Published in final edited form as:

J Phys Chem B. 2011 May 19; 115(19): 6130–6137. doi:10.1021/jp111259e.

Simple physics-based analytical formulas for the potentials of mean force of the interaction of amino-acid side chains in water. VI. Oppositely-charged side chains

Mariusz Makowski^{1,2,*}, Adam Liwo^{1,2}, and Harold A. Scheraga²

¹Faculty of Chemistry, University of Gdańsk, Sobieskiego 18, 80-952 Gdańsk, Poland ²Baker Laboratory of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853-1301

Abstract

The two-site coarse-grained model for the interactions of charged side chains, to be used with our coarse-grained UNRES force field for protein simulations proposed in the accompanying paper, has been extended to pairs of oppositely-charged side chains. The potentials of mean force of four pairs of molecules modeling charged amino-acid side chains, i.e., propionate – n-pentylamine cation (for aspartic acid – lysine), butyrate...n-pentylamine cation (for glutamic acid – lysine), propionate – 1-butylguanidine (for aspartic acid – arginine), and butyrate – 1-butylguanidine (for glutamic acid – arginine) pairs were determined by umbrella-sampling molecular dynamics simulations in explicit water as functions of distance and orientation, and the analytical expression was fitted to the potentials of mean force. Compared to pairs of like-charged side chains discussed in the accompanying paper, an average quadrupole-quadrupole interaction term had to be introduced to reproduce the Coulombic interactions, and a multi-state model of charge distribution had to be introduced to fit the potentials of mean force of all oppositely-charged pairs well. The model reproduces all salt-bridge minima and, consequently, is likely to improve the performance of the UNRES force field.

Keywords

charged side chains; new model of side-chain – side-chain interactions; potential of mean force; molecular dynamics; umbrella sampling; multipole expansion

Introduction

Continuing our study of the development of physics-based side chain – side chain interaction potentials,^{1–4} for use in our coarse-grained UNRES force field,^{1–17} in the accompanying paper¹⁸ we proposed a new model of charged amino-acid side chains and analytical expressions for the respective contributions to the potential of mean force (PMF) of charged side chain – side chain interactions and applied it to systems modeling pairs of like-charged side chains. The new potentials will replace the knowledge-based potentials⁶, which were determined from the Protein Data Bank (PDB)¹⁹ and have the Gay-Berne functional form.²⁰ These new potentials take into account some anisotropy of the interactions; the charged side chains contain both a charged “head” and a nonpolar “tail”, i.e., they are amphiphilic and, consequently, the symmetry of the potential of their interactions is lower than spheroidal. Moreover, the Gay-Berne potential fails to reproduce

*Corresponding author: momo@chem.univ.gda.pl.

the desolvation maxima present in the potentials of mean force between pairs of amino-acid side chains in water.

We showed¹⁸ that use of an analytical function, consisting of the Gay-Berne term, an electrostatic potential, the generalized Born term, a polarization energy term, an isotropic cavity contribution to the free energy of hydration of the two charges, and a cavity term to compute hydrophobic association, fitted the potentials of mean force between pairs of six like-charged amino acids well. Their PMFs have the typical shape with solvent-separated minima, and intervening maxima. The parameters of the energy components also have reasonable values and physical meaning. In this paper, we treat systems modeling the pairs of oppositely-charged side chains, viz., propionate – n-pentylamine cation (Pr p[−] ... Pna⁺), butyrate – n-pentylamine cation (But[−] ... Pna⁺), propionate - 1-butylguanidine (Pr p[−] ... BtG⁺), and butyrate - 1-butylguanidine (But[−] ... BtG⁺), as representing aspartic acid – lysine, glutamic acid – lysine, aspartic acid – arginine, and glutamic acid – arginine, respectively.

Theory

Analytical expressions for potential of mean force

The new model of interactions between charged side chains developed in the accompanying paper¹⁸ is illustrated in Figure 2 of the accompanying paper.¹⁸ Each such side chain is represented by two sites: a nonpolar site (represented by an ellipsoid of revolution in Figure 2 of the accompanying paper)¹⁸ and a charged/polar site (represented by shaded spheres in Figure 2 of the accompanying paper¹⁸). Both, nonpolar and charged/polar sites are located on the C^α-SC axis. The side chain center is located between the polar/charged and nonpolar centers.

For the systems modeling pairs of oppositely-charged side chains in water considered in this study, we found that assuming a fixed distance of the center of the charged site from side-chain center does not reproduce the shape and structure of the contact (salt-bridge) minima in the PMF surface corresponding to head-to-head orientations of the side chains; consequently, we assumed that the charged site can exist in two states, which differ from each other in the distance of the charged center from the side-chain center. The introduction of the two-state model also enables us to differentiate the head-to-head and side-to-side orientations from each other. The two state model of two interacting side chains is shown in Figure 1.

