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Unexpectedly Enhanced Solubility of Aromatic Amino Acids and Peptides in an Aqueous Solution of Divalent Transition-Metal Cations

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We experimentally observed considerable solubility of tryptophan (Trp) in a $CuCl_2$ aqueous solution, which could reach 2–5 times the solubility of Trp in pure water. Theoretical studies show that the strong cation-π interaction between Cu^{2+} and the aromatic ring in Trp modifies the electronic distribution of the aromatic ring to enhance significantly the water affinity of Trp. Similar solubility enhancement has also been observed for other divalent transition-metal cations (e.g., Zn^{2+} and Ni^{2+}), another aromatic amino acid (phenylalanine), and three aromatic peptides (Trp-Phe, Phe-Phe, and Trp-Ala-Phe).

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Dispersion behavior of biomolecules in aqueous electrolyte solutions has fundamental importance in a large variety of physical, biological, and chemical processes [1–8], and understanding this behavior is a prerequisite for discovering the physical mechanism of their biological functions. For example, whether biomolecules are dispersed or aggregated can strongly affect their physiological functions [3–5], drug absorption and bioavailability [6], and the reaction efficiency of chemical catalysis [7,8]. The controlling biomolecule dispersion has thus attracted wide attention and it may open up many fascinating prospects in various applications such as the crystallization of proteins and nucleic acids [9,10], preparation of drugs [11,12], and synthesis of macromolecules [13,14].

As the simplest biomolecules and essential building blocks of many complex biomolecules, such as proteins, the dispersion and aggregation properties (i.e., solubility) of aromatic amino acids largely affect the solubility of the relative biomolecules in solution [15,16]. The aromatic amino acids usually have low solubility in water because aromatic rings are usually regarded as hydrophobic [17,18]. These aromatic rings are believed to provide the hydrophobic interaction, which is one of the important driving forces in the functions of proteins, such as protein folding, maintaining protein structure, protein-ligand interactions, and even drug activity of involving proteins [19–22].

In many conditions, including physiological and pathological surroundings, as well as contaminated water and soils, ions are rich. The concentration of copper ions reached about 400 μM in the amyloid plaques of Alzheimer's disease (AD) patients, which is near 30 times in the plasma copper concentration (about 14 μM) in healthy people [23,24]. The multivalent transition-metal ions, such as Cu^{2+}, Ni^{2+}, Cd^{2+}, and Co^{3+}, in the contaminated water and soils are usually several hundred times that in the natural water and soils, and can enter food chains (e.g., cadmium contaminated rice) easily via plant uptake [25,26]. Generally, in aqueous solution with low ion concentrations, the solubility of the biomolecules will slightly increase [27], but in aqueous solution with high ion concentrations, it will sharply decrease [28]. In particular, in solution with many multivalent transition-metal ions, such as Cu^{2+}, Pt^{2+}, Pd^{2+}, and Co^{3+}, the solubility of aromatic amino acids significantly decreases because most of them will form complex precipitates with these ions [29–32]. Moreover, many aromatic amino acids directly act as drugs [33,34], and their dispersion in water or aqueous solution itself is greatly important for the drug's bioavailability and absorption in the body.

In this Letter, we show considerably increased solubility of tryptophan (Trp) in a $CuCl_2$ aqueous solution observed experimentally, reaching 2–5 times that of Trp in pure

water. Based on first principles calculations, this unexpected experimental phenomenon is found to be attributed to the strong interaction between Cu^{2+} and the aromatic ring in Trp, referred to as the cation-π interaction, which has been further demonstrated by fluorescence and ultraviolet (UV) spectroscopy. This cation-π interaction modifies the electronic distribution of the aromatic ring in Trp, which gives rise to the remarkable enhancement of the water-aromatic ring interaction and thus significantly increases the water affinity of Trp. This unexpected experimental discovery is attributable to our new experimental design based on the above understanding that a high local concentration of Cu^{2+} at the surface of Trp is present. In contrast, in experiments using the conventional method [29,35], which involve a low local concentration of Cu^{2+} at the surface of Trp, the solubility of Trp in a $CuCl_2$ aqueous solution significantly decreased because most Trp will form complex precipitates with Cu^{2+}. We also show that the other divalent transition-metal cations (e.g., Zn^{2+} and Ni^{2+}), another aromatic amino acid phenylalanine (Phe), and three aromatic peptides (Trp-Phe, Phe-Phe, and Trp-Ala-Phe) have similar behaviors. Considering that the aromatic ring structure widely exists in biomolecules and its hydrophobic interaction provides an important driving force in biomolecule functions, these findings provide new insights in understanding many fundamental biological phenomena induced by metal ions.

