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EXPERIMENTAL AND THEORETICAL STUDIES OF THE EFFECTS OF HYDRATION ON PROTON EXCHANGE EQUILIBRIA

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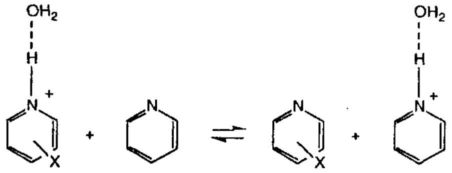
Theoretical calculations with the *ab initio* molecular orbital STO-3G basis set on the effect of trihydration on the relative acidities of 3- and 4-substituted phenols, 4-substituted quinuclidinium ions and 4-substituted bicyclo [2.2.2] octylammonium ions are reported. These results are contrasted with calculations on non-hydrated species and compared with results in aqueous solution and in the gas phase. Unlike results for smaller molecules such as substituted acetic acids and methylammonium ions, the solvation effects of three molecules of water are far short of that observed in going from the gas phase to aqueous solution. Reasons for this are discussed in the context of solvent attenuation factors for various molecules.

INTRODUCTION

Most reactions have been studied in solution, particularly in water, rather than in the gas phase. However, in recent years, new experimental techniques (notably ICR, high-pressure mass spectrometry and flowing afterglow spectrometry) have permitted the measurement of equilibria in the gas phase. These data allow a direct comparison with corresponding values in solution, thus providing information on the effect of the solvent. Within series of related compounds, such as certain substituted phenols or benzoic acids, it is found[1] that the effects of different substituents in water are approximately linear versus those in the gas phase, but of smaller magnitude. The reduction factors for water are in the range of one quarter to one tenth of that in the gas phase.

There is evidence[1–5] for specific solvation effects for certain substituents, and when these occur it is common to observe a change in relative acidities between the gas phase and solution.[6]

Limited experimental results are also available on the effect of a restricted number of solvent molecules on the gas-phase equilibria of organic molecules. Thus, experimental results[7] have been published for equilibrium (1) in the gas phase.



(1)

The attenuation of substituent effects compared with the non-hydrated equilibrium was about 1·4; the attenuation from the gas phase non-hydrated pyridines to aqueous solution, by comparison, is approximately 2·6 for weakly solvated substituents. Calorimetric studies[8] of relative solvation entropies have shown that most of the effect arises from the solvation of the ion rather than of the neutral molecule. Related work[9] also showed that the relative acidity of the 4-cyanopyridinium ion with up to three molecules of water in the gas phase still did not approach the value for aqueous solution.

Theoretical calculations at the *ab initio* molecular

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orbital level are very useful in investigating these solvation effects. Such calculations, even at the minimal STO-3G basis level, have proved capable of closely following the relative gas-phase acidities or basicities for a whole range of compounds, including substituted methylamines,[10] quinuclidines,[11] pyridines,[12,13] bicyclooctylcarboxylic acids,[14] phenols[15] and cyanides.[16] Further, such calculations also reproduce[1,7] the experimental figures for equilibrium (1) when a water molecule, appropriately optimized as to geometry, is included in the calculations for the pyridinium ions. This gives confidence that such calculations have validity for hydrated systems based on the series above.

In recent work, we have studied two series of relatively small molecules, namely substituted methylamines[17] and acetic acids.[4] Here the calculated relative basicities or acidities, respectively, are found to be close to those observed in aqueous solution when only three molecules of water are bonded in primary hydration shells to the charged centres in the ions. Thus, for example, the calculations give results close to the gas-phase experimental results for equilibrium (2) and to the aqueous solution results for equilibrium (3).

$$\mathrm{XCH_2NH_3^+ + CH_3NH_2 \rightleftharpoons XCH_2NH_2 + CH_3NH_3^+} \tag{2}$$

$$\mathrm{XCH_2NH_3^+ \cdot 3H_2O + CH_3NH_2 \rightleftharpoons XCH_2NH_2 + CH_3NH_3^+ \cdot 3H_2O} \tag{3}$$

The molecules of water are directed so that each of the acidic protons of the ion is hydrated by one of them. The use of these isodesmic processes minimizes any effect of entropy.

The agreement with solution results is improved further if one molecule of water is bonded to the nitrogen on the neutral amine. Similar results are found for the acetic acids.

