ΔS = 24 ± 2 cal mol^{-1} K^{-1}			ΔS = 33 ± 1 cal mol^{-1} K^{-1}			ΔS = 38 ± 2 cal mol^{-1} K^{-1}		

[a] Ratio of intensities of C(2) ^{13}C resonances for tetramer/dimer. [b] Ratio of populations for tetramer/dimer from ^1H line shape analysis. [c] Ratio of intensities of C(4) ^{13}C resonances for tetramer/dimer.

Table VIII. ^{13}C Chemical Shifts for Lithium Phenolates in Dioxolane

			$\delta_{^{13}C}$				
substituents	concn, M	temp, °C	C(1)	C(2)	C(3)	C(4)	$-\Delta\delta_{C(4)}$
3,5-dimethoxy	0.51	26	169.3	98.1	163.1	89.0	4.7
		−50	169.4	97.7	162.8	88.7	5.0
			169.4	98.8	162.8	89.4	4.3
3,5-dimethyl	0.2	26	167.5	117.8	139.3	117.2	5.8
		−60	167.6	117.9	139.2	117.3	5.7
			167.6	119.3	139.4	117.5	5.5
3,5-diethyl	0.3	26	167.6	116.7	146.0	114.8	5.8
		−30	167.7	116.6	145.9	114.8	5.8
			167.7	117.9	145.9	115.2	5.4
		−85	167.6	117.9	145.9	115.9	5.2
4-bromo	0.5	26	166.7	121.5	133.0	106.3	7.0
		−90	168.9	121.7	133.4	103.3	10.0
			166.8	121.1	133.1	106.4	6.9
			166.4	123.1	132.9	107.5	5.8

Table IX. Equilibrium Constants as a Function of Concentration and Temperature and Thermodynamic Parameters for Tetramer ⇌ $^2/_3$ Hexamer for Lithium 3,5-Dimethoxyphenolate in Dioxolane

temp, K	concn,[a] M	$I(h)/I(t)^b$	K_{eq}, mol$^{-1/3}$
218	0.78	1.15	1.86
218	0.51	0.99	1.89
218	0.27	0.75	1.86
218	0.12	0.57	1.96
195	0.51	4.73	7.65
201	0.51	3.42	5.65
205	0.51	2.23	3.83
210	0.51	1.66	2.95
216	0.51	1.16	2.16
221	0.51	0.88	1.72
227	0.51	0.64	1.33

ΔH = −4.7 ± 0.3 kcal mol^{-1} ΔS = −20 ± 1.7 cal deg^{-1} mol^{-1}

[a] Nominal concentration of salt. [b] Ratio of intensities of C(2) ^{13}C resonances.

by greater ordering of solvent atmosphere of the product.

The enthalpies are in agreement with qualitative predictions. Thus, the higher value for 3,5-dimethyl- vs 4-bromophenolate is a consequence of the stronger solvating power of pyridine compared to THF. The higher endothermicity for tetramer formation by 2-isopropylphenolate relative to the 4-bromo derivative in the same solvent reflects the fact that steric factors are more serious in tetramers than dimers.

Hexamers. Lithium 3,5-dimethoxyphenolate in dioxolane at low temperatures coexists as two species having values of $\Delta\delta_{C(4)}$ (Table VIII) in the range usually characteristic of tetramers. The stoichiometric relation between these two species has been established by integrating the C(2) resonances in the spectra for different phenolate concentrations (Table IX), and assuming that the species with $\Delta\delta_{C(4)}$ of −5.0 ppm is a tetramer, and the other species (−4.3) must be a hexamer. The thermodynamic constants calculated from the dependence of the pseudoequilibrium constant on temperature (Table IX) show that the hexamer is more highly solvated than the tetramer.

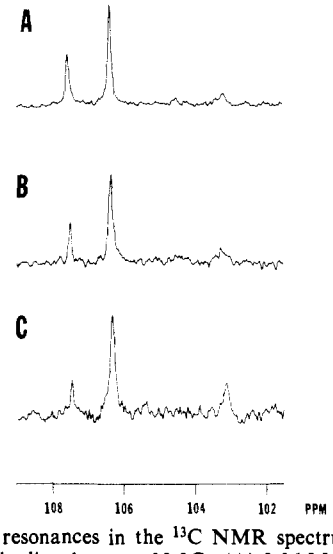


Figure 2. C(4) resonances in the ^{13}C NMR spectrum of lithium 4-bromophenolate in dioxolane at −90 °C: (A) 0.96 M, (B) 0.50 M, (C) 0.25 M.

