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Biophysical Chemistry 51 (1994) 253–261

Biophysical Chemistry

The hydration and solvent polarization effects of nucleotide bases

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Received 3 December 1993; accepted 14 January 1994

Abstract

A combined Monte Carlo quantum mechanical and molecular mechanical (QM/MM) simulation method is used to determine the free energy of hydration and the solvent polarization effect for the nucleotide bases. In the present AM1/TIP3P model, the solute molecule is characterized by valence electrons and effective nucleus cores with Hartree–Fock molecular orbital theory incorporating a solute–solvent interaction Hamiltonian. It is found that polarization energy contributes up to 37%–61% of the total solute–solvent interaction for the systems considered. The computed free energies of hydration are compared with previous theoretical results.

Key words: Monte Carlo simulation; Hydration; Polarization; Nucleotide bases

1. Introduction

Due to the high solubility and lack of volatility, experimental determination of the free energies of hydration of nucleotide bases has been difficult [1]. Yet, they are important in the understanding of the structure and properties of nucleic acids in aqueous solution [2]. Consequently, these quantities are primarily obtained based upon theoretical treatments [3–6]. Most simulation studies make use of the molecular mechanics-type potential functions [3–8], which are parametrized by fitting against experimental or ab initio data [9–11]. Although these calculations can provide valuable insights into solute–solvent interactions, a major concern is the lack of specific consideration of the solute electronic polarization in solution. This is echoed by the finding of significant polarization contributions to the relative energies and dipole moments of heterocyclic compounds from a combined quantum and statistical mechanical simulation approach, and from continuum self-consistent reaction field (SCRF) calculations [12–14]. Classical studies of solute polarization in water also demonstrated the significance of these effects [15–17]. Despite these concerns, progress has been slow to incorporate electric polarization effects into molecular mechanical force fields because of a lack of quantitative understanding of the condensed-phase polarization effect [18,19]. Thus, it is of interest to evaluate the free energies of hydration of nucleotide bases with the inclusion of solute electronic relaxations in condensed-phase simulations.

We adopt a combined quantum mechanical and molecular mechanical (QM/MM) approach in this study. The method centers on the division of the condensed-phase system into a quantum mechanical region for the solute, and an empirical, molecular mechanical region for the surrounding solvent (for reviews see refs. [20,21])

SSDI 0301-4622(94)00046-M

[22]. Solute–solvent interaction energies are determined by including the partial charges of the classical water molecules into the QM Hamiltonian of the nucleotide bases.

The combined QM/MM approach has been pioneered by several groups. Warshel and co-workers investigated numerous chemical and biological systems, using empirical valence bond (EVB) theory and molecular orbital method [20]. Karplus and co-workers, employing the semiempirical AM1 and MNDO Hamiltonian, carried out a molecular dynamics simulation to determine the free energy of activation for an S_N2 reaction in water [23]. Recently, we have adopted the same AM1/TIP3P model and developed a method to determine condensed-phase polarization energies and the free energies of hydration of organic compounds [13]. Encouraging results have been obtained in these studies. In addition, a number of groups have combined ab initio molecular orbital method with MM programs in energy minimization studies [24].

In this paper, we present the results from analyses of the solute electric polarization in nucleotide base–water interactions. In addition, the absolute free energies of hydration for the five nucleic acid bases and the polarization contributions are determined. Section 2 summarizes the theoretical model used in the present calculation, while the performance of the combined QM/MM-AM1/TIP3P potential is verified in section 3 via comparison with the results from ab initio 6-31G(d) and QM/MM calculations for bimolecular complexes of heterocyclic compounds with water. The results from the fluid simulations are presented and discussed in sections 4 and 5, followed by conclusions.

