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Role of twisting and sliding on the solvation of a stacked cytosine dimer: an ab initio study

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Abstract. Ab initio calculations with inclusion of correlation effects at the MP2/6-31G* level have been used to predict the interaction energy of stacked cytosine dimer (C/C) as a function of twisting and sliding in the gas phase. Systematic calculations have also been carried out on the solvation free energies of various rotated and translated C/C dimers using a polarized continuum model approach at the HF/6-31G* level with a view to probe the role of various degrees of freedom on the free energy of solvation of the C/C dimer. The interaction energy of the C/C dimer decreases upon changing from a parallel to an antiparallel conformation in the gas phase. The 180°-rotated conformation has been found to be the most stable arrangement when compared to other rotated positions. The rotated and translated dimers exhibit lower solvation free energy than the parallel conformation. The decrease in the dipole moment upon rotation from the parallel to the antiparallel conformation indicates the cancellation of charge distribution upon rotation in the z direction of one cytosine base with respect to the other. The calculation reveals that the present approach could not yield association energy, $\Delta\Delta G_{\mathrm{Asso}}$, in a solvent medium. This may be due to the fact that in the case of floppy molecules the contribution from translational, rotational and vibrational free energies plays a significant role in the calculation of $\Delta\Delta G_{\mathrm{Asso}}$.

Key words: DNA base dimers – Twist – Slide – Solvation

1 Introduction

Stacking and hydrogen-bonding interactions between nucleic acid bases are important in stabilizing the three-dimensional DNA double helix [1, 2]. Electrostatic interactions are dominant in hydrogen-bonded base pairs, whereas dispersion forces determine the stability of stacked nucleic acid complexes [3]. The energy of the stacked aromatic DNA bases is quite complex since the π-stacking energy arises from van der Waals interactions, electrostatic interactions between partial atomic charges, electrostatic interactions between the charge distributions associated with out-of-plane π-electron density, and electrostatic interactions between the charge distributions associated with out-of-plane π-electron density and the partial charges [4, 5]. Hunter [6] has made a systematic analysis of the sequence-dependent structure of DNA on the basis of these base-stacking interactions as a function of sliding, rolling, shifting, tilting, rising and twisting, which describe the degrees of freedom within a single base pair. Sponer et al. [7, 8] have made exhaustive theoretical studies on the structure, energetics and dynamics of nucleic acid bases using ab initio quantum chemistry. Hobza and Sponer [9] have recently reviewed various theoretical techniques employed to probe DNA bases, base pairs and stacked pairs and salient findings from such investigations.

Hydration of nucleic acids plays an essential role in determining their structure and is responsible for their conformational transition and hence the effect of water and other solvents on the interaction between nucleotides has been a subject of great importance. Numerous investigations in quantum chemistry have focused on gaining insight into chemical and biochemical processes in solvent phases [1, 10]. Statistical-mechanics-based methods, such as Monte Carlo and molecular dynamics calculations have been used to study the hydration of the DNA double helix [11]. In the prediction of the free energy of association of DNA base pairs and stacked pairs, Cieplak and Kollman [12, 13] have made a seminal contribution using free-energy perturbation theory. The free-energy calculations revealed that the stacked dimers are more stable in water than the hydrogen-bonded DNA base pairs and the free energy of association of nucleic acid bases in water ranges between 0 and -2 kcalmol^{-1}.

Even though several techniques have been used to represent solute–solvent interactions, the recently developed self-consistent reaction field (SCRF) has proved to

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be a powerful tool in representing the bulk solute–solvent interactions [14]. To understand the changes in the molecular geometry, vibrational and electronic spectra and other electronic properties, the SCRF approach has been found to be a useful method. Solvation of DNA bases, base pairs and stacked base pairs has been studied using the SCRF approach [15, 16]. Orozco and Luque [17] have reviewed theoretical methods for the description of solvent effects in biomolecular systems. The SCRF approach based on Onsager's model [18] is the simplest approach and describes the solvation phenomenon at slightly higher computational cost than that required by gas-phase calculations. Sivanesan et al. [19] have employed the Onsager-based SCRF approach to model solvation of a stacked cytosine dimer. Among the quantum reaction field methods, the polarized continuum model (PCM) developed by Miertus, Scrocco and Tomasi [20] to analyze the solvent effect on the basis of molecular shaped cavities [21] and the molecular electrostatic potential [22] has received widespread attention owing to its adaptability and accuracy. The description of solvent effects by means of Langevin dipoles has been pioneered by Warshel's group [23]. They have investigated possible conformations of stacked DNA base dimers using a MP2/6-31G*(0.25) calculation combined with a Langevin dipole model.

There are many studies on the explicit solvation of DNA bases and base pairs [12, 13, 24]. Gadre and coworkers have exploited the topographical features associated with the molecular electrostatic potential (electrostatic potential for intermolecular complexation, EPIC) to study the explicit solvation of uracil [25]. Recently, Sivanesan et al. [26] have studied the hydration pattern and energetics of cytosine dimers using both EPIC and ab initio calculations. This study again reinforces the earlier predictions of Cieplak and Kollman [12, 13] that stacked pairs become hydrated better than the hydrogen-bonded pair.

