Energetics of Base Pairs in B-DNA in Solution: An Appraisal of Potential Functions and Dielectric Treatments

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The energetics of base pairs in B-DNA in solution has been estimated via recently reported versions of some empirical potential energy functions, namely, AMBER, CHARMM, GROMOS, and OPLS used commonly in biomolecular simulations. The electrostatic component of the interaction energy between bases involved in Watson−Crick pairing in B-DNA in aqueous environment, evaluated via the finite difference Poisson−Boltzmann methodology with all the above force fields, is in the range of −2 to −3 kcal/mol per H-bond. An examination of different dielectric functions used in conjunction with the above force fields suggests that a sigmoidal function, with an estimate of −2 kcal/mol per H-bond, comes closest to mimicking the electrostatics of AT and GC base pairs under aqueous conditions.

Introduction

Evidence emerging from the structural and computer simulation data over the past few years suggests that B-DNA in solution is a flexible macromolecule, sensitive to the effects of solvent and counterions. It is able to undergo major structural transitions between different allomorphic forms and some minor ones involving base pair opening, bending or modulations in sugar pucker and backbone torsions, induced intrinsically by the base sequence or extrinsically by proteins or drug molecules.[1−15] The integral role of hydrogen bonds in the stability of the double helical structure of B-DNA, in the flexibility of nucleic acids in general that allows for structural adaptation in the presence of proteins and drug molecules, and the attendant energetics are yet to be fully understood in molecular terms.

Theoretical descriptions of DNA fine structure, the intra- and inter-base pair degrees of freedom, in particular, and DNA−ligand interactions involving base atoms exposed in the grooves, critically depend on the charge distribution on the base pairs and the manner in which electrostatic interactions are treated. Any force field attempting to model DNA and its interactions requires a satisfactory representation of hydrogen bonding between complementary base pairs both in gas phase and in solution. As a number of new and carefully parametrized force fields have been put forward recently, an assessment of these diverse force fields and dielectric models for estimating nucleic acid−base interactions in aqueous environment assumes significance for an accurate model of DNA, drug−DNA, and protein−DNA interactions. As a step toward this goal, in this study, a comparison of the diverse force fields and dielectric functions is undertaken, together with an estimation of the base pair energies in B-DNA in solution.

Numerous studies, both experimental and theoretical, were initiated to understand the specificity of base pairing and to evaluate quantitatively the energetics involved in this interaction. The mass spectroscopic values of −13.0 kcal/mol and −21.0 kcal/mol for AT and GC, respectively,[16] have been valuable reference points for studies on base pairing enthalpies in the gas phase. Early attempts to estimate the base pairing energies in solution[17,18] revealed that base stacking, rather than pairing of mononucleotides, is favored in aqueous environment, as considerable competition is expected from the solvent. Experimental studies thus employed nonaqueous solvents to study the properties of specific H-bonded complexes. Kyogoku et al.[19−21] reported a value of −6.2 ± 0.2 kcal/mol (−3.1 kcal/mol per H-bond) for the enthalpy of formation of 9-ethyladenine and 1-cyclohexyluracil base pair in chloroform. Newmark and Cantor[22] estimated, from NMR spectra, an enthalpy change of −5.8 kcal/mol (−1.9 kcal/mol per H-bond) and an entropy change of −16 eu for the formation of a GC base pair from solvated monomers in dimethyl sulfoxide (DMSO). They rationalized the observed enthalpy change as being due to the formation of hydrogen bonds. As DMSO is a strong proton acceptor, the degree of H-bonding was considered to be closer to that in water.[22] Turner et al.[23] derived free energy increments for H-bonds in nucleic acid base pairs from measurements of optical melting curves. They predicted a maximum $\Delta\Delta G_{HB}$ of −2.0 kcal/mol per H-bond for double helical oligoribonucleotides of GC in aqueous medium. The enthalpic contribution may be expected to be slightly larger since pairing involves some entropy loss. It is equally conceivable that this loss in entropy attendant upon pairing of bases, which are already anchored to the sugar−phosphate backbone, is offset by a favorable hydrophobic contribution originating in the formation of a smaller cavity in water for a pair than for unpaired bases, leading to similar magnitudes for both enthalpy and free energy of pairing. Also, there is no a priori reason to expect that the hydrogen bond energetics is drastically different in oligodeoxyribonucleotides. A subtle point to be noted is that the values of Turner et al. are more a reflection of the interaction strength of a hydrogen bond in a base pair and the associated free energy cost for switching off a hydrogen bond, rather than free energy of base pair formation/H-bond. Sinden (ref 3, p 13) proposes a value of −2 to −3 kcal/mol as the strength of hydrogen bond in DNA.

