Accurate Solvation Free Energies of Acetate and Methylammonium Ions Calculated with a Polarizable Water Model

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Received August 4, 1994

A significant challenge in simulations of organic and biological molecules is the accurate representation of ion solvation. Although effective two-body models can do an excellent job in the calculation of solvation free energies of neutral molecules,[1] much larger errors often arise when they are used to describe the solvation of charged species. One can easily adjust the parameters of monatomic ions to reproduce the experimental solvation free energies within effective two-body models,[2] but how to do this for more complex ions is not obvious. It is also straightforward in parametrized continuum solvation models (*e.g.*, DelPhi[3] or AMSOL[4]) to force the reproduction of solvation free energies. However, it would be highly desirable to have a more general, "first principles" approach to the accurate calculation of solvation free energies of organic ions.

We present such an approach here. Using the same method of charge derivation previously described for neutral systems,[5] we show that, with no further adjustable parameters, the solvation free energies of methylammonium and acetate ions are calculated in near-quantitative agreement with experiment in polarizable water (the POL3 model[6]). In contrast, the energies obtained with a pairwise-additive water model, TIP3P,[7] are more than 10 kcal/mol too negative.

Free energy perturbations were carried out using the standard windows procedure in a modified version of AMBER (see footnotes below Table 2).[8] Studies were performed with the TIP3P[7] and POL3[6] water models. Both sets of simulations employ the standard Lennard-Jones and Coulombic energy terms; the POL3 simulations also include the polarization energy, as described previously.[9,10] The perturbations were done in separate electrostatic and van der Waals (VDW) stages. Additionally, in the POL3 systems, solute polarizability contributions to the solvation energies were calculated.

Acetate and methylammonium point charges were obtained with the RESP method of restrained fits to 6-31G* electrostatic potentials[5] and are listed with the remaining nonbonded parameters in Table 1.[5,6,11,12] The bond, angle, and torsional parameters (not listed) are from the Weiner *et al.* force field.[13]

Table 1. Nonbonded Parameters

	atom type	r (Å)[a]	ϵ (kcal/mol)[a]	q (e)	α (Å^3)[b]
H_2O (POL3)[c]	OW	1.7980	0.1560	−0.7300	0.528
	HW	0.0000	0.0000	0.3650	0.170
$CH_3CO_2^-$	CT	1.9080	0.1094	−0.2072	0.878
	HC	1.4870	0.0157	0.0015	0.135
	C	1.9080	0.0860	0.8911	0.616
	O2	1.6612	0.2100	−0.8442	0.434
$CH_3NH_3^+$	CT	1.9080	0.1094	−0.0375	0.878
	HP	1.1000[d]	0.0157[d]	0.1138	0.135
	N3	1.8240	0.1700	−0.1931	0.530
	H	0.6000	0.0157	0.2964	0.161

[a] Reference 5 for solute atom types, except where noted otherwise. [b] Reference 12 for solute atom types. [c] Reference 6. [d] Reference 11.

Calculated and experimental free energies are given in Table 2.[4,5,14−17] As anticipated, the calculated solvation energies of these ions are dominated by electrostatics; the VDW and solute polarizability contributions are relatively small. Thus, it was not considered necessary for the present study to carry out the much longer perturbations required for a high level of precision in the calculated VDW free energy. The greater polarizability contribution for acetate relative to methylammonium is consistent with expectations for anions and cations of similar size. The nonadditive water results are in good agreement with experiment, especially for acetate; the solvation free energy of methylammonium is slightly too negative. In contrast, the additive water model yields values about 10−15 kcal/mol too negative, once the Born correction is included. It may seem counterintuitive that a polarizable water model yields smaller solvation energies; however, overestimating the favorable energy of ion solvation is a general tendency of pairwise-additive water models, at least in part because there is no term that reflects the energy cost of polarization.[18] Previous Monte Carlo studies of acetate and methylammonium in TIP4P water gave reasonable accord with experimental heats of solution, but no cutoff contribution was included.[19,20]

