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Theoretical Studies of Interactions between O-Phosphorylated and Standard Amino-Acid Side-Chain Models in Water

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Abstract

Phosphorylation is a common post-translational modification of the amino-acid side chains (serine, tyrosine, and threonine) that contain hydroxyl groups. The transfer of the negatively charged phosphate group from an ATP molecule to such amino-acid side chains leads to changes in the local conformations of proteins and the pattern of interactions with other amino-acid side-chains. A convenient characteristic of the side chain–side chain interactions in the context of an aqueous environment is the potential of mean force (PMF) in water. A series of umbrella-sampling molecular dynamic (MD) simulations with the AMBER force field were carried out for pairs of O-phosphorylated serine (pSer), threonine (pThr), and tyrosine, (pTyr) with natural amino acids in a TIP3P water model as a solvent at 298 K. The weighted-histogram analysis method was used to calculate the four-dimensional potentials of mean force. The results demonstrate that the positions and depths of the contact minima and the positions and heights of the desolvation maxima, including their dependence on the relative orientation depend on the character of the interacting pairs. More distinct minima are observed for oppositely charged pairs such as, e.g., O-phosphorylated side-chains and positively charged ones, such as the side-chains of lysine and arginine.

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Notes

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Supporting Information

Table of box dimensions and number of water molecules in molecular dynamics simulations and figures showing partial atomic charges and PMF curves. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpcb.5b04782.

INTRODUCTION

Post- and cotranslational phosphorylation plays a key role in controlling and regulating intracellular processes. Phosphorylation of specific hydroxylated amino-acid side chains such as serine (Ser), threonine (Thr), and tyrosine (Tyr) by protein kinases can activate numerous enzymes; this effect can be reversed by the activation of protein phosphatases.¹ The activity of protein kinases and phosphatases is controlled by hormones, secondary messenger pathways and many more.² A range of classes of protein kinases occurs in living cells, which have the representative group of target enzymes. The primary sequences immediately surrounding phosphorylated particles of substrate play an important role in a substrate recognition.^{3–5} The kinases might recognize short specific amino-acid sequences with phosphate neighbors. Protein phosphorylation is one of the most widespread processes in living cells. More than one-third of proteins in eukaryotic organisms are the subject of this process. Protein phosphorylation is a key signaling mechanism in diverse cellular processes including metabolism, ion channel regulation, cell cycle progression, and controlling the activity of glycodegradation of enzymes.^{1,6–13} Intercellular signaling enables cells to coordinate their vital functions in response to signals that reach them. Most of the information about the environment received by a single cell has a chemical character. A signal transporter is a concentration of a particular chemical compound which acts as a signaling molecule.¹⁴ It is characteristic that the vast majority of well-known signaling molecules do not penetrate the cell. A strong enhancement of a signal is often a result of phosphorylation. For example, one molecule of activated kinase can in short time phosphorylate hundreds of target proteins which, when they are enzymes, convert a large amount of substrate.¹⁵ Moreover, protein phosphorylation regulates certain metabolic pathways, gene translation and transcription, membrane transport, hormonal response, cell division and cell growth, muscle contraction, light harvesting and photosynthesis, learning and memory.^{16–18} Knowledge of how phosphorylation alters the structure and function of proteins is still limited. The phosphate group by itself bears a -2 charge at physiological pH, which could perturb the local electrostatic potential in protein(s) and often induces local conformational changes that influence function¹¹ or modulate protein–protein interactions.¹

Hydrogen-bonding interactions are important in stabilizing protein structure. Phosphorylated residues can act as hydrogen-bond acceptors, owing to the presence of negatively charged oxygen atoms of the phosphate group. In particular, the phosphate groups can form salt bridges with the positively charged lysine or arginine side chains. The salt-bridge energy depends strongly on the identity, proximity, and orientation of the side chains involved in its formation and the surrounding environment.^{19–23} The contribution of a salt bridge to protein stability has been investigated experimentally^{19,20} and theoretically.^{21–27} A number of theoretical studies are concerned with the strength of the hydrogen bonds involving phosphorylated amino-acid side chains. In particular, Mandell and co-workers,²⁸ and Masunov and Lazaridis²⁹ used molecular dynamics simulations to estimate the free energies of salt bridges between all charged standard amino-acid side chains in the most convenient orientations.