For pairs including arginine, the spread of the charge distribution must also be included by introducing a term corresponding to averaged quadrupole-quadrupole interactions and, for all pairs, an explicit Lennard-Jones term must be included between the charged centers. The approximate analytical expression for the PMF of oppositely-charged side chains is given by eq 1.

$$W_{cc} = E_{GBerne} + \Delta F_{cav} - RT \ln \sum_{i=1}^N w^{(i)} \exp \left(- \frac{E_q^{(i)} + E_{qd}^{(i)} + E_{LJ}^{(i)} + E_{pol}^{GB(i)} + E_{pol}^{(i)} + \Delta F_{cav}^{iso(i)}}{RT} \right) + RT \ln \sum_{i=1}^N w^{(i)} \quad (1)$$

where E_{GBerne} is the van der Waals term corresponding to the interactions between the nonpolar sites expressed by Gay-Berne potential, ΔF_{cav} is the difference between the cavity contribution to the free energy of hydration of the nonpolar sites of the dimer and those of the isolated monomers, E_q is the Coulombic term for the interaction between the charged sites, E_{qd} is the average quadrupole-quadrupole interaction term, E_{LJ} is the Lennard-Jones

term representing the dispersion interactions and valence repulsion between the charged headgroups, E_{pol} is the polarization energy coming from the interactions between the charged and nonpolar sites (but not from their interactions with the solvent), E_{pol}^{GB} is the energy contribution due to solvent polarization by the charged sites; it is computed by using the generalized Born (GB) model,^{21–25} ΔF_{cav}^{iso} is the cavity term corresponding to the charged sites (the superscript “iso” indicates that the sites involved are isotropic), ΔF_{cav} is the cavity term corresponding to the nonpolar sites, the superscript (*i*) indicates the index of the microstate, $w^{(i)}$ is the weight of this microstate (also treated as an adjustable parameter in fitting eq 1 to the PMF), N is the number of microstates ($N = 4$ in this work) R is the universal gas constant and T is the absolute temperature ($T = 298$ K in this work). Each of the microstates corresponds to different distances between the center of the charged headgroups and the side-chain center (see Figure 1). We assume two possible states for the centers of the charged headgroups for each side-chain model of a pair, which gives a total of four microstates (in one state the headgroup is closer and in the other one farther from the side-chain center).

Except for E_{qd} the terms in eq 1 have been defined and their physical origin discussed in the accompanying paper.¹⁸ The average energy of interactions of two point quadrupoles (E_{qd}) *i* and *j* is expressed by eq. 2 (see Appendix for derivation; eqs A1 – A9):

$$E_{qd} = \frac{A}{f_{GB}(r'_{ij})^5} \left[5 + 3(\cos^2 \alpha_{ij} - 1) - \frac{75}{2}(\cos^2 \theta_{ij}^{(1)} + \cos^2 \theta_{ij}^{(2)}) + \frac{315}{2} \cos^2 \theta_{ij}^{(1)} \cos^2 \theta_{ij}^{(2)} - 45 \cos \alpha_{ij} \cos \theta_{ij}^{(1)} \cos \theta_{ij}^{(2)} \right] \quad (2)$$

where A is a parameter to be determined by least-squares fitting, r'_{ij} is the distance between the centers of the charged groups, the angles $\theta_{ij}^{(1)}$ and $\theta_{ij}^{(2)}$ are the angles (see Figure 1 in the accompanying paper¹⁸) between the vector linking the side-chain centers of the charged headgroups and the $C^\alpha \dots SC$ axes of the side chains *i* and *j*, respectively, α_{ij} is the angle between the $C^\alpha \dots SC$ axes of the side chains (which are identified with the axes about which the quadrupoles rotate), and f_{GB} is expressed by eq 3.

$$f_{GB}(r'_{ij}) = \sqrt{r_{ij}'^2 + a_i a_j \exp\left(-\frac{r_{ij}'^2}{4a_i a_j}\right)} \quad (3)$$

where a_i and a_j are the Born radii of sites *i* and *j*, respectively.

Methods

We used the same computational procedure, the AMBER force field as well as water model as described in detail in the Methods section of our accompanying paper.¹⁸ The box dimensions as well as the number of water molecules for the pairs of solute molecules studied in this work are collected in Table 1. The charges and the AMBER atom types are shown in Figure 3 in our accompanying paper.¹⁸ Fitting of analytical approximations to the PMFs was accomplished as described in our accompanying paper.¹⁸

Results and Discussion

Figure 2a–d shows the PMFs of the pairs considered (dashed lines), together with the approximations computed with the fitted analytical expressions (eq 1; solid lines). The

PMFs are plotted as functions of the distance between the centers of the molecules (see Figure 1) for the four selected side-chain orientations: side-to-side, side-to-head, head-to-side, and head-to-head (see Figure 4 of the accompanying paper¹⁸).

The PMF curves for the four side-chain orientations resulting from MD simulations (dashed lines) shown in Figure 2 have characteristic shapes with two minima, and an intervening desolvation maximum. As expected from side-chain anisotropy, the minima corresponding to the head-to-head orientation appear at the longest distance (about 7 Å for Pr p⁻ ... Pna⁺, and But⁻ ... Pna⁺ and about 7.5 – 8.0 Å for Pr p⁻ ... BtG⁺ and But⁻ ... BtG⁺), while those corresponding to the side-to-side orientation appear at the shortest distances (about 4.0 Å - 4.6 Å). The basins containing the minima corresponding to the head-to-head, head-to-side, and side-to-head orientations are the broadest and exhibit fine structure (several shallow minima). This fine structure arises because, for flexible side chains, the charged headgroup can be positioned at various distances from the side-chain center depending on side-chain conformation. As opposed to the head-to-head, head-to-side, and side-to-head orientations, the energy of headgroup interactions is independent of the distance of the headgroups from the side centers for the side-to-side orientation and, consequently, the PMF has only one minimum for the side-to-side orientation.

