Strength of Hydrogen Bonds in α Helices

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ABSTRACT: The intramolecular helix backbone >C═O - - - H— N< hydrogen bonding energies in poly(L-alanine) α helices have been estimated both *in* vacuum and in an aqueous environment using the parameter sets of five of the most commonly used force fields for modeling biomolecules, namely AMBER, CHARMM, ECEPP, GROMOS, and OPLS. The relative capabilities of these force fields in describing the H-bonding interactions with different dielectric continuum models have been assessed. A modified Hingerty–Lavery function is proposed for the treatment of electrostatic interactions of biomolecules in an aqueous environment. The helix backbone H-bonding energies predicted by this function (~ -1 kcal/mol) correspond closely with the experiment. © 1997 by John Wiley & Sons, Inc. *J Comput Chem* **18:** 1245–1252, 1997

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Introduction

A large number of hydrogen bonds (H-bonds) holding the native polypeptide chain into stable secondary structures naturally implicates their significance in determining the internal architecture of proteins. H-bonding and its effect on biomolecular structure has been a matter of intense research interest[1,2] since Mirsky and Pauling[3] first stressed the dominant role of H-bonding in protein folding. This further led to the discovery of secondary structures,[4] namely α helices, and parallel and antiparallel β sheets by Pauling and coworkers.[5,6] The NH - - - O bond, in general, is linear (to within 10°) and the nitrogen–oxygen distance is around 2.79 ± 0.12 Å with the oxygen atom lying on the extension of the NH-bond axis.[7] A recent review by Baker and Hubbard[8] ascribes a mean N ⋯ O distance of 2.99 Å in the α helices and 2.91 Å in the β sheets to H-bonds in >C═O - - - H—N< type interactions.

Accurate modeling of side chains and their interactions has been the cynosure of a number of studies in recent years for a better understanding of the folding and binding processes. An interest in backbone H-bonds surfaced when Baker and

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Hubbard[8] followed by Stickle et al.[9] concluded that a large majority of protein (82%) is involved in an H-bonded secondary structure, of which 68% of the H-bonds occur between backbone polar groups. With the availability of some improved parameter sets for modeling biomolecules, a reexamination and characterization of the H-bonding energy in diverse biochemical contexts becomes a research topic of considerable value in developing a molecular view of stability and recognition. In this study we focus on the energetics of hydrogen bonding in α helices as captured by different potential functions and dielectric continuum models.

Background

Investigations on the dimerization enthalpies of model compounds in aqueous solutions and organic media, both experimental and theoretical, were the first to give a clue to the magnitude of intramolecular hydrogen bonding in α helices. Schellman's[10,11] evaluation of the urea dimerization enthalpy in water was one of the first attempts in this direction, which yielded a value of -2.1 kcal/mol. Mizushima et al.[12] estimated the intramolecular H-bonding energies in model compounds in CCl_4 to be -1.7 ± 0.2 kcal/mol. Spectroscopic studies of Klotz and Franzen[13] on the H-bonding involved in the dimerization of *N*-methyl acetamide (NMA) suggested negligible enthalpies in aqueous solutions. However, higher enthalpy values were obtained in CCl_4 (-4.2 kcal/mol) and dioxane (-0.8 kcal/mol). These were also supported by $\Delta H_{\text{dimerization}}$ of -3.9 and -2.9 kcal/mol for NMA and for *N*-methyl formamide.[14] Monte Carlo computer simulations of Jorgensen[15] on the NMA dimerization energetics showed no net attraction between the NMA molecules in water due to competition for H-bonding with the solvent. In CCl_4, however, the interaction free energy was computed to be -3.5 kcal/mol.

Particularly relevant to the present work are the results of the two independent studies of Scholtz et al.[16] and Ooi and Oobatake.[17] Scholtz et al. determined a binding enthalpy of -1.3 kcal/mol/residue in α helices of a 50 residue alanine-rich polypeptide in aqueous solution.[16] This calorimetric study concludes that the major contribution to the enthalpy of helix formation comes from the backbone–backbone interactions. Ooi and Oobatake, on the other hand, evaluated the enthalpies of unfolding in an alanine α helix in water (40 residue polypeptide).[17] Their results suggest that helix formation is an enthalpy driven process with the enthalpy of folding (-0.86 kcal/mol/residue) in the same range as that of Scholtz et al.[16] Ben Naim[18] estimated an H-bonding energy of ~ -1 kcal/mol in α helices when the interacting functional groups were partially exposed to the solvent. However, the free energy was positive and of the order of $+6.4$ kcal/mol when the functional groups were completely removed from the solvent. Fersht and Serrano[19] concluded that individual H-bonds contribute around -0.5 to -2.0 kcal/mol to binding free energy. In a recent review Shirley et al.[20,21] assign a similar value of -1.5 ± 1.0 kcal/mol to $\Delta(\Delta G)$ of hydrogen bonding based on mutant studies on Rnase T1 and further conclude that hydrogen bonding and hydrophobic interactions make large but comparable contributions to the conformational stability of globular proteins in solution.