To illustrate the impact of the water affinity of biomolecules with aromatic ring structures by divalent transition-metal cations due to cation-π interactions, using density functional theory (DFT) (PS11 in the Supplemental Material [36]), we computed the interaction energy between the aromatic ring structure in Trp with Cu^{2+} adsorption (referred to as the Cu^{2+}–Trp complex) and the nearest neighboring water [Fig. 1(a)], which is -10.9 kcal/mol (more computational results in PS1 of the Supplemental Material [36]). This energy is close to 2 times the hydrogen-bonding energy and is much stronger than the interaction energy (-1.6 kcal/mol) between the aromatic ring structure in Trp without Cu^{2+} adsorption and the nearest neighboring water. The distance between the oxygen atom in the water and the hydrogen atom in the aromatic ring structure in the Cu^{2+}–Trp complex is also computed, which is 2.0 Å. This value is much smaller than the corresponding value of 2.4 Å without Cu^{2+} adsorption. Molecular orbitals (PS2 in the Supplemental Material [36]) show a clear coupling of the lone pair of electrons of the oxygen atom in the water, delocalized π states of the aromatic ring structure in Trp, and the empty orbitals of Cu^{2+} (Fig. S2). All of these data show that the affinity of the indole ring structure in Trp for water would be greatly enhanced because of the cation-π interaction between Cu^{2+} and the aromatic ring structure in Trp.

To show how the strong Trp water affinity affects the behaviors of Trp, we performed an experiment on the

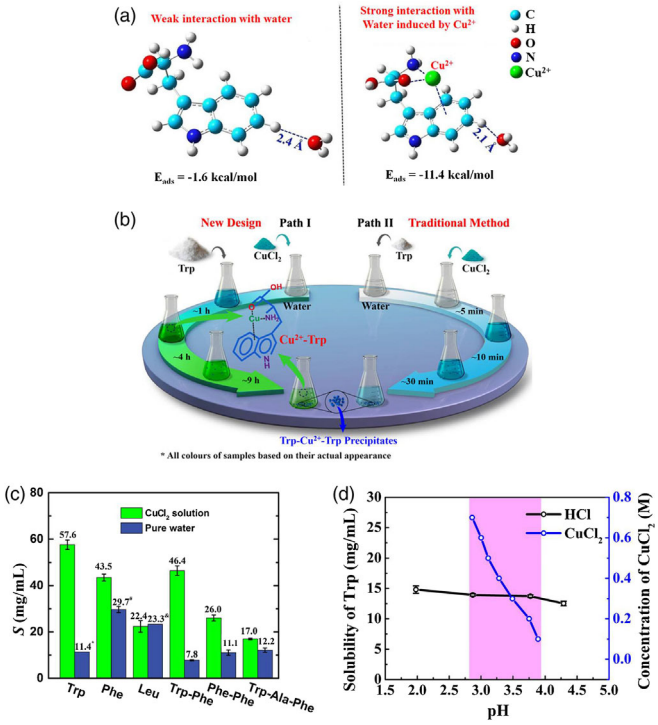

FIG. 1. (a) Optimized geometric structures and interaction energies ($\mathbf{E}_{ads}$) between water molecule and Trp with and without Cu^{2+} adsorption. (b) Schematic drawings of experimental observations. In path I, tryptophan is added into 0.5 mol/L (M) $CuCl_2$ solution. Only a small amount of blue precipitate is observed in 4 h, but a large amount of blue precipitate forms after ~9 h. In contrast, the $CuCl_2$ solid or solution is added into Trp aqueous solution in path II. After only ~10 min min, some blue precipitates are observed; after ~30 min, a large amount can be observed. (c) Solubility ($\boldsymbol{S}$) of Trp, phenylalanine (Phe), leucine (Leu), and three aromatic peptides (Trp-Phe, Phe-Phe, and Trp-Ala-Phe) in 0.5M $CuCl_2$ aqueous solution (green pillar) and pure water (royal blue pillar) at room temperature. (d) $\boldsymbol{S}_{\mathbf{Trp}}$ with pH (black line) and the pH (blue line, right blue axis) with a solution concentration of $CuCl_2$ at room temperature. The shaded part is the pH of the $CuCl_2$ solution used in our experiment. * data from Ref. [42], # data from Ref. [43], & data from Ref. [44].

