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Origin of the Inversion of the Acidity Order for Haloacetic Acids on Going from the Gas Phase to Solution

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The change in the relative acidities of the haloacetic acids on going from the gas phase to aqueous solution has been studied via ab initio calculations for the gas phase, the SCIPCM reaction field model for an aprotic polar solvent, and Monte Carlo statistical mechanics for aqueous solution. The relative gas phase acidities of acetic acid, the haloacetic acids and trifluoroacetic acid are well reproduced at the B3P86/6-311+G** and G2 levels of theory. The reaction field model reduced the relative acidities of fluoro- and bromoacetic acids to a value close to that found in aqueous solution, but it only reproduced half of the observed net effect of going from the gas phase to aqueous solution. Since the remainder of the solvent effect was probably due to hydrogen bonding, Monte Carlo calculations were carried out and they were in satisfactory accord with the aqueous solution pK_a's.

It has frequently been found that the relative acidities for a series of related compounds are different in the gas phase than in solution. For example, benzoic acid is more acidic that formic acid in the gas phase,[2] but formic acid is the more acidic in DMSO.[3] In many cases this may be attributed to the need for internal Coulombic stabilization in the gas phase, which is provided by nearby polarizable groups. In solution, this becomes less important, and other factors may control relative acidities. In the above case, ab initio calculations for the gas phase have reproduced the acidities, and the corresponding calculations for a polar solvent using the SCIPCM reaction field model[4] reproduced the reversed acidity for solutions.[5]

Another interesting case of acidity reversal is found with the haloacetic acids. In the gas phase, the order of increasing acidity is[2]

$$H_3CCO_2H < FCH_2CO_2H < ClCH_2CO_2H < BrCH_2CO_2H$$

whereas in aqueous solution it is[3]

$$H_3CCO_2H < BrCH_2CO_2H < ClCH_2CO_2H < FCH_2CO_2H$$

The origin of this change in order has been examined by Kawata, Ten-no, Kato and Hirata[6] using their RISM model. They concluded that hydrogen bonding was a dominant factor in giving the order found in aqueous solution. However, whereas the difference in ionization free energy in solution for fluoro and chloroacetic acid is 0.4 kcal/mol, their calculated energy difference was 2.8 kcal/mol.

On the other hand, it seemed likely that the change in order might be accounted for more simply by considering Coulombic interactions. In the gas phase, the large and polarizable bromine should be able to stabilize the charge in the carboxylate ion better than either chlorine or fluorine. Thus, the gas phase order might result simply from internal stabilization. The solution phase order is that which one might reasonably expect based on the inductive effect and C−X bond dipole of the halides. These compounds are of special interest since the classical Westheimer-Kirkwood treatment of substituent effects on acidity[7] was developed to explain the difference in acidity between chloroacetic and acetic acids.

To gain further information, ab initio calculations were carried out at the B3P86/6-311+G** level for the acids and their anions.[8] It is known that the conformation of the acids in which the halogen eclipses the C═O bond is the more stable in the gas phase,[9] and it was also found to be the more stable in preliminary HF/6-31+G* calculations. Whereas with acetic acid, a CH bond eclipses the carbonyl group in the lower energy conformation, in acetate ion the preferred conformation has the hydrogens staggered with respect to the C−O bonds. However, the difference in energy between the acetate conformers was negligible, and it may be considered to be a free rotor.

The B3P86/6-311+G** energies are summarized in Table 1. To compare the calculated energy differences with those determined experimentally, it was necessary to convert the data to 298 K. This made use of the B3P86 vibrational frequencies. The calculated ΔH_{acid} and ΔG_{acid} values are in close agreement with the calculated values, considering the experimental uncertainties. The relative calculated energies are in even better agreement with experiment (Table 2).

However, the solvent effect studies presented below suggested that the difference in acidity between acetic and fluoroacetic acid should be somewhat smaller than that calculated at the B3P86/6-311+G** level. Therefore, we also calculated the energies of the acids and their anions at the G2 level which usually gives quite good relative energies. The data are shown in Table 3, and energy differences are given in Table 2. The difference between the B3P86 and G2 relative energies are small, but the latter are usually considered to be more satisfactory.

