Proton Acceptor Abilities of Anions and Possible Relevance to the Hofmeister Series

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Abstract: Proton acceptor abilities of a variety of common anions are reported using phenol and water as proton donors. Equilibrium quotients for 1:1 complexes in organic solvents are given. Anions such as ClO_4^- and BF_4^- are much poorer proton acceptors than SO_4^{2-} and Cl^-, as determined by equilibrium quotients, ir frequency shifts, and the average degree of solvation. The trend in proton acceptor ability is inversely related to the destabilizing effects of these anions on macromolecules. This work suggests that the anions which denature the best can bind effectively because they are poorly solvated.

The proton acceptor properties of anions can be studied using conventional infrared and nmr techniques.[2-4] We have used these methods to study ion association in organic solvents.[5] In a previous experiment[3] we noticed that the proton acceptor abilities of the anions then under study were inversely related to their ability to "salt-in" macromolecules.[6] We have extended our results to include a wider variety of anions and to include the use of water as a proton donor.

Experimental Section

Phenol and water were used as proton donors. They were used as dilute solutions in methylene chloride (for the phenol experiments) and deuteriochloroform (for the water experiments). All measurements were made on a Beckman IR-12 spectrometer as previously described.[3] The $CDCl_3$ (Diaprep or Matheson Coleman and Bell) was used without further purification. No ethanol was present in either lot. Stock salt solutions were prepared and mixed with appropriate amounts of stock solutions containing phenol or water such that the final concentrations were 0.01–0.10 *M* for the salts, 0.05–0.10 *M* for the phenol, or 0.02–0.05 *M* for the water. Detailed procedures for the phenol experiment have been published.[7] The experiments with water as a proton donor were carried out in similar fashion except that the low solubility of water in $CDCl_3$, as well as some interfering absorbance of the solvent in the 3600-cm^{-1} region, required 1.5-mm KBr cells and the use of the variable scale expansion accessory of the IR-12. The amount of water in freshly opened $CDCl_3$ was low (*ca.* 0.005 *M*) and could be directly determined. The water associated with the more hygroscopic salts presented greater difficulties. These materials were dried to constant weight in the flasks used for the final solutions. Blanks (*i.e.*, salt $CDCl_3$, but no added water) were examined, but corrections were not straightforward because an unknown fraction of the detectable water was hydrogen bonded. The water introduced with the salt was the largest source of experimental uncertainty in the final water concentration. No proton–deuterium exchange with $CDCl_3$ could be detected in 12 hr at the equilibrium temperature of the ir compartment (40°). Control experiments showed that the dimerization of phenol and water were negligible at our concentrations in these solvents.

We used tetraalkylammonium and methyltriphenylphosphonium salts, most of which were commercially available or were synthesized earlier.[3,5] Previous experiments suggest that these cations are relatively inert and do not interfere with solvent hydrogen bonding to anions.[1,3,4] Salts of smaller cations (*e.g.*, Li^+, Me_4N^+) for which interferences are likely were not sufficiently soluble under our conditions to be included in this study. All salts were recrystallized and dried at least 24 hr before use. Tetrapropylammonium hydroxide in methanol. The solvent was removed by evaporation and the product was recrystallized from acetonitrile–carbon tetrachloride.

Results

The ir experiment provides a direct measure of the concentration of "free" proton donor, ϕ_f, as a function of initial proton donor and salt concentration.[3,8] From these quantities we prepared a plot: ϕ_f *vs.* $\bar{n}$ ($\bar{n}$ is the average degree of solvation, that is, the concentration of bound proton donor divided by the initial salt concentration) (Figures 1 and 2). These graphs can be analyzed for multiple equilibria of the type

$$n(\mathrm{AH}) + \mathrm{B} \overset{K_n}{\rightleftharpoons} ((\mathrm{AH})_n\cdots\mathrm{B})$$

K_1, for example, is the limiting slope, $d\bar{n}/d\phi_f$, as $\phi_f \rightarrow 0$. We fit the data to a maximum of three equilibria.[3] Equilibrium quotients are reported in Table I. We have assumed unit activity coefficients for all species present and have not corrected for interactions between the anions and the bulk solvents ($CDCl_3$ or CH_2Cl_2).

Discussion

We find substantial differences in the proton acceptor abilities of the anions studied. With both proton donors the spread in equilibrium quotients is at least 500-fold (of order 4 kcal/mol) for the 1:1 species. This suggests very sizable differences for the fully solvated species at high donor concentrations. The general trends are the same for phenol and water over the limited range of anions examined. Water, as expected, is a weaker proton donor than phenol. From simple electrostatic theory the equilibrium quotient should increase with anionic charge and decrease with increasing anionic radius. Our data are qualitatively consistent with these predictions, although the very weak binding of ClO_4^- and BF_4^- may be dominated by other factors.[9] We note a rough correlation between the anion ac-

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[2] (a) A. Allerhand and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **85**, 1223 (1963); (b) J. S. Martin, W. B. M. Cassie, and J. B. Hyne, *Can. J. Chem.*, 47, 1639 (1969).