2. Method

2.1. Intermolecular potential functions

We employ the combined AM1/TIP3P model to describe solute–solvent interactions in solution. The method has been described in detail previously [13,20–22]. Thus, only a brief summary is given here. In this approach, the solute molecule is treated by Hartree–Fock molecular orbital theory using the AM1 Hamiltonian [25], while the solvent molecules are represented by the three-site TIP3P model for water [26]. Thus, the total effective Hamiltonian for the system is given by

$$\hat{H}_{\text{eff}} = \hat{H}^0 + \hat{H}_{\text{qm/mm}} + \hat{H}_{\text{mm}}, \tag{1}$$

where $\hat{H}^0$ is the Hamiltonian for the QM solute, $\hat{H}_{\text{mm}}$ is the solvent–solvent interaction energy, and $\hat{H}_{\text{qm/mm}}$ is the solute–solvent interaction Hamiltonian, which can be further divided into electronic and van der Waals terms,

$$\hat{H}_{\text{qm/mm}} = \hat{H}^{\text{el}}_{\text{qm/mm}} + \hat{H}^{\text{vdW}}_{\text{qm/mm}}. \tag{2}$$

The solute–solvent interaction energy in the combined QM/MM model is evaluated using

$$E_{\text{qm/mm}} = \langle \Phi | \hat{H}^{\text{el}}_{\text{qm/mm}} | \Phi \rangle + \sum_{i}^{\text{solute}} \sum_{s}^{\text{water}} 4\epsilon_{is} \times \left[(\sigma_{is}/R_{is})^{12} - (\sigma_{is}/R_{is})^{6} \right], \tag{3}$$

where Φ is the wavefunction of the solute in aqueous solution. The Lennard-Jones terms account for dispersion interactions between QM and MM regions, which do not have orbital overlap in the present treatment [13]; they contain the only parameters for the solute, which have been adjusted to reproduce ab initio 6-31G(d) hydrogen-bonding complexes, and are given in a previous publication [13]. To form the QM/MM interaction Hamiltonian, a solute–solvent cutoff distance of 9 Å was used. Thus, water molecules that are within the cutoff distance from any solute atoms are included in the calculation of $E_{\text{qm/mm}}$.

Clearly, to compute the energies for the QM solute molecule throughout the fluid simulation, a computationally efficient method must be used. Therefore, the semiempirical Austin Model 1 (AM1) theory developed by Dewar and co-workers is employed in this study [25]. The validity of this combination for the calculation of hydration free energies of nucleotide bases is further tested below.

2.2. Free energy calculations

Free energies of hydration for the five nucleotide bases are evaluated using the free energy perturbation method (Eq. (4)) in the context of Monte Carlo simulations [27]

$$\Delta\Delta G_{AB} = -kT \ln\langle e^{-\Delta\hat{H}(A\rightarrow B)/kT}\rangle_A, \qquad (4)$$

where k is Boltzmann's constant, T is temperature, $\Delta\Delta G_{AB}$ is the difference in solvation free energy between molecules A and B, $\Delta\hat{H}(A\rightarrow B)$ is the difference between the Hamiltonians for A and B. The brackets $\langle\ \rangle_A$ in Eq. (4) implies that the statistical ensemble average is obtained based on the Hamiltonian for A. In practice, the convergence of Eq. (4) is slow for solutes with large size differences. Consequently, a series of simulations are needed to gradually 'mutate' one molecule into another through a coupling parameter λ, which varies from 0, representing state A, to 1, representing state B. The total free energy difference is then enumerated with

$$\Delta\Delta G_{AB} = \sum_{\lambda=0}^{\text{steps}} \Delta G(\lambda\rightarrow\lambda+\Delta\lambda), \qquad (5)$$

where $\Delta\lambda$ is the percent change in each step of the mutation. Significantly, the free energy of hydration of A can be determined through a procedure used by Cieplak and Kollman [28], in which A is made to vanish in solution. In this study the QM/MM interaction Hamiltonian (consisting both electrostatic and van der Waals terms, Eq. (2)) is converted to one that contains only the van der Waals term to yield the electrostatic contribution, ΔG_{elec}. Then, the 'van der Waals molecule' is gradually annihilated by perturbing the Lennard-Jones parameters to zero to give ΔG_{vdW}. Combining the results from the electrostatic decoupling [4] and van der Waals parameters annihilation, the absolute free energy of hydration ΔG_{hyd} can be computed using Eq. (6) below based on a thermodynamic cycle [28],

$$\Delta G_{hyd} = -\Delta G_{elec} - \Delta G_{vdW}. \qquad (6)$$

This type of calculations have been used to determine binding free energies of nucleotide base pairs and other host–guest systems [29].