The minima corresponding to the head-to-head (red curves) and side-to-side (black curves) orientations are remarkably deeper compared to those corresponding to the head-to-side (blue curves) and side-to-head (green curves) orientations (their depth is about -2.0 kcal/mol for pairs involving Pna⁺ and -2.5 kcal/mol for those involving BtG⁺, respectively). One reason for this is that the oppositely charged headgroups can make contact with each other for the head-to-head and the side-to-side orientations forming a salt bridge, while they are also in contact with the nonpolar parts of the other side chain for the head-to-side and side-to-head orientation.²⁶ Another reason is that, for these orientations, the electrostatic interactions between the headgroups are less attractive because fewer hydrogen bonds can be formed if a carboxylic group faces the side of an ammonium/guanidine group or vice versa. This observation is supported by the fact that the minima corresponding to the head-to-head orientation are remarkably deeper for pairs involving the n-butylguanidine cation compared to those corresponding to the side-to-side orientation because the guanidine group is a large unit and contains five hydrogen-bonding protons.

In the free-energy function corresponding to the interactions in which charged headgroups are involved, the spread of the charge distribution is accounted for by the interactions between point quadrupoles. From Figure A2-b, it follows that, for the oppositely-charged groups, the quadrupole-quadrupole term exhibits the global maximum when the axis (about which one quadrupole is rotated) is perpendicular to and the axis of the other one is aligned with the vector linking the quadrupoles (as in the head-to-side ($\theta_{ij}^{(1)}=0^\circ$ or 180° and $\theta_{ij}^{(2)}=90^\circ$) and side-to-head ($\theta_{ij}^{(1)}=90^\circ$ and $\theta_{ij}^{(2)}=0^\circ$ or 180°) orientations). The global minimum (Figure A2-b) appears when the rotation axes of both quadrupoles are aligned with the vector linking them (as for the head-to-head ($\theta_{ij}^{(1)}=0^\circ$ or 180° and $\theta_{ij}^{(2)}=0^\circ$ or 180°) orientation). It should also be noted that, for the like-charged groups, the quadrupole-quadrupole term is at a minimum for the head-to-side and side-to-head orientations which explains why the side chains in the Arg...Arg pairs are usually perpendicular to each other²⁷ (see the Appendix for discussion).

The results of fitting the PMFs, using the analytical expressions given by eq 1 are also shown in Figure 2 (solid lines). We present the fitted parameters of the expressions of the PMF components for E_{GBerne} (eq 2 of ref 18), E_{pol}^{GB} (eq 11 of ref 18), E_{pol} (eq 13 of ref 18),

ΔF_{cav}^{iso} (eq 14 of ref 18), ΔF_{cav} (eq 16 of ref 18), E_{LJ} (eq 19 of ref 18), and E_{qd} (eq 2 derived and introduced in this work), in Table 2 together with the distances of the interacting sites from the respective side-chain centers shown in Figure 1 (which occur implicitly in these equations because they are needed to compute the site-site distances): $d_i^{(1,1)}$ and $d_i^{(1,2)}$ (the distances of the center of headgroup of side chain i from its center in the first and in the second possible state for that side chain), $d_i^{(2)}$ (the distance of the nonpolar center of side chain i from side-chain center), $d_j^{(1,1)}$ and $d_j^{(1,2)}$ (as above for side chain j), and $d_j^{(2)}$ (as above, for side chain j). The values of ϵ_{ij} in eq 4 was fixed at 0.01 kcal/mol; varying this parameter did not result in remarkable improvement of the fit of the approximate expressions to the simulated PMFs, while worsening the convergence of the fitting procedure. For the same reason, we did not include the anisotropy of the well-depth of the Gay-Berne term of the interactions between the nonpolar parts of the side chains (eq 3–5 of the accompanying paper¹⁸).

Conclusions

We implemented the two-site coarse-grained model of charged amino-acid side chains, proposed in the accompanying paper,¹⁸ which consists of a charged head and a nonpolar tail positioned on the C $^{\alpha}$...SC axis to develop effective energy functions for the interactions between oppositely-charged side chains. In contrast to like-charged pairs discussed in the accompanying paper,¹⁸ it was necessary to introduce multiple states of a charged headgroup corresponding to its varying position with respect to the center of the side chain, which results in the expression of the interactions between the charged groups as a potential of mean force accruing from multiple microstates. In this work, we introduced four microstates corresponding to two possible distances between the charged headgroups and the centers of the nonpolar (spheroidal) sites. Only with this modification was the analytical expression able to reproduce both the side-to-side and head-to-head minima, the latter corresponding to salt-bridge formation. Compared to pairs of like-charged side-chains it was necessary to introduce a quadrupole-quadrupole interaction term for all four pairs to distinguish the side-to-side, side-to-head, and head-to-head orientations. The introduction of quadrupole-quadrupole interactions is reasonable in view of evidently non-spherical charge distributions of the guanidine and carboxylate head groups. The introduction of the quadrupole term also improves the fit of the approximate analytical expressions to the PMFs of like-charged side chain pairs; however, this improvement is only minor and we did not think it worthwhile to apply the extended expression to such pairs.

The ability to reproduce salt-bridge minima is the most remarkable feature of the new energy function. The salt bridges do not occur very frequently but their formation can be a critical factor determining protein-structure stability or the early stages of proteins folding (as demonstrated, e.g., in our recent work²⁸ on the folding of the C-terminal β -hairpin of immunoglobulin binding protein). Consequently, the new potentials are likely to increase the performance of the UNRES force field. The increase of computational cost due to the multistate model will be negligible because there are only four possible pairs of oppositely-charged amino-acid side chains.