Attempts to theoretically estimate base pair energetics focused mainly on base−base interactions in the gas phase via the application of ab initio methods [refs 24−28 and references

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therein]. An accurate description of the solution thermodynamics of base pairs in DNA requires an extensive sampling of the configurational space of the bases in a DNA-like environment, with explicit solvent. A computationally expeditious alternative lies in using a dielectric continuum representation of the medium with a thorough calibration of the parameters in lieu of explicit solvent. The utility of distance dependent dielectric functions in modeling DNA was already commented upon by Mazur and Jernigan.[29] Our original intention was to arrive at a dielectric function to be used in conjunction with OPLS parameters,[30] which would capture the hydrogen bonding and electrostatic interactions in protein−DNA and drug−DNA systems as realistically as possible, to facilitate a discussion of specificity and biomolecular recognition with relative computational ease.[31] The minimum that is expected of any such dielectric function is to reproduce the base−base interaction energies in solution. The current study gives us an opportunity to characterize some of the recent and popular force fields used in conjunction with different dielectric screening functions, with base pair energies providing a convenient testing ground. Specifically, we have examined the interaction energies between complementary bases involved in Watson−Crick hydrogen bonding adopting a sigmoidal dielectric function (also referred to hereinafter as a modified Hingerty−Lavery function: MHLF),[32−36] to capture the aqueous environment, employing parameters from AMBER,[37] CHARMM,[38] GROMOS,[39] and OPLS[30,40] force fields. As H-bonds are considered to be mostly electrostatic in nature, it is of interest to estimate the electrostatic contribution to the energetics of base pairs by some state of the art techniques such as the finite difference Poisson−Boltzmann (FDPB) methodology.[41−48] While this work was in progress, a comparison of base pair energies in gas phase was attempted by several research groups.[26,28,38,40,49] Hobza et al.[49] recently reported a critical assessment of the interaction energies of bases in gas phase as predicted by diverse empirical potential functions and quantum mechanical calculations. We focus here on the energetics of base pairs as embedded in B-DNA in solution and estimated with different force fields and dielectric treatments.

Methodology and Calculations

The structures of poly(dA)−poly(dT) and poly(dG)−poly(dC) homopolymers, 14 base pairs long, were generated in the canonical B-DNA conformation using the coordinates of Arnott and co-workers[50] along with BIOSYM software.[51] No further optimization of the canonical structure was undertaken to avoid any force field dependent changes in the conformation. The subsequent procedure involves considering each of the central 10 base pairs separately and obtaining their interaction energies using AMBER, CHARMM, GROMOS, and OPLS parameters.

To compare the performance of different parameter sets and dielectric models we deemed it fit to use a single structure. Energy minimization, in our preliminary studies, led to slightly different structures with each force field as expected. Moreover, the energy minimization results on the base pairs in B-DNA are sensitive to several protocol issues dealing particularly with solvent and counterions.[7] Thus canonical B-DNA (B80) structure[50] formed a natural choice for a comparative study.

The total base−base interaction energy E_{bp} is represented by the following expression.

$$E_{bp} = \sum [E_{el} + E_{vdW}]$$

E_{el} is the electrostatic contribution to the total energy, E_{vdW} is the van der Waals term, and the summation runs over all the atoms of a base on one strand and its complementary base on the opposite strand. The effect of inclusion of sugar−phosphate backbone atoms on the base pair interaction energy has also been considered separately.