2.3. Monte Carlo simulations

Statistical mechanical Monte Carlo simulations have been carried out using Metropolis sampling in the isothermal–isobaric (NPT) ensemble at 25°C and 1 atm. A cubic box consisting of 260 water molecules (about $20\times20\times20$ Å^3) plus one solute is used. The Owicki-Scheraga preferential sampling technique with $1/(r^2+C)$ weight, where $C = 150$ Å^2, was adopted to facilitate the statistics near the solute molecule. The free energy was computed with both forward and reverse perturbations through double-wide sampling [30], from which the error ranges for the computed quantities were estimated. Ten simulations (windows) were used for each system in the electrostatic decoupling. In the second step, ten simulations were used to transform purine bases to pyrimidine, followed by ten additional perturbations to convert pyrimidine into methane. The free energy of hydration for methane has been determined previously [22,31]. For each simulation, 5×10^5 to 10^6 configurations were taken in the equilibration, followed by 1.5×10^6 configurations for data collection. During the calculation, solute-solvent interaction energies are evaluated by single-point Hartree–Fock SCF calculations using the effective Hamiltonian of Eq. (1). All calculations were carried out on a SUN Sparc10 workstation and a Titan 3000 computer in our laboratory using the BOSS/MCQUB programs [32], in which the QM energies are determined with the MOPAC program [33].

3. Gas-phase bimolecular complexes

An important criterion on the reliability of a force field for liquid simulations is to be able to predict the structural and energetic properties of bimolecular complexes. In the course of the development of the OPLS parameters for the nucleotide bases, Jorgensen and co-workers performed ab initio calculations for complexes of these bases and the monocyclic fragments of adenine and guanine with water [10]. For each base, several orientations of the water hydrogen-bonded complex were considered with 6-31G(d) partial

geometry optimization (Fig. 1). Since the 6-31G(d) basis set is known to provide good descriptions of hydrogen bonding interactions for a variety of systems, these results may be used to verify the performance of the combined AM1/TIP3P potential used in the present study. Consequently, these bimolecular complexes are investigated using the combined AM1/TIP3P model. Now, the heterocyclic compounds are treated by the AM1 theory, and the water molecule is treated by the TIP3P model. Partial geometry optimizations are executed using a program developed in our laboratory with fixed monomer geometries. The AM1 geometries are used throughout in the present