Acknowledgments

This work was supported by grants from the Polish Ministry of Science and Higher Education (N N204 152836), from the U.S. National Institutes of Health (GM-14312), and the U.S. National Science Foundation (MCB05-41633). This research was conducted by using the resources of (a) our 880-processor Beowulf cluster at the Baker Laboratory of Chemistry and Chemical Biology, Cornell University, (b) the National Science Foundation Terascale Computing System at the Pittsburgh Supercomputer Center, (c) our 45-processor Beowulf cluster at the

Faculty of Chemistry, University of Gdansk, (d) the Informatics Center of the Metropolitan Academic Network (IC MAN) in Gdansk, and (e) the Interdisciplinary Center of Mathematical and Computer Modeling (ICM) at the University of Warsaw.

Appendix

Average energy of quadrupole-quadrupole interactions

The energy of interactions of two point quadrupoles i and j with quadrupole-moment tensors $\mathbf{Q}_i$ and $\mathbf{Q}_j$, respectively, and described by the relative position vector $\mathbf{r}_{ij} = [x_{ij1}, x_{ij2}, x_{ij3}]^T$ [separated by the distance $r_{ij} = (x_{ij1}^2 + x_{ij2}^2 + x_{ij3}^2)^{1/2}$], is expressed by eq. (A1).²⁹

$$E_{ij}(\mathbf{r}_{ij}) = \frac{1}{3!} \mathbf{Q}_i : \nabla \nabla \varphi_j(\mathbf{r}_{ij}) = \frac{1}{6} \sum_{k=1}^3 \sum_{l=1}^3 Q_{ikl} \frac{\partial^2 \varphi_j(\mathbf{r}_{ij})}{\partial x_{ijk} \partial x_{ijl}} \quad (\text{A1})$$

with

$$\varphi_j(\mathbf{r}_{ij}) = \frac{1}{2!} \frac{\widehat{\mathbf{r}}_{ij}^T \mathbf{Q}_j \widehat{\mathbf{r}}_{ij}}{2r_{ij}^3} = \frac{1}{4r_{ij}^5} \sum_{k=1}^3 \sum_{l=1}^3 Q_{jkl} x_{ijk} x_{ijl} \quad (\text{A2})$$

$$\widehat{\mathbf{r}}_{ij} = \frac{1}{r_{ij}} \mathbf{r}_{ij} \quad (\text{A3})$$

where $E_{ij}(\mathbf{r}_{ij})$ is the energy of quadrupole-quadrupole interaction, $\varphi_j(\mathbf{r}_{ij})$ denotes the electrostatic potential of quadrupole j and $\widehat{\mathbf{r}}_{ij}$ denotes the unit vector of the position vector $\mathbf{r}_{ij}$.

We assume that the quadrupole-moment tensor can rotate freely about the C ^{α} ...SC axes, the angles of rotation being ψ_i and ψ_j (for clarity, in Figure A1 we show the rotation of the quadrupole for only one side chain and, consequently, only ψ_i ; ψ_j can be visualized likewise). These angles are clearly independent of each other (Figure A1). These are the variables averaged over when deriving the approximate contribution to the UNRES energy function arising from the interactions of the head groups of charged residues with spatially-distributed charges (Arg, Glu, and Asp). As in our previous work,⁶ we take the first non-vanishing central moment of the quadrupole-quadrupole interaction contribution to that energy, which is the first moment (average quadrupole-quadrupole interaction energy) in this case. To obtain the average energy, we first note that, because ψ_i and ψ_j are independent variables, the average energy can be expressed in terms of the quadrupole-moment tensors averaged over ψ_i and ψ_j , respectively:

$$\langle E_{ij} \rangle_{\psi_i \psi_j} = \left\langle \frac{1}{24} \mathbf{Q}_i(\psi_i) : \nabla \nabla \frac{\widehat{\mathbf{r}}_{ij}^T \mathbf{Q}_j(\psi_j) \widehat{\mathbf{r}}_{ij}}{r_{ij}^3} \right\rangle_{\psi_i \psi_j} = \frac{1}{24} \langle \mathbf{Q}_i(\psi_i) \rangle_{\psi_i} : \nabla \nabla \frac{\widehat{\mathbf{r}}_{ij}^T \langle \mathbf{Q}_j(\psi_j) \rangle_{\psi_j} \widehat{\mathbf{r}}_{ij}}{r_{ij}^3} \quad (\text{A4})$$

where $\langle \dots \rangle_y$ denotes an average over variable y . The right-hand side of eq A4 is straightforward to derive if one notes that the components of the quadrupole-moment tensors are independent of $\mathbf{r}_{ij}$ and averaging over ψ_i is independent of that over ψ_j .

As in Figure A1, we align the axis of the first side chain with the x axis; the axis of the second side chain is expressed by the unit vector $\hat{\mathbf{u}}_{jx}$ and the remaining two axes of the reference system of side chain SC_j are expressed by unit vectors $\hat{\mathbf{u}}_{jy}$ and $\hat{\mathbf{u}}_{jz}$, respectively; these three vectors form an orthonormal right-handed reference system denoted by matrix $\mathbf{U}_j = (\hat{\mathbf{u}}_{jx}, \hat{\mathbf{u}}_{jy}, \hat{\mathbf{u}}_{jz})$; we also define the matrix $\mathbf{U}_i$ corresponding to the reference system of SC_i , which is a unit matrix when the settings are as in Figure A1. The quadrupole-moment tensors of side chains SC_i and SC_j are expressed by eq A5.