Lithium 3,5-dimethylphenolate in dioxolane (0.44 M) has been shown[8] by vapor pressure barometry to be a tetramer at room temperature with a ^7Li quadrupole splitting constant of 66 kHz.[14] The 3,5-diethylphenolate (0.3 M) has similar $\Delta\delta_{C(4)}$ and QSC values [63 ± 4 kHz; $T_1(C(4))$ = 0.339, $T_1(^7Li)$ = 0.415 s at 30 °C], and the values (Table VIII) of $\Delta\delta_{C(4)}$ for the two salts are consistent, with tetramers being the predominant species. At lower temperatures, however, both salts, like the 3,5-dimethoxy derivative, are converted to hexamers, and in the case of the 3,5-diethylphenolate, at −85 °C this is the only species observable in the ^{13}C NMR spectrum.

Lithium 4-bromophenolate in dioxolane coexists as three species at low temperatures (Figure 2; Table VIII). The chemical shifts of the C(4) resonances and the qualitative order of the dependence

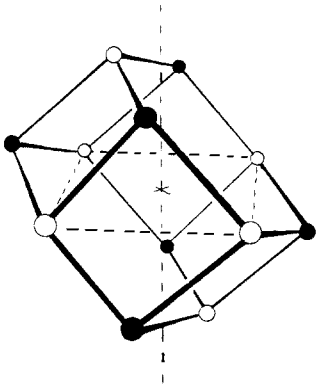


Figure 3. Hexamer structure based on that for the unsolvated lithium enolate of 3,3-dimethyl-2-butanone.[27] The lithium atoms are represented by open circles.

of their intensities on concentration indicate that they are the dimer, tetramer, and hexamer with $\Delta\delta_{C(4)}$ = 10.0, 6.9, and 5.8 ppm, respectively. Similar behavior appears to be exhibited by lithium 4-chlorophenolate, but in this system, the C(2) and C(4) resonances of the various coexisting species are badly overlapped, and a complete assignment of the spectrum was not undertaken.

The similarity between the C(4) chemical shifts for the hexamers and tetramers indicates that, in the former, each oxygen anion is bonded to three lithium cations. This situation prevails in the crystal structures of $[Li(C_6H_{11})]_6$,[23] $(LiSiMe_3)_6$,[24] $[LiN{:}C(NMe_2)_2]_6$,[25] and $(LiN{:}C\text{-}t\text{-}Bu)_2)_6$[26] as well as in that of the unsolvated hexamer of 1-lithio-3,3-dimethyl-2-butanone.[27] In all these systems, the $(LiX)_6$ unit can be regarded as having an approximately hexagonal-prismatic structure[27] in which the six lithium atoms occupy the six corners of a distorted octahedron[25] (Figure 3). All these compounds are unsolvated in the crystalline state, although this is due to the fact that they were prepared in and crystallized from hydrocarbon solvents. The occurrence of hexameric lithium phenolates in dioxolane is, however, not because the hexamer is the preferred structure for an unsolvated salt. As pointed out above, the hexamer is more heavily solvated than the tetramer. Evidently, it is more difficult to solvate the tetramer with such a weak donor solvent (see below) as dioxolane. In better donor solvents such as THF, complete solvation of the tetramer is presumably possible, and the hexamer is no longer formed even at low temperatures.

There is evidently a significant effect of anion basicity on hexamer formation. Thus, at −90 °C the ratio of hexamer to tetramer in a 0.96 M solution of lithium 4-bromophenolate is 1:2.7 in contrast to the complete conversion of 0.3 M 3,5-diethylphenolate to hexamer at −85 °C.