Hydrogen-bond and salt-bridge formation between natural amino-acid side chains was investigated in our previous work.^{30–35} On the basis of molecular dynamics simulation data, the potential of mean force (PMF) surfaces were calculated and analyzed for like-charged and oppositely charged side chains. We showed that the most significant are the interactions between oppositely charged amino-acid side chains.^{36–38} The stabilizing electrostatic free energy of the salt bridges arises from the attraction between opposite charges. Because the charged side chains are flexible, two minima are observed for the head-to-head orientation, one corresponding to extended and one to more compact side-chain conformations, while only one minimum is observed for the side-to-side orientation, in which the distance between the two charged headgroups is not so sensitive to side-chain conformation.³⁸ However, the salt-bridge interactions are meaningful for both the head-to-head and side-to-side orientations. The negatively charged headgroup of Glu or Asp side-chains could make contact with positively charged groups of Lys or Arg and form salt bridges. In PMF plots, we observed two or more minima, which are wider and deeper than for head-to-side or side-to-head orientations. These minima correspond to the bridges, which are formed by the oxygen atoms from water, or the hydroxyl group of the other side-chain (where Glu and Asp are involved). Another type of bridge is mediated by two oxygen atoms of the carboxyl group, each of them being hydrogen-bonded to a guanidinium or ammonium groups of the protonated Arg or Lys models, respectively, and localized roughly in the plane associated with the counterion. These two oxygen atoms could belong to different groups or to the same group. Magalhaes et al.³⁹ showed that the addition of water molecules or counterions to the system progressively increases the stabilization energy of a dimer. They found that the bridging role of the water molecules or counterions is an important structural and energetic feature between interacting groups in a pair.

The studies of pairs of simple ions in water³⁶ showed complexity of their interactions. The presence of noncontact minima in the PMF curves could be explained by the local concentration of water molecules or counterions in the space between the interacting charged species. Additionally, the PMF minima become shallower or disappear for a number of pairs of ions. The authors³⁶ explained this situation by the creation of strong hydrogen-bonds with water molecules. The bridging of two ions by water molecule/counterion is less favorable than complete solvation of these ions. This effect could be

reflected in the interacting ions and have a significant influence on charged side chains in water.

The potential of mean force is one of the free-energy properties with which to calculate the physicochemical properties of systems studied. The calculated potentials of mean force can subsequently be used to compute measurable physicochemical characteristics of the systems studied such as, e.g., association constants^{25,26} and, consequently, validate the use of the force field of choice. PMF calculations are also suitable when the direct experiment is inapplicable (for example to study hydrophobic association) or to lower the cost of experiment.⁴⁰

In this work, we determined the PMF of pairs of compounds modeling phosphorylated and natural amino-acid residues to analyze the interactions between phosphorylated amino-acid side-chains and natural amino-acid side chains, including those that are involved in hydrogen-bond and salt-bridge formations with the phosphate groups (lysine and arginine). The latter were divided into four groups based on the properties of the side chains: hydrophobic (Gly, Ala, Pro, Val, Leu, Ile, Phe, Met, Trp), polar (Ser, Thr, Cys, Asn, Gln, His, Tyr), charged (Asp, Glu, Lys, Arg), and phosphorylated (pSer, pThr, pTyr). The pSer, pThr, and pTyr hydrogen-bond acceptors tend to participate in a stable interaction. The phosphate group of the acceptors studied bear the -2 net charge, which prefers to participate in hydrogen-bond or salt bridge creation.

The PMFs were determined from explicit-solvent umbrella-sampling molecular dynamics simulations, with subsequent processing of the results with the weighted histogram analysis method (WHAM).^{41,42} These PMFs provide insight into the relative intrinsic strength of various types of interactions and help to address the behavior of phosphorylated and other side chains of amino acids.

