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Monte Carlo Simulations of Guanidinium Acetate and Methylammonium Acetate Ion Pairs in Water

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Free energy profiles of guanidinium acetate and methylammonium acetate ion pairs in water were calculated using Monte Carlo simulations. Both systems display a single shallow free energy minimum at a distance corresponding to a contact ion pair. Hydrogen bonding between the ions is an important feature in the association. The weakness of association is attributed to weaker solute–solvent interaction as the ions approach one another, as reflected in the loss of some of the water molecules hydrating the ions.

INTRODUCTION

Many different types of interactions contribute to the process of protein folding, including electrostatics, hydrogen bonding, and hydrophobic interactions (*1*). Current opinion generally recognizes hydrophobic interactions as the dominant force; however, the relatively minor contributions that arise from electrostatic interactions may also be important, as evidenced by the large number of salt bridges present in many different proteins (*2*). Salt bridges are formed when a positively charged side chain, such as arginine or lysine, interacts with a negatively charged side chain, such as aspartate or glutamate. In this article we report some computational investigations of guanidinium acetate (Gn–Ac) and methylammonium acetate (Ma–Ac) ion pairs. The former serves as a simple model for the arginine–aspartate (or glutamate) salt bridge, the latter for the lysine–aspartate (or glutamate) salt bridge.

The work described here relies on Monte Carlo simulations as the primary computational method (*3*). Calculations of this type have been reported for a variety of ion pairs, including, for example, *t*-butyl chloride (*4*) and tetramethylammonium chloride (*5*). A similar study investigated the pairing of tetramethylammonium cation with a variety of anions, including fluoride, chloride, bromide, and acetate (*6*). In fact, the two ion pairs included in this study have been investigated before (*7, 8*). However, in these previous simulations the relative orientations between the two ions were constrained. Such constraints can have a significant effect on the results. A recent study provides evidence of this (*9*).

In this work no such constraints were imposed during the Monte Carlo simulation, allowing complete orientational averaging. Compared to the earlier studies (*7, 8*),

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we also used a different set of parameters, particularly in the partial charge distribution and in the use of an explicit, all-atom model rather than a united atom representation for the methyl group. The suitability of our parameters was tested by comparison with ab initio calculations. Not surprisingly, our results are quite different from the earlier ones, particularly for the Gn–Ac ion pair.

COMPUTATIONAL METHODS

Monte Carlo simulations are employed to compute the structural and thermodynamic properties of a system as statistical mechanical averages (*3*). The particular system in this instance consists of the ion pair plus 316 (for Gn–Ac) or 318 (for Ma–Ac) water molecules confined in a rectangular box with approximate dimensions $18.6 \times 18.6 \times 27.9$ Å^3. Periodic boundary conditions were employed, i.e., the box was surrounded by images of itself in all directions. This allows the simulation of bulk properties of a fluid while keeping the system size manageable. The simulations were performed at a constant temperature of 25°C and constant pressure of 1 atm.

OPLS potential functions were used to calculate the system's energy (*10*). In this scheme, intermolecular interaction energies are calculated from Coulombic and Lennard–Jones interaction terms between sites primarily centered on the nuclei (Eq. [1]).

$$E_{ab} = \Sigma_{i \text{ on } a} \Sigma_{j \text{ on } b} \left(q_i q_j r_{ij}^{-1} + A_{ij} r_{ij}^{-12} - C_{ij} r_{ij}^{-6} \right) \qquad [1]$$

Water molecules are represented by the TIP4P model (*11*), while for the ionic solutes standard OPLS Lennard–Jones parameters were employed (*10*). Partial atomic charges were determined by fitting to electrostatic potentials generated for the isolated ions using *ab initio* calculations at the HF/6-31 + G level (*12*). The parameters used in these simulations are listed in Table 1. This procedure has been well tested and is currently the most commonly used method for deriving potentials for molecular simulations (*13*), and its suitability in the present context is discussed in more detail below. The intermolecular interactions are truncated using spherical cutoffs at 9.0 Å, with quadratic feathering over the last 0.5 Å.

In addition to intermolecular energies, a contribution from intramolecular conformational energies of the ions is also included. Thus, rotations around the C–C bond of acetate and the C–N bonds of guanidinium and methylammonium were sampled. The torsional energies were calculated using the parameters in the AMBER force field (*14*). Note that the scheme used in AMBER also includes intramolecular nonbonded interactions, including 1–4 interactions, which receive special treatment in that they are scaled by a factor of 8.0 (*10*) compared to other types of nonbonded interactions. This convention is followed in our calculations.