Solvent Effects. Lithium 4-bromophenolate, which can exist as a dimer, tetramer, or hexamer in solution, provides an excellent system for studying the effect of the solvent on the degree of aggregation. Some pertinent data are assembled in Table X. We will attempt to interpret these data in terms of the following equilibria

$$\underset{2}{Li_2A_2S_4} \rightleftharpoons \underset{3}{Li_2A_2S_2} \rightleftharpoons \underset{4}{Li_4A_4S_m} \rightleftharpoons \underset{5}{Li_4R_4S_n} \rightleftharpoons \underset{6}{Li_6A_6S_p}$$

where A is the phenolate anion and m, n, and p are integers with $m > n$. The values of $\Delta\delta_{C(4)}$ for the dimers observed in THF and dioxolane at low temperatures correspond to the species **2** and **3**, respectively, the difference being due to the greater localization of the anionic charge on oxygen by the neighboring, *unsolvated* lithium cations. Similar observations have been made for lithium secondary arylamides.[14] It is evident that, in the absence of steric factors, dimer formation increases, relative to tetramer, with increasing Lewis basicity of the solvents as assessed by their heats of reaction (ΔH_{BF_3}) with boron trifluoride, which have been determined by Maria and Gal.[28,29] Thus, at room temperature, the proportion of dimer increases in the order dioxolane < THF < pyridine. Dimethoxyethane is presumably somewhat less basic than THF but can promote dimer formation by functioning as a bidentate ligand.

Two tetrameric systems are observed. That in THF is the species **4** and is characterized by having $\Delta\delta_{C(4)}$ = 7.5 ppm, whereas the species in diethyl ether, dioxolane, and 2,6-lutidine have values in the range 6.8–7.0 ppm and are accordingly assigned the less solvated structure **5**. The salt in triethylamine has the same $\Delta\delta_{C(4)}$ as the hexamer, but the possibility that it has the structure **5** with an even lower value of n cannot be excluded.

The relative solvating power for the series THF, dioxolane, and diethyl ether is confirmed by the comparison of the ^{13}C spectra of lithium 2-isopropylphenolate in these solvents (0.5 M at −80 °C). The relative proportions of tetramer/dimer are 39:61, 88:12, 100:0, respectively.

Table X. Effects of Solvent on $\Delta\delta_{C(4)}$ for Lithium 4-Bromophenolate

solvent	$-\Delta H_{BF_3}$, kcal mol^{-1}	concn, M	temp, °C	$-\Delta\delta_{C(4)}$,[a] ppm	species
pyridine	30.8[b]	0.17	26	10.6	**2** + **4**
DME		0.50[c]	26	8.4	**2** + **4**
THF	21.6[b]	0.42	26	7.7	**4**
			−60	7.5	**4**[d]
				11.5	**2**[d]
dioxolane	16.4[e]	0.51	26	7.0	**5**
			−90	5.8	**6**[f]
				6.9	**5**[f]
				10.0	**3**[f]
diethyl ether	18.8	0.50	26	6.8	**5**
			−40	6.8	**5**
2,6-lutidine	23.3	0.50	26	7.0	**5**
triethylamine	32.5	0.10[g]	26	5.9	**6** or **5**[h]

[a] Footnote *a*, Table I. [b] Reference 8. [c] Poor solubility at lower temperatures. [d] 2:4 ≈ 2:1. [e] Reference 29. [f] 6:5:3 ≈ 1:3.8:0.2. [g] Poor solubility. [h] See text.

Summary

i. Lithium phenolates in a variety of weakly polar aprotic solvents can exist as monomers, dimers, tetramers, or hexamers.

ii. The basicity of the anion is a factor in controlling the degree of aggregation, increased aggregation being favored by increasing basicity.

iii. Most ortho substituents favor dimers relative to tetramers, presumably for steric reasons.

iv. The chelating ortho substituent, $-CH_2OCH_3$, induces tetramer formation.

v. Increased Lewis basicity of the solvent promotes dimer formation. In the case of diethyl ether, 2,6-lutidine, and triethylamine, steric factors outweigh inherent basicity and result in tetramer formation.

vi. The effect of the solvent is an interplay of entropic and enthalpic effects, which favors the more highly solvated species at low temperatures.

vii. 1,3-Dioxolane is unique among the solvents studied in that it promotes the formation of hexamers at low temperatures.

viii. Monomer formation has so far only been observed[8] for a very highly hindered phenolate in a strongly basic solvent (lithium 2,6-di-*tert*-butylphenolate in pyridine).

Acknowledgment. We gratefully acknowledge support for this research by a grant (CHE85-03502) from the National Science Foundation.