Since properties of various DNAs depend on various degrees of freedom, like sliding, rolling, shifting, tilting, rising and twisting, in this work an attempt has been made to unravel the solvation of stacked cytosine dimer by varying the twist angle and the sliding. In the present investigation, the interaction energy of stacked cytosine (C/C) dimers (both undisplaced and displaced) was investigated using a MP2/6-31G* calculation. In addition, the free energy of solvation of both the undisplaced and the displaced C/C dimer was calculated as a function of the twist angle and the sliding to understand the electrostatic interaction associated with the solvation phenomenon using the PCM. In the calculation of the binding energy of molecular association, the contribution from entropy was not included.

In the molecular association, there is an entropic cost associated with any molecular interactions, which arises from the degrees of freedom lost when two molecules are rigidly constrained within a complex on motion [27]. In the formation of stacked dimers, the entropic contributions (translational, rotational and vibrational) have to be accounted for to derive a clear picture about the interaction in solution. The prediction of this entropy contribution is difficult for various reasons. First, the entropies of the molecules in the solvent are subject to uncertainties. Second, the residual motion present in a complex formed by association in a solvent is also uncertain. Third, the amount of residual motion in a complex may change as a function of the nature and the extent of intermolecular forces responsible for binding [27]. On the basis of the statistical thermodynamics of binding put forth by Ben Naim [28], Gilson et al. [29], Janin [30, 31] and Atkins [32] attempts have been made to calculate the entropic cost involved in the dimerization of cytosine bases in a stacked conformation. Recently, a theoretically rigorous and computationally tractable methodology for the prediction of the free energies of binding of protein–ligand complexes has been presented [33]. This study has also highlighted the importance of the calculation of the translational, rotational and vibrational contributions in the calculation of the binding free energies of HIV-I protease-inhibitor binding. In the present study, an attempt has been made to estimate the entropic cost involved in the freezing of the translational and rotational degrees of freedom upon dimerization in a solvent using the approach adopted by Doig and Williams [34]. The calculation of the vibrational entropy is highly complicated owing to the nature of the potential-energy surface of the C/C stacked arrangement. The problems associated with the calculation of the vibrational entropy contributions are also highlighted in the investigation.

2 Methodology

2.1 Calculation of entropy associated with cytosine dimerization

Molecular association in the solvent phase needs more attention as the thermodynamic process of association involves changes in the translational, rotational and vibrational entropies of the unbound species. Any bimolecular binding phenomenon is entropically unfavorable owing to the formation of a single complex molecule with the loss of translational and rotational entropy. The approach to the study of solvation thermodynamics has been well developed by Ben-Naim [28], Gilson et al. [29] and Atkins [32]. The free energy of bimolecular association can be written as

$$\Delta G = \Delta G_{\mathrm{Tra}} + \Delta G_{\mathrm{Rot}} + \Delta G_{\mathrm{Vib}} + \Delta G_{\mathrm{Sol}} + \Delta G_{\mathrm{Ele}} \ , \tag{1}$$

where G_{Tra}, G_{Rot} and G_{Vib} are the translational, rotational and vibrational parts, respectively, of the free energy involved in the molecular association, G_{Sol} is the solvation free energy and G_{Ele} is the electronic free energy. As the thermodynamic process of molecular association is highly influenced by the entropic cost of bimolecular associations, we calculated the entropic penalty involved in the dimerization of cytosine. The translational part of the entropy can be calculated from the Sackur–Tetrode equation.

$$S_{\mathrm{trans}} = 5R/2 + (5R/2)\ln T - R\ln P + R\ln\left[\left(2\pi m/h^2\right)^{3/2}k^{5/2}\right] \ , \tag{2}$$

i.e.

$$S_{\mathrm{trans}} = 108.8 + 12.47\ln M_{\mathrm{r}}\ \mathrm{JK^{-1}mol^{-1}} \ . \tag{3}$$

The rotational entropy is given by

$$S_{\mathrm{rot}} = R + R\ln\left[\pi^{7/2}\left(8kT/h^2\right)^{3/2}\left(I_{\mathrm{A}}I_{\mathrm{B}}I_{\mathrm{C}}\right)^{1/2}\right] \ , \tag{4}$$

where R is the ideal gas constant, T is the temperature, P is the pressure, m is the mass of the molecule, h is Plank's constant, k is Boltzmann's constant, I_{A}, I_{B} and I_{C} are the moments of inertia about the three perpendicular axes and M_{r} is the relative molecular mass of the molecule.

The change in translational entropy on going from the gas phase to aqueous solution (1 M) was calculated by considering

the phase transition in two steps: transition from the gas phase to a "pure liquid" phase where all the molecules present in the gas phase are condensed into a liquid; the pure liquid is then diluted to a concentration of 1 M. The entropy of condensation for water is reported as 109 $JK^{-1}mol^{-1}$ [35]. The change in translational entropy on dimerization has been observed to be 100 $JK^{-1}mol^{-1}$ and has been used by Doig and Williams [34] for the calculation of the dimerization of amide. The change in entropy on dilution is given by

$$\Delta S = R\ln(M_1/M_2) \quad . \tag{5}$$

Since the initial concentration for a pure liquid is $1000/M_r$ and the final concentration is 1 M, the change in entropy on dilution is therefore approximately