(a) Electrostatic Term. The electrostatic contribution to the interaction energy between an atom i of one base with that of its complementary base atom j is computed as

$$E_{el} = \frac{332 q_i q_j}{D(r) r_{ij}}$$

where q_i and q_j are the partial atomic charges taken from each specified force field[30,37−39] for the two interacting atoms, r_{ij} is the distance between the atoms i and j, and $D(r)$ is a dielectric function. A series of calculations were performed with different values for $D(r)$, namely 1, 4, 80, r_{ij}, and 4 r_{ij} and also with $D = 46.7$ as appropriate for dimethyl sulfoxide (DMSO). In studies employing a modified Hingerty−Lavery function (MHLF), the $D(r)$ was taken as

$$D(r) = D - \left[\left(\frac{D - D_i}{2}\right)(\alpha^2 + 2\alpha + 2)e^{-\alpha}\right]$$

$D(r)$ is a sigmoidal function. $D = 78$, $D_i = 4$, and $\alpha = sr$, where $s = 0.395$.[31] This choice of s in our preliminary studies led to total interaction energies (electrostatic + van der Waals) of ~ -4 and -6 kcal/mol for AT and GC base pairs, respectively (with OPLS parameters), in close correspondence to the experimentally obtained enthalpy values of -1.9 kcal/mol per H-bond as determined by Newmark and Cantor[22] in DMSO for base pair formation. The enthalpy of formation of a dimer from monomers here is equated with the effective interaction energy. Also, desolvation effects on enthalpy are implicit to some extent in any dielectric function introduced as a modulation in Coulomb's expression. In addition, in a continuum solvent representation, the dielectric constant of DMSO is high enough to mimic water environment. Calculations performed with DMSO and with water (presented in sequel) with solvent treated as a dielectric continuum support this view. The magnitude of the interaction strength is also in conformity with the measurements of Turner et al.[23] in aqueous solution which are closer to this study in design. This sigmoidal function appears to fare well in other contexts as well. The hydrogen bond strength in α-helices without any additional parametrization of MHLF was estimated to be -1 kcal/mol[52] consistent with some recent experiments.[53,54] Usage of this function for DNA counterion interactions and for mapping out B to Z-DNA conformational energy profiles and integration into JUMNA have already been reported previously.[34−36]

The electrostatic contribution to the interaction energy with the sigmoidal function is amenable to expression in a more familiar form[55−57] as the sum of Coulomb and shielding terms (due to solvent) for each pair of interacting atoms.

$$\frac{q_i q_j}{D(r) r_{ij}} = \frac{q_i q_j}{r_{ij}} - \left(1 - \frac{1}{D}\right)\frac{q_i q_j}{\rho_{ij}}$$

$$\rho_{ij} = \left\{\frac{\left(1 - \frac{1}{D}\right)}{\left(1 - \frac{1}{D(r)}\right)}\right\} r_{ij}$$

ρ_{ij} is an effective distance parameter. Other symbols have been defined above. This, combined with the Born type self-energies

TABLE 1: Watson-Crick Base Pair Energies (in kcal/mol) for Isolated Bases in Gas Phase[e]

	base pair	AMBER	CHARMM	GROMOS	OPLS
present work	AT	−12.9	−13.1	−8.7	−9.8
	GC	−27.6	−23.5	−19.3	−22.0
lit. values	AT	−11.9[a]	−14.0[c]		−10.6[d]
		−12.8[b]	−13.6[b]		−10.5[b]
	GC	−25.4[a]	−24.8[c]		−22.1[d]
		−28.0[b]	−25.5[b]		−23.1[b]

[a] Reference 37. [b] Reference 49. [c] Reference 38. [d] Reference 40. [e] $D(r) = 1$. The geometry of base pairs corresponds to the B-DNA[50] structure. Each base is made neutral by placing the residual charge on a hydrogen located at the position of C1' atom.

of atoms i and j,[55] in principle, defines the total electrostatic energy of the system of charges i and j in a solvent of dielectric constant D.