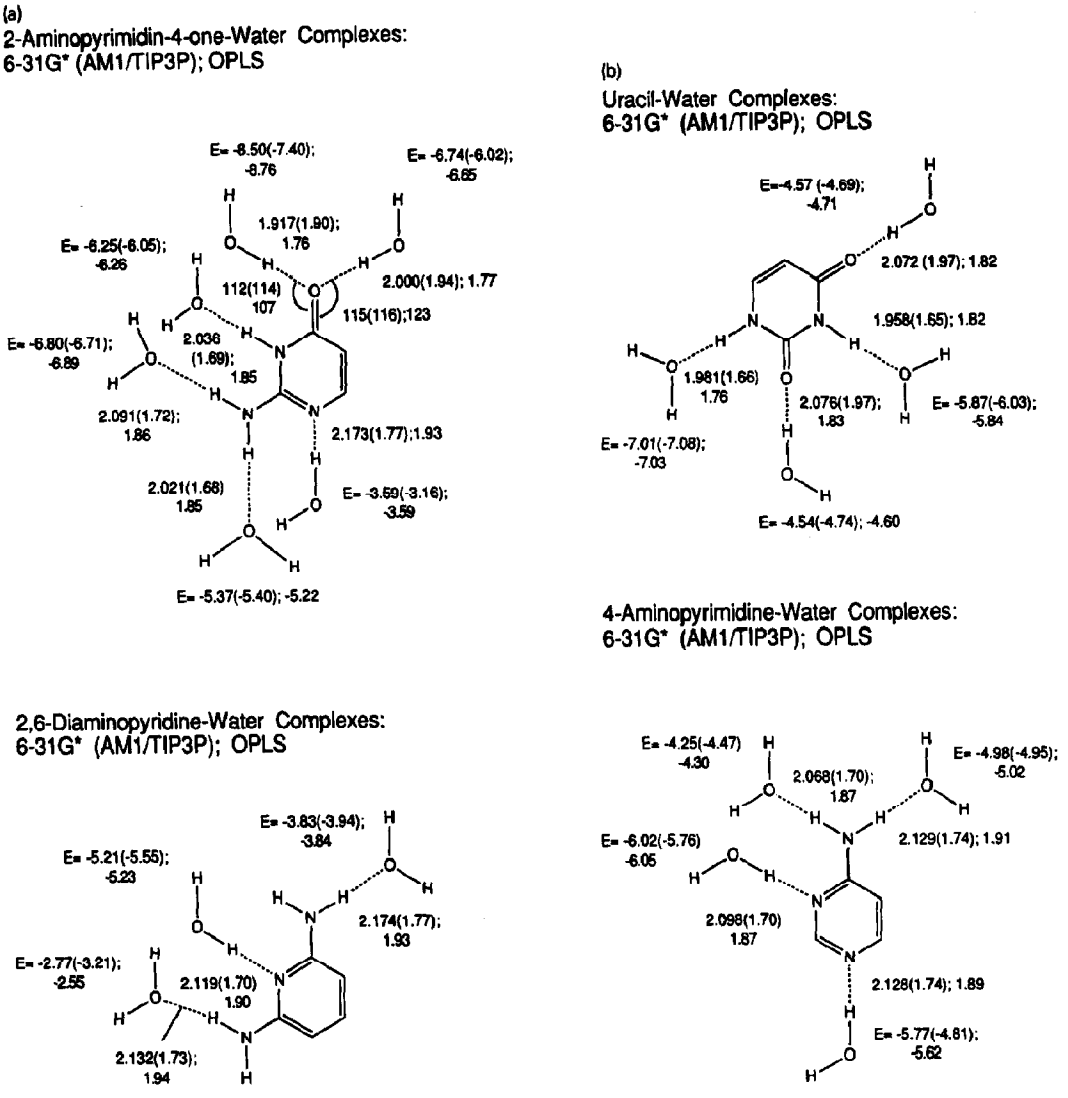

Fig. 1. Base–water complexes. 6-31G(d) results are given first, followed by the AM1/TIP3P values in parentheses, and the OPLS data last. Interaction energies are given in kilocalories per mole, and distances in angstroms. Both the ab initio and OPLS data are taken from ref. [10].

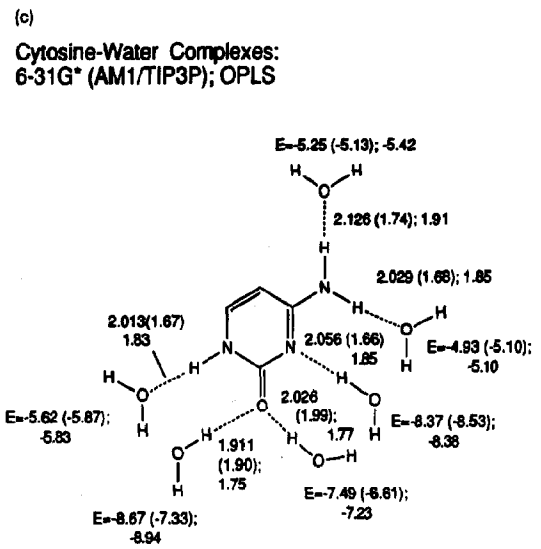

Fig. 1 (continued).

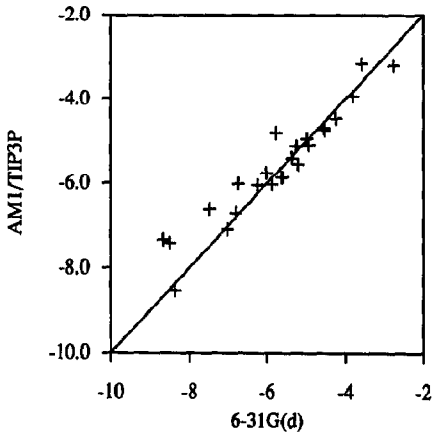

Fig. 2. Comparison between ab initio 6-31G(d) and AM1/TIP3P interaction energies (kcal/mol).

study for the bases, while the experimental configuration is adopted for water. The results are shown in Fig. 1.