solubility of Trp ($\boldsymbol{S}_{\mathbf{Trp}}$) in a $CuCl_2$ aqueous solution [path I in Fig. 1(b)]. As shown in Fig. 1(c), the $\boldsymbol{S}_{\mathbf{Trp}}$ is 57.6 ± 2.0 mg/mL in 0.5 mol/L (M) $CuCl_2$ aqueous solution, which is over 5 times that in pure water (11.4 mg/mL [42]). The significant enhanced solubility of Trp in Cu^{2+} aqueous solution is consistent with the theoretical prediction. Figure S3 shows that the $\boldsymbol{S}_{\mathbf{Trp}}$ increases monotonically with respect to the $CuCl_2$ concentration, which at high solution concentration can reach over 5 times that in pure water, and about 2 times even at low solution concentration. This increase can be well fitted by, $\boldsymbol{S}_{\mathbf{Trp}} = \boldsymbol{A}_{\mathbf{Cu}}\boldsymbol{C}_{\mathbf{Cu}} + \boldsymbol{S}^{0}{}_{\mathbf{Trp}}$, where $\boldsymbol{S}_{\mathbf{Trp}} \sim \boldsymbol{C}_{\mathbf{Cu}}$ ($\boldsymbol{A}_{\mathbf{Cu}}$, $\boldsymbol{C}_{\mathbf{Cu}}$, and $\boldsymbol{S}^{0}{}_{\mathbf{Trp}}$ are the water affinity factor (94.1) of Trp induced by Cu^{2+}, the Cu^{2+} concentration, and solubility of Trp in pure water, respectively, PS3 in the Supplemental Material [36]).

We note that conventional experiments [29,35] showed that most of Trp in solution would form blue precipitates with Cu^{2+} (PS4 in SM [36]), indicating that $\boldsymbol{S}_{\mathbf{Trp}}$ is very low in the solution with Cu^{2+} presence, different from our theoretical prediction and experimental observation. Careful examination shows that the main difference between them is the local molecular ratio of Trp to Cu^{2+}. The molecular ratio of Trp to Cu^{2+} in the Cu^{2+}–Trp complex [Fig. 1(a)] predicted in our theoretical calculation is 1:1, but this ratio was 2:1 in the blue precipitates (Trp–Cu^{2+}–Trp complexes) observed in experiments using the conventional method [29,35]. Thus, we speculate that the favorable structure (Cu^{2+}–Trp complex) for the high solubility of Trp including cation-π interaction, is mainly formed when the local concentration of Cu^{2+} at the surface of Trp is higher. In contrast, the blue precipitates (Trp–Cu^{2+}–Trp complex) would be mainly formed when the local concentration of Cu^{2+} at the surface of Trp is lower. These patterns indicate that we could observe a considerable enhancement of the $\boldsymbol{S}_{\mathbf{Trp}}$ when the local Cu^{2+} concentration at the surface of Trp is higher because the Cu^{2+}–Trp complex of $\boldsymbol{S}_{\mathbf{Trp}}$ enhancement is the main product at this condition. The experiments presented in this Letter are based on our new design, which relies on this understanding [path I in Fig. 1(b)]. In the experiment, we first divided the total Trp powder into many small shares and gradually put these small shares into an aqueous $CuCl_2$ solution to ensure that only a small amount of Trp was added to the solution each time. In this process, Trp molecules are gradually dissolved into the solution from the Trp powder (Fig. R2a). Generally, every dissolving Trp molecule will fall into the environment surrounded by many Cu^{2+} ions in a high solution concentration of Cu^{2+}, resulting in a high local Cu^{2+} concentration at the surface of Trp.

Experimentally, the Cu^{2+}–Trp complex can stably exist for a long time and at a large temperature range (PS5 in the Supplemental Material [36]). The infrared (IR) spectra, terahertz (THz) spectra, and soft x-ray absorption experiments show both precipitates from path I and the conventional method (path II) are consistent with the Trp–Cu^{2+}–Trp complexes in the early study (PS6 in the Supplemental Material [36]) [29].