Dielectric continuum solvent methods over the last few years have proved to be highly successful in arriving at quantitative estimates of the energetics of solvation and binding and in sketching a molecular thermodynamic picture of these processes.[22] Yang and Honig[23] used a dielectric continuum solvent approach (the finite difference Poisson–Boltzmann method, FDPB) (see ref. 22 and references therein) to obtain binding enthalpies of -2.08 kcal/mol/residue in alanine polypeptides in solution. Osapay et al.[24] estimated an H-bond energy of -2.4 kcal/mol for a linear dimer of alanine and concluded that the peptide solutes responded in qualitatively similar ways when solvation was treated either by explicit solvent models or by using continuum solvent methods. Computational demands of explicit solvent simulations preclude their usage in studies involving extensive searches of the conformational space of a polypeptide or a protein,[25] thus encouraging the use of implicit models for investigating their structure in solution. The above cited studies thus motivate more extensive development and testing of the continuum solvation methods[24,26] for understanding protein stability and function.

Recently we found that the peptide backbone of a regulatory protein λ repressor contributes about one-third of the total interaction energy toward recognition of its operator binding site,[27,28] signifying the importance of the local fold/structural motif of the protein and its packing in the major groove of DNA. The important role of the backbone, not only in specifying the secondary structure of the protein, but also in DNA–protein inter-

actions, has led to this renewed interest in the strength and contribution of the backbone >CO - - - HN< H-bonds to stability and recognition.

In this study we employed a modified Hingerty–Lavery function (MHLF) to capture the electrostatics in an aqueous environment. This is a fairly superior function to the other commonly used dielectric constants/scaling parameters. Earlier studies showed that the MHLF along with a Lennard–Jones 12–6 potential can represent H-bond interactions in aqueous solution for base pairing in B-DNA,[29] in close agreement with the experiment. We propose this simple and computationally inexpensive treatment as a substitute for the more expensive explicit solvent representation in simulations of biomolecules in an aqueous environment. Although no explicit solvent simulations have been undertaken here, the results are in reasonable agreement with experimental values. The calculations reported here employ parameters from five of the most commonly used potential functions to ensure force field independence of the conclusions regarding the appropriateness of this function in evaluating biomolecular interaction energies. This study should have implications for ongoing efforts to develop more accurate and computationally less expensive theoretical tools for modeling biomolecules under aqueous conditions.

Methodology

A nonapeptide of poly(L-alanine) in α_R conformation was generated using BIOSYM software.[30] The (i)–(i + 4) H-bond length (N ⋯ O distance) was noted to be 3.10 Å in this canonical conformation. No further minimizations were done on this structure. There are five backbone hydrogen bonds in this nonapeptide. Only the three central hydrogen bonds were considered for calculating the average hydrogen bond energy. Collinear CO and NH group structures were also generated wherein the C═O bond length was fixed at 1.24 Å and the N—H-bond length at 1.00 Å.[7,31]

The total H-bond energetics was calculated as a sum of the contributions due to electrostatic and van der Waals interactions between the carbonyl of the ith residue and amide of the $(i + 4)$th residue by assigning partial atomic charges and van der Waals parameters from AMBER,[32] CHARMM,[33] ECEPP,[34,35] GROMOS[36] and OPLS[37] force fields followed subsequently by an evaluation of the interaction energy. The total interaction energy for AMBER, GROMOS and OPLS, $E_{(CO-HN)}$ is represented by the following expression:

$$E_{CO-HN} = \sum [E_{el} + E_{vdW}],$$

for CHARMM and ECEPP an additional hydrogen bonding term was incorporated to be consistent with the force fields employed. The H-bond energy in these cases is computed as

$$E_{(CO-HN)} = \sum [E_{el} + E_{vdW} + E_{hb}],$$

where E_{el} is the electrostatic contribution to the total energy, E_{vdW} is the van der Waals term, E_{hb} is the hydrogen bonding term, and the summation runs over the carbonyl atoms of the ith residue and the amide atoms of the $(i + 4)$th residue.