These results are in contrast with the earlier initial results on the hydration of pyridines[7,9] discussed above. We wished to examine in which series of molecules specific hydration at the charged site was sufficient to account for most of the effects for non-solvated substituents in transferring the equilibrium from gas to water. Further, we wished to try to understand why this was so in some systems and not in others.

Accordingly, we report here theoretical investigations of the effect of hydration on the acidities of substituted phenols and the basicities of 4-substituted quinuclidines and 4-substituted bicyclooctylamines. These results are compared with experimental results in both the gas phase and in aqueous solution.

CALCULATIONS AND RESULTS

All calculations were performed at the *ab initio* molecular orbital level, using the Gaussian 86 series of programs[18] with the STO-3G basis set. The geometries of trihydrated phenol and trihydrated phenoxide were optimized as far as the positions and geometries of the water molecules were concerned. These geometries were then used for the series of substituted phenols and phenoxides. A similar procedure was used for the hydrated quinuclidinium and bicyclootylammonium ions.

Table 1 lists the energies for the trihydrated phenols and phenoxides, Table 2 those for both mono- and trihydrated quinuclidinium ions and Table 3 those for the trihydrated bicyclooctylammonium ions.

Table 1. *Ab initio* molecular orbital calculations (STO-3G) on the trihydrated substituted phenols and phenoxides ($-E$ in hartrees)

	X-phenol		X-phenoxide	
X	*meta*	*para*	*meta*	*para*
H	526·65771		525·96636	
Me		565·24118		564·54821
F	624·11706	624·11570	623·43076	623·42639
CF_3		857·62238		856·94057
CN	617·20918	617·21108	616·53142	616·53744
NO_2	727·34818	727·35124	726·67416	726·68368

Table 2. *Ab initio* molecular orbital calculations (STO-3G) on mono- and tri-hydrated 4-substituted quinuclidinium ions ($-E$ in hartrees)

X	$\mathrm{QuinH^+ \cdot H_2O}$	$\mathrm{QuinH^+ \cdot 3H_2O}$
H	398·67546	548·60651
NMe_2	530·11945	
NH_2[a]	452·97211	602·90303
OH	472·50072	622·43248
OMe	511·06913	661·00074
Me	437·25718	587·18799
F	496·12245	646·05462
COMe	548·46645	698·39792
CF_3	729·63145	879·56365
CN	489·20779	639·14088
NO_2	599·34733	749·28116

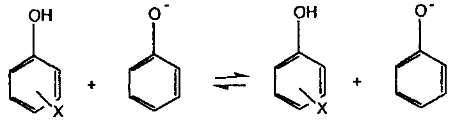
[a] Planar NH_2.

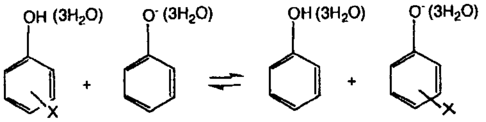
Table 3. *Ab initio* molecular orbital calculations (STO-3G) on trihydrated 4-substituted bicyclooctylammonium ions

X	$-E$ (hartrees)	X	$-E$ (hartrees)
H	587·23742	COMe	737·03738
NH_2	641·53270	CO_2Me	810·89071
OMe	699·63143	CN	677·77541
Me	625·81024	NO_2	787·91649
F	684·68742	CF_3	918·19703

DISCUSSION

In Table 4, we give the experimental [$\Delta G^\circ_{(g)}$] and calculated[15] [$\Delta E^\circ_{(g)}$] values for the energies for equilibrium (4) together with the experimental values for aqueous solution [$\Delta G^\circ_{(Aq)}$] and those calculated for process (5).


(4)


(5)

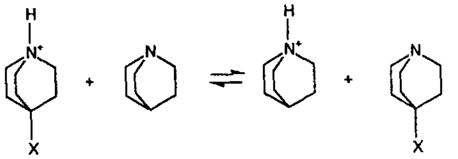
The calculated results for the gas phase[15] are broadly linear versus the experimental values, with a slope close to unity, except for the 3-NO_2, 4-NO_2 and 4-CN substituents, where the calculated value of $-\Delta E^\circ$ is overestimated. The aqueous results show an average solvent attenuation factor (*SAF*) of about 6, compared with the gas-phase results as discussed above (the actual *SAF* varies according to substituent, depending on any specific solvation of the group). The calculated results for the trihydrated species, by contrast, show a much smaller attenuation (approximately 1·8), compared with the results calculated for equilibria 4, as shown in equation (6).