The enhancement of $\boldsymbol{S}_{\mathbf{Trp}}$ in $CuCl_2$ solution does not come from the pH effect induced by hydrolysis of Cu^{2+} (PS7 in the Supplemental Material [36]). We note that the solution concentration of $CuCl_2$ from $0.1M$ to $0.6M$ used in our experiment is acidic (pH from 2.8 to 3.9) as reported previously [45]. Figure 1(e) shows that $\boldsymbol{S}_{\mathbf{Trp}}$ slightly decreases from pH 2.0 to 4.3 in the HCl aqueous solution, consistent with the early experiment [46]. This value is close to that of $\boldsymbol{S}_{\mathbf{Trp}}$ in pure water.

The self-diffusion behavior of the Trp water solution with and without Cu^{2+} has been determined using quasielastic neutron scattering (QENS) on the PELICAN instrument at Australian Nuclear Science and Technology Organization [47] (PS10 in the Supplemental Material [36]). To determine the Trp self-diffusion, D_2O and partially deuterated Trp (active H atoms replaced by D) have been used for two samples: $\mathrm{Trp}-D_2O$ (mol ratio of 1:100) and $\mathrm{Trp}-D_2O-CuCl_2$ (1:100:1). Because of the strong incoherent cross section of H, the H atoms in Trp dominate the QENS signal, thus to first approximation the QENS signal reflects the Trp dynamics. The measured QENS spectra were fitted with a Lorentzian function. The fitted values of half width at half maximum (HWHM) of the Lorentzian function as a function of Q^2 are shown in Fig. 2(a), where Q is the momentum transfer covering the range from 0.4 to 1.8 Å^{-1}. An estimate of self-diffusion coefficients are obtained by fitting the linear part of HWHM versus Q^2 with Fick's law [48]. The values are $(2.6 \pm 0.1) \times 10^{-5}$ cm^2/s and $(1.9 \pm 0.1) \times 10^{-5}$ cm^2/s for $\mathrm{Trp}-D_2O$ and $\mathrm{Trp}-D_2O-CuCl_2$, respectively. These values reflect the dynamics of the entire system; however, this will be dominated by Trp and as such the significant difference indicates that Trp in D_2O containing Cu^{2+} moves much more slowly as compared with that without Cu^{2+}. This observation supports our theoretical predication of the enhancement of water affinity of Trp due to the presence of Cu^{2+}.

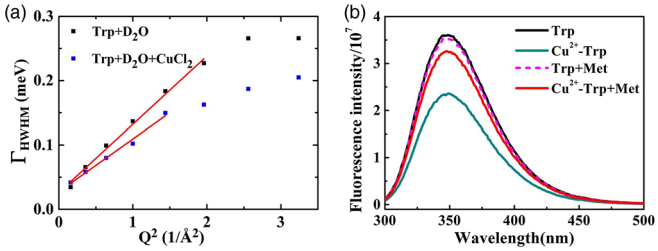

FIG. 2. (a) The half width at half maximum (HWHM) of the Lorentz function and the corresponding fitting curves (red lines) of Fick's law for $\mathrm{Trp} + D_2O$ (black squares) and $\mathrm{Trp} + D_2O + CuCl_2$ (blue squares) as a function of Q^2 (momentum transfer), respectively. (b) Fluorescence spectra of the Trp (40 μM, black solid line), methionine (Met, 200 μM, orange dashed line) and $CuCl_2$ (80 μM, green dashed line) in water solution and the mixed solution of Trp with $CuCl_2$ (royal blue solid line), Trp with Met (pink dash line) and Trp with $CuCl_2$ with Met (red solid line).