[3] R. P. Taylor and I. D. Kuntz, Jr., *J. Phys. Chem.*, 74, 4573 (1970).

[4] S. C. Mohr, W. D. Wilk, and G. M. Barrow, *J. Amer. Chem. Soc.*, 87, 3048 (1965).

[5] R. P. Taylor and I. D. Kuntz, Jr., *ibid.*, **92**, 4813 (1970).

[6] P. H. von Hippel and T. Schleich in "Structure and Stability of Biological Macromolecules," S. N. Timasheff and G. D. Fasman, Ed., Marcel Dekker, New York, N. Y., 1969, p 417.

[7] L. Joris, Ph.D. Thesis, Princeton University, 1967.

[8] We measured the peak absorbance of the phenol OH stretch at 3584 cm^{-1} or that of the symmetric water OH stretch at 3609 cm^{-1}. The asymmetric water band (3697 cm^{-1}) was frequently obscured by the corresponding vibration of the "free" OH in the 1:1 water–anion complex.[4]

[9] E. R. Nightingale, *J. Phys. Chem.*, **64**, 162 (1960).

Table I. Hydrogen Bonding Properties of Anions

	Equilibrium quotients (40°)[a]				Frequency shifts[b]		
	Phenol[c]			Water[c]	Phenol[c]	Water[c]	Methanol[c]
Anion	K_1	K_2	K_3	K_1	$\Delta\nu$	$\Delta\nu$	$\Delta\nu$
BF_4^-	10 ± 2	2 ± 2			120		
ClO_4^-	16 ± 4	2 ± 2		4 ± 1	180	63	
Pic$^-$ [d]	20	5			340		188
I^-	30	10			330		233
HSO_4^-	50 ± 20	10 ± 5			240		
SCN^-	55 ± 10	5 ±			340		
Br^-	100	20	7	11 ± 2	400	224	275
NO_3^-	165 ± 30	8 ± 5	12 ± 6		350		
Cl^-	400	25	25	25 ± 2	>400	273	305
SO_4^{2-}	>5000	?	?	>5000	>400	296	

[a] The equilibrium quotients for the phenol–anion systems are sufficient to describe the data within experimental error, except for SO_4^{2-} where terms up to K_6 are needed. Higher K's are needed for all the water–anion systems except for ClO_4^-. [b] Based on "free" bands at 3584 cm^{-1} for phenol, 3609 cm^{-1} for the symmetric band of water, and 3652 cm^{-1} for methanol. [c] Bulk solvents were CH_2Cl_2 for phenol and methanol, $CDCl_3$ for water. [d] Picrate.

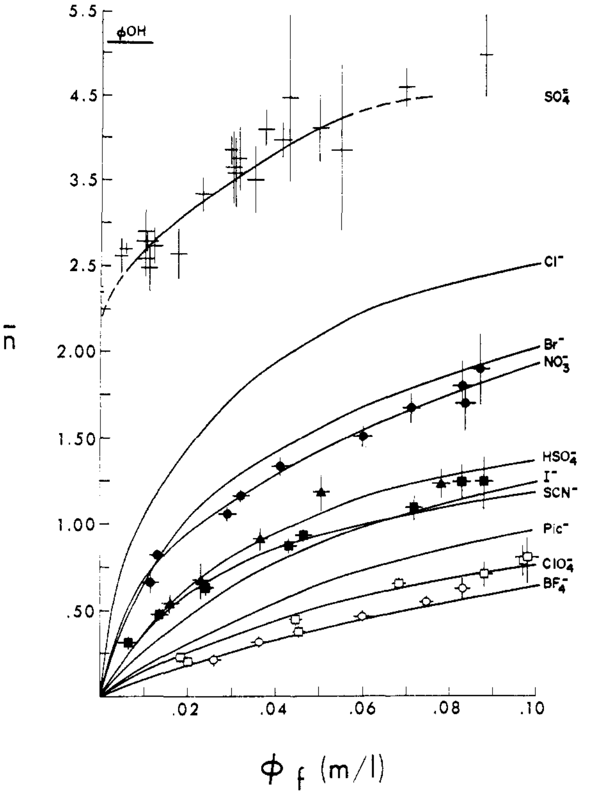

Figure 1. $\bar{n}$ *vs.* concentration of free phenol (ϕ_f) for phenol–anion interactions. The lines drawn through the experimental points were calculated based on the K_n values of Table I, except for SO_4^{2-}. Error estimates are shown. CH_2Cl_2 is the "inert" solvent. Data for Cl^-, Br^-, I^-, Pic$^-$ are from ref 3.