ELECTROSTATIC TERM

The electrostatic component of the interaction between the carbonyl atom j of the ith residue with that of the amide atom k of the $(i + 4)$th residue is computed as

$$E_{el} = \frac{332 q_j q_k}{D(r) r_{jk}},$$

where q_j and q_k are the partial atomic charges on the two interacting atoms (taken from each specified force field), r_{jk} is the distance between the atoms j and k, and $D(r)$ is a dielectric function. To gauge the effect of different dielectric continuum models for representing proteins in the gas phase and in aqueous solution, a series of calculations were performed with different values for $D(r)$, namely 1, 4, 80, r_{jk}, etc. In the studies employing the MHLF,[38,39] $D(r)$ was taken as

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

Here $D(r)$ is a sigmoidal function. $D = 78$, $D_i = 4$, and $\alpha = sr$, where $s = 0.395$. D_i and s were calibrated previously on the base pairing energies to yield −2 kcal/mol/H-bond in close correspondence with the experiment.[27–29]

VAN DER WAALS TERM

The van der Waals interactions were modeled using a 12–6 Lennard–Jones potential between the

atom pairs jk of the ith carbonyl and the $(i + 4)$th amide.

$$E_{\mathrm{vdW}} = \left[\frac{C_{12}^{jk}}{r_{jk}^{12}} - \frac{C_6^{jk}}{r_{jk}^{6}} \right].$$

For the OPLS force field C_{12}^{jk} and C_6^{jk} are obtained as geometric means from the individual atomic 12, 6 parameters. For AMBER, calculations require computing the R_{jk} and ε_{jk} as

$$R_{jk}^{*} = R_j^{*} + R_k^{*}$$

and

$$\varepsilon_{jk} = (\varepsilon_j \varepsilon_k)^{1/2}.$$

ε_j is the well depth parameter and R_j^{*} is half of the half distance at the well depth. $\sigma_{jj} = 2^{-1/6} R_{jj}^{*}$, and $R_{jj}^{*} = R_j^{*} + R_j^{*}$; alternatively $\sigma_{jj} = 2^{5/6} R_j^{*}$. The R_j^{*} values for AMBER calculations were taken from the van der Waals parameters listed in table 14 of ref. 32. The 12–6 parameters were then obtained as

$$C_{12}^{jk} = \varepsilon_{jk} (R_{jk}^{*})^{12}$$

and

$$C_6^{jk} = 2 \varepsilon_{jk} (R_{jk}^{*})^{6}.$$

The GROMOS force field prescribes the values of $\sqrt{C_{12}^{jj}}$ and $\sqrt{C_6^{jj}}$ to be used directly for calculations after forming the appropriate jk products. The CHARMM and ECEPP force fields, however, employ the Slater–Kirkwood equation[40] for estimating C_6^{jk}.

$$C_6^{jk} = \frac{3}{2} \left(\frac{1}{4\pi\varepsilon_0} \right)^{1/2} e\hbar m_e^{-1/2} \frac{\alpha_j \alpha_k}{\left(\frac{\alpha_j}{N_j} \right)^{1/2} + \left(\frac{\alpha_k}{N_k} \right)^{1/2}}.$$

The C_{12}^{jk} are then computed from C_6^{jk} values as

$$C_{12}^{jk} = \frac{1}{2} C_6^{jk} (R_j + R_k)^{6}.$$

In the preceding two equations α_j is the polarizability, N_j the effective number of outer shell electrons, R_j the van der Waals radius, m_e the electron rest mass, $\hbar = h/2\pi$ where h is the Planck's constant, e the electron charge, and ε_0 the permittivity of vacuum.