Registry No. Lithium phenolate, 555-24-8; lithium 3,5-dimethylphenolate, 83859-28-3; lithium 4-bromophenolate, 114299-83-1; lithium

(23) Zerger, R.; Rhine, W.; Stucky, G. *J. Am. Chem. Soc.* **1974**, *96*, 6048.
(24) Schaaf, T. F.; Butler, W.; Glick, M. D.; Oliver, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 7593. Ilsley, W. H.; Schaaf, T. F.; Glick, M. D.; Oliver, J. P. *Ibid.* **1980**, *102*, 3769.
(25) Clegg, W.; Snaith, R.; Shearer, H. M. M.; Wade, K.; Whitehead, C. *J. Chem. Soc., Dalton Trans.* **1983**, 1309.
(26) Shearer, H. M. M.; Wade, K.; Whitehead, G. *J. Chem. Soc., Chem. Commun.* **1979**, 943.
(27) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462.
(28) Maria, P.-C.; Gal, J.-F. *J. Phys. Chem.* **1985**, *89*, 1296.
(29) Maria, P.-C., private communication.

4-chlorophenolate, 1121-75-1; lithium 4-chloro-3,5-dimethylphenolate, 114299-84-2; lithium 4-fluorophenolate, 114299-85-3; lithium 4-methoxyphenolate, 1122-94-7; lithium 3,5-dimethyl-4-methoxyphenolate, 114299-86-4; lithium 4-(trifluoromethyl)phenolate, 114299-87-5; lithium 2-methylphenolate, 83859-26-1; lithium 2-ethylphenolate, 114299-88-6; lithium 2-propylphenolate, 114299-89-7; lithium 2-isopropylphenolate, 114299-90-0; lithium 2-*tert*-butylphenolate, 114299-91-1; lithium 2-(methoxymethyl)phenolate, 114299-92-2; lithium 2-(trifluoromethyl)-phenolate, 114299-93-3; lithium 3,5-dimethoxyphenolate, 114299-94-4; lithium 3,5-diethylphenolate, 114299-95-5; phenol, 108-95-2; 3,5-dimethylphenol, 108-68-9; 4-bromophenol, 106-41-2; 4-chlorophenol, 106-48-9; 4-chloro-3,5-dimethylphenol, 88-04-0; 4-fluorophenol, 371-41-5; 4-methoxyphenol, 150-76-5; 3,5-dimethyl-4-methoxyphenol, 4962-29-2; 4-(trifluoromethyl)phenol, 402-45-9; 2-methylphenol, 95-48-7; 2-ethylphenol, 90-00-6; 2-propylphenol, 644-35-9; 2-isopropylphenol, 88-69-7; 2-*tert*-butylphenol, 88-18-6; 2-(methoxymethyl)phenol, 5635-98-3; 2-(trifluoromethyl)phenol, 444-30-4; 3,5-dimethoxyphenol, 500-99-2; 3,5-diethylphenol, 1197-34-8.

Low-Spin Cyanide Adduct of Transferrin

Susan K. Swope,[†] N. Dennis Chasteen,*[,†] Katherine E. Weber,[†] and Daniel C. Harris[‡]

Contribution from the Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824-3598, and Chemistry Division, Research Department, Naval Weapons Center, China Lake, California 93555-6001. *Received September 22, 1987*

Abstract: The interaction between cyanide and the high-spin iron(III) centers of diferric human serum transferrin was investigated to gain insight into the nature of mixed-ligand complexes that are formed between iron, the protein, and exogenous chelators. The binding of cyanide forms a low-spin adduct at only the C-terminal iron(III) binding site of transferrin. The characteristic $g' = 4.3$ EPR spectrum of the high-spin Fe(III) at this site is converted to a low-spin spectrum exhibiting $g_x = 2.34$, $g_y = 2.15$, and $g_z = 1.92$. Analysis of the g factors according to a crystal field perturbation model indicates that the unpaired electron is in a d_{xy} orbital and that the metal site has nearly complete "rhombic" symmetry. The cyanide adduct is formed according to the reaction Fe_c-Tf-$HCO_3^z + 3CN^- \rightarrow Fe_c$-Tf-$(CN)_3^{z-2} + HCO_3^-$ where the synergistic anion HCO_3^- normally required for iron(III) binding to the protein is displaced from the first-coordination sphere by cyanide. This result demonstrates that the presence of bicarbonate is not essential for the formation of stable mixed-ligand complexes with the protein. The stoichiometry of the reaction implies that three CN^- anions are bound to the metal and, by inference, three coordination sites are accessible to exogenous ligands in the iron(III)-protein complex. The possibility that some of the CN^- simply binds elsewhere on the protein is not precluded by the data, however. Ultraviolet difference and visible spectral measurements on the C-terminal monoferric transferrin suggest that the phenolate groups of two tyrosine residues are coordinated to the iron. A possible structure for the metal site is proposed.