$$\Delta S = R\ln(1000/M_r) \quad . \tag{6}$$

The fundamental frequency of the vibration was calculated using Eq. (7) with the assumption that vibration behaves as a simple harmonic oscillator. The expressions for the vibrational free energy, entropy and enthalpy are as follows:

$$G_{vib} = RT\ln\left(1 - e^{-\theta/T}\right) \quad , \tag{7}$$

$$S_{vib} = -R\ln\left(1 - e^{-\theta/T}\right) + R\theta/T\ln\left(e^{\theta/T} - 1\right) \quad , \tag{8}$$

$$H_{vib} = R\theta\Big/\left(e^{\theta/T} - 1\right) \quad , \tag{9}$$

where $\theta = h\nu/k$ and ν is the fundamental frequency of vibration.

Cytosine as an unbound species has large translational, S_{trans}, and rotational, S_{rot}, entropy in solution. On dimerization, there is a large loss in the translational and rotational entropy, which is compensated by the noncovalent interactions. S_{trans} and S_{rot} of cytosine in the gas phase were calculated using the equations given earlier. It has been established that the conformation of the stacked cytosine dimer is not in the global minimum of the potential-energy surface at the Hartree–Fock level [8] and the optimization of stacked cytosine dimer results in an unstacked conformation where both the bases try to form a paired (hydrogen-bonded) geometry. Hence, the fundamental vibrational modes of the stacked cytosine cannot be calculated accurately using the available computational techniques and is the reason for not calculating the vibrational frequencies of the stacked cytosine dimer.

2.2 Calculation of the solvation free energy of the C/C dimer

Various twisted conformations of C/C dimers were generated using the optimized cytosine monomer at the HF/6-31G* level. Keeping the lower cytosine base fixed, the upper cytosine base was rotated in a clockwise direction (we denote this as "twist") from 0 to 180° in increments of 20°. A displacement of ±1 Å from the origin was introduced along both the *x*- and *y*-axes (we denote this as "slide"). A schematic representation of the twisting and sliding applied on the C/C dimer is shown in Fig. 1. Single-point-energy calculations were performed on these geometries at the MP2/6-31G* level. The interaction energy of the C/C dimers in the gas phase, $E_{Int,G}$, was calculated as a function of twisting and sliding from the energy of the cytosine monomers, E_{Mono1} and E_{Mono2}, using a supermolecule approach and the basis set superposition error was corrected using the method of Boys and Bernardi [36]:

$$E_{Int,G} = E_{Com} - (E_{Mono1} + E_{Mono2}) \quad . \tag{10}$$

The binding energy, $E_{Bind,G}$, was calculated as the negative of the interaction energy, i.e.

$$E_{Bind,G} = -E_{Int,G} \tag{11}$$

The free energy of solvation, ΔG_{Sol}, was calculated using the PCM in the framework of the Hartree–Fock method. The ΔG_{Sol} of any molecule in solution is written as the sum of electrostatic and nonelectrostatic interactions, i.e.

$$\Delta G_{Sol} = \Delta G_{Ele} + \Delta G_{Cav} + \Delta G_{Dis} + \Delta G_{Rep} \quad , \tag{12}$$

where ΔG_{Cav}, ΔG_{Dis} and ΔG_{Rep} are nonelectrostatic terms which describe the energy needed to build the solute cavity and solute–solvent dispersion and repulsion interactions [20]. ΔG_{Ele} is the electrostatic interaction between the solute and solvent. The free energy of association, $\Delta\Delta G_{Asso}$, of the C/C dimer in water was calculated as the difference between the free energy of solvation of the complex, $\Delta G_{Sol,Com}$), and the individual monomers, $\Delta G_{Sol,Mono}$, i.e.

$$\Delta\Delta G_{Asso} = \Delta G_{Sol,Com} - \left(\Delta G_{Sol,Mono1} + \Delta G_{Sol,Mono2}\right) \quad . \tag{13}$$

A dielectric constant of 78.5 was used to represent water as a continuum medium. All the calculations were performed using the GAUSSIAN98W package [37]. It is known that the continuum calculation of the solvation free energy is sensitive to the solute radii, the cavity size and the shape. The standard default parameters present in GAUSSIAN98W were used for the PCM calculation.