$$-\Delta E^\circ_{(g)} = -1{\cdot}83\Delta E^\circ_{(3H_2O)} - 0{\cdot}2 \qquad r = 0{\cdot}995 \quad (6)$$

Clearly, the inclusion of three molecules of water in the calculations does not mirror the magnitude of the effect in moving experimentally from the gas phase to aqueous solution. This was earlier commented on using calculated results for just phenol and 4-cyanophenol.[9]

A closer examination of the calculated effect of three molecules of water is shown in the last column of Table 4. The experimental $-\Delta G^\circ_{(gas)}$ value corrected for the calculated effect of three molecules of water is divided by the experimental $-\Delta G^\circ_{(Aq)}$ value. A value close to unity would have indicated that the inner solvation shell was almost entirely responsible for the overall solvation, as found with the substituted methylamines and acetic acids. However, the value found is around 3·3 ± 0·3 for substituents where significant specific solvation does not occur. As expected when the aqueous results involve specific substituent solvation effects, the ratio depart appreciably from the value 3·3: for 4-CN it is 2·2 and for 4-NO_2 it is 1·9.

Table 5 shows similar results for equilibrium (7) and also with one or with three molecules of water attached to the quinuclidinium ions (earlier results[17] on pyridines and methylammonium ions showed that the effect of water on the neutral amines was relatively minor).


(7)

The results are similar to those found for the phenols. The calculated gas-phase results can be seen to be in fair agreement with the experimental figures, except that the calculated $\Delta E^\circ_{(g)}$ value for X = CF_3 is 2·4 kcal mol^{-1} (1 kcal = 4·184 kJ) too low. However, the effect of even three molecules of water is only about half of the experimental difference between the gas phase and aqueous solution.

Table 6 lists a series of acidities of substituted bicyclooctylammonium ions. Only relatively few experimental results are available for comparison. However, once again, it is clear that the effect of three molecules of water is significantly less than the experimental

Table 4. Effect of hydration on the relative acidities of substituted phenols (ΔG° and ΔE° in kcal mol^{-1})

X	$-\Delta E^\circ_{(g)}$	$-\Delta E^\circ_{3H_2O}$	$\delta_{(3H_2O)}\Delta E^{\circ a}$	$-\Delta G^\circ_{(g)}$	$-\Delta G^\circ_{(Aq)}$	$\delta_{(Aq)}\Delta G^{\circ b}$	$-\Delta G^\circ - \delta_{(3H_2O)}\Delta E^\circ / -\Delta G^\circ_{(Aq)}$
H	0·0	0·0	0·0	0·0	0·00	0·0	
4-NH_2	−4·9	−5·3	0·4	−3·2	−0·44	−2·8[c]	6·4[d]
4-Me	−1·0	−1·0	0·0	−1·1	−0·35	−0·7	3·1
4-F	1·6	1·4	−0·2	2·3	0·12	2·2	—
4-CF_3	11·5	6·1	5·4	11·9	1·81	10·1	3·6
4-CN	21·4	11·2	10·2	16·6	2·76	13·8[c]	2·3[d]
4-NO_2	29·2	15·5	13·7	20·9	3·89	17·0[c]	1·9[d]
3-F	5·4	3·2	2·2	5·3	1·08	4·2	2·9
3-CN	14·5	8·6	5·9	13·0	1·88	11·1	3·7
3-NO_2	18·1	10·9	7·2	14·4	2·21	12·2	3·3

[a] $\delta_{(3H_2O)}\Delta E^\circ = -\Delta E^\circ_{(g)} + \Delta E^\circ_{(3H_2O)}$.

[b] $\delta_{(Aq)}\Delta G^\circ = -\Delta G^\circ_{(g)} + \Delta G^\circ_{(Aq)}$

[c] Involves significant substituent solvation.

[d] Appreciable difference from value of 3.3 ± 0.3 shows the effect of substituent solvation on $-\Delta G^\circ_{(aq)}$ value.

observation on going from the gas phase to aqueous solution.