Fluorescence and UV absorption spectral experiments were performed to show evidence of the cation-π interactions between Cu^{2+} and the aromatic ring (indole) structure in Trp. The fluorescence spectrum of Trp excited at 279 nm has an emission peak at 349 nm, which is assigned to a conjugate double bond of the indole group that easily generated the $\pi - \pi*$ transition [49,50]. Compared with the fluorescence intensity of Trp in water, the intensity of Trp in the 80 μM $CuCl_2$ solution markedly decreased (Fig. 2), indicating that the conjugate double bonds of the indole group in Trp are greatly affected in the

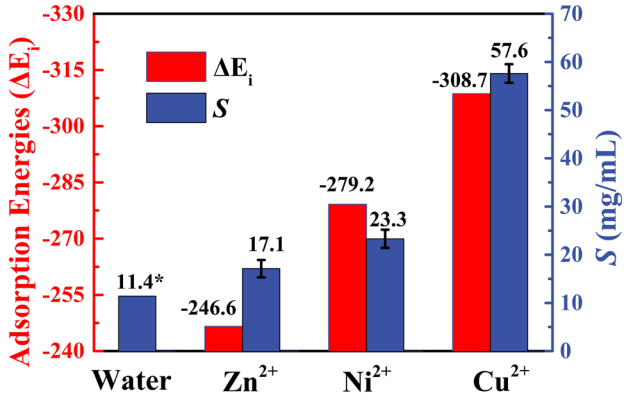

FIG. 3. Adsorption energies (ΔE_i, red rectangles) of different divalent transition-metal cations (i.e., Zn^{2+}, Ni^{2+}, and Cu^{2+}) with Trp, and water solubilities of Trp (S_{Trp}, royal blue rectangles) in 0.5M $ZnCl_2$, $NiCl_2$, and $CuCl_2$ aqueous solutions, respectively.

$CuCl_2$ solution, even under a physiological Cu^{2+} concentration [23]. Subsequently, we added methionine (Met), which can strongly bind Cu^{2+} by a Cu–S bond [51], to the mixed solution of Trp with $CuCl_2$. Figure 3 shows that the fluorescence intensity of Trp in $CuCl_2$ solution obviously recovered in the presence of Met. For comparison, as shown in Fig. 2, there is no fluorescence emission of Met and $CuCl_2$ in the same condition, and Met does not clearly affect the fluorescence intensity of Trp. These results demonstrate that the main effect of the fluorescence intensity of the conjugate double bonds of the indole group in Trp arises from Cu^{2+} in $CuCl_2$ solution.

Moreover, we observed that the UV absorption spectra of Trp was also affected by the cation-π interactions between the indole ring in Trp and Cu^{2+} in solution (PS8 in the Supplemental Material [36]), which is important evidence for the existence of cation-π interactions [52]. Altogether, fluorescence and UV absorption spectral experiments show the existence of cation-π interactions between the aromatic ring structure of Trp and Cu^{2+} in solution, which is consistent with the theoretical prediction.

Solubility of Phe with an aromatic ring structure (C_6H_5-), and leucine (Leu) without the aromatic ring structure was observed in 0.5M $CuCl_2$ aqueous solution at room temperature. Figure 1(c) shows that S_{Phe} was 43.5 ± 1.5 mg/mL in the solution, about 1.5 times the value in pure water (29.7 ± 1.3 mg/mL [43]). When the aromatic rings structure was replaced by a methyl (CH_3-) group, the S_{Leu} in the solution (22.4 ± 2.5 mg/mL) was close to that in pure water (23.3 mg/mL [44]). These results indicate that the main impact on the water solubility of amino acids in $CuCl_2$ solution is the aromatic ring structure, which is consistent with our theoretical prediction.

The aromatic peptides show similar behavior as aromatic amino acids in the $CuCl_2$ aqueous solution. We performed experiments on the solubilities of three peptides with aromatic amino acids, i.e., Trp-Phe, Phe-Phe, and Trp-Ala-Phe, in 0.5M $CuCl_2$ aqueous solution and pure water at room temperature. Their solubilities, $S_{Trp\text{-}Phe}$, $S_{Phe\text{-}Phe}$, and $S_{Trp\text{-}Ala\text{-}Phe}$ were 46.4, 26.0, and 17.0 mg/mL in the solution, about 5.9, 2.3, and 1.4 times the solubility of the corresponding aromatic peptides in pure water (7.8, 11.1, and 12.2 mg/mL), respectively [Fig. 1(c)].