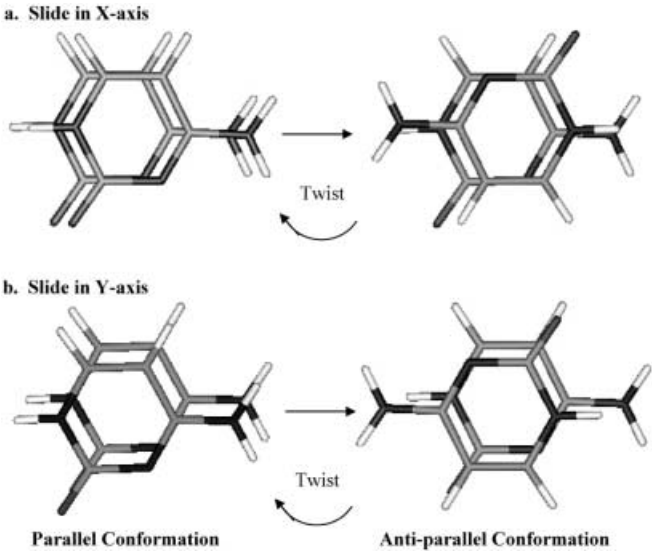

Fig. 1a, b. A sketch of how the twist and slide are defined

3 Results and discussion

3.1 Solvation free energy of the C/C dimer

All the calculations were made on coplanar cytosine bases with a vertical base separation (*z*-axis) of 3.4 Å, which is the vertical separation observed in crystals of DNA constituents [38]. The dependence of $E_{Int,G}$ and ΔG_{Sol} of the undisplaced and displaced (to a distance of ±1 Å along both the *x*- and *y*-axes) C/C dimer on rotation from 0° to 180° (in a clockwise direction) was calculated. The variations in $E_{Int,G}$, $E_{Corr,G}$ and the dipole moment upon rotation for both the *x*- and *y*-translated dimers are shown in Figs. 2, 3 and 4. Figures 2a, 3a and 4a show the variation with respect to the sliding along the *x*-axis and Figs. 2b, 3b and 4b illustrate the variation on the *y*-axis. It was observed that the translation of the upper cytosine monomer in the *y* direction induces considerable changes in $E_{Int,G}$, $E_{Corr,G}$ and the dipole moment.

3.1.1 Variation of $E_{Int,G}$ on twisting and sliding

The interaction energies calculated at the MP2/6-31G* level for various twisted and translated geometries of the C/C dimer are shown in Fig. 2. The interaction energy of

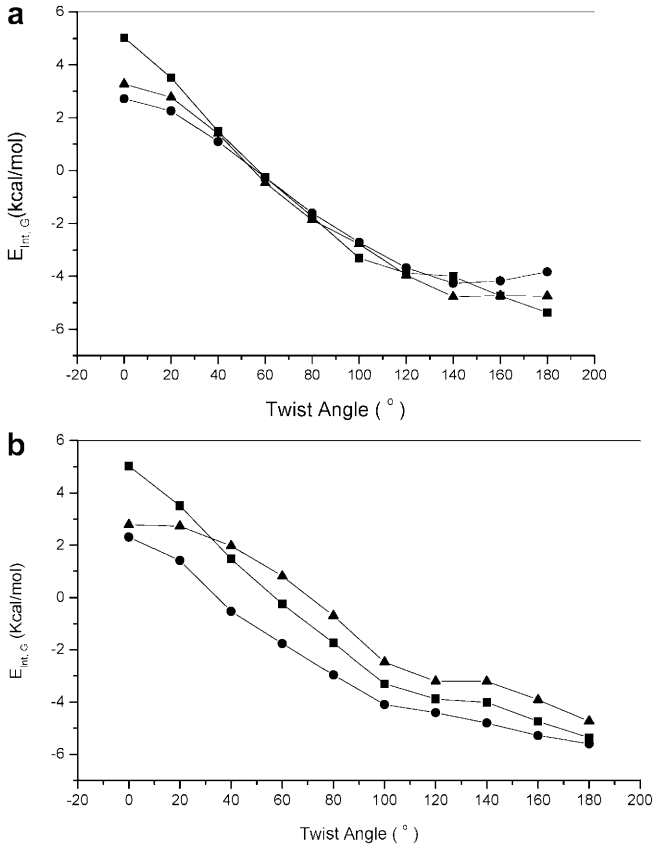

Fig. 2. Variation of the interaction energy, $E_{\mathrm{Int,G}}$, of the stacked cytosine dimer (*C*/*C*) without sliding (*squares*) and with sliding (*circles* +1 Å; *triangles* –1 Å) along **a** the *x*-axis and **b** the *y*-axis

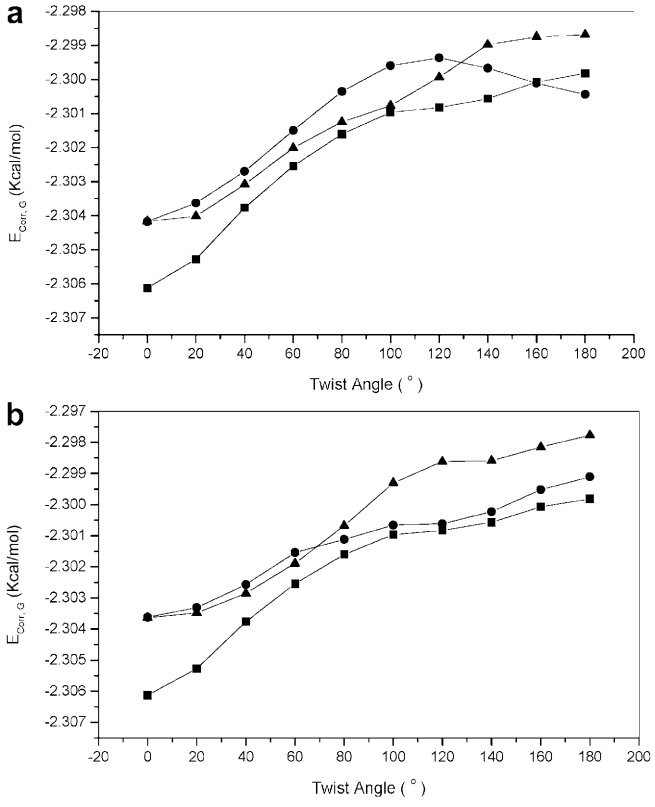

Fig. 3. Variation of the correlation energy, $E_{\mathrm{Corr,G}}$, of the C/C dimer without sliding (squares) and with sliding (circles +1 Å; triangles −1 Å) along **a** the *x*-axis and **b** the *y*-axis