(b) van der Waals Term. The van der Waals interactions were modeled using a (12,6) Lennard-Jones potential between the atoms of the two complementary bases.

$$E_{\mathrm{vdW}} = \left[\frac{C_{12}^{\mathrm{ij}}}{r_{\mathrm{ij}}^{12}} - \frac{C_{6}^{\mathrm{ij}}}{r_{\mathrm{ij}}^{6}}\right]$$

For the OPLS force field, C_{12}^{ij} and C_{6}^{ij} are obtained as geometric means from the individual atomic 12,6 parameters while for AMBER and CHARMM, the calculations involve computing the R_{ij} and ϵ_{ij} as

$$R_{\mathrm{ij}}^{*} = R_{\mathrm{i}}^{*} + R_{\mathrm{j}}^{*}$$

and

$$\epsilon_{\mathrm{ij}} = (\epsilon_{\mathrm{i}}\epsilon_{\mathrm{j}})^{1/2}$$

ϵ_{i} above is the well depth parameter and R_{i}^{*} is half the distance to the well depth ($\sigma_{\mathrm{ii}} = 2^{-1/6}R_{\mathrm{ii}}^{*}$ and $R_{\mathrm{ii}}^{*} = 2R_{\mathrm{i}}^{*}$; alternatively, $\sigma_{\mathrm{ii}} = 2^{5/6}\,R_{\mathrm{i}}^{*}$. This relation of R^{*} is valid for both AMBER and CHARMM force fields). The R_{i}^{*} values for AMBER calculations were taken from the van der Waals parameters listed in Table 14 of ref 37. For CHARMM calculations ($R_{\mathrm{i}}^{*} = R_{\mathrm{i,min}}/2$), these were adapted from the Lennard-Jones parameters in Table 5 of Appendix in the Supporting Information of ref 38. The 12,6 parameters C_6 and C_{12} are then obtained as

$$C_{12}^{\mathrm{ij}} = \epsilon_{\mathrm{ij}}(R_{\mathrm{ij}}^{*})^{12}$$

and

$$C_{6}^{\mathrm{ij}} = 2\epsilon_{\mathrm{ij}}(R_{\mathrm{ij}}^{*})^{6}$$

The GROMOS force field prescribes the values of the square roots of C_{12}^{ii} and C_{6}^{ii} to be used directly for calculations after forming the appropriate ij products.

As a first step, the interaction energies of the neutral isolated base pairs have been evaluated (at $D(r) = 1.0$) in gas phase with each force field, for the purpose of comparing them with the results of previous experimental and theoretical studies. Such calculations on free base pairs normally include a hydrogen or a methyl group at N1 (pyrimidines) or N9 (purines) at a position that is taken up by the C1′ atom of the sugar ring in DNA. In our studies, the residual charge on each base is placed on a hydrogen at the C1′ position and the interaction energies are computed and compared with the literature values (Table 1).

The focus of this study is on the base atoms as embedded in the double helix. This is a more realistic treatment of base pair energetics in DNA, as the bases are considered a part of the polynucleotide chain rather than as single isolated species. These have been considered in a second series, and interaction energies have been evaluated both in gas phase and in solution (Table 2). Essentially, the contributions of C1′ of sugar or other attachments in its place are not included in the base pair interaction energies in this series.