METHODS

MD simulations were performed with the AMBER 9.0 force field.⁴³ The phosphorylated and regular amino-acid side chains were modeled by the compounds collected in Table 1. All 66 pairs composed of each of the 3 phosphorylated amino-acid side chains and all amino-acid side chains considered in this work (20 regular and 3 phosphorylated) were treated.

Each of the pairs of molecules was placed in a periodic box containing TIP3P water molecules.⁴⁴ Box sizes and the number of water molecules in a respective box are collected in Table S1, Supporting Information.

Molecular dynamics simulations were carried out in two steps. First, each system was equilibrated for 100 ps in the *NPT* ensemble (constant number of particles, pressure and temperature) at 298 K and $p = 1$ atm. Production simulations were run in the *NVT* ensemble (constant number of particle, volume and temperature) at 298 K for 10 ns. The integration time step was 2 fs. A 10 Å distance was used as a cutoff for Lennard-Jones interactions. The particle-mesh Ewald summation⁴⁵ was used for estimating long-range effects of electrostatic

interactions. Consequently, the PMFs must tend to zero with increasing solute–solute distance.⁴⁰

To cover the distance range between amino-acid residues, the umbrella-sampling⁴⁶ method was used. For each system, a series of 10 windows of 10 ns simulations per window was run. The distance between the molecules was restrained with a biasing harmonic potentials defined by eq 1.

$$V(\xi)=k(\xi-d_0)^2 \quad (1)$$

where k is the force constant ($k = 2 \text{ kcal/mol/\AA}^2$), ξ is the distance between the centers of the side-chain models, and d_0 is the equilibrium distance equal to 3, 4, ..., 12 Å, for the respective simulation windows (10 windows total). Snapshots from MD simulations were saved after every 0.2 fs; as a result, 50 000 trajectory frames were written (i.e., every 100th frame was written) for each window at 298 K. To determine the potential of mean force (PMF) of the systems studied, the weighted histogram analysis method (WHAM)^{41,42} was used.

The charges on the atoms of the solute molecules needed for the AMBER 9.0 force field⁴³ were determined from the molecular electrostatic potentials calculated with Hartree–Fock and the 6-31G* basis set. The program GAMESS⁴⁷ was used to carry out quantum mechanical calculations. The partial charges were obtained by fitting to the molecular-electrostatic potentials, computed as described above, by using the program RESP⁴⁸ of the AMBER 9.0⁴³ package. The structures used as models of regular and phosphorylated amino-acid side chains are shown in Figure S1. The charges and atom force-field types used in MD simulations are presented in the same Figure S1 in electron charges units.

The PMFs are defined by eq 2.

$$W(r;\theta^{(1)};\theta^{(2)};\phi;T)=-RT\ln g(r;\theta^{(1)};\theta^{(2)};\phi;T) \quad (2)$$

where $W(r; \theta^{(1)}, \theta^{(2)}, \phi; T)$ is the PMF at distance r , which is defined here as a distance between the geometric centers of the interacting particles, and absolute temperature T , $g(r; \theta^{(1)}, \theta^{(2)}, \phi; T)$ is the pair correlation function (determined from MD simulations) at distance r and absolute temperature T , R is the universal gas constant and T is the absolute temperature (equal to 298 K in this work). Because the method used to calculate the PMFs cannot provide the absolute value of a PMF, the region over 12 Å was used as baseline to superimpose the PMFs calculated by WHAM.

The resulting PMFs depend on the distance between side-chain geometric centers and their relative orientations (four variables altogether). As observed in earlier studies,^{29,36–38} the PMFs are plotted as functions of the distance for selected orientations. Four-dimensional

histograms of r_{ij} , $\theta_{ij}^{(1)}$, $\theta_{ij}^{(2)}$, and ϕ_{ij} (Figure 1) were constructed. The ranges and bin sizes were 3 Å r_{ij} 12 Å with bin side length $r = 0.2$ Å, with angles 0° $\theta^{(1)}$ 180° with bin side length $\theta^{(1)} = 60^\circ$, 0° $\theta^{(2)}$ 180° with bin side length $\theta^{(2)} = 60^\circ$, and -180° ϕ

180° with bin side length $\varphi = 60^\circ$. Consequently, each distance corresponded to 54 bins, each containing counts from different orientations of the molecules.