These results are in marked contrast to our earlier reported results of the effect of water on the acidities of substituted methylammonium ions[17] [equilibria (2) and (3)] and on substituted acetic acids.[4] Here, placing three molecules of water around the charged site gave calculated results differing from the unhydrated equilibria to about the same extent as the experimental change in going from the gas phase to aqueous solution. This is illustrated in Table 7 for the acidity of substituted acetic acids, equilibria (8).

$$XCH_2CO_2H + CH_3CO_2^- \rightleftharpoons XCH_2CO_2^- + CH_3CO_2H \qquad (8)$$

The calculated results are for processes (8) and (9),

Table 5. Effect of hydration on the relative acidities of 4-substituted quinuclidinium ions (ΔG° and ΔE° in kcal mol^{-1})

X	$-\Delta E^\circ_{(g)}$	$-\Delta E^\circ_{(H_2O)}$	$-\Delta E^\circ_{(3H_2O)}$	$\delta_{(3H_2O)}\Delta E^\circ$	$-\Delta G^\circ_{(g)}$	$-\Delta G^\circ_{(Aq)}$	$\delta_{(Aq)}\Delta G^\circ$
H	0·0	0·0	0·0	0·0	0·0	0·0	0·0[d]
NMe_2	−0·7	−0·4	−0·1[a]	−0·6	−0·3	1·43	1·7[c]
OH	3·5	3·0	2·5	1·0	4·9	2·29	2·6
OMe	3·0	2·6	2·3	0·7	(3·4)[b]	2·47	0·9
Me	−0·9	−0·6	−0·5	−0·4	0·0	0·15	−0·2
F	5·4	4·4	3·7	1·7	7·1	3·51	3·6
COMe	2·6	2·3	2·0	0·6	(5·0)[b]	2·31	2·7
CF_3	5·7	4·8	4·1	1·6	8·3	2·34	6·0[c]
CN	10·5	8·6	7·3	3·2	11·3	4·15	7·1[c]
NO_2	14·0	12·2	10·4	3·6	(12·0)[b]	4·75	7·3[c]

[a] NH_2

[b] Estimated from equation (6) in Ref. 11.

[c] Significant substituent solvation effects are involved.

[d] Average value of the rates $-\Delta G^\circ_{(g)} - \delta_{(3H_2O)}\Delta E^\circ / -\Delta G^\circ_{(Aq)}$ is 2.1 ± 3.

Table 6. Effect of hydration on the relative acidities of 4-substituted bicyclooctylamines (ΔG° and ΔE° in kcal mol^{-1})

X	$-\Delta E^\circ_{(g)}$	$-\Delta E^\circ_{(3H_2O)}$	$\delta_{3H_2O}E^\circ$	$-\Delta G^\circ_{(g)}$	$-\Delta G^\circ_{(Aq)}$	$-\delta_{(Aq)}\Delta G^\circ$
H	0·0	0·0	0·0	0·0	0·0	0·0
NH_2	1·0	−0·7	1·7	(1·2)[a]	—	—
OMe	2·1	1·5	0·6	1·1	1·15	0·0
Me	−0·5	0·0	−0·5	−0·8	0·00	−0·8
F	3·7	2·2	1·5	5·4	1·54	3·9
CF_3	3·9	2·9	1·0	(5·0)[a]	—	—
CN	7·4	4·9	2·5	(7·1)[a]	—	—
NO_2	10·1	7·5	2·6	(7·7)[a]	2·10	5·6
COMe	2·1	1·6	0·5	(2·7)[a]	—	—
CO_2Me	2·2	0·6	1·6	(2·5)[a]	1·05	1·4
Cl	—	—	—	5·3	1·50	3·8

[a] Estimated from equation (7) in Ref. 11.

Table 7. Effect of hydration on the relative acidities of substituted acetic acids (ΔG° and ΔE° in kcal mol^{-1})

X	$-\Delta G^\circ_{(g)}$	$-\Delta E^\circ_{(g)}$	$-\Delta G^\circ_{(Aq)}$	$-\Delta E^\circ_{(3H_2O)}$	$-\delta_{(Aq)}\Delta G^\circ$	$-\delta\Delta E^\circ$
H	0·0	0·0	0·0	0·0	0·0	0·0
Me	1·2	0·7	−0·08	−0·4	1·3	1·1
Et	2·0	1·2	−0·09	−0·3	2·1	1·5
Ph	6·9	8·6	0·61	3·2	6·3	5·4
F	9·6	9·2	2·96	3·4	6·6	5·8
OMe	6·0	5·6	1·62	1·4	4·4	4·2
CF_3	13·0	14·8	2·31	3·2	11·7	11·6
CN	15·3	22·7	3·12	8·5	12·1	14·2

but the results are similar if the single water molecule is omitted from the neutral acids.