HYDROGEN BOND TERM

The hydrogen bond term was essentially considered as a 12–10 interaction between the hydrogen bonding atoms H - - - O for ECEPP and donor–acceptor atoms N - - - O for CHARMM.

$$E_{\mathrm{hb}} = \left(\frac{A'}{r_{jk}^{12}} - \frac{B'}{r_{jk}^{10}} \right) \cos^{m} \theta_{(A-\mathrm{H}-D)} \times \cos^{n} \theta_{(AA-A-\mathrm{H})}.$$

The 12–10 terms were calculated for CHARMM from the nonbonded parameters given in appendix I of ref. 33 and for ECEPP with parameters from ref. 34; m and n were assigned values of 4 and 2, respectively, for α-helix calculations in CHARMM while $m = n = 0$ was used for ECEPP. Besides this, $\theta_{(A-\mathrm{H}-D)}$ and $\theta_{(AA-A-\mathrm{H})}$ take values of 151.63° and 142.20°, respectively, in the α-helix calculations (default angles in canonical α-helix conformation) while both θ angles take values of 180° in linear >CO - - - HN< interaction.

Results and Discussion

All the force fields considered here (AMBER,[32] CHARMM,[33] ECEPP,[34,35] GROMOS[36] and OPLS[37]) describe the structure and dynamics of proteins and their interactions quite effectively. Because H-bonds are crucial contributors to the stability of secondary structures of proteins, it is of interest to appreciate the relative performance of each of these force fields in estimating intraprotein interaction energies and this is presented here.

LINEAR >CO - - - HN< HYDROGEN BOND STRENGTHS

Prior to the evaluation of >CO - - - HN< interaction energies in helices, wherein the relative position and orientation of the CO and NH groups as defined by their configuration in the helix may have a role to play, it is necessary to characterize the force field preferences when the CO and NH groups approach each other linearly. Force field characterization for H-bond length and strength in >CO - - - HN< interactions was done by varying the N ⋯ O distance and computing the interaction of the CO group with the NH group as they approach each other along a straight line. Total interaction energies were evaluated as N ⋯ O distance was varied from 1.1 to 4.0 Å with an increment of 0.1 Å, retaining the collinear geometry for the >CO - - - HN< atoms. It may be noted, however, that this geometry does not necessarily repre-

sent the H-bond interactions in real molecules but serves to elicit information on the location of the energy minimum with each force field.

All the force fields show minima at N···O distances of 2.9–3.0 Å (Table I) for $D(r) = 1$. The interaction strengths at the minimum obey the following trend: GROMOS > OPLS > AMBER > CHARMM > ECEPP. A value greater than −2.0 kcal/mol/H-bond at $D(r) = 1$ appears to be an underestimate of the interaction energy in vacuum inferred from the experiment (−4.4 to −5.2 kcal/mol).[41] The distance dependent dielectric function, however, leads to relatively stronger interactions. The minima for $D(r) = r$ occur in the range of 2.7–2.9 Å N···O. The energies with $D(r) = r$ for OPLS are closer to the experimentally determined values. The interaction energies with $D(r) = 4.0$ and 80.0 do not accurately represent the energies in the gas phase and aqueous phase, respectively. As is apparent from Table I, the MHLF in the case of all force fields yields an interaction energy of ∼ −1.0 kcal/mol in solution close to the experimental enthalpy[16,17] of −0.86/− 1.3 kcal/mol without any extra parametrization for proteins. Also, the minima are obtained at the same interatomic distance of ∼ 3.1 Å (with MHLF) as the (i)–$(i + 4)$ N···O distance in the canonical structure of the α helix of alanine.

An interesting result emerges upon a variation of the list of atoms considered for H-bond interaction. As in the case of >CO---HN< interaction, if only >O---HN< interaction is considered, the energetics with $D(r) = r$ is stronger with all the force fields except ECEPP (H-bond energies in kcal/mol: OPLS −6.02, GROMOS −5.35, AMBER −4.18, CHARMM −3.60, ECEPP −1.50); the results, as calculated with the MHLF in an aqueous environment, are almost unaffected by any such change in the list of atoms considered and are still within the experimental range (AMBER −1.25, CHARMM −0.94, ECEPP −1.11, GROMOS −1.26, OPLS −1.46 kcal/mol). $D(r) = 1$ does not give any meaningful results except with GROMOS parameters (results not tabulated).

An alternative approach for calculating H-bond energies involves evaluation of neutral group interactions (CO---HN for GROMOS and CO---HNCα for OPLS and CHARMM). It may be noted that for AMBER and ECEPP, interaction of CO---HNCαHα was evaluated, which still bears a nonnegligible residual charge. From Table II it is apparent that there is a modest improvement in the H-bond strengths with all the force fields. The trends with both $D(r) = 1$ and $D(r) = r$ are as follows: OPLS > AMBER > GROMOS > CHARMM > ECEPP. The results with the MHLF are still within the expected range.