$$\mathbf{Q}_i(\psi_i) = \mathbf{R}(\psi_i) \mathbf{Q}_i(0) \mathbf{R}(\psi_i)^T, \mathbf{Q}_j(\psi_j) = \mathbf{U}_j \mathbf{R}(\psi_j) \mathbf{Q}_j(0) \mathbf{R}(\psi_j)^T \mathbf{U}_j^T \quad (\text{A5})$$

with

$$\mathbf{R}(\psi) = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \cos\psi & -\sin\psi \\ 0 & \sin\psi & \cos\psi \end{pmatrix} \quad (\text{A6})$$

The average quadrupole-moment tensors in the local coordinate systems of side chain SC_i and SC_j , respectively, are expressed by eq A7.

$$\begin{aligned} & \langle \mathbf{R}(\psi_i) \mathbf{Q}_i(0) \mathbf{R}(\psi_i)^T \rangle_{\psi m} \\ &= \begin{pmatrix} Q_{m11} & 0 & 0 \\ 0 & \frac{Q_{m22} + Q_{m33}}{2} & 0 \\ 0 & 0 & \frac{Q_{m22} + Q_{m33}}{2} \end{pmatrix} \\ &= Q_{m11} \begin{pmatrix} 1 & 0 & 0 \\ 0 & -\frac{1}{2} & 0 \\ 0 & 0 & -\frac{1}{2} \end{pmatrix} \\ &= Q_{m11} \left[\frac{3}{2} \begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} - \frac{1}{2} \mathbf{I}_{3 \times 3} \right], \quad m \in \{i, j\} \end{aligned} \quad (\text{A7})$$

because the quadrupole-moment tensor is traceless, $Q_{m11} + Q_{m22} + Q_{m33} = 0$; thus, only the quadrupole-moment components along the side-chain axes occur in the expression for the average quadrupole-quadrupole interaction energy (eq A5). Eq A7 provides the final expression of the average quadrupole-moment tensor of side chain SC_i , while that of side chain SC_j needs to be transformed by the matrix $\mathbf{U}$ to the global reference system and is expressed by eq A8.

$$\langle \mathbf{Q}_j(\psi_j) \rangle = Q_{j11} \left[\begin{pmatrix} \frac{3}{2} u_{jx1}^2 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} - \frac{1}{2} \hat{\mathbf{u}}_{jx} \hat{\mathbf{u}}_{jx}^T \right] \quad (\text{A8})$$

Inserting eqs A7 and A8 into the right-hand side of eq A4, we obtain eq A9, which is actually eq 2 of the main text.

$$\begin{aligned} \langle E_{ij} \rangle &= \frac{Q_{i11}Q_{j11}}{48r_{ij}^3} \left[3 \frac{\partial^2 \varphi_{ij}}{\partial x_{ij1}^2} - \widehat{\mathbf{u}}_{jx}^T \nabla \nabla \varphi_{ij} \widehat{\mathbf{u}}_{jx} \right] \\ &= \frac{Q_{i11}Q_{j11}}{1680r_{ij}^5} \left\{ 5 + 3 \left[(\widehat{\mathbf{u}}_{ix} \bullet \widehat{\mathbf{u}}_{jx})^2 - 1 \right] - \frac{75}{2} \left[(\widehat{\mathbf{u}}_{ix} \bullet \widehat{\mathbf{r}}_{ij})^2 + (\widehat{\mathbf{u}}_{jx} \bullet \widehat{\mathbf{r}}_{ij})^2 \right] + \frac{315}{2} (\widehat{\mathbf{u}}_{ix} \bullet \widehat{\mathbf{r}}_{ij})^2 (\widehat{\mathbf{u}}_{jx} \bullet \widehat{\mathbf{r}}_{ij})^2 - 45 (\widehat{\mathbf{u}}_{ix} \bullet \widehat{\mathbf{u}}_{jx}) (\widehat{\mathbf{u}}_{ix} \bullet \widehat{\mathbf{r}}_{ij}) (\widehat{\mathbf{u}}_{jx} \bullet \widehat{\mathbf{r}}_{ij}) \right\} \end{aligned}$$

(A9)

It should be noted that $\widehat{\mathbf{u}}_{ix} \bullet \widehat{\mathbf{u}}_{jx} = \cos \alpha_{ij}$, $\widehat{\mathbf{u}}_{ix} \bullet \widehat{\mathbf{u}}_{ij} = \cos \theta_{ij}^{(1)}$ and $\widehat{\mathbf{u}}_{jx} \bullet \widehat{\mathbf{u}}_{ij} = \cos \theta_{ij}^{(2)}$. Plots of the surface corresponding to eq A9 for the angle $\phi_{ij} = 0$ (Figure 1 in our accompanying paper¹¹), for the like- (e.g., Arg-Arg; $Q_{i11}Q_{j11} > 0$) and opposite-charge (e.g., Asp-Arg; $Q_{i11}Q_{j11} < 0$) pairs of side chains with spread charge distribution of the head group are shown in Figures A2a and A2b, respectively.