TABLE 2: Interaction Energies (in kcal/mol) between Complementary Bases in B-DNA with Different Force Fields and Dielectric Models

dielectric function	base pair	AMBER	CHARMM	GROMOS	OPLS
$D(r) = 1.0$	AT	−11.8	−5.1	−8.7	−3.4
	GC	−27.6	−18.7	−19.3	−18.7
$D(r) = R_{\mathrm{ij}}$	AT	−14.2	−13.6	−9.4	−10.2
	GC	−27.0	−20.6	−17.9	−21.5
$D(r) = 4.0$	AT	−3.0	−1.4	−3.8	−1.5
	GC	−5.6	−3.8	−6.0	−4.2
$D(r) = 46.7$	AT	−0.2	−0.3	−2.3	−0.9
(DMSO)	GC	1.1	0.7	−2.0	0.2
$D(r) = 80.0$	AT	−0.1	−0.3	−2.2	−0.9
	GC	1.4	0.9	−1.8	+0.4
$D(r) = 4R_{\mathrm{ij}}$	AT	−3.5	−3.6	−4.0	−3.2
	GC	−5.5	−4.3	−5.7	−4.9
MHLF[a]	AT	−4.3	−4.3	−4.3	−3.7
(D = 46.7)	GC	−7.0	−5.8	−6.6	−6.2
MHLF[a]	AT	−4.2	−4.3	−4.3	−3.7
(D = 80)	GC	−6.5	−5.2	−6.2	−5.7

[a] MHLF: Calculations with a modified Hingerty−Lavery function: $D_{\mathrm{i}} = 4$ and $s = 0.395$.

TABLE 3: Nucleotide−Nucleotide Interactions Energies (in kcal/mol) in B-DNA in Solution[a]

base pair	AMBER	GROMOS	OPLS
AT	−4.2	−4.4	−3.8
GC	−6.4	−6.5	−5.6

[a] $D(r)$ = Modified Hingerty−Lavery function: $D_{\mathrm{i}} = 4$ and $s = 0.395$. Interactions of all the atoms in a nucleotide on one strand with those in the complementary strand are considered in B-DNA[50] geometry. Partial atomic charges and radii employed are according to the force field specified.

TABLE 4: Electrostatic Component of the Interaction Energy (in kcal/mol) between Bases in Watson−Crick Base Pairs in B-DNA Calculated with Finite Difference Poisson−Boltzmann Method

base pair	AMBER	CHARMM	GROMOS	OPLS
(in water, $D = 80$)				
AT	−5.8	−5.6	−2.8	−3.9
GC	−11.1	−9.8	−6.0	−9.1
(in DMSO, $D = 46.7$)				
AT	−5.8	−5.5	−2.8	−3.8
GC	−11.3	−9.9	−6.2	−9.2

In our third series of calculations, interactions of all the atoms in one nucleotide with all the atoms of the complementary nucleotide were considered to gauze the effect of the number of atoms included in estimating the base pair energies in solution (Table 3).

Electrostatic component of the interactions between the complementary bases in a DNA-like environment in solution was also evaluated using the finite difference Poisson−Boltzmann methodology (FDPB) along with parameters from diverse force fields, in a fourth series of calculations (Table 4). A resolution of 4 grids/Å was employed in all the FDPB calculations. It may be noted that for FDPB calculations the results correspond to calculations on the central base pair of an oligomer which effectively eliminates the role of end effects on the calculated electrostatic potentials and the energetics. The

results are presented and discussed below. Also the interaction energies are divided by 2 for AT base pairs and 3 for GC base pairs when reported as the energy per H-bond.

Results and Discussion

The gas phase ($D(r) = 1$) base pair energies (Table 1) are in line with the values reported in the literature,[28,38,40,49] indicating the correctness of the application of the force fields from the published data. The differences between the present set and the literature values are attributable to the differences in the geometry of the base pairs and also to the presence of a methyl group in place of a H on the N9 or N1 of purine or pyrimidine, respectively.