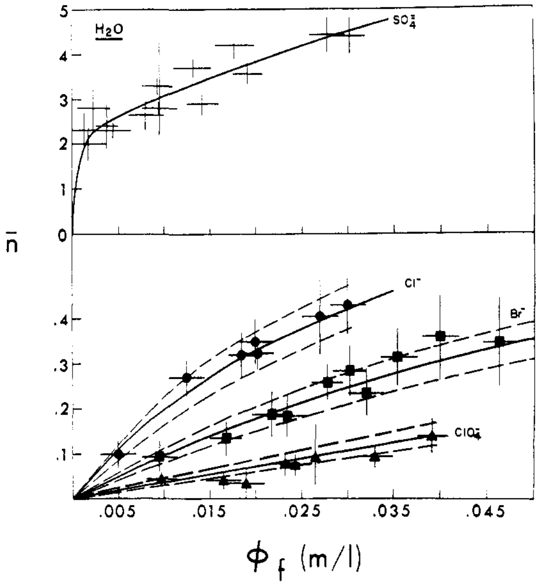

Figure 2. $\bar{n}$ *vs.* concentration of free water (ϕ_f) for water–anion interactions. $CDCl_3$ is the "inert" solvent. Note change of scale for SO_4^{2-}.

ceptor ability and basicity (pK_b), but trends of this type might be partly fortuitous.[10] The frequency differences between the free and bonded proton donor bands ($\Delta\nu$'s) are observed to be only approximate measures of the equilibrium quotients.[10b,11]

Although we are aware that $CDCl_3$ and possibly CH_2Cl_2 can competitively bind to anions[1,11] and thus reduce the magnitude of the K's, our earlier studies with CCl_4, CH_2Cl_2, and nitromethane together with this work indicate that the *relative* values of the equilibrium quotients are not very sensitive to choice of solvents.[3] Thermodynamic data on ion solvation in a variety of organic solvents permit the same conclusion.[12]

Extension of this discussion, based as it is on results obtained in low dielectric organic solvents, to a consideration of anions in aqueous solutions is an uncertain but challenging problem. The present data suggest that all these anions are appreciably hydrated in strongly aqueous environments. It seems likely that the same trend in water binding will persist. Support for this suggestion comes from several sources. Hartman[13] as well as Brink and Falk[14] have examined the ir of HOD in salt solutions. Their results indicate quite weak hydrogen bonds between water and ClO_4^- and BF_4^-. Combining these results, one can order the anions' effect on HOD stretching frequencies: $BF_3^- > ClO_4^{2-} > I^- > NO_3^- = Br^- = SCN^- > Cl^-$. In each case the center of gravity of the band shifts to

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(10) (a) E. M. Arnett and E. J. Mitchell, *J. Amer. Chem. Soc.*, **93**, 4053 (1971); (b) E. M. Arnett, L. Joris, T. S. S. R. Murty, T. M. Gorrie, and P. v. R. Schleyer, *ibid.*, **92**, 2365 (1970), and references therein.

(11) G. C. Pimental and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman, San Francisco, Calif., 1960.

(12) J. Padova in "Water and Aqueous Solutions," R. A. Horne, Ed., Wiley-Interscience, New York, N. Y., 1972, pp 109–174.

(13) K. A. Hartman Jr., *J. Phys. Chem.*, 70, 271 (1966).

(14) G. Brink and M. Falk, *Can. J. Chem.*, **48**, 3019 (1970).

Table II. Comparison of Spectroscopic and Thermodynamic Properties of Anions

	In organic solvents			HOD in H_2O						
Anion	PhOH K_{eq}^{a}	PhOH $\Delta\nu^{a}$	HOD $\Delta\nu^{a,b}$	$\Delta\nu^{c}$	$\Delta\delta^{c}$	$\Delta H^{\circ\, d}$	$\Delta S^{\circ\, e}$	ΔV^{f}	Affinity for Dowex 2	Polyacrylamide^{g}
BF_4^-	10	120		$(74)^h$ 152		−71.2	40	44.2		
ClO_4^-	16	180	116	$(107)^h$ 170	30	−57.1	43.2	44.1	32	0.10
I^-	30	330		212	26	−69.7	26.1	36.2	8–13	0.086
HSO_4^-	50	240					30.5	35.7		
SCN^-	55	340		229	23			35.7	19	0.086
Br^-	100	400	277	227	24	−79.8	19.3	24.7	3.4	0.062
NO_3^-	165	350		224	20		35.0	29.0	3.3	0.07
Cl^-	400	>400	326	239	18	−87.6	13.2	17.8	1.0	0.036
SO_4^{2-}	>5000	>400	347				4.1	14.0		0.022