The solvent effect was calculated using the SCIPCM model for a dielectric constant of 80.[10] In this model the solute is placed in a cavity in the solvent, and the volume and shape of the cavity are determined by the 0.0004 e/au^3 electron density surface which closely approximates the experimental molar volumes. The surface charges that are derived from the dipole and higher moments, and including the charge in the anions, are calculated

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TABLE 1: B3P86/6-311+G Energies and Gas Phase Acidities**[a]

compd	ZPE[b]	E (H)	$H° - H_0^0$	$G_0 - H_0^0$	ΔH_{acid}(calc)[c]	ΔH_{acid}(obs)	ΔG_{acid}(calc)	ΔG_{acid}(obs)
CH_3CO_2H	38.77	−229.73104	3.49	−17.27	346.6	348.7 ± 3.0	338.7	341.5 ± 2.0
$CH_3CO_2^-$	30.12	−229.16576	3.39	−17.51				
FCH_2CO_2H	34.44	−329.12199	3.94	−17.86	335.2	338.4 ± 3.0	327.9	331.0 ± 2.0
$FCH_2CO_2^-$	26.03	−328.57489	3.59	−17.73				
$ClCH_2CO_2H$	33.51	−689.64896	3.89	−18.63	332.1	336.3 ± 3.0	325.2	328.9 ± 2.0
$ClCH_2CO_2^-$	25.09	−689.10613	3.20	−18.47				
$BrCH_2CO_2H$	33.06	−2804.05695	4.02	−19.56	331.4	333.9 ± 3.0	324.0	327.4 ± 2.0
$BrCH_2CO_2^-$	24.65	−2803.51628	3.92	−19.24				
F_3CCO_2H	24.56	−527.94172	4.49	−19.67	321.0	322.9 ± 4.0	312.6	317.4 ± 2.0
$F_3CCO_2^-$	16.15	−527.41761	4.41	−20.36				

[a] The total energies are given in Hartrees, and the other energies are given in kcal/mol. The thermodynamic functions were calculated using the B3P86/6-311+G* frequencies and the moments of inertia obtained from the B3P86 geometry optimizations. The temperature is 298.15K. [b] The zero point energies are obtained from B3P86/6-311+G* calculations. For this level of theory, the scaling factor is close to unity. [c] The convention that the enthalpy of the proton is temperature independent was used, and the RT factor was included. At 298 K, $G_0 - H_0^0 = 7.76$ kcal/mol.

TABLE 2: Relative Free Energies of Ionization in the Gas Phase and in Solution, kcal/mol

	gas phase			aqueous solution[a]		
	calc			calc		
acid	B3P86	G2	obs[c]	SCRF[b]	MC	obs
acetic acid	0.0	0.0	0.0	0.0	0.	0.0
fluoroacetic acid	−10.8	−10.3	−10.3	−6.5	−4.4	−3.0
chloroacetic acid	−13.5	−12.6	−12.4	−6.5	−4.1	−2.6
bromoacetic acid	−14.6	−13.7	−14.8	−6.6	−3.8	−2.5
trifluoroacetic acid	−26.0	−23.6	−25.8	−16.3	−8.3	−5.8

TABLE 3: G2 Calculated Energies of Acids and Anions

compd	G2-H[a]	G2-G[b]	ΔH_{acid}	ΔG_{acid}
CH_3CO_2H	−228.74745	−288.77999	345.1	338.0
$CH_3CO_2^-$	−228.19844	−228.22886		
FCH_2CO_2H	−327.89141	−327.92580	335.8	327.7
$FCH_2CO_2^-$	−327.35718	−327.39114		
$ClCH_2CO_2H$	−687.88948	−687.92535	330.6	323.4
$ClCH_2CO_2^-$	−687.35878	−687.39438		
$BrCH_2CO_2H$	−2800.72509	−2800.76249	332.5	324.3
$BrCH_2CO_2^-$	−2800.19625	−2800.23331		
F_3CCO_2H	−526.22218	−526.26053	322.3	314.4
$F_3CCO_2^-$	−525.70855	−525.74708		

[a] The G2 energy corrected for the enthalpy change at 25 °C. [b] The G2 energy corrected for the free energy change to 25 °C.