ENERGETICS OF INTRAHELICAL H-BONDS

Interaction energies between the ith CO and $(i + 4)$th NH groups were calculated for poly(L-alanine) in the α_R conformation and these are shown in Table III. For simulations with explicit solvent, $D(r) = 1$ is the obvious choice. The gas phase values obtained with the dielectric function $D(r) = 1$, however, fall severely short (−1.2 to −2.7 kcal/mol/H-bond) of the expected H-bond energy.[41] An H-bond strength of ∼ −1.0 kcal/mol in solution is estimated by the MHLF for all the force fields considered and is close to the experimental enthalpy of −0.86/− 1.3 kcal/mol.[16,17] Similar results are obtained with neutral group (CO—HNCαHα) type interaction energies evalu-

TABLE I.
Calculated Hydrogen Bond Energies Considering Linear >CO---HN< Interactions with Different Force Fields and Dielectric Models.

Dielectric Function	AMBER		GROMOS		CHARMM		OPLS		ECEPP	
	E_{min}	r_{min}	E_{min}	r_{min}	E_{min}	r_{min}	E_{min}	r_{min}	E_{min}	r_{min}
$D(r) = 1.0$	−2.19	3.0	−3.24	2.9	−2.04	2.9	−2.56	2.9	−1.46	2.9
$D(r) = 4.0$	−0.67	3.2	−0.81	3.2	−0.56	3.1	−0.66	3.2	−1.07	3.0
$D(r) = 80.0$	−0.32	3.4	−0.22	3.4	−0.18	3.3	−0.28	3.4	−0.94	3.0
$D(r) = r$	−3.62	2.9	−3.74	2.8	−3.07	2.9	−5.14	2.7	−2.09	2.9
MHLF	−1.11	3.1	−0.98	3.1	−0.91	3.1	−1.29	3.1	−1.27	3.0

All E_{min} values are in kcal/mol H–bond and r_{min} values are in Å.
r_{min} refers to the N···O distance at which the energy is a minimum.

TABLE II.
Calculated Hydrogen Bond Energies Considering Neutral Group Interactions.

Dielectric Function	AMBER		GROMOS		CHARMM		OPLS		ECEPP	
	E_{iin}	r_{min}	E_{min}	r_{min}	E_{min}	r_{min}	E_{min}	r_{min}	E_{min}	r_{min}
$D(r) = 1.0$	−3.48	3.0	−3.24	2.9	−3.21	2.9	−4.96	2.8	−1.95	2.9
$D(r) = r$	−4.45	2.9	−3.74	2.8	−3.73	2.9	−6.50	2.7	−2.51	2.9
MHLF	−1.44	3.1	−0.98	3.1	−1.17	3.0	−1.71	3.0	−1.50	3.0

All E_{min} values are in kcal / mol / H-bond and r_{min} values are in Å.
r_{min} refers to the N ⋯ 0 distance at which the energy is a minimum. See text for a definition of neutral groups.

ated in the context of the poly(alanine) helix. The H-bond energies with the MHLF are still of the order of −1 kcal/mol (AMBER −1.27; CHARMM −1.12; ECEPP −1.26; GROMOS −0.91; OPLS −1.55 kcal/mol). A further ancillary issue highlighted by this study here is that the van der Waals component is almost negligible (of the order of −0.1 kcal/mol) at the 3.1 Å H-bonding distance.

For *in vacuo*/gas phase calculations, all the force fields considered here, appear to work better with $D(r) = r$ rather than with $D(r) = 1$ for both proteins and nucleic acids,[29] despite the lack of physics in such a dielectric function. Interactions with $D(r) = 4$ and 80 merely correspond to scaling down the electrostatics and do not yield satisfactory results for the gas phase and aqueous phase, respectively. For an implicit solvent treatment, the MHLF appears to be best suited. All other dielectric models considered here are to be discouraged in view of their performance on the energetics. A possible *lacuna* in this study is that the energetics refers to single point energies. Boltzmann averaging would only make the H-bond strengths weaker than given by the minima and the experiment, a point to be addressed in further refinements of the force fields.