In Figure 2a–d, a scheme for four selected orientations: “side-to-side” (parallel), “head-to-head” (linear), “tail-to-tail” (linear), and “side-to-head” (perpendicular) for which the distance dependence of the PMF is discussed in the next section is shown.

Figure 3 shows the dependence of the PMF of pSer-Ala on the total simulation time. The convergence is achieved simultaneously with increasing number of steps during MD simulations. The convergence of the PMF as a function of distance between the geometric center of each particles in a pair, took place after 4 ns of simulation time for the O-phosphorylated serine and alanine pair. All pairs show the same tendency. We concluded, that the 10 ns simulation time is sufficient to obtain proper statistical results.

RESULTS AND DISCUSSION

We determined the PMFs [$W(r; \theta^1, \theta^2, \varphi; T)$ of eq 2] for pairs of amino-acid side-chain models in water, calculated with MD simulations performed in the NVT scheme at 298 K. Because the side-chain–side-chain interaction potentials of mean force depend on distance and orientation, we analyzed the PMFs for four selected orientations, namely, side-to-side (a), head-to-head (b), tail-to-tail (c), and side-to-head (d), defined in Figure 2. The PMF curves (plotted as functions of the distance between side-chain centers for the four selected orientations) for 60 six pairs of molecules are shown in Figures 4a–c (pairs of O-phosphorylated and positively charged side-chains of amino-acids), 5a–c (pairs of O-phosphorylated and negatively charged side-chains of amino-acids), 6a–f (pairs of O-phosphorylated and O-phosphorylated side-chains of amino-acids), 7a–c (pairs of O-phosphorylated and polar side-chains of amino-acids), and 8a–c (pairs of O-phosphorylated and hydrophobic side-chains of amino-acids), as well as Figures S2–S5 in the Supporting Information. The black, green, red, and blue lines correspond to the PMFs determined for the side-to-side, head-to-head, tail-to-tail, and side-to-head, respectively. The definitions of those four orientations are indicated below each plot.

The positions and depths of the contact minima and the positions and heights of the desolvation maxima, including their mutual orientation depend on the character of the interacting pairs. More distinct minima are observed for oppositely charged pairs, such as O-phosphorylated side-chains, and positively charged ones (lysine and arginine Figures 4a–c, and Figures S2a–c, respectively). The same effect was observed in our previous work.³⁸

O-Phosphorylated and Charged or O-Phosphorylated Amino-Acid Side Chain Models

The PMF curves for oppositely charged and like-charged amino-acid side chain models are shown in Figures 4a–c and 5a–c and in Figures S2a–c and S3a–c of the Supporting Information, respectively, while those corresponding to pairs of O-phosphorylated side chains are shown in Figure 6a–f. It can be seen from Figures 4–6 that the contact minima in the side-to-side and side-to-head orientations are wider and deeper for the pairs of larger oppositely charged molecules (Figures 4 and S2, respectively) than for those for pairs of negatively charged molecules (Figures 5, 6, and S3, respectively).

For pairs of positively charged and O-phosphorylated amino-acid side chains, the PMF curves exhibit deep minima except for the tail-to-tail orientation (Figures 4 and S2). The basins of minima are narrower for the side-to-side orientations, while the basins are wider or exhibit multiple minima (for the pThr-Arg pair, Figure S2b) for the head-to-head and head-to-side orientation, i.e., in which the positively charged side chains are oriented headwards toward the O-phosphorylated side chain. Clearly, this feature arises because both the Arg and the Lys side chains have long and flexible hydrocarbon sections, which results in multiple conformational states. The resulting widening of the minimum basin or appearance of multiple minima were also observed in our earlier work on pairs of oppositely charged side chains.³⁸ Because the Lys and Arg side chains are prolate, the minima for the head-to-head and head-to-side orientation occur at larger distances compared to those for the side-to-side orientation. For all three orientations mentioned above, the minima are of contact type and correspond to the formation of salt bridges between the phosphate groups and the positively charged groups of the side chains.