[a] This work. Units: K's, l./mol; $\Delta\nu$, cm^{-1}. [b] Based on 3662 cm^{-1} as an estimate of the HOD monomer frequency in CCl_4. [c] References 13 and 14. Center of gravity of HOD band includes HOD···HOD interactions; 5 m salt solutions. Measured from 3662 cm^{-1} to compare with previous column. Nmr values in Hz at 60 MHz. [d] Reference 16, in kcal/mol. [e] Reference 15, in eu. [f] Reference 17, in cc/mol, includes electrostrictive terms. [g] Reference 20. [h] HOD···anion band resolved, ref 14.

higher frequency although separate bands are only resolved for ClO_4^- and BF_4^-. Hartman also gives nmr data with a similar ordering of anion effects.[13] The water nmr shifts are upfield with these anions. We feel that all these data are explicable if water–anion hydrogen bonds are replacing water–water hydrogen bonds. If we make the usual assumption that higher ir or nmr frequencies are associated with weaker hydrogen bonds, water–anion bonding is found to parallel the K's or ν's given in Table I. Thermodynamic data on aqueous solutions, while not providing such direct implication of hydrogen bonding effects, show that the partial molal entropy,[15] the absolute hydration enthalpy,[16] and the partial molal volumes[17] of the anions follow essentially the same trend as our results. The anions that hydrogen bond best give the most negative enthalpies and the smallest entropies and partial molal volumes (Table II).

Hofmeister Effects

As we have indicated, the general ordering of anions in terms of proton acceptor abilities is very similar to the Hofmeister or lyotropic order for denaturing effects. The following statement appears generally true: those anions which are most effective at denaturing ("salting-in") decrease the activity of polar solutes in water,[18] bind the best to anion-exchange resins[19] and polyamides,[20] and are the poorest proton acceptors. These observations can be rationalized with a very simple molecular model.[21] We assume that the decrease in activity (increase in solubility) comes from the direct binding of the anions through charge-dipole interactions with the macromolecular solute.[6, 20] Poorly hydrated anions are bound more strongly either because their hydrated radii are less than the strongly hydrated anions or because the binding involves a dehydration which is more facile with the poorly hydrated anions. Those anions which interact most favorably with water (*e.g.*, SO_4^{2-}) might act to dehydrate the macromolecule at sufficiently high salt concentrations. Such an effect could decrease solvent–macromolecule interactions and generally favor salting out and/or stabilization of the best folded states of the macromolecule.[22]

We note in passing that similar arguments are unlikely to be the dominant effect in cationic denaturation where the strongly hydrated species (*e.g.*, Li^+) are the best denaturants. One possible explanation for the cation behavior is suggested by the work of Zundel[23] who has shown that the polarization of the water by the cation electric field can increase the proton donor ability of the hydrated ion and presumably thereby improve its ability to bind to a dipolar site on the macromolecule.

Acknowledgment. Helpful discussions with Professors P. H. von Hippel and T. Spiro and partial support of this work by the National Science Foundation (GP-31564) are gratefully acknowledged.

(15) G. N. Lewis and M. Randall, "Thermodynamics," 2nd ed, revised by K. S. Pitzer and L. Brewer, McGraw-Hill, New York, N. Y., 1961, p 400.

(16) H. F. Halliwell and S. C. Nyburg, *J. Chem. Soc.*, 4603 (1960).

(17) F. J. Millero in ref 12, p 519.

(18) U. P. Strauss and P. D. Ross, *J Amer. Chem. Soc.*, **81**, 5295 (1959).

(19) H. P. Gregor, J. Belle, and R. A. Marcus, *ibid.*, 77, 2713 (1955).

(20) P. H. v. Hippel, V. Schleich, L. Schack, and L. Karlson, manuscript in preparation; T. Schliech, B. Rollefson, and P. H. von Hipple, *J. Amer. Chem. Soc.*, **93**, 7070 (1971).

(21) Our discussion is applicable to fairly concentrated salt solutions (above 1 M); at low salt concentrations (below 10^{-2} M), nonspecific Debye–Hückel effects aid in stabilizing all charged macromolecules.

(22) H. R. Mahler and E. H. Cordes, "Biological Chemistry," 2nd ed, Harper and Row, New York, N. Y., 1971, p 99.

(23) G. Zundel, "Hydration and Intermolecular Interaction," Academic Press, New York, N. Y., 1969.