the undisplaced C/C dimer varies from 5.03 to −5.37 kcalmol^{-1} on twisting from a parallel to an antiparallel conformation. For the C/C dimers displaced along the *x*-axis, $E_{\mathrm{Int,G}}$ varies from 2.72 to −3.84 kcalmol^{-1} for a +1-Å displacement and from 3.27 to −4.76 kcalmol^{-1} for a –1-Å displacement. The calculated $E_{\mathrm{Int,G}}$ is negative only for undisplaced and displaced (*x*-axis) C/C dimers twisted between 60 and 180° twist angle, which indicates the binding of the C/C dimer in these twisted conformations. The calculated $E_{\mathrm{Int,G}}$ varies from 2.31 to −5.59 kcalmol^{-1} and from 2.78 to −4.74 kcalmol^{-1} for the C/C dimers displaced in positive and negative directions of the *y*-axis, respectively. In the translation of a distance of about +1 Å along the *y*-axis, bound conformations of the C/C dimer were achieved when the upper cytosine monomer of the C/C dimer was rotated between 40 and 180° of twist angle. However, the negative displacement along the *y*-axis favors the binding of the C/C dimer from 80 to 180° rotations. The dependence of $E_{\mathrm{Int,G}}$ on twisting and sliding is depicted in Fig. 2b. The dependence of the C/C stacking energy on twisting has been reported by Sponer et al. [8] at the MP2/6–31G*(0.25) level. They noticed that on rotation, the stacking energy for the undisplaced C/C dimer decreases from 1.5 to −7.0 kcalmol^{-1} and for the displaced dimer, the energy ranges from –1.0 to –8.0 kcalmol^{-1}. The rotation of the C/C dimer (both displaced and undisplaced) from a parallel to an antiparallel conformation decreases $E_{\mathrm{Int,G}}$ by about 7–9 kcalmol^{-1}, which is in good agreement with the results of Sponer et al. [8]. The observed difference in the calculated $E_{\mathrm{Int,G}}$ may be attributed to the different basis sets used in this calculation (6-31G*) and the ones used by Sponer et al. [6-31G*(0.25)]. It is evident from Fig. 2 that the stable conformation for the C/C dimer with higher binding energy is obtained at 180° rotated conformations.

It is known that the correlation energy, $E_{\mathrm{Corr,G}}$, that arises from the interaction between the π-electron clouds plays a significant role in the stabilization of the stacked dimer and is prone to change according to the orientation of the base dimer. The correlation energy is attractive for the undisplaced C/C dimer stacked in a parallel fashion. It was observed that the introduction of a twist as well as a slide on the upper cytosine base decreases $E_{\mathrm{Corr,G}}$ considerably. The variation of $E_{\mathrm{Corr,G}}$ with respect to the twist angle for the translated (in both positive and negative directions of the *x*- and *y*-axes) dimer is shown in Fig. 3.

3.1.2 Variation of ΔG_{Sol} on twisting and sliding

The advantage of the PCM approach is that the solvation phenomenon can be well understood by various solute–solvent interactions, such as electrostatic and nonelectrostatic energies. The electrostatic energy is derived from the polar and nonpolar solute–solvent interactions and the solute polarization. The electrostatic

energy of a solute specifies its tendency of solvation in a solvent. As the electrostatic behavior of the solute originates predominantly from its dipole moment, the rotation and translation might also induce certain marginal changes in the electrostatic energy.

The variation in the electrostatic energy of the C/C dimer on twisting and sliding (± 1 Å along both the x and y-axes) is given in Tables 1 and 2. The undisplaced C/C dimer at 0° rotation contributes −46.05 kcalmol^{-1} of electrostatic energy to the solvation energy and this decreases gradually to −35.01 kcalmol^{-1} on twisting from 0 to 180°. The rotation of the cytosine monomer introduces considerable changes in the electrostatic distribution and results in a difference of 11 kcalmol^{-1} on moving from parallel to antiparallel stacking. A similar trend was observed in the case of displaced dimers and is given in Table 2. It is observed from Table 2 that the parallel displacement of the upper cytosine does not change the electrostatic energy significantly. The PCM calculates the nonelectrostatic energy from the van der Waals interaction between the solute and solvent molecules and the cavitation energy involved in the formation of the solute cavity. The rotated and translated cytosine dimers contribute about 7 kcalmol^{-1} of nonelectrostatic energy for solvation and the variation due to rotation and translation is much less.