The PMFs of positively charged and O-phosphorylated amino-acid residues at the head-to-head orientation were determined by Mandell et al.²⁸ It can be observed that the PMF minima from their work are by 0.5 kcal/mol on average deeper compared to the depths of the head-to-head-orientation minima determined in our work. Because Mandell et al. also used umbrella sampling and WHAM to determine the PMFs (however, as opposed to our work, they fixed the orientation of the interacting particles), the differences in the PMF values probably result from the different force field used (OPLS in ref 28 compared to AMBER 9 used in our work). Similar differences between our values and the values of the PMFs at contact minima computed earlier by Luo et al.²² who used the CHARMM 22.0 force field and the generalized Born model of the solvent. Our values are closer to the experimental values of the free energies of association of phosphate anions with the guanidine cation being about -0.8 kcal/mol.⁴⁹

The PMFs for pairs of negatively charged and O-phosphorylated side chains and those for pairs of O-phosphorylated side chains exhibit similar features, because both groups contain pairs of negatively charged particles with headgroups that can act as proton acceptors. The deepest minima occur for the tail-to-tail orientation in most cases except for pSer-Asp, pTyr-Asp, pSer-pSer, and pSer-pThr (where other orientations exhibit deeper minima); those correspond to hydrophobic association of the nonpolar hydrocarbon sections of the interacting particles (Figures 5 and S3). However, minima are also observed for the side-to-side and side-to-head orientations (Figures 5 and S3). As observed in our earlier work on pairs of like-charged side chains,^{36,37} these minima arise because of the high concentration of water molecules and counterions at the interface of the two solute molecules and can, therefore, be considered solvent- or counterion-separated minima. These minima are deeper and more structured for the pairs composed of O-phosphorylated side chains because the phosphate group contains more oxygen atoms that can be bridged by water molecules or counterions than the carboxylate group (Figure 6).

O-Phosphorylated and Uncharged Amino-Acid Side Chain Models

The interactions between O-phosphorylated and polar amino-acid side-chains are shown in Figures 7a–c and S4a–r (Supporting Information). For the head-to-head orientation, the PMF has the highest value and either exhibits the shallowest minima or does not have minima. Depending on the O-phosphorylated and polar side chain (mostly on the extent of the nonpolar section), either the side-to-side or the tail-to-tail orientation corresponds to the deepest minimum, which demonstrates that hydrophobic association is an important component of the interactions. It can be seen, that the strongest interactions take place for pTyr-Ser (~ -1.5 kcal/mol) and pSer-His (~ -1.7 kcal/mol) for tail-to-tail orientation. In the remaining pairs of such type, the lowest energy values of the PMFs at hydrogen-bond distance have values about -1 kcal/mol and depend strongly on orientation. The deepest minima for the side-to-side, head-to-side and head-to-head orientations occur for pairs involving the histidine model, because it contains a proton-donor NH group.

The PMFs of the pairs composed of O-phosphorylated serine, threonine, tyrosine and nonpolar side-chains of amino-acids (alanine, proline, isoleucine/leucine, valine, phenylalanine, methionine, and tryptophan) are shown in Figures 8a–c and S4 (Supporting Information).

The interactions between two the nonpolar segments of the interacting particles are of hydrophobic-association nature.^{50–53} From the PMF plots (Figures 8 and S5), it can be seen that the interactions between pSer, pTyr, pThr, and hydrophobic amino-acid side chain models are much weaker than those involving charged and polar amino-acid side chains. The deepest minima are observed for the side-to-side and tail-to-tail orientations, suggesting that the interactions between the O-phosphorylated and nonpolar side chains are of hydrophobic nature.