The accord for the interaction energies between the AM1/TIP3P and ab initio 6-31G(d) results is illustrated in Fig. 2. Overall, the root-mean-square (RMS) deviation is 0.5 kcal/mol for a total of 23 complexes. This may be compared with the best fit between the OPLS and ab initio data, which has an RMS deviation of 0.13 kcal/mol [10]. The interaction distances from the AM1/TIP3P calculations are also in reasonable agreement with the ab initio results (Fig. 1). Large deviations are primarily from hydrogen bonding interactions involving nitrogen atoms, for which the AM1 method typically underestimates the charge separation. In this case, the interaction distances from the AM1/TIP3P optimization are about 0.4 Å shorter than the ab initio results (Fig. 1). Similar features are also necessary in the empirical OPLS function and in other molecular mechanical force fields, with which the interaction distances are typically 0.2–0.3 Å shorter than the 6-31G(d) values [9–11]. For complexes with QM hydrogen-bond acceptors, the predicted interaction distances using the QM/MM model are in good accord with the ab initio data.

The results shown in Figs. 1 and 2 strongly support the use of the present AM1/TIP3P model for nucleotide bases, suggesting that the simulations can provide reasonable estimates of the hydration free energies.

Table 1
Computed free energies of hydration for nucleotide bases at 25°C (kcal/mol)

Method	Adenine	Cytosine	Guanine	Thymine	Uracil
MC QM/MM	−5.1 ± 0.6	−16.3 ± 0.8	−13.5 ± 1.1	−8.5 ± 0.5	−9.9 ± 0.7
OPLS [a]	0.0	−8.5	−10.1	−1.5	−1.2
AMBER [b]	−12.6 ± 1.7	−12.7 ± 2.4	−19.6 ± 2.2	−7.5 ± 2.1	
AM1-SM2 [c]	−23.7	−21.7	−26.9	−16.5	−18.2
SCRF(AM1) [d]	−11.3	−14.4	−18.1	−8.6	
SCRF(6-31G*) [e]	−6.5	−13.0	−16.1	−8.9	−10.0
FDPB [f]	−10.8	−16.8	−19.7	−10.4	

[a] Ref. [8], relative free energies for methylated bases. [b] Ref. [9], for methylated bases. [c] Ref. [12]. [d] Ref. [34]. [e] Ref. [35], for methylated bases. [f] Ref. [6], for methylated bases.

4. Free energies of hydration

The absolute free energies of hydration, ΔG_{hyd} for the five nucleotide bases are computed using the free energy perturbation method in Monte Carlo simulations. The results are listed in Table 1 along with previous findings. In early studies, hydration free energies are typically computed for the 1-methylated pyrimidine and 9-methylated purine bases, which are about 1 to 2 kcal/mol less negative than the parent nucleotide bases considered here [12]. Thus, this difference should be taken into account in the following discussion. In Table 1, a noticeable difference is the results predicted by the AM1-SM2 model which employs a self-consistent reaction field (SCRF) approach in Hartree–Fock AM1 calculations [12]. The AM1-SM2 model tends to yield greater solvation free energies by about 8–12 kcal/mol over those obtained with other methods. The reason for this discrepancy is not clear, particularly in view of the good agreement with our results on the aqueous dipole moments for these compounds (see below). It is difficult to predict which calculation is 'correct' since experimental data are not available.

For cytosine and thymine, our AM1/TIP3P values are in good accord with the results from molecular dynamics simulations using the AMBER force field [4] and from continuum models [6,34,35]. For uracil, the present value is consistent with a recent molecular dynamics simulation study by Elcock and Richards [8], who predicted the relative free energies of hydration for uracil and thymine to be similar. The agreement with Young and Hillier's results was also good [35]. The numbers reported by Cramer and Truhlar are 5–8 kcal/mol more negative than our results.

ΔG_{hyd}s are estimated to be −5.1 and −13.5 kcal/mol for the two purine bases, adenine and guanine, respectively, using the AM1/TIP3P potential. In comparison with the literature data (Table 1), these numbers are about 6 kcal/mol smaller. The difference might be due to limitations of the AM1 theory employed in the present Monte Carlo simulations, although it is not clear whether the results based on empirical, molecular-mechanics potentials are sufficiently accurate to make this conclusion. It should be noted that the partial charges used in these force fields are typically fitted to reproduce gas-phase properties, such as molecular electrostatic potentials and dipole moments, which do not include the solvent polarization effects [9–11]. The discrepancy probably can only be unambiguously resolved by experiments when they are eventually performed. Nevertheless, the present results represent a *consistent* estimate of the free energies of hydration for these nucleotide bases without parameter adjustments in these calculations. Further, our Monte Carlo simulations take into account specific electric polarizations of the bases in solution. It is interesting to notice that the most recent results, which were obtained from a seven-order multipole expansion using the 6-31G(pd) basis set in the SCRF treatment and appeared after the submission of this manuscript [35], are in good accord with the present findings, particularly for adenine.