It should be noted that, for the opposite-charge pair, the global minimum corresponds to the head-to-head orientation ($\theta_{ij}^{(1)} = 0^\circ$ or 180° and $\theta_{ij}^{(2)} = 0^\circ$ or 180°), which enables the formation of strong hydrogen bonds between these groups; the side-to-side configuration ($\theta_{ij}^{(1)} = 90^\circ$ and $\theta_{ij}^{(2)} = 90^\circ$) in which hydrogen bonds can also be formed also is a minimum. The perpendicular configuration is the global maximum, which is understandable because, in this orientation, the side charges of the quadrupole along the SC direction face the like central charge of the quadrupole of the second side chain. As seen from the PMF of the Asp-Arg pair (Figure 2c), the relationship between the depths of the head-to-head, side-to-side and side-to-head configurations of the two side chains corresponds exactly to those of the plot in Figure A2b. For the like-charge pair/s, the perpendicular configuration is the global energy minimum, which corresponds to the relations between the depths of the minima in the plot of the PMF of the Arg-Arg pair (Figure 5e in accompanying paper¹⁸). However, introduction of the quadrupole-quadrupole term does not seem to be necessary to fit the PMFs of the Arg-Arg pair.¹⁸ It should be noted that the fact that the quadrupole-quadrupole energy is negative at the minimum for the like-charge side-chain pairs explains, in addition to the presence of water bridges between arginine head groups, the occurrence of close Arg-Arg contacts as found by Magalhaes et al.²⁷; from Figures 1 and 2 in ref. 20 and from the data analysis presented in that reference²⁷, it can be gathered that the Arg-Arg contacts occur in perpendicular arrangement.

Appendix

Figure A1.

A model of the quadrupole-moment tensor Q_i rotation about the $C^\alpha \dots SC$ axes, the angle of rotation being Ψ_i . Q_{i11} , Q_{i22} , Q_{i33} are the relative position of the quadrupole-moment tensors. Primes refer to the quadrupole-moment tensor positions after rotation about an angle Ψ_i .

Figure A2.

Plots of the energy surface corresponding to eq A9 for the angle $\phi_{ij} = 0$ (Figure 1 in our accompanying paper¹¹), for the (a) like- (e.g., Arg-Arg; $Q_{iII}Q_{jII} > 0$) and (b) opposite-charge (e.g., Asp-Arg; $Q_{iII}Q_{jII} < 0$) pairs of side chains with spread charge distribution of the head group.

References and Notes

1. Makowski M, Liwo A, Scheraga HA. J. Phys. Chem. B. 2007; 111:2910–2916. [PubMed: 17388416]
2. Makowski M, Liwo A, Maksimiak K, Makowska J, Scheraga HA. J. Phys. Chem. B. 2007; 111:2917–2924. [PubMed: 17388417]
3. Makowski M, Sobolewski E, Czaplewski C, Liwo A, Oldziej S, Scheraga HA. J. Phys. Chem. B. 2007; 111:2925–2931. [PubMed: 17388418]
4. Makowski M, Sobolewski E, Czaplewski C, Oldziej S, Liwo A, Scheraga HA. J. Phys. Chem. B. 2008; 112:11385–11395. [PubMed: 18700740]
5. Liwo A, Pincus MR, Wawak RJ, Rackovsky S, Scheraga HA. Prot. Sci. 1993; 2:1697.
6. Liwo A, Oldziej S, Pincus MR, Wawak RJ, Rackovsky S, Scheraga HA. J. Comput. Chem. 1997; 18:849.
7. Liwo A, Kaźmierkiewicz R, Czaplewski C, Groth M, Oldziej S, Wawak RJ, Rackovsky S, Pincus MR, Scheraga HA. J. Comput. Chem. 1998; 19:259.
8. Liwo A, Czaplewski C, Pillardy J, Scheraga HA. J. Chem. Phys. 2001; 115:2323.
9. Oldziej S, Kozłowska U, Liwo A, Scheraga HA. J. Phys. Chem. A. 2003; 107:8035.
10. Liwo A, Oldziej S, Czaplewski C, Kozłowska U, Scheraga HA. J. Phys. Chem. B. 2004; 108:9421.
11. Oldziej S, Łągiewka J, Liwo A, Czaplewski C, Chinchio M, Nancias M, Scheraga HA. J. Phys. Chem. B. 2004; 108:16950.
12. Kozłowska U, Liwo A, Scheraga HA. J. Phys.: Condens. Matter. 2007; 19:285203.

13. Liwo A, Khalili M, Czaplewski C, Kalinowski S, Ołdziej S, Wachucik K, Scheraga HA. *J. Phys. Chem. B.* 2007; 111:260. [PubMed: 17201450]
14. Shen H, Liwo A, Scheraga HA. *J. Phys. Chem. B.* 2009; 113:8738. [PubMed: 19480420]
15. Liwo, A.; Czaplewski, C.; Ołdziej, S.; Rojas, AV.; Kaźmierkiewicz, R.; Makowski, M.; Murarka, RK.; Scheraga, HA. Chapter 8. In: Voth, G., editor. *Coarse-Graining of Condensed Phase and Biomolecular Systems*. Taylor & Francis; 2008. p. 107-122.
16. He Y, Xiao Y, Liwo A, Scheraga HA. *J. Comput. Chem.* 2009; 30:2127. [PubMed: 19242966]
17. Kozłowska U, Maisuradze GG, Liwo A, Scheraga HA. *J. Comput. Chem.* 2010; 31:1143. [PubMed: 20073062]
18. Makowski M, Liwo A, Sobolewski E, Scheraga HA. *J. Phys. Chem. B.* 2010 accompanying paper.
19. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE. *Nucleic Acid Research.* 2000; 28:235.
20. Gay JG, Berne BJ. *J. Chem. Phys.* 1981; 74:3316.
21. Born M. *Z. Phys.* 1920; 1:45.
22. Still WC, Tempczyk A, Hawley RC, Hendrickson T. *J. Am. Chem. Soc.* 1990; 112:6127.
23. Hawkins GD, Cramer CJ, Truhlar DG. *J. Phys. Chem.* 1996; 100:19824.
24. Bashford D, Case DA. *Annu. Rev. Phys. Chem.* 2000; 51:129. [PubMed: 11031278]
25. Wojciechowski M, Lesyng B. *J. Phys. Chem. B.* 2004; 108:18368.
26. Némethy G, Steinberg IZ, Scheraga HA. *Biopolymers.* 1963; 1:43.
27. Magalhaes A, Maigret B, Hoflack J, Gomes JN, Scheraga HA. *J. Prot. Chem.* 1994; 13:195.
28. Lewandowska A, Ołdziej S, Liwo A, Scheraga HA. *Biophys. Chem.* 2010; 151:1. [PubMed: 20494507]
29. Podolsky, B.; Kunz, KS. *Fundamentals of Electrodynamics*. Marcel Dekker Inc.; New York: 1969. p. 58-66.