along with their interaction with the solvent taken as a dielectric continuum with the experimental dielectric constant. The latter gives the electrostatic stabilization afforded by the solvent. This model will reproduce the electrostatic effect of a dielectric continuum, but it will not include specific solvent−solute interactions such as hydrogen bonding. The calculated energies are given in Table 3. Since the electron distribution in the molecule is allowed to relax during the calculation, it is not surprising that the dipole moments increase on going from the gas phase to a polar medium. Geometry optimization in the polar medium was carried out in all cases, and although there were some changes in bond lengths and angles, they were relatively small.[11]

Normally, as the size of the cavity is reduced, the solvation energy increases. This is found with all of the acids (Table 3). However, with the anions, the solvation energy decreases when the cavity size is decreased. With anions, the electron density distribution is fairly diffuse, and as a result, some of the electron density will lie outside the cavity and will not be taken into account in the solvation calculation. As the cavity size is decreased, the amount of electron density outside the cavity will increase, leading to the anomalous decrease in solvation energy. In these cases, it is necessary to scale the electron density distribution so that all of it will reside within the cavity. When this is done (Table 3), the normal effect of cavity size on solvation energy is found. With the neutral acids, the effect of scaling the electron density is negligible because essentially all of it resides within the solvent cavity.

The SCI−PCM calculations are adapted to account for the presence of solute electron density outside of the cavity by scaling the image charges on the cavity surface. An SCRF calculation for a conducting solvent would suffer from the same "loss" of charge, and since the electrostatic potential at the cavity surface should be exactly zero for the case of a conducting solvent, we compute the scale factor for each image charge which would be required to compensate exactly for the missing change in the conductor case. The same scale factors are used to compensate for the actual (dielectric) calculations.

The relative energies based on these calculation are summarized in Table 2. As noted above, the gas phase relative energies are reproduced well within the experimental uncertainties. The relative acidities of fluoroacetic and bromoacetic acids have been reduced from 4.0 kcal/mol in the gas phase to 0.1 kcal/mol, which is close to the aqueous solution difference. Approximately half of the net observed change on going from the gas phase to solution has been accounted for by the reaction field model. It seems reasonable to assume that the other half of the effect is due to changes in hydrogen bonding.

To further examine the experimental observations, Monte Carlo simulations with free energy perturbation theory were carried out for the aqueous solutions.

Monte Carlo Simulations. Classical MC calculations were performed for a single solute in a periodic cube with 265 TIP4P water[12] molecules at 25 C and 1 atm in the NPT ensemble.[13] Free-energy perturbation (FEP) calculations[14] were performed to yield the free-energy changes in water for the conversions of acetic acid or acetate ion to the corresponding fluoro, chloro, bromo, or trifluoromethyl derivatives. The geometries of the solutes were taken from the solution phase B3P86/6-311+G** optimizations. The intermolecular interactions between two molecules a and b were evaluated using Coulomb and Lennard-Jones terms:

$$\Delta E_{\mathrm{ab}} = \sum_{i}^{\text{on a}} \sum_{j}^{\text{on b}} \left\{ \frac{q_i q_j e^2}{r_{ij}} + 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] \right\}$$

The Lennard-Jones σ and ϵ values were taken from the OPLS-AA force field,[15] and the combining rules are $\sigma_{ij} = (\sigma_{ii}\sigma_{jj})^{1/2}$ and $\epsilon_{ij} = (\epsilon_{ii}\epsilon_{jj})^{1/2}$. The partial charges for the solutes were obtained from single-point calculations on the B3P86/6-311+G** geometries via the CM1A procedure.[16] This method, which uses AM1 wave functions, yields excellent gas-phase dipole moments.[15] However, for solution-phase simulations the partial charges for neutral molecules need to be enhanced. It was previously shown that a scaling factor of 1.2 is appropriate and yields improved free energies of hydration over FEP calculations with charges obtained from fitting to the electrostatic potential surfaces from 6-31G* wave functions.[17] Thus, the CM1A partial charges for the acids were also scaled here by 1.2.