Table 2 lists the computed dipole moments for

Table 2
Computed dipole moments (D)

Base	AM1	Exp.	OPLS [a]	AMBER [b]	QM/MM [c]	AM1-SM2 [d]	SCRF [e]
Adenine	2.17	3.16	2.54	2.17	3.81	3.1 (3.1)	2.9
Cytosine	6.33	7.10	7.20	5.67	9.40	9.0 (10.0)	7.4
Guanine	6.18	6.76	6.44	6.14	9.42	8.5 (9.3)	6.6
Thymine	4.24	3.58	4.12	3.20	5.89	6.2 (6.6)	5.2
Uracil	4.28	3.86	3.71	3.37	6.15	6.4 (6.9)	5.2

[a] Ref. [10]. [b] Ref. [9]. [c] The estimated standard deviation is about 0.01 D. [d] Ref. [12]. Data in parentheses are obtained for fully relaxed (both geometry and wave function) systems. [e] Ref. [36].

the five nucleotide bases in the gas phase and in aqueous solution, which provide some support to the computed hydration free energies. Table 2 also compares our results with those obtained by Katritzky and Karelson [36] and by Cramer and Truhlar [12]. The overall increase in dipole moment for the five compounds are 39%–75%, in excellent accord with the finding of 41%–60% in ref. [12]. The agreement is particularly encouraging in view of the difference in the two computational methods. In our calculation, water molecules are explicitly represented by the TIP3P model, whereas the SCRF AM1-SM2 calculation includes solvent as a continuum dielectric medium [12]. However, it should be noted that the AM1-SM2 calculation also allows solute geometry relaxation in solution, which further increases the dipole moments by 6%–11% (data in parentheses). Nevertheless, the change induced by such a geometry variation only alters the computed solvation free energy by 5% (or less than 1 kcal/mol). The observed dipole increase reported in ref. [36] is only 12%–32%, substantially smaller than our Monte Carlo and the AM1-SM2 data. Cramer and Truhlar have attributed the smaller increase in that study to the omission of multipole contributions of the solute [12].

Of particular interest is the comparison of the trends of the computed hydration free energies (Table 1) and aqueous dipole moments (Table 2). In the present QM/MM Monte Carlo calculation, ΔG_{hyd}s follow nicely the change of the computed dipole moments of these bases in water. Although the hydration free energies for adenine and guanine are much smaller than other predictions, the trend is consistent with the relative magnitude of the aqueous dipole moments. On the other hand, the patterns are more complex in other calculations. Bash et al. noted that 9-methyladenine has a greater ΔG_{hyd} than 1-methylthymine, but the former has a much smaller dipole moment [4]. The same ordering was, too, obtained by Cramer and Truhlar; however, the explanation for this reversal in terms of the low-order multipole moments was considered to be insufficient for these complex molecules [12]. Previous molecular dynamics simulations of these nucleotide bases in water exclude solute electronic relaxations, whereas continuum models do not consider specific intermolecular interactions explicitly. Of course, the latter approach takes into account the $\hat{H}_{qm/mm}$ term through the SCRF treatment [12,14,37]. The trends noted above might be an indication that both aspects are of considerable importance in modeling solute–solvent interactions, which are, of course, included in the present approach.