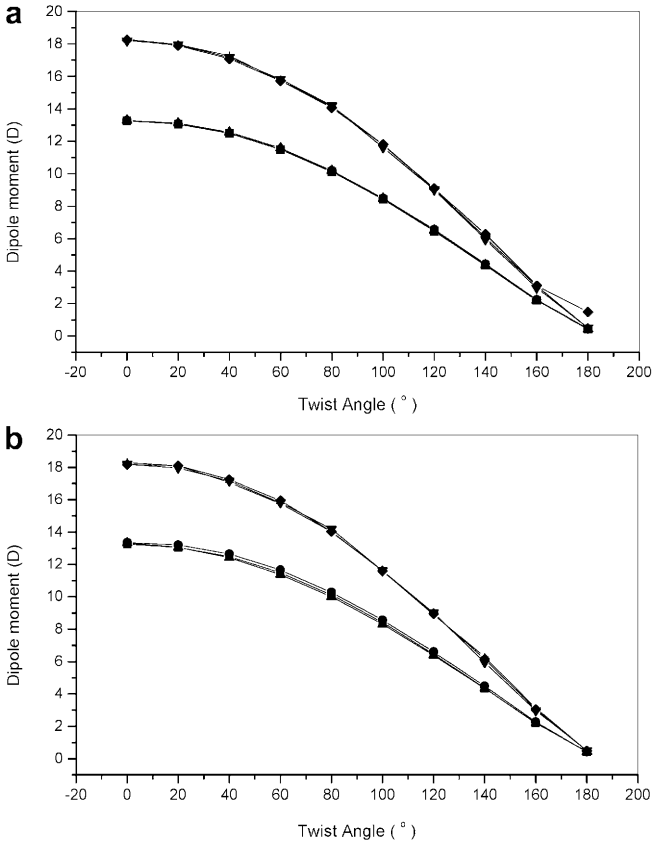

Fig. 4. Variation of the dipole moment of the C/C dimer in the gas phase without sliding (*squares*) and with sliding (*circles* +1 Å; *up triangles* −1 Å) and in water without sliding (*down triangles*) and with sliding (*diamonds* +1 Å; *crosses* –1 Å) along **a** the x-axis and **b** the y-axis

It was noticed that ΔG_{Sol} depends on the orientation of the stacked geometry. The free energy of solvation of the dimers at different orientation and translation is also listed in Tables 1 and 2. The variation observed in ΔG_{Sol} shows a linear dependence on the changes observed in the major component, namely the electrostatic energy. The dimers show that free energy of solvation changes from −40 to −27 kcalmol^{-1} on rotation from 0 to 180°. It was observed that the solvation free energy of the C/C dimer varies with respect to the displacement of the upper cytosine monomer. This observation indicates that the stability of the C/C dimers depends on the twisting and sliding of the upper monomer.

3.1.3 Dependence of the dipole moment on twisting and sliding

The variation of the dipole moment of the C/C dimer with respect to a twist angle from 0 to 180° as well as a slide of 1 Å (in both positive and negative directions of the x- and y-axes) in the gas phase and in water is shown in Fig. 4. In the gas phase, the variation of the dipole moment of the stacked cytosine dimer was found to be between 13.26 and 0.43 D. It is seen that the displacement of the cytosine monomer to a distance of ± 1 Å (both x- and y-axis) results in a similar variation in the

Table 1. Calculated solvation free energy of the stacked cytosine dimer (C/C) on twisting and sliding along the x-axis

Angle (degrees)	Free energy of solvation (kcalmol^{-1})								
	Electrostatic Displacement (Å)			Nonelectrostatic Displacement (Å)			Total Displacement (Å)		
	0.0	+1.0	−1.0	0.0	+1.0	−1.0	0.0	+1.0	−1.0
0	−46.05	−46.23	−46.43	6.49	6.82	6.81	−39.57	−39.41	−39.62
20	−45.57	−45.55	−45.38	6.76	7.00	6.77	−38.81	−38.55	−38.61
40	−45.32	−43.73	−45.50	6.93	7.09	6.78	−38.39	−36.64	−38.72
60	−42.60	−41.97	−42.21	6.91	7.44	6.72	−35.69	−34.53	−35.49
80	−41.42	−40.42	−41.32	6.92	7.85	6.81	−34.50	−32.58	−34.51
100	−37.66	−38.70	−39.02	6.95	7.35	6.93	−30.71	−31.35	−32.09
120	−36.60	−37.28	−36.81	7.01	7.25	7.10	−29.59	−30.03	−29.71
140	−35.21	−37.05	−35.82	7.22	7.34	6.05	−27.99	−29.71	−28.65
160	−35.77	−36.35	−35.00	7.62	7.65	6.05	−28.16	−28.69	−27.65
180	−35.01	−40.92	−34.86	7.65	7.80	6.09	−27.36	−33.11	−27.29

Table 2. Calculated solvation free energy of the C/C dimer on twisting and sliding along the *y*-axis