The solute was initially placed in an equilibrated box containing 267 water molecules and the 2 water molecules with the highest interaction energies with the solute were discarded. The intermolecular interactions were truncated at 9 Å based on the OO distance for water pairs and the solute C1−water O distance for solute−water pairs. The interactions were quadratically smoothed to zero within 0.5 Å of the cutoff. Standard protocols were used for the FEP calculations;[13] each perturbation was carried out over six windows with double-wide sampling yielding a total of 12 free energy increments to sum to the total free energy change in each case. Each window entailed 2.1 million configurations for equilibration and 4 million configurations of averaging. Statistical uncertainties were estimated with the batch-means procedure using 4 batches of 1 million configurations.[12] The TIP4P water molecules and the solutes underwent rigid-body translations and rotations, while the sampling of the solutes also included free torsional motion about the C−C bonds. Solute and volume moves were attempted every 60 and 1625 configurations, respectively. Acceptance rates of ca. 40% for new configurations were obtained using ranges of ca. ±0.12 Å and ±12° for the rigid-body motions and ±10° for the torsions.

The MC simulations and CM1A calculations were carried out with the BOSS program, version 4.1,[18] on a Dell PC using dual 500-MHz Pentium III processors and Windows NT. Each complete FEP calculation required 5−6 h on one processor. Thus, all 8 FEP calculations for this study could be completed within 1 day.

The results of the calculations are summarized in Table 5, and the resulting free energy differences are given in Table 2. The calculated ionization energies in solution for the haloacetic acids are in good agreement with the experimental results, with an average deviation of only 1.5 kcal/mol. The deviation between calculations and experiments for trifluoroacetic acid is somewhat larger, 2.5 kcal/mol, but still in a satisfactory range.

It was of interest to see how the solvation changed with substituents. The average number of hydrogen bonds for each species are given in Table 6. With the anions, the average number of hydrogen bonds decreases with increasing size of the substituent, and probably is a steric effect. The same trend is seen with the acids, but here the number of hydrogen bonds is much smaller. Trifluoroacetic acid and its anion are the poorest hydrogen-bond acceptors, which is expected to also reflect their lower oxygen basicity owing to electron withdrawal by the trifluoromethyl group.

An interesting feature of the work of Katawa, et al.[6] is the observation of a well-defined hydrogen-bond peak between the F atom of fluoroacetic acid and the H atoms of water. In our MC simulations, we find that the F−HOH radial distribution function is featureless, just a broad band with no distinct first peak. F−O has a weak first peak at 3.2 Å. The anion is basically the same with F−HOH having a maximum height of 1.14 at 4.4 Å, and F−O having a weak first peak of height 1.16 at 5.3 Å. It appears that the previous results are incorrect.

TABLE 4: Calculated Energies in Solution, B3P86/6-311+G, $e = 80$**

a. Total Energies

	unscaled		scaled	
compd	$\rho = 0.0004^a$	$\rho = 0.001^b$	$\rho = 0.0004^a$	$\rho = 0.001^b$
$\mathrm{CH_3CO_2H}$	−229.73924	−229.74382	−229.73920	−229.74359
$\mathrm{CH_3CO_2^-}$	−229.25514	−229.25496	−229.26266	−229.27174
$\mathrm{FCH_2CO_2H}$	−329.13377	−329.13976	−329.13368	−329.13938
$\mathrm{FCH_2CO_2^-}$	−328.66199	−328.66178	−328.66922	−328.67790
$\mathrm{ClCH_2CO_2H}$	−689.65962	−689.66526	−689.65962	−689.66516
$\mathrm{ClCH_2CO_2^-}$	−689.18784	−689.18579	−689.19582	−689.20419
$\mathrm{BrCH_2CO_2H}$	−2804.06750	−2804.07318	−2804.06753	−2804.07310
$\mathrm{BrCH_2CO_2^-}$	−2803.59587	−2803.59335	−2803.60430	−2803.61251
$\mathrm{F_3CCO_2H}$	−527.95127	−527.95681	−527.95119	−527.95641
$\mathrm{F_3CCO_2^-}$	−527.49732	−527.49484	−527.50425	−527.51039