5. Free energy of polarization

The present investigation along with early works that explicitly include solute electronic relaxations demonstrates the significance of the polarization contribution to the aqueous solvation process [12,13,38]. In our previous study, we have found that the solute electronic polarization increases the solute–solvent interaction energy by about 20% for organic compounds representing amino acids and nucleotide bases [13]. Cramer

Table 3
Contributions to the total free energy of hydration (kcal/mol)

Base	ΔG_{hyd}	ΔG_{elec}	ΔG_{vdW}	ΔG_{pol}	ΔG_{pol} AM1-SM2 [a]
Adenine	−5.1 ± 0.6	−5.5 ± 0.5	0.4 ± 0.3	−3.1 ± 0.2	−4.5 (−4.9)
Cytosine	−16.3 ± 0.8	−16.8 ± 0.8	0.5 ± 0.3	−6.4 ± 0.4	−4.4 (−5.5)
Guanine	−13.5 ± 1.1	−13.3 ± 1.0	−0.2 ± 0.3	−7.3 ± 0.3	−5.6 (−6.6)
Thymine	−8.5 ± 0.5	−9.3 ± 0.3	0.8 ± 0.3	−3.4 ± 0.2	−3.1 (−3.7)
Uracil	−9.9 ± 0.7	−10.1 ± 0.6	0.3 ± 0.3	−3.7 ± 0.3	−3.8 (−4.4)

[a] Ref. [12]. Data in parentheses are for fully relaxed bases in water.

and Truhlar reported increase in ΔG_{hyd} by 26–34% for nucleic acids with Φ relaxation [12]. Here, we report an average of the polarization contribution to the total free energies of hydration for the nucleotide bases, or polarization free energy of hydration $\Delta G_{h,pol}$ (Eq. (7)),

$$-\Delta G_{h,pol} = -kT \ln\left\langle \exp\left\{-\left[E_{sx}(\Phi^0) - E_{sx}(\Phi_{aq})\right] /kT\right\}\right\rangle_{\Phi_{aq}}, \quad (7)$$

where Φ^0 and Φ_{aq} are solute wave functions in the gas phase and water, respectively, and $E_{sx}(\Phi^0)$ and $E_{sx}(\Phi_{aq})$ are interaction energies for the 'unpolarized' and polarized solute with the solvent. The brackets $\langle\ \rangle_{\Phi_{aq}}$ indicates that the ensemble average was computed using the fully relaxed solute wavefunction. For additional insights of these quantities, see ref. [13].

Table 3 shows the van der Waals dispersion and electrostatic contributions to the total free energy of hydration. The latter component also includes the solute polarization contributions, which are compared with the data by Cramer and Truhlar for the geometry relaxed bases [12]. The quantitative agreement between the two calculations is remarkable. Our results suggest that the solute electronic polarization effects contribute significantly to the aqueous solvation of the nucleotide bases, which amount to 37%–61% in the AM1/TIP3P simulation calculation. These findings have crucial implications in computer simulation of nucleic acids in aqueous solution using pairwise, empirical potentials, which treat the polarization effects in an average way through the parametrization process. However, the partial atomic charges for the nucleotide bases used in these studies typically yield dipole moments in close agreement with the gas phase experimental values. Clearly, explicit inclusion of the polarization terms in the empirical force field is desirable.

It is interesting to compare the results predicted by the AM1-SM2 model and by the present AM1/TIP3P simulation since the molecular wavefunctions used in the two methods are the same, but differing significantly in the treatment of solvent effects. For properties including molecular dipole moments and the polarization free energies, the two approaches are in excellent agreement (Tables 2 and 3), suggesting that the electronic polarization of the nucleotide bases are well represented by both methods. On the other hand, the computed absolute free energies of hydration for the five bases differ by 5.4–18.6 kcal/mol. The departure is particularly surprising in view of the accord in the computed solvation free energies for other organic compounds representing amino acid sidechains [13,39]. Although one may speculate about the difference in the parametrization procedure used in the two methods, it is not clear from this study where it specifically originates.

6. Conclusion

We have presented quantitative evidence, suggesting a significant solute electronic polarization contributions to the total free energy of hydration for nucleotide bases. Undoubtedly, the solvent polarization effects should be included in fluid simulations of biopolymers including nucleic acids in aqueous solution. The results obtained here using a combined quantum mechanical and statistical mechanical simulation approach may be used in the parametrization of future models that include these terms. The computed absolute free energies of hydration of the pyrimidine bases are within the range of previous theoretical values, while our prediction for the purine bases is smaller than the early data. The trend of the hydration free energies, however, is consistent with the magnitude of the aqueous dipole moments for these bases, and the qualitative picture of the significance of the solvent polarization effect should be valuable.

Acknowledgement

Gratitude is expressed to the National Institutes of Health and the National Science Foundation for support of our research.

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