The primary objective of our simulations is to calculate a free energy profile $\omega(r)$, also called potential of mean force (PMF), as a function of the interionic separation r. This is done using an application of statistical perturbation theory

TABLE 1

Parameters Used for the Ions in the Monte Carlo Simulations[a]

Ion	Atom	q	σ, Å	ε, kcal · mol^{-1}
Acetate	C (carbonyl)	1.133	3.75	0.105
	O	−0.954	2.96	0.210
	C (methyl)	−0.273	3.50	0.066
	H	0.016	2.50	0.030
Guanidinium	C	1.393	2.25	0.050
	N	−1.167	3.25	0.170
	H	0.518	0.0	0.0
Methylammonium	C	−0.014	3.50	0.066
	H (on C)	0.114	2.50	0.030
	N	−0.306	3.25	0.170
	H (on N)	0.326	0.0	0.0

[a] The Lennard–Jones parameters σ and ε are related to A and C in Eq. [1] by the relation $A_{ii} = 4\ \varepsilon_i\sigma_i^{12}$ and relation $C_{ii} = 4\ \varepsilon_i\sigma_i^6$; for mixed terms geometric combining rules were used: $A_{ij} = (A_{ii}A_{jj})^{1/2}$ and $C_{ij} = (C_{ii}C_{jj})^{1/2}$.

that allows the computations of the free energy difference between two similar systems i and j as the statistical mechanical average of a function of the potential energy difference between those two systems (Eq. [2]) (*15*).

$$G_j - G_i = -kT \ln \langle \exp[-(H_j - H_i)\ (kT)^{-1}] \rangle_i \qquad [2]$$

In the present context, the two systems i and j are simply the ion pair with slightly different interionic separations. In each simulation, the free energy changes associated with increasing and decreasing the separation by 0.1 Å are calculated simultaneously, a procedure known as doublewide sampling (*16*). Separate simulations are performed with separations ranging from about 3 to 7.5 Å, and the free energy differences are then combined to generate the PMF. Note that because only free energy *differences* are calculated, the absolute energies are not obtained from these calculations.

Each simulation consists of the generation of at least 10^6 configurations for equilibration, followed by averaging over the next 4×10^6 configurations. Averages were also computed separately for blocks of 2×10^5 configurations to provide estimates in the statistical uncertainties in the free energies. For each simulation, the free energy differences computed were generally less than 1 kcal/mol (except for the region where the ions are nearly in contact with each other), while the standard deviations after 4×10^6 configurations were less than 0.2 kcal/mol. It was also observed that the standard deviations generally decrease with increased number of configurations from 1 to 4×10^6, ensuring that adequate sampling has been obtained.

The choice of parameters such as the ones in Table 1 is always a matter of concern in performing molecular simulations. A particular issue is the suitability

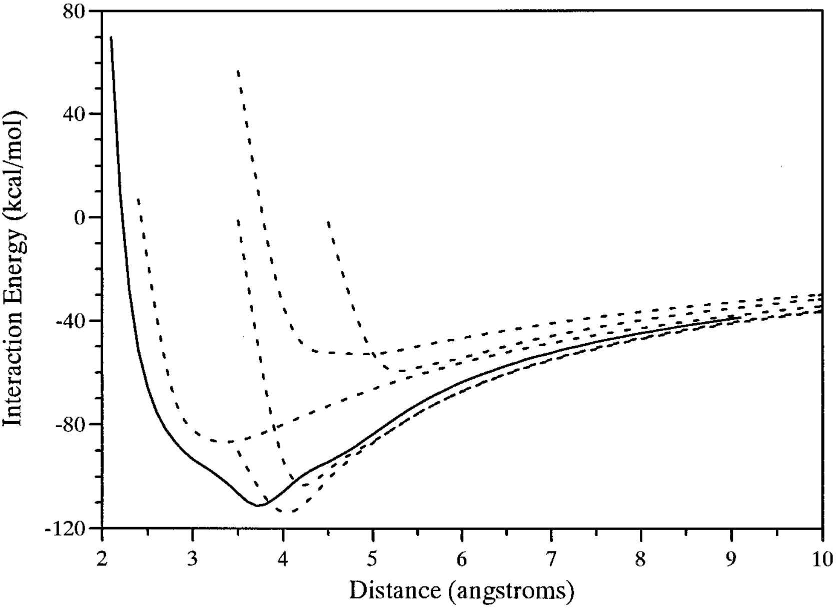

FIG. 1. Gas-phase interaction energy between guanidinium and acetate. The horizontal axis is the distance between the central carbon atom of guanidinium and the carbonyl carbon atom of acetate. Dashed lines, ab initio interaction energy profiles at various orientation. Solid line, Monte Carlo free energy profile.