Figure 1.

Illustration of the new model for the interactions of charged and polar side chains. A side chain of this type is assumed to consist of the charged (shaded) and nonpolar (ellipsoidal) parts. The geometric centers of side chains i and j are denoted as SC_i and SC_j , respectively and represented by small black circles located between the centers of the charged and nonpolar sites. The charged site of each side chain can exist in two possible states; hence two shaded spheres are shown for each charged site. The spheres corresponding to alternative positions of the charged sites (farther away from the centers of side chain i and j , respectively) are bordered by dashed lines and are transparent to indicate that each of them corresponds to the alternative state of a single site and does not represent an additional site.

The vector $\hat{\mathbf{u}}_{ij}^{(1)}$ is the unit vector of the long axis of side chain i , $\hat{\mathbf{u}}_{ij}^{(2)}$ is the unit vector of the long axis of side chain j , $\hat{\mathbf{r}}_{ij}$ is the unit vector pointing from the geometrical center of the nonpolar site of side chain i to that of side chain j , r_{ij} is the distance between these two centers, r'_{ij} is the distance between the charged/polar centers of the head groups of side chains i and j , r''_{ji} and r''_{ji} are the distances between the charged centers of particle i and the center of particle j , and the charged center of particle j and the center of particle i , respectively (for clarity sake we show only the distances that involve the polar/charged center in the first possible state), $d_i^{(1,1)}$, $d_i^{(1,2)}$ and $d_j^{(1,1)}$, $d_j^{(1,2)}$ are the distances from the geometrical center of side chain i and j , respectively, to the center of the charge of head group i and j respectively, and $d_i^{(2)}$ and $d_j^{(2)}$ are the distances from the geometrical center of side chain i and j , respectively, to the nonpolar center of particles i and j respectively.

Figure 2.

The PMF curves for dimers of (a) propionate – n-pentylamine cation, (b) butyrate – n-pentylamine cation, (c) propionate - 1-butylguanidine cation, (d) butyrate - 1-butylguanidine cation. The dashed black, red, blue, and green lines correspond to PMFs determined for the side-to-side, head-to-head, head-to-side, and side-to-head, respectively (Figures 4a–d in our accompanying paper¹¹), obtained by MD simulations. The solid lines with the same color code correspond to the analytical approximation to the PMFs, with coefficients determined by least-squares fitting (eq. 21 in the accompanying paper¹¹) of the analytical expression to the PMF (eq. 1), determined by MD simulations.

Table 1

Box dimensions and number of water molecules in molecular dynamics simulations using the AMBER 9.0 force field for the systems studied in this work.

System ^a	box dimension [$\text{\AA}^3$]	number of water molecules
Pr p ⁻ ... Pna ⁺	40×40×40	2102
But ⁻ ... Pna ⁺	40×40×40	2065
Pr p ⁻ ... BtG ⁺	43×43×43	2628
But ⁻ ... BtG ⁺	43×43×43	2683

^a Abbreviations: Pr p⁻ - propionate; But⁻ - butyrate; Pna⁺ - n-pentylamine cation; BtG⁺ - 1-butylguanidine cation.

Table 2

Parameters of E_{GBerne} , E_{pol}^{GB} , E_{pol} , ΔF_{cav}^{iso} , ΔF_{cav} and E_{LJ} (eqs 2, 11, 13, 14, 16, and 19, respectively of the accompanying paper¹¹) and E_{qd} (eq 2 in this paper) determined by fitting of the analytical approximation to the PMF determined from MD simulations.