$$XCH_2CO_2H \cdot H_2O + CH_3CO_2^- \cdot 3H_2O \rightleftharpoons XCH_2CO_2^- \cdot 3H_2O + CH_3CO_2H \cdot H_2O \quad (9)$$

Obviously, solvation in the methylamines and acetic acids is different from that in the pyridines, phenols, quinuclidines and bicyclooctylamines. It seems that with the smaller molecules, hydration at the charged site accounts for most of the effect when the reaction is transferred from the gas phase to aqueous solution. On the other hand, such specific hydration accounts for less than half of the overall effect for the larger molecules. Separate work[3,5] indicates that hydration at the substituents is not large enough to be significantly involved in this difference.

It would therefore seem that the difference between the smaller and larger molecules is related to a general continuum effect of water. Certainly, the transfer of an ion from the gas phase to aqueous solution involves considerable energy in creating a cavity and then charging it. However, it is not clear why this should differ greatly between one, say, substituted quinuclidinium ion and another. However, in the larger molecules, the lines of force between the charged centres and the substituents are likely to travel significantly through the solvent compared with the more compact smaller molecules.

In order to look at this more simply, we need to dissociate field effects from other mechanisms of transfer of substituent electronic effects. Accordingly, in Table 8 we list ρ_F values for a variety of proton-transfer equilibria, both for the gas phase and for aqueous solution. The solvent attenuation factors (*SAF*) are $\rho_{F(g)}/\rho_{F(Aq)}$. The factors are generally larger for carboxylic acids than amines for corresponding geometries because of the larger dispersal of charge by the carboxylate anion into water than for the ammonium salt. This is the most extensive set of data yet published as far as distance versus *SAF* is concerned. It shows clearly that not only do ρ_F values fall off with distance as expected, but also the *SAF* increases markedly. Put another way, the ρ_F values in the gas phase do not fall at anything like the rate of decrease observed in $\rho_{F(Aq)}$ values. By contrast, the SAF factors between calculated $\rho_{F(g)}$ and $\rho_{F(3H_2O)}$ values (Table 9) decreased only from 1·8 for the substituted methylammonium ions to 1·4 for the bicyclooctylamines.

Table 8. Solvent attenuation factors (*SAF*) for field effects in various systems (ρ from Ref. 2, unless stated otherwise)

Species	$\rho_{F(g)}$	$\rho_{F(Aq)}$	$SAF_{calc.}$
$XCH_2NH_3^+$	33·1	10·5	3·2
$XCH_2NMe_2H^+$	28·6	13·7	2·1
XCH_2CO_2H	24·6	4·1	6·0
4-X-Quin·H$^+$	18·0	7·0	2·6
4-X-Pyr·H$^+$	21·8	8·3	2·6
4-X-$C_8H_{12}NH_3^+$	12·8	3·2	4·0
4-X-$C_6H_4NH_3^+$	18·9	4·6	4·1
4-X-C_6H_4OH	18·6	3·1	6·0
4-X-$C_8H_{12}CO_2H$	13·3	0·9	14·8
4-X-$C_6H_4CO_2H$	15·0	1·0	15·0

Table 9. Transmission of substituent electronic effects in various proton-transfer equilibria

Species	X	Calc.$_{(g)}$	Calc.$_{(3H_2O)}$	$SAF_{calc.}$
$XCH_2NH_3^+$	F	9·4	6·36	1·48
	CF_3	10·2	5·35	1·91
	CN	16·7	8·33	2·01
	NO_2	23·9	13·64	1·76
				Av. 1·8
4-X-Quin·H$^+$	F	5·37	3·72	1·44
	CF_3	5·74	4·11	1·40
	CN	10·48	7·34	1·43
	NO_2	13·96	10·44	1·34
				Av. 1·4
$4XC_8H_{12}NH_3^+$	F	3·75	2·35	1·59
	CF_3	3·88	2·90	1·34
	CN	7·45	5·68	1·31
	NO_2	10·08	7·77	1·29
				Av. 1·4

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