Whether the backbone H-bonds contribute favorably or unfavorably to the free energy of helix formation is an issue of considerable topical interest. Yang and Honig[23] suggest that the electrostatic contribution to the free energy of H-bond formation in aqueous solution, in a helical context, can be approximated as the sum of solvation free energy (obtained with 2, 1 and 2, 80 dielectrics with the FDPB method) and Coulombic interaction energy in the gas phase for an i–$(i + 4)$ interaction evaluated with $D(r) = 1$, wherein the charges on all atoms, except those involved in H-bond formation, have been switched off (method I).

$$\Delta G^{\text{h-b}} = \Delta G^{\text{h-b}}_{\text{solv}} + \Delta U^{\text{h-b}}_{\text{elec}}.$$

Alternatively, the binding energy can be evaluated in one step (with solute dielectric constant set at 2, and solvent dielectric constant at 80 in the FDPB calculation), when the charges on all atoms except those on the ith CO are switched off and

TABLE III.
Calculated Hydrogen Bond Energies in Poly(L-alanine) α Helix with Different Force Fields and Dielectric Models.

Dielectric Function	AMBER	GROMOS	CHARMM	OPLS	ECEPP
$D(r) = 1.0$	−1.72	−2.66	−1.65	−1.80	−1.17
$D(r) = 4.0$	−0.53	−0.69	−0.54	−0.53	−0.93
$D(r) = 80.0$	−0.15	−0.07	−0.18	−0.13	−0.86
$D(r) = r$	−2.81	−2.81	−2.38	−3.33	−1.56
MHLF	−1.02	−0.91	−0.89	−1.18	−1.10

All values are in kcal / mol / H-bond.

TABLE IV.
Calculated Hydrogen Bond Energies Considering >CO - - - HN< Interactions with Finite Difference Poisson–Boltzmann Methodology.

	AMBER	GROMOS	CHARMM	OPLS	ECEPP
Method I	3.96	−0.85	3.15	5.07	3.18
Method II	−1.15	−1.16	−0.89	−1.38	−0.28

All values are in kcal / mol / H-bond and correspond to electrostatic contribution to the binding free energy of the central >CO—HN< unit involved in the hydrogen bond. Resolution employed was 4 grids / Å.

the potentials generated on the corresponding $(i + 4)$th NH atoms are then multiplied by their charges to obtain the H-bonding energy (method II).

$$\Delta G^{h-b} = \sum q_i \phi_i,$$

where i now refers to NH atoms only.

An application of the above two methodologies with diverse force fields considered here yields inequivalent results (Table IV). With method I the computed free energy change is positive except for GROMOS, while the binding free energy using method II is negative and of the order of −1 kcal/mol for all the force fields considered, except ECEPP. The inference following from method I, as also reported by Yang and Honig,[23] is that H-bond formation does not add to helix stability. Contrary to this, the results from method II indicate that H-bond formation does add to the stability of α helices. An alteration in the list of atoms to accommodate neutral groups in the H-bond formation does not affect the conclusions, although the magnitudes of H-bond contributions vary (Table V). Also, this conclusion with method II is not dependent on the solute dielectric considered. A higher solute dielectric of course diminished the contribution but did not make it unfavorable. Method II suffers from the artifact of grid potentials that is eliminated in method I by taking differences. This notwithstanding, that the difference in the charging pattern in the two methodologies leads to divergent conclusions on the H-bond contribution to α-helix stability needs further investigation.

Conclusions

In this article, we attempted to characterize the intramolecular H-bond strengths in α helices as described by the AMBER, CHARMM, ECEPP, GROMOS, and OPLS parameter sets. Also suggested is a simple dielectric function (MHLF) to mimic the aqueous environment for the purpose of estimating intramolecular electrostatic interactions as a substitute for explicit solvent consideration. Irrespective of the force field and the list of atoms considered, the MHLF captures the energetics in solution (∼ −1.0 kcal/mol/H-bond) close to the experimentally predicted enthalpy of −0.86/− 1.3 kcal/mol.[16,17] The same function leads to a value of −2.0 kcal/mol for base pairing without any modification indicating the role of contextual effects and geometry on the H-bond energies.

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TABLE V.
Calculated Hydrogen Bond Energies Considering Neutral Group Interactions with Finite Difference Poisson—Boltzmann Methodology.

	AMBER	GROMOS	CHARMM	OPLS	ECEPP
Method I	1.48	−0.85	0.50	−0.18	1.74
Method II	−1.25	−1.16	−0.97	−1.62	−0.34

All values are in kcal / mol / H-bond and correspond to electrostatic contribution to the binding free energy of the central neutral units involved in the hydrogen bond. Resolution employed was 4 grids / Å.

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