Other divalent transition-metal cations show similar behavior to the Trp because of the strong cation-π interactions. We performed theoretical computations of the adsorption of other divalent transition-metal cations (i.e., Zn^{2+} and Ni^{2+}) on Trp (Fig. 3) and found that all of them have the strong interaction. S_{Trp} in 0.5M $ZnCl_2$ and $NiCl_2$ aqueous solution was also observed, respectively. Figure 3 shows that S_{Trp} clearly enhanced from Zn^{2+} to Ni^{2+} to Cu^{2+}, which is consistent with the change tendency of the adsorption energies between these cations and Trp. Even the smallest S_{Trp} in $ZnCl_2$ solution is still considerably higher than that in pure water. We note that the cation-π interactions between an alkali (Li^+, Na^+, and K^+) or alkaline-earth (Mg^{2+}) metal cation and benzene, indole, or phenol are only about 100 kcal/mol or less [47,48], significantly lower than the interaction (over 200 kcal/mol) of the divalent transition-metal cations with aromatic amino acids since there are stronger cation-π interactions and additional interactions between the carboxyl and amino groups in the side chains of these divalent transition-metal cations. Although recent theoretical [53,54] and gas phase experimental [54] studies have shown that the cation-π interactions of an alkali (Li^+, Na^+, and K^+) or alkaline-earth (Mg^{2+}) metal cation with benzene, indole, or phenol influence the hydrogen bonding of a water molecule with the benzene, indole, or phenol, the effect on the solubility of the benzene, indole, or phenol in the solution with the alkali (Li^+, Na^+ and K^+) or alkaline-earth (Mg^{2+}) metal cations might be much more difficult to be observed from experiment.

In summary, considering that divalent transition-metal cations are prevalent in many situations, we investigate the solubility of two aromatic amino acids (Trp and Phe) and three aromatic peptides (Trp-Phe, Phe-Phe, and Trp-Ala-Phe) in aqueous solutions of divalent transition-metal cations (e.g., Cu^{2+}, Ni^{2+}, and Zn^{2+}). In contrast to the conventional approach, a significant enhancement of the solubility has been experimentally observed. Particularly, in $CuCl_2$ solution, the solubility of Trp reaches 2–5 times that of Trp in pure water. Theoretical studies show that the key to this unexpectedly experimental phenomenon is the strong cation-π interaction between the cations and the aromatic ring in aromatic amino acids, which modifies the electronic distribution of the aromatic ring to enhance significantly the amino acid's water affinity. It should be pointed out that the important roles of cation-π interactions have been investigated in biological systems [52,55–57] in the hydrogen bonding of water molecules with the benzene,

indole, or phenol [53,54], and the enhancement of wetting and enrichment of ions on graphitic (e.g., graphite, graphene, and carbon nanotubes) surfaces have also been observed [58–61]. Here, we see for the first time that the cation-π interaction causes a strong interaction, short binding distance, and an effective molecular orbital coupling between the water molecule and aromatic ring structure in aromatic amino acids, like a hydrogen bond, which significantly enhances the water affinity of aromatic amino acids.

Aromatic ring structure widely exists in drug molecules, and even many aromatic amino acids directly act as drugs [33,34]. Their solubility in water or aqueous solution is of great importance for the drug's bioavailability and absorption in the body. Our finding provides a new insight to improve the solubility of these drugs. Along this direction, we have found that the solubility of theophylline, which includes aromatic ring structures and is a widely used drug, is clearly enhanced in $CuCl_2$ aqueous solution (PS9 in the Supplemental Material [36]).

It should be pointed out that this unexpected experimental discovery arises from our new design for the experimental process which is different from the conventional approach [29,35]. In the present experiment, we gradually added the aromatic amino acid powder to the divalent transition-metal cation (e.g., Cu^{2+}, Ni^{2+}, and Zn^{2+}) aqueous solution, producing a high local concentration of the cations at the Trp surface. In contrast, in the conventional experiment, the divalent transition-metal cation (e.g., Cu^{2+}, Ni^{2+}, and Zn^{2+}) aqueous solution is directly added to the Trp aqueous solution, resulting in a low local concentration of the cations at the Trp surface. This approach also provides a method for controlling two basic noncovalent interactions, i.e., complexing action and cation-π interaction in biology, and the related dispersion and aggregation behaviors of biomolecules by adjusting the local ion concentration of the aromatic amino acid surface.

As essential building blocks of many complex biomolecules, the water affinity of aromatic amino acids and peptides is crucial in the structure and functions of such biomolecules. Our findings enrich the view of biomolecular solubility in aqueous electrolyte solution and provide new insights for the understanding of physiological functions of multivalent metal ions and are expected to play important roles in the functions of proteins, such as protein folding, maintaining protein structure, and protein-ligand interactions.

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