Parameter ^a	System ^b			
	Pr p ⁻ ... Pna ⁺	But ⁻ ... Pna ⁺	Pr p ⁻ ... BtG ⁺	But ⁻ ... BtG ⁺
ϵ_{ij}^0 [kcal/mol]	0.01 ^d	0.01 ^d	0.01 ^d	0.08 ^d
σ_{ij}^0 [Å]	5.14	5.49	3.52	4.17
σ_i^{iso} [Å]	4.00 ^d	4.00 ^d	4.00 ^d	4.00 ^d
σ_j^{iso} [Å]	5.28	3.35	8.29	7.79
$a_{ij}^{iso(1)}$ [kcal/mol]	0.04	0.03	0.999	0.15
$a_{ij}^{iso(2)}$ [kcal/mol]	0.04	0.03	0.999	0.15
$a_{ij}^{iso(3)}$ [kcal/mol]	0.04	0.03	0.999	0.15
$a_{ij}^{iso(4)c}$	14.63	15.05	34.01	16.38
a_i [Å]	2.00 ^d	2.00 ^d	2.00 ^d	3.34 ^d
a_j [Å]	3.66	3.43	3.72	2.51
$\chi_{ij}^{(1)c}$	0.071	-0.859	-0.924 ^d	-0.279
$\chi_{ij}^{(2)c}$	0.131	0.200	0.050	0.227
$\chi_{ij}'^{(1)c}$	0.00 ^d	0.00 ^d	0.00 ^d	0.00 ^d
$\chi_{ij}'^{(2)c}$	0.00 ^d	0.00 ^d	0.00 ^d	0.00 ^d
$\chi_{ij}''^{(1)c}$	0.198	0.009	0.052	0.431
$\chi_{ij}''^{(2)c}$	-0.998 ^d	0.230	0.657	-0.991 ^d
a_{ij}^{pol} [kcal/mol·Å ⁴]	1.99	1.80	1.62	1.55
a_{ji}^{pol} [kcal/mol·Å ⁴]	1.34	1.72	1.50	1.34
ϵ_{ij}' [kcal/mol]	0.01 ^d	0.01 ^d	0.01 ^d	0.01 ^d
σ_{ij}' [Å]	4.15	4.60	5.54	5.74
σ_i [Å]	3.15	3.73	3.22	3.29
σ_j [Å]	5.68	6.79	5.86	6.00
$a_{ij}^{(1)}$ [kcal/mol]	7.26	15.97	9.53	14.67

Parameter ^a	System ^b			
	Pr p ⁻ ... Pna ⁺	But ⁻ ... Pna ⁺	Pr p ⁻ ... BtG ⁺	But ⁻ ... BtG ⁺
$a_{ij}^{(2)}$ [kcal/mol]	0.19	-0.01	-0.16	-0.07
$a_{ij}^{(3)}$ [kcal/mol]	0.63	0.35	0.34	0.29
$a_{ij}^{(4)c}$	13.71	13.04	13.61	13.21
A_{ij} kcal/mol·Å ⁵	26.41	43.61	18.31	39.77
$d_i^{(1,1)}$ [Å]	1.24	1.30	0.14	0.50
$d_i^{(1,2)}$ [Å]	2.20	2.25	1.40	1.84
$d_i^{(2)}$ [Å]	0.26	1.13	0.53	0.83
$d_j^{(1,1)}$ [Å]	0.20 ^d	0.20 ^d	0.20 ^d	0.10 ^d
$d_j^{(1,2)}$ [Å]	1.93	2.25	2.35	2.27
$d_j^{(2)}$ [Å]	0.13 ^d	0.13 ^d	0.13 ^d	0.03 ^d
ϵ_{in}^c	8.92	5.99	2.32	2.28
ϵ_{out}^c	80.00 ^d	80.00 ^d	80.00 ^d	80.00 ^d
$w_{ij}^{(1)c}$	0.40	0.20	1.16	1.24
$w_{ij}^{(2)c}$	1.16	1.41	0.18	0.47
$w_{ij}^{(3)c}$	1.00 ^d	1.00 ^d	1.00 ^d	1.00 ^d

$a_{ij}^0, \sigma_{ij}^0, \chi_{ij}^{(1)}, \chi_{ij}^{(2)}, \chi_{ij}'^{(1)}$, and $\chi_{ij}'^{(2)}$ are the parameters of the Gay-Berne potential for the interaction between the nonpolar sites (eqs 2 – 9 of ref 11), ϵ_{ij} and σ_{ij} are the well depth and the diameter of the Lennard-Jones potential for the interaction between the charged sites (eq 19 of ref 11), $\sigma_i^{iso}, \sigma_j^{iso}, \alpha_{ij}^{iso(1)}, \alpha_{ij}^{iso(2)}, \alpha_{ij}^{iso(3)}$, and $\alpha_{ij}^{iso(4)}$ are the parameters for the cavity potential corresponding to the charged sites (eq 14 of ref 11) α_{ij}^{pol} and α_{ji}^{pol} are the constants in the expression for the polarization energy (eq 13 in ref 11), ϵ_{in} and ϵ_{out} are the dielectric constant of the interior of the interacting sites and of the environment, respectively (eq 11 of ref 11), a_i and a_j are the Born radii of the charged sites (eqs 11–12 in ref 11), $\sigma_i, \sigma_j, \alpha_{ij}^{(1)}, \alpha_{ij}^{(2)}, \alpha_{ij}^{(3)}$ and $\alpha_{ij}^{(4)}$ are the parameters of the cavity potential corresponding to the nonpolar sites (eq 16 of ref 11), A_{ij} is the constant in eq 2 for the quadrupole-quadrupole interaction term, $w_{ij}^{(1)}, w_{ij}^{(2)}, w_{ij}^{(3)}$ and $w_{ij}^{(4)}$ are the weights of the states of pairs of charged sites contributing to the partition function in eq 1, $d_i^{(1,1)}, d_i^{(1,2)}, d_j^{(1,1)}$, and $d_j^{(1,2)}$ are the distances of the centers of the charged sites from side-chain centers and $d_i^{(2)}$ and $d_j^{(2)}$ are the distances of the nonpolar sites from side-chain centers (Figure 1).

^b Abbreviations: Pr p⁻ - propionate; But⁻ - butyrate; Pna⁺ - n-pentylamine cation; BtG⁺ - 1-butylguanidine cation.

^c Dimensionless.

^d This value was fixed during minimization.