b. Scaled Solvation Energies, kcal/mol

	ΔG_{solv}		relative $\Delta\Delta G_{\mathrm{solv}}$	
compd	$\rho = 0.0004$	$\rho = 0.001$	$\rho = 0.0004$	$\rho = 0.001$
$\mathrm{CH_3CO_2H}$	−5.12	−7.88	0.00	0.00
$\mathrm{CH_3CO_2^-}$	−60.81	−66.50		
$\mathrm{FCH_2CO_2H}$	−7.34	−10.91	3.84	4.89
$\mathrm{FCH_2CO_2-}$	−59.19	−64.64		
$\mathrm{ClCH_2CO_2H}$	−6.69	−10.17	6.10	7.26
$\mathrm{ClCH_2CO_2-}$	−56.28	−61.53		
$\mathrm{BrCH_2CO_2H}$	−6.64	−10.13	7.10	8.37
$\mathrm{BrCH_2CO_2^-}$	−55.23	−60.38		
$\mathrm{F_3CCO_2H}$	−5.94	−9.22	7.26	9.62
$\mathrm{F_3CCO_2^-}$	−54.37	−58.22		

[a] This value of ρ usually accurately reflects experimental molar volumes and is the recommended value for these calculations. [b] This value of ρ is used to test the calculations. A decrease in ρ would be expected to give a small increase in the solvation energy, whereas the opposite is found with anions in the unscaled calculations.

TABLE 5: Results Using B3P86/6-311+G Geometries and CM1A Charges**

	$\mathrm{CH_3COOH + A^- \rightarrow CH_3COO^- + AH}$		
AH	$\Delta G_{\mathrm{aq}}(\mathrm{AcOH{-}AH})$	$\Delta G_{\mathrm{aq}}(\mathrm{AcO^-{-}A^-})$	rel $\Delta\Delta G_{\mathrm{solv}}$
$\mathrm{CH_3COOH}$	0.0	0.0	0.0
$\mathrm{FCH_2COOH}$	−0.87 ± 0.05	−5.07 ± 0.11	5.94 ± 0.12
$\mathrm{ClCH_2COOH}$	−0.03 ± 0.06	−8.43 ± 0.17	8.46± 0.18
$\mathrm{BrCH_2COOH}$	0.15 ± 0.08	−10.09 ± 0.21	9.94 ± 0.22
$\mathrm{F_3CCOOH}$	−0.72 ± 0.05	−15.01 ± 0.18	15.73 ± 0.19

TABLE 6: Average Number of Donated and Accepted Hydrogen Bonds in Water (25 °C, 1 atm)[a]

AH	donor	acceptor	$\mathrm{A^-}$	donor	acceptor
$\mathrm{CH_3CO_2H}$	1.00	2.53	$\mathrm{CH_3COO^-}$	0.00	6.66
$\mathrm{FCH_2CO_2H}$	1.01	1.98	$\mathrm{FCH_2CO_2^-}$	0.00	6.61
$\mathrm{ClCH_2CO_2H}$	1.02	2.24	$\mathrm{ClCH_2CO_2^-}$	0.00	5.99
$\mathrm{BrCH_2CO_2H}$	1.02	2.20	$\mathrm{BrCH_2CO_2-}$	0.00	6.00
$\mathrm{F_3CCO_2H}$	1.03	1.38	$\mathrm{F_3CCO_2^-}$	0.00	5.34

[a] A hydrogen bond is defined as having an O−OH distance of less than 2.5 Å.

Summary. The change in relative acidity for the haloacetic acids on going from the gas phase to aqueous solution appears to result from two factors. The first is the change from internal stabilization by a polarizable substituent to stabilization by the medium having a large dielectric constant. This part is obtained in the reaction field calculations, and it reduces the gas phase energy difference between fluoro- and bromoacetic acids of 4 kcal/mol to 0.1 kcal/mol which is close to the observed energy difference in aqueous solution. It, however, only reproduced about half of the net effect on pK_a on going from the gas phase to water. It should be noted that a consistent application of a reaction field model will lead to the same solvation energies for a polar solvent such as acetonitrile and water. The additional effect of water may be attributed to hydrogen bonding. The Monte Carlo simulations reflect well the sum of the dielectric stabilization and hydrogen bonding. In conjunction with the G2 or B3P86 results, accurate relative free energies in aqueous solution can be obtained.

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Supporting Information Available: A table of the calculated changes in geometry at the B3P86/6-311+G** level on going from the gas phase to a polar medium. The material is available free of charge via the Internet at http://pubs.acs.org.

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