of the partial charges. In some cases accurate free energies can only be obtained when the partial charges are allowed to vary among the different conformations of a molecule, or at least adjusted so that they are representative for all the different conformations rather than for a single one (*17*). The issue in the present case is whether the partial charges should be varied as a function of interionic distance and the relative orientation between the ions. We have investigated this issue for the Gn–Ac ion pair. This was done by comparing the performance of the OPLS model with the results of *ab initio* calculations in the gas phase.

Ab initio interaction energies were calculated for the Gn–Ac ion pair for five different relative orientations and different interionic distances. These are displayed in Fig. 1. Monte Carlo simulations were performed, using the OPLS parameters in Table 1 and in the absence of solvent, to generate the gas-phase free energy profile. This is also shown in Fig. 1. A single curve is obtained for the OPLS interaction energies, because sampling of different relative orientations is allowed and thus the system will tend to adopt the most favored orientation at any given distance. It is evident that the chosen parameters are quite successful in reproducing the *ab initio* results. The distances are slightly smaller than the *ab initio* results, and only relative energies are obtained from the Monte Carlo simulations, but it is clear that OPLS energy curve follows that of the most stable *ab initio* structure at any given

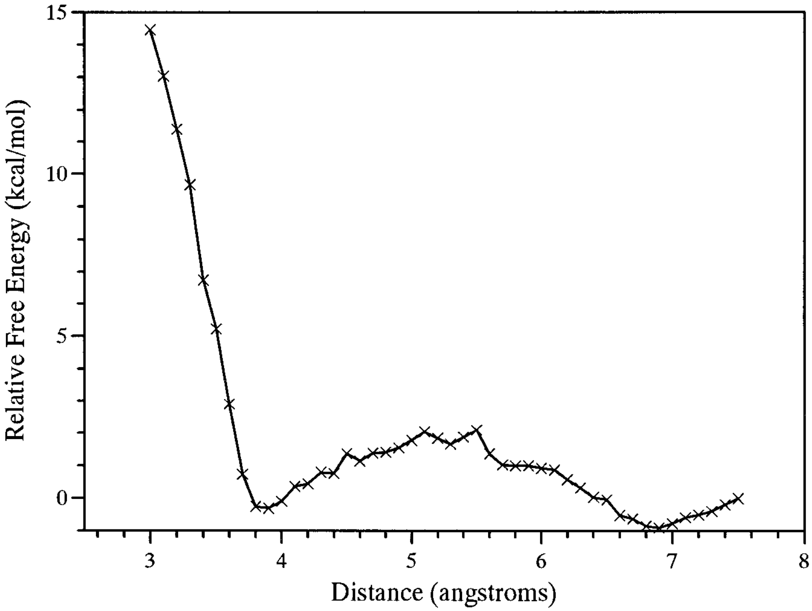

FIG. 2. PMF for guanidinium acetate in water. The horizontal axis is the distance between the central carbon atom of guanidinium and the carbonyl carbon atom of acetate. The PMF is set to zero at 7.5 Å.

distance. Moreover, the relative orientation is the same for the Monte Carlo and *ab initio* calculations. For example, at the energy minimum (distance *ca* 4 Å) the orientation is essentially coplanar, with two hydrogen bonds between two different nitrogen atoms of guanidinium and the two oxygens of acetate, while at smaller distances (below 3 Å) the orientation is perpendicular, with the two acetate oxygens facing the plane of the guanidinium cation.

We have also investigated the variability of the partial charges. The charges were fitted for the ion *pair* at various distances and relative orientations. The greatest variation was observed for the carbon atom of guanidinium; it was less than 0.15. Thus, we conclude that *for this system* a single charge distribution obtained from the isolated ions is sufficient. It was assumed that the same situation will hold for the Ma–Ac ion pair.

The Monte Carlo simulations were performed using the BOSS program (*18*), and the *ab initio* calculations were performed using Gaussian-92 (*19*). All computations were run on Silicon Graphics Indigo R-4000 computers.

RESULTS AND DISCUSSION

The PMF's for Gn–Ac and Ma–Ac are shown in Figs. 2 and 3, respectively. For the purpose of display both PMF's are set to 0 kcal · mol^{-1} at 7.5 Å; as mentioned