The Watson−Crick base pair energies with different parameter sets and dielectric models are reported in Table 2. Results with a dielectric constant of unity ($D(r) = 1$) in most cases fall in the range expected from the experimental gas phase values. Force field dependent variations are of course noticeable across the row. The interaction strengths of the AT pair and to an extent that of the GC pair with CHARMM and OPLS charges in particular are seen to be underestimated. This however, is not the case for the interaction of isolated base pairs (Table 1). Results in Tables 1 and 2 taken together suggest that CHARMM and OPLS charge distributions for the base pairs are distinct from the remaining force fields. The significance assumed by the sugar C1′ atom on the energetics as evidenced by the differences between Tables 1 and 2 for $D(r) = 1$, with these two force fields, is striking. It may be further noted that the partial atomic charges for bases with GROMOS force field add up to zero for each base, even without the hydrogens at N1/N9. Bases in DNA, with all other force fields considered here, carry a net negative charge. While these may be matters of how the charges are derived, special attention needs to be paid to correlations between the force field dependent charge distributions and the spatial disposition of the bases and sugars in analyzing the dynamical trajectories of DNA. On the basis of the energetics in Tables 1 and 2, a description of the DNA fine structure with AMBER, CHARMM, and GROMOS is expected to differ unless the explicit solvent used in simulations (TIP3P or SPC/E) can some how compensate for these differences.

Results with $D(r) = r$ appear to significantly mask the differences seen with $D(r) = 1$ while simulating gas phase environment (Table 2). An interesting feature of the base−base interaction energies is that they are more negative with $D(r) = r$ than with $D(r) = 1$. This can never be the case for isolated charges for distances greater than 1 Å, and indeed $D(r) = 1$ is seen to yield much larger values for each pair of atoms considered individually. It is the algebraic sum over all the pairs that alters the trend. Molecules which are electrostatically complementary can exhibit such a behavior with suitable charge distributions. Results with $D(r) = 80$ severely underestimate the base−base attractions as expected. The computed interaction energies in dimethyl sulfoxide, treated as a continuum solvent of dielectric constant 46.7, are too small in relation to experiment. A uniform dielectric constant (a fixed constant value for D) appears to be inappropriate for modeling DNA in solution using continuum solvent methods. Results with $D(r) = 4$ are closer to solution values than to gas phase values, a point of relevance to molecular dynamics protocols and modeling studies on DNA in vacuo. Overall, the relative strength of the base pair energetics in gas phase, considering either $D(r) = 1$ or $D(r) = r$ as representative, obeys the following trend AMBER > CHARMM > OPLS > GROMOS.

It is also apparent from Table 2 that the sigmoidal dielectric function (MHLF) is able to describe the solution energetics both in DMSO and water, in good agreement with the experimental enthalpy values[22] irrespective of the choice of the force field parameters. Another dielectric function $D(r) = 4r$, is also in vogue along with AMBER parameters[37,58] for molecular mechanics protocols involving DNA in solution. This function with AMBER yields −3.6 and −5.5 kcal/mol for the AT and GC base pairs, respectively. We note that the interaction energies with this dielectric function are slightly on the weaker side with AMBER and GROMOS parameters in comparison with the MHLF results and experiment, and more so with CHARMM and OPLS parameters (Table 2). Nonetheless, an inescapable general observation emerging from the results presented here is the diminution of differences between diverse force fields with distance dependent dielectric functions particularly with the sigmoidal function in contrast to the results obtained with a fixed dielectric constant.

The list of atoms included in theoretical estimates of base pair energies in B-DNA may have an effect on the energetics. One such instance is the inclusion/noninclusion of a charge at C1′ position, the consequences of which with $D(r) = 1$, are discussed above (Table 2). An alternative is to include interactions of all the atoms in one nucleotide with all the atoms in the complementary nucleotide. Results of such a computation with the MHL function are very similar (Table 3) to the results obtained considering only the base atoms (Table 2) and consistent with expectations based on experiment.[22,23] Thus the sigmoidal dielectric function appears to perform well for any reasonable choice of the atoms included in evaluating the base pair energetics in solution.