The transferrins are a class of iron-binding and -transport proteins that play an essential role in the metabolism of iron in vertebrates. All transferrins contain two metal-binding sites, bind iron strongly in the 3+ oxidation state, and display EPR signals at $g' = 4.3$, which are characteristic of high-spin Fe(III) in a ligand environment of low symmetry.[1,2] While serum transferrin functions as the iron-transport protein of the circulation, ovotransferrin from egg white and lactoferrin from milk and other secretions have bacteriostatic functions as well as other possible roles.[3-5]

The mechanism by which serum transferrin exchanges iron with its environment is not well understood, but it is clear that anions are important in this process. The binding of (bi)carbonate to the iron is required for the metal to bind at the specific sites of the protein.[6] In addition, anions such as chloride and perchlorate are known to affect the kinetics of iron exchange between chelators and the protein and to influence the relative thermodynamic stability of iron binding in the two sites.[7-11] Recent studies of iron exchange between transferrin and anionic chelators have detected the formation of unstable mixed-ligand intermediate complexes of the type chel-Fe-transferrin in which both the chelator and protein are presumably coordinated to the iron.[12,13] Little is known about the metal-site coordination in these intermediates and whether the (bi)carbonate remains bound.

Knowledge of labile coordination sites in the iron-transferrin complex is particularly important in light of the recently published X-ray structure of lactoferrin, which indicates that the protein contributes four amino acid ligands to the metal: two tyrosines, one histidine, and one aspartate.[14] It is likely that the remaining two positions are filled by (bi)carbonate and possibly water (or hydroxide) to give a six-coordinate complex. Therefore, it appears that at least two ligand sites on the iron may be accessible to small anions and chelators, which participate in removal of the metal from the protein.

[†] University of New Hampshire.
[‡] Naval Weapons Center.

(1) Chasteen, N. D. In *Iron Binding Proteins without Cofactors or Sulfur Clusters*; Theil, E. C., Eichorn, G. L., Marzilli, L. G., Eds.; Advances in Inorganic Chemistry Vol. 5; Elsevier: New York, 1983; pp 201-233.
(2) Aisen, P.; Listowski, I. *Annu. Rev. Biochem.* **1980**, *49*, 357-393.
(3) Schade, A. L.; Caroline, L. *Science (Washington, D.C.)* **1944**, *100*, 14-15.
(4) Alderton, G.; Ward, W. H.; Fevold, H. L. *Arch. Biochem. Biophys.* **1946**, *11*, 9-13.
(5) Montreuil, J.; Mazuerier, J.; Legrand, D.; Spik, G. In *Proteins of Iron Storage and Transport*; Spik, G., Montreuil, J., Crichton, R. R., Mazuerier, J., Eds.; Elsevier: New York, 1985; pp 25-38.
(6) Schlabach, M. R.; Bates, G. W. *J. Biol. Chem.* **1975**, *250*, 2182-2188.
(7) Williams, J.; Chasteen, N. D.; Moreton, K. *Biochem. J.* **1982**, *201*, 527-532.
(8) Chasteen, N. D.; Williams, J. *Biochem. J.* **1981**, *193*, 717-727.
(9) (a) Baldwin, D. *Biochim. Biophys. Acta* **1980**, *623*, 183-188. (b) Baldwin, D. A.; de Sousa, D. M. R. *Biochem. Biophys. Res. Commun.* **1981**, *99*, 1101-1107.
(10) Folajtar, D. A.; Chasteen, N. D. *J. Am. Chem. Soc.* **1982**, *104*, 5775-5780.
(11) Thompson, C. P.; McCarty, B. M.; Chasteen, N. D. *Biochem. Biophys. Acta* **1986**, *870*, 530-537.
(12) Cowart, R. E.; Kojima, N.; Bates, G. W. *J. Biol. Chem.* **1982**, *257*, 7560-7565.
(13) Cowart, R. E.; Swope, S.; Loh, T. T.; Chasteen, N. D.; Bates, G. W. *J. Biol. Chem.* **1986**, *261*, 4607-4614.
(14) Anderson, B. F.; Baker, J. M.; Dodson, E. J.; Norris, G. E.; Rumball, S. V.; Waters, J. M.; Baker, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 1769-1773.

0002-7863/88/1510-3835$01.50/0