Angle (degrees)	Free energy of solvation (kcalmol^{-1})					
	Electrostatic Displacement (Å)		Nonelectrostatic Displacement (Å)		Total Displacement (Å)	
	+1.0	−1.0	+1.0	−1.0	+1.0	−1.0
0	−45.20	−45.24	9.03	7.54	−36.17	−37.70
20	−45.14	−45.94	6.90	6.78	−38.25	−39.16
40	−43.07	−45.02	7.03	6.94	−36.04	−38.08
60	−40.58	−43.63	6.90	8.01	−33.68	−35.62
80	−39.21	−41.57	7.16	7.16	−32.05	−34.40
100	−37.76	−40.18	6.89	6.01	−30.87	−33.01
120	−36.35	−37.44	6.80	7.43	−29.55	−30.01
140	−36.82	−38.49	7.01	7.49	−29.82	−31.00
160	−35.97	−37.27	7.18	7.57	−28.79	−29.70
180	−35.55	−35.92	6.89	7.62	−28.67	−28.23

dipole moment as that of the cytosine dimer on rotation alone. The dipole moment of the cytosine dimer gradually decreases from 18.31 to 0.49 D as the monomer is rotated from a parallel to an antiparallel direction in water. In general, the cytosine dimers show an increase of 26–28% in the dipole moment in water, except for the conformation at 180°. The enhanced dipole moment in water agrees well with the results reported by Cramer and Truhlar [15] for the polarization of nucleic acid bases in an aqueous medium. The observed increase in the dipole moment indicates that polarization is induced in the presence of water. The smooth variation of the dipole moment from a higher to a lower value reflects the fact that the rotation of the stacked cytosine (upper monomer) gradually cancels out the net dipole of the other cytosine by the twist of 0 to 180°. In the antiparallel conformation, where both cytosine bases are stacked exactly opposite each other, the alignment of electronic charges is reversed, which results in almost zero dipole moment (the dipole of the C/C dimer at an orientation of 180° is 0.4 D). Hence, the conformation at 180° has much lower solubility than the other conformations. An interesting observation is that the undisplaced and displaced C/C dimer in an antiparallel orientation has a dipole moment of 0.4 D in both the gas phase and in water. This observation reveals that the C/C dimer in an antiparallel conformation is not influenced by the presence of water. All the results indicate that the C/C dimer at an orientation of 180° is much more hydrophobic than at other geometries owing to the low dipole moment. Hence, on twisting, these dimers solvate less than the undisplaced C/C dimer in water.

3.1.4 Calculation of $\Delta\Delta G_{\text{Asso}}$

The calculated $\Delta\Delta G_{\text{Asso}}$ of all the C/C dimers are given in Table 3. It is observed that the free energy of association varies in the range 0.03–12.24 kcalmol^{-1} for the undisplaced stacked dimer. As the cytosine dimer shows only marginal differences in the solvation free energy on rotation, the calculated $\Delta\Delta G_{\text{Asso}}$ was found to be quite large. It is evident from the work of Cieplak and Kollman [12] that the free energy of association of various hydrogen-bonded and stacked DNA base pairs

Table 3. Calculated free energy of association of the C/C dimer on twisting and sliding

Angle (degrees)	$\Delta\Delta G_{\text{Asso}}$ (kcalmol^{-1})				
	Slide on *x*-axis (Å)			Slide on y-axis (Å)	
	0.0	+1.0	−1.0	+1.0	−1.0
0	0.03	0.19	−0.02	3.43	1.90
20	0.79	1.05	0.99	1.35	0.44
40	1.21	2.96	0.88	3.56	1.52
60	3.91	5.07	4.11	5.92	3.98
80	5.10	7.02	5.09	7.55	5.20
100	8.89	8.25	7.51	8.73	6.59
120	10.01	9.57	9.89	10.05	9.59
140	11.61	9.89	10.95	9.78	8.60
160	11.44	10.91	11.95	10.81	9.90
180	12.24	6.49	12.3	10.93	11.37

ranges between 0 and −2 kcalmol^{-1}. Since the values of $\Delta\Delta G_{\text{Asso}}$ obtained using the PCM are very high, the application of the PCM could not reproduce the values reported by Cieplak and Kollman. The introduction of sliding on the upper monomer is found to increase the free energy of association to a greater extent. In the calculation of $\Delta\Delta G_{\text{Asso}}$, contribution from ΔG_{Tra}, ΔG_{Rot}, and ΔG_{Vib} would influence the dimerization significantly. In addition to these contributions, basis set superposition error in the calculation of $\Delta\Delta G_{\text{Asso}}$ would also influence the calculated values. Owing to computational limitation we could not include basis set superposition error correction in the calculation of $\Delta\Delta G_{\text{Asso}}$.

3.2 Translational and rotational entropy cost of dimerization of cytosine in an aqueous medium

The dimerization of cytosine can be represented as 2C→C/C, where C/C is the stacked dimer. Generally, any bimolecular association leads to the loss of three degrees of translational and rotational freedom. It was found in our previous study [39] that cytosine is surrounded by 14 (coordination number) water molecules, whereas the stacked C/C dimer is associated with 17 water molecules. These coordination numbers were

used to compute the entropy of dimerization of cytosine in water.

The translational entropy for cytosine dimerization is shown in Fig. 5. It was observed that the translational entropy, $\Delta S_{trans}(g)$, in the gas phase is -177 J $K^{-1}mol^{-1}$ and is -83 $JK^{-1}mol^{-1}$ in aqueous medium of concentration 1 M [ΔS_{trans} (1 M, aq)]. It is evident from these values that the entropy of translation upon dimerization approximately halves on transfer from the gas phase to 1 M aqueous solution. It is a known fact that the internal rotations of cytosine also affect the entropy of cytosine dimerization. The rotational entropies for C and the C/C dimer were calculated as 188 and 200 $JK^{-1}mol^{-1}$, respectively. The change in the rotational entropy on dimerization was calculated as -176 $JK^{-1}mol^{-1}$. Similar to the findings of Doig and Williams [34] and Finkelstein and Janin [40], about half the translational and rotational entropy of a substrate is lost upon complex formation. It is evident from the dimerization of urea in water and CCl_4 that the new low-frequency vibrational modes lead to the stabilization of the dimer. Since C/C is not a global minimum in the calculated potential-energy surface, owing to computational limitations, favorable vibrational modes could not be identified.