Finite Difference Poisson−Boltzmann (FDPB) Calculations. H-bonding interactions, which are central to Watson−Crick base pairing, are sensitive not only to the partial atomic charges on the donor and acceptor groups but also to the environment.[41,52] The FDPB method is known to depict the electrostatics of molecular systems quite accurately considering both the shape of the solute molecule and dielectric inhomogeneities in solution.[41] The electrostatic component of the interaction energy between the complementary bases in aqueous solution is evaluated in a single step as follows: the solute dielectric constant is set at 2, the solvent dielectric constant at 80, and the charges on the atoms on either of the two bases forming the base pair are switched on (the charges on the complementary base atoms being switched off). The potentials generated on the complementary base atoms upon solving the Poisson equation (the linearized PB equation at zero ionic strength) numerically are then multiplied by their charges to obtain the interaction energy.

$$\Delta A^{\mathrm{h-b}} = \sum q_{\mathrm{i}} \phi_{\mathrm{i}}$$

where i refers to the complementary base atoms only. This methodology is of course not new and has been in vogue since the work of Kirkwood and co-workers[59] for estimating solvent mediated interactions. The corresponding experiments would involve turning one or both charge distributions on or off as by a mutation or via a titration as feasible/applicable. As opposed to this, binding studies typically involve bringing the two interacting species initially separated to their final state, which require inter alia, an explicit consideration of desolvation and the problem configured in the framework of a thermocycle. Binding energies can be postive/unfavorable even for oppositely charged distributions. Identification of the forces driving the double helix formation is beyond the purview of this study. The

focus here is on interaction energy between the Watson−Crick partners as embedded in the double helix in water.

The base pair interaction energies (Table 4) are negative and are in the range of −2 to −3 kcal/mol/H-bond with all the force fields considered here. In a previous study, this methodology led to a base pair energy of ∼ −2 kcal/mol/H-bond [Nidhi Arora, Jayaram, Honig, 1993, unpublished results with AMBER united atom parameters].[60] Also, Zakrzewska et al.[61] reported a value around −2 kcal/mol/H-bond with Flex force field parameters after adding the nonelectrostatic contributions to the FDPB results.

A notable inference emerging from the present calculations is that the inter-base interaction strengths obey the following order AMBER > CHARMM > OPLS > GROMOS. The implication is that base pair opening may be relatively facile during a dynamics run with GROMOS parameters. The earlier GROMOS[62] parameters had to be supplemented with a restraint potential for maintaining Watson−Crick base pairing in MD simulations on B-DNA in solution to prevent the base pairs from opening up.[63] On the other hand, base pairing with AMBER parameters is expected to be relatively stable during a dynamics run on B-DNA in solution.[11−14] Tapia and Velazquez[64] however, recently reported stable B-DNA trajectories with GROMOS[39] parameters with a hydrophoicity correction and a weak external force constraint on the counterions. The results provided here, particularly the striking influence of sugar atoms on the base pair energies (as seen in Tables 1 and 2 with $D(r) = 1$), do point to some scope for further finetuning of the partial atomic charges for an accurate modeling of DNA in solution. Molecular dynamics simulations on B-DNA and on A to B-DNA transitions[11−14,65−68] with explicit solvent, are better equipped to bring these issues to a sharper focus. In studies involving an implicit/continuum representation of the solvent, it is hoped that the results presented here would help in making a judicious choice of the dielectric function. A full thermodynamic account of base pair/double helix formation requires an estimation of the standard free energy of binding. Interaction energy presented here is but one component of the binding energy.

The base pair energetics is expected to be senstive to temperature, solvent environment and sequence (context) effects as well as the presence of ligands. All these factors, as noticeable from the crystal structures and theoretical investigations,[1−15] influence the relative disposition of the bases affecting the inter-base interaction energetics and the results reported here hopefully provide a reference point for judging the consequences of these factors on B-DNA stability and flexibility in solution.

Conclusions

An analysis of the base pair energies in canonical B-DNA with different dielectric treatments suggests that a sigmoidal function is more apt for solution conditions in implicit solvent treatments. The finite difference Poisson−Boltzmann calculations indicate that the electrostatic component of the interaction energy between complementary bases in B-DNA in solution in the canonical form is around −2 to −3 kcal/mol per H-bond, the relative H-bond strengths with different force fields obeying the following order AMBER > CHARMM > OPLS > GROMOS.

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