CONCLUSIONS

In this work, we determined the potentials of mean force for 66 pairs composed of O-phosphorylated amino-acid side chains (pSer, pThr, and pTyr) and nonpolar, polar, and like-charged amino-acid side chain models, as functions of the distances between the interacting particles and their orientations.

The deepest minima in PMF plots are observed for pairs composed of positively charged amino-acid side chains and O-phosphorylated residues, which is understandable because the particles involved in interactions bear opposite charge (Figures 4 and S2). The electrostatic character of the interactions between the negatively charged phosphate group and the positively charged side chains of lysine or arginine is manifested in the presence of deep contact minima for the head-to-head, head-to-side, and side-to-side orientations, which correspond to the formation of salt bridges. For the head-to-head and head-to-side orientations, the minima are broad or multiple minima occur because the positively charged side chain, whose headgroup faces the phosphate group has multiple conformational states, which differ in the length of the linear hydrocarbon chain.

For pairs of like-charged or uncharged particles (negatively charged, O-phosphorylated, or uncharged side chains and O-phosphorylated side chains), the hydrophobic component of the net interaction becomes very important or even dominant; consequently, deep minima are observed for the tail-to-tail orientation (Figures 5–8, and S3–S5). Additionally, for the pairs of like-charged particles, the other orientation results in the appearance of solvent, or counterion-separated minima, as observed in earlier work on pairs of like-charged solute molecules in water (Figures 5, 6, and S3).^{29,36–38} These minima are more pronounced for pairs composed of O-phosphorylated amino-acid side chains (Figure 6), because their headgroups contain more oxygen atoms that can be bridged. The polar headgroups of polar amino-acid side chains can form hydrogen bonds with the phosphate groups, which results in greater depths of the PMF minima at the side-to-side, head-to-head, and head-to-side orientation than for pairs involving nonpolar amino-acid residues; this effect is especially remarkable for pairs involving histidine (Figure 7).

Finally, the coarse-grained model of the interactions of the O-phosphorylated amino-acid side chains with natural amino-acid side chains and the respective potentials developed in this work will be introduced into the UNRES force field,⁵⁴ which will enable us to simulate the proteins containing O-phosphorylated amino-acid residues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Definition of variables describing the location of two spheroidal particles (i and j) with respect to each other. The vector $\hat{u}_{ij}^{(1)}$ is the unit vector of the long axis of particle i , $\hat{u}_{ij}^{(2)}$ is the unit vector of the long axis of particle j , $\hat{r}_{ij}$ is the unit vector pointing from particle i to particle j , $\theta_{ij}^{(1)}$ and $\theta_{ij}^{(2)}$ are the angles between the vector $\hat{r}_{ij}$ and vectors $\hat{u}_{ij}^{(1)}$ and $\hat{u}_{ij}^{(2)}$, respectively, and ϕ_{ij} is the angle of counterclockwise rotation of the vector $\hat{u}_{ij}^{(2)}$ about the vector $\hat{r}_{ij}$ from the plane defined by the vector $\hat{u}_{ij}^{(1)}$ and vector $\hat{r}_{ij}$ when looking from the center of particle j toward the center of particle i .

Figure 2.

Illustration of the (a) side-to-side, (b) head-to-head, (c) tail-to-tail, and (d) side-to-head orientation of two interacting side-chain of amino-acids. The orientation variables (see

Figure 2 for definition) are $\theta_{ij}^{(1)}=90^\circ$, $\theta_{ij}^{(2)}=90^\circ$, and $\varphi_{ij}=0^\circ$ (a), $\theta_{ij}^{(1)}=90^\circ$, $\theta_{ij}^{(2)}=90^\circ$, and $\varphi_{ij}=0^\circ$ (a), $\theta_{ij}^{(1)}=0^\circ$, $\theta_{ij}^{(2)}=180^\circ$, and φ_{ij} undefined (b), $\theta_{ij}^{(1)}=180^\circ$, $\theta_{ij}^{(2)}=0^\circ$, and $\varphi_{ij}=0^\circ$ (c), and $\theta_{ij}^{(1)}=90^\circ$, $\theta_{ij}^{(2)}=180^\circ$, and φ_{ij} undefined (d). Filled circles at one of the ends of each particles refer to the charged or polar “head” of the particle.