4 Conclusion

In the present study, the stability of the C/C dimer was analyzed as a function of twisting and sliding. The entropic penalty involved in the dimerization of cytosine was also highlighted. Some interesting conclusions from our analysis are as follows:

- $E_{Int,G}$ calculated at the MP2/6-31G* level shows changes as a function of twisting and sliding and the trends are in good agreement with the results obtained by Sponer et al. It was found that the displacement of the upper cytosine base along the *x*- and *y*-axes reduces the correlation energy of the C/C dimers.
- Studies on the dependence of the solvation free energies and the dipole moment of the C/C dimer on twisting and sliding at the HF/6–31G* level show that the free-energy profile of the C/C dimer is sensitive to twisting and sliding. The dipole moment of the C/C dimer varies gradually from -18.31 to -0.49 D as the conformation changes form parallel to antiparallel in water.
- The free energy of association calculated as a function of the twist angle is very high and does not agree with the values reported earlier. This may be due to the fact that the PCM method may not adequately describe the solvation process. The contributions from the entropic cost have to be included in the calculation of the binding energy to derive a clear picture of the interaction upon dimerziation of cytosine.
- Though the interaction energy of the cytosine dimer was corrected for basis set superposition error, $\Delta\Delta G_{Asso}$ was not corrected for basis set superposition error. This correction would also influence the values obtained in this study. To make basis set superposition error correction in the calculation of

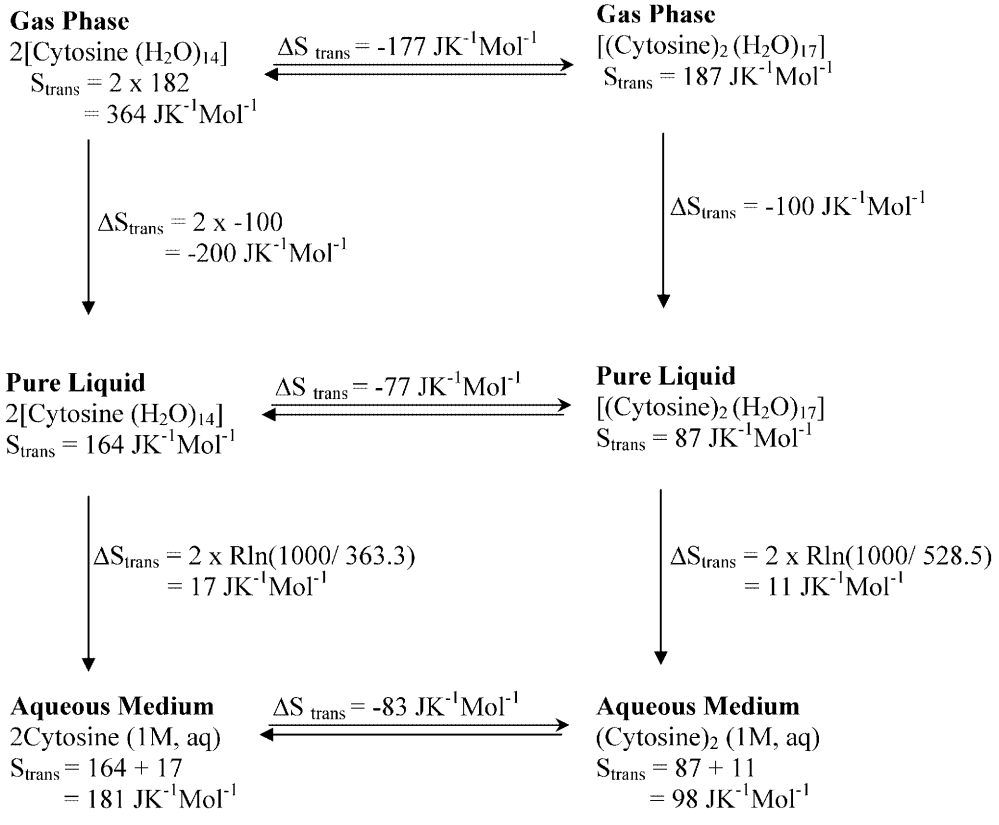

Fig. 5. Calculation of ΔS_{trans} for cytosine dimerization in an aqueous medium

ΔG, the necessary computational codes have to be developed.

– The changes in entropy associated with the translational and rotational contributions are −83 and −176 $JK^{-1}mol^{-1}$, respectively. Since the conformation of C/C is not a global minimum in the HF/6-31G** potential-energy surface, its optimization leads to a hydrogen-bonded complex; hence, the vibrational contributions from the stacked geometry of cytosine could not be estimated. To make this prediction, a different theoretical methodology has to be developed.

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