As an alternative to the Born correction, cutoff contributions calculated with DelPhi[3] were also examined (Table 2). These are obtained analogously to solvation energies (in DelPhi), except that solute VDW radii are set to the cutoff used in the simulations (8 Å). While the assumptions are similar to those of the Born equation, the shape and charge distribution of the molecules are taken into account (the Born equation involves only the solute net charge and the cutoff). Corrections of −18.4 and −18.1 kcal/mol were obtained for acetate and methylammonium, respectively. When these are used in place of the Born value of −20.5 kcal/mol, the methylammonium solvation energy matches experiment but the acetate solvation energy is slightly too positive (although now within error range of the experimental value). It should be pointed out that the reported uncertainties are not true upper bounds on the magnitude of error, but represent the hysteresis in the perturbations. Also,

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Table 2. Calculated[a] and Experimental Solvation Free Energies (kcal/mol)

	additive model		nonadditive model			
	elect.[b]	total[c]	elect.[b]	solute pol.	total[d]	exptl
$CH_3CO_2^-$	−89.6 ± 0.4	−87.6 ± 2.0	−76.6 ± 0.7	−3.38 ± 0.12	−77.5 ± 1.7 (−75.4 ± 1.7)[g]	−77,[e] −79.9[f]
$CH_3NH_3^+$	−88.8 ± 0.4	−87.1 ± 1.2	−75.1 ± 0.2	−0.83 ± 0.03	−74.0 ± 1.0 (−71.6 ± 1.0)[g]	−70,[e] −71.3[f]

[a] Simulations employed periodic boundary conditions, with coupling constants[14] of 0.2 ps to the target temperature and pressure, 298 K and 1 bar. An 8.0-Å cutoff was used, and the one to four VDW and electrostatic interactions were scaled by factors of 1/2.0 and 1/1.2, respectively.[5] All bonds were constrained with SHAKE,[15] and the time step was 1 fs. In each case, the fully charged solute was placed in the center of a cube of waters, 26 Å in each dimension. After minimization and 20 ps of equilibration, the solute was "annihilated" in separate electrostatic and VDW stages. Each stage consisted of 100 windows, 500 steps of equilibration and 500 steps of collection per window. In the VDW portion, all bonds were shrunk to 0.5 Å; the bond-PMF correction[16] is included in the result. Additionally, in POL3 water, solute atom polarizabilities were introduced over 20 windows, each 1000 steps of equilibration and 1000 steps of data collection. Perturbations were carried out in both directions and with double-wide sampling; the calculated free energies are reported as the average of the four values ± the maximum deviation. [b] Electrostatic contribution including a Born cutoff correction of −20.5 kcal/mol. [c] Electrostatic and VDW contributions. [d] Electrostatic, solute polarizability, and VDW contributions. [e] Reference 4. [f] Reference 17. [g] Includes the DelPhi correction (see text) instead of the Born correction.

the VDW parameters for sp^3 nitrogens and their attached hydrogens have recently been refined.[21] We had used parameters for methylammonium nitrogen and hydrogen developed for amide nitrogens and hydrogens;[5] however, mutating the radii into the new, slightly larger values[21] increases the free energy of the ion in TIP3P water by 1.4 kcal/mol. Adding this value to the free energy found with the nonadditive model brings the calculated *absolute* solvation energy close to experiment using either cutoff protocol (−72.6 and −70.2 kcal/mol with the Born and DelPhi corrections, respectively) and also improves agreement with the experimentally determined *relative* solvation energy of methylammonium and acetate.

Overall, the accord with experimental solvation energies is good. It is especially notable as no *post hoc* parameter adjustment has been done; charges were generated with the standard RESP procedure,[5] and the remaining solute parameters came from other work.[5,11–13,21] Finally, the POL models have already proved successful in reproducing pure liquid properties as well as water−water and water−ion cluster energies and geometries.[6,9,10]

Our results demonstrate the usefulness and wide applicability of the RESP charge model and nonadditive (POL) water models. It is also likely that the usefulness and importance of nonadditive effects are not confined to the specific model we have developed.[22–24] Our method for including polarization is more computationally expensive than that employed in ref 22 in that it increases the CPU time by approximately a factor of 5, but it appears to be simpler to generalize to more complex solutes. More detailed analyses of the structure and energy of POL3 water as a function of solute properties are under way.

Acknowledgment. This work was supported by NSF Grant CHE9113472.

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