Figure 3. PMF plots of O-phosphorylated serine and alanine pair at 298 K in water TIP3P model as solvent for an increasing MD simulation time. The lines denote the duration of a run in each window.

Figure 4. PMF curves for O-phosphorylated and oppositely charged side-chain of amino-acid models interactions of (a) pSer-Lys, (b) pThr-Lys, and (c) pTyr-Lys pairs. The black, green, red, and blue lines correspond to PMFs determined for the side-to-side (Figure 2a), head-to-head (Figure 2b), tail-to-tail (Figure 2c), and side-to-head (Figure 2d) orientation, respectively obtained by MD simulations at 298 K.

Figure 5.

PMF curves for O-phosphorylated and identical charged side-chain of amino-acid models interactions of (a) pSer-Asp, (b) pThr-Asp, (c) pTyr-Asp pairs. The black, green, red, and blue lines correspond to PMFs determined for the side-to-side (Figure 2a), head-to-head (Figure 2b), tail-to-tail (Figure 2c), and side-to-head (Figure 2d) orientation, respectively obtained by MD simulations at 298 K.

Figure 6.

PMF curves for O-phosphorylated and O-phosphorylated side-chain of amino-acid models interactions of (a) pSer–pSer, (b) pThr–pThr, (c) pTyr–pTyr, (d) pSer–pThr, (e) pSer–pTyr, and (f) pThr–pTyr pairs. The black, green, red, and blue lines correspond to PMFs determined for the side-to-side (Figure 2a), head-to-head (Figure 2b), tail-to-tail (Figure 2c), and side-to-head (Figure 2d) orientation, respectively obtained by MD simulations at 298 K.

Figure 7.

PMF curves for O-phosphorylated and polar side-chain of amino-acid models interactions of (a) pSer-His, (b) pThr-His, and (c) pTyr-His pairs. The black, green, red, and blue lines correspond to PMFs determined for the side-to-side (Figure 2a), head-to-head (Figure 2b), tail-to-tail (Figure 2c), and side-to-head (Figure 2d) orientation, respectively obtained by MD simulations at 298 K.

Figure 8.

PMF curves for O-phosphorylated and hydrophobic side-chain of amino-acid models interactions of (a) pSer-Leu/Ile, (b) pThr-Leu/Ile, and (c) pTyr-Leu/Ile pairs. The black, green, red, and blue lines correspond to PMFs determined for the side-to-side (Figure 2a), head-to-head (Figure 2b), tail-to-tail (Figure 2c), and side-to-head (Figure 2d) orientation, respectively obtained by MD simulations at 298 K.

Table 1

Solute Molecules Represented by Model Systems, Which Refer to the Corresponding Side-Chain Models of Amino-Acid Molecules Used in This Work

system	model	symbol
ethane	alanine	Ala
<i>n</i> -propane	proline	Pro
isobutane	valine	Val
isopentane	leucine/isoleucine	Leu/Ile
ethylbenzene	phenylalanine	Phe
methyl propyl sulfide	methionine	Met
indole	tryptophan	Trp
propionate anion	aspartic acid	Asp
butyrate anion	glutamic acid	Glu
<i>n</i> -pentylamine cation	lysine	Lys
1-butylguanidine cation	arginine	Arg
ethanol	serine	Ser
phenol	tyrosine	Tyr
2-propanol	threonine	Thr
5-ethylimidazole	histidine	His
ethyl sulfide	cysteine	Cys
ethanamide	asparagine	Asn
propanamide	glutamine	Gln
ethyl phosphate dianion	O-phosphorylated serine	pSer
isopropyl phosphate dianion	O-phosphorylated threonine	pThr
<i>p</i> -ethylphenyl phosphate dianion	O-phosphorylated tyrosine	pTyr