Solvation of Anionic Water-Soluble Porphyrins: A Computational Study

TEOBALDO R. CUYA GUIZADO,[1] SONIA R. W. LOURO,[1] PEDRO G. PASCUTTI,[2] CELIA ANTENEODO[1,3]

[1]Departamento de Física, PUC-Rio, Rio de Janeiro, Brazil
[2]Laboratório de Modelagem e Dinâmica Molecular, Inst. de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil
[3]National Institute of Science and Technology for Complex Systems, Rio de Janeiro, Brazil

ABSTRACT: Explicit solvent molecular dynamics simulations of meso-tetra[4-sulfonatophenyl] porphyrin ($TPPS^{4-}$) in water were performed. The relation solute–solvent was examined through the radial distribution function $g(r)$ of water molecules around different groups of the solute. The outcomes of the simulations show that, despite the presence of charged side groups in the particular case of $TTPS^{4-}$, it displays a global hydrophobic character. Moreover, the hydropathic pattern of the different groups of the solute (central ring and side chains) is also characterized. Additionally, we show that this heterogeneous hydropathicity profile remains basically unaltered by complexing $TPPS^{4-}$ with Fe^{2+}.   © 2010 Wiley Periodicals, Inc. Int J Quantum Chem 110: 2094–2100, 2010

Key words: porphyrins; hydropathicity; molecular dynamics; radial distribution function

1. Introduction

Besides playing important roles for life, porphyrins and their compounds are of interest in biomaterials research. In particular, the meso-tetra[4-sulfonatophenyl] porphyrin ($TPPS^{4-}$)

and its Fe^{2+} complex ($Fe(II)TPPS^{4-}$), whose structures are depicted in Figure 1, are well known hydrosoluble porphyrins used in photodynamic therapy [1] and in molecular electronics devices [2]. There are also studies showing the possibility of employing the $Fe(II)TPPS^{4-}$ for oxygen storage and transport, hence as a potential candidate in artificial blood research [3].

As in any biophysical process, the hydrophobic effect is fundamental for most phenomena in which porphyrins are involved. The hydropathic properties of porphyrins are relevant in aggregation,
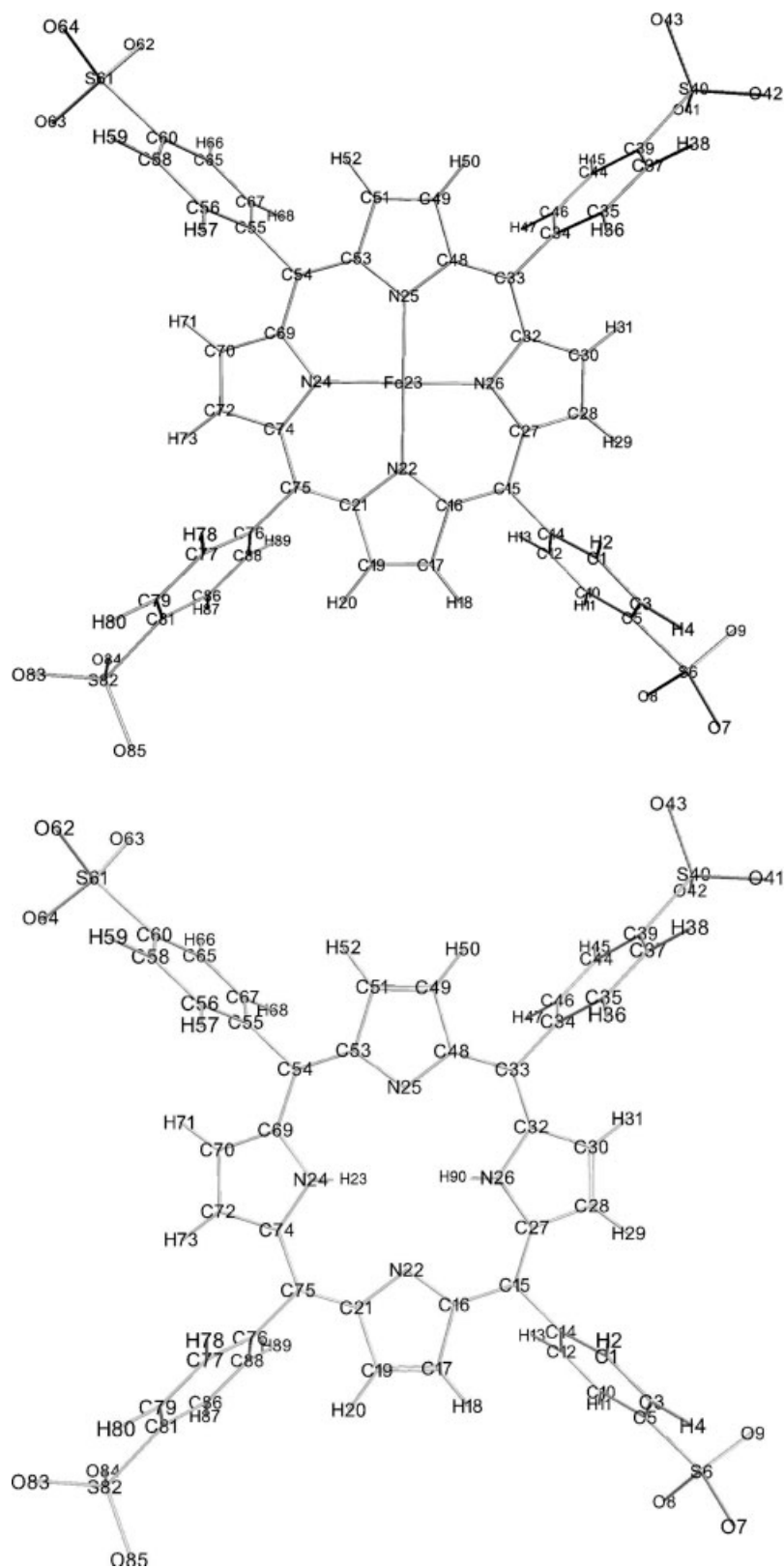
FIGURE 1. Representation of the TPPS^{4-} (lower panel) and Fe(II)TPPS^{4-} (upper panel) porphyrins, the numeric labels are the same used in Table I.

transport, interaction with biomembranes, and binding to receptors, and may guide the design of new synthetic porphyrins.

In previous computational work [4], the solvation properties of the protoporphyrin XI and its Fe^{2+} complex, the heme, were analyzed. The global hydrophobicity and local heterogeneous solute–water affinity were characterized in such case. It is our present goal to investigate, by means of molecular dynamics (MD) simulations, to which extent the side-chains in $TPPS^{4-}$, with excess negative charge, affect the solute-water interaction.

The solvation properties are discussed on the basis of the computation of the radial distribution function (RDF) $g(r)$. Regions of different affinity of the solute for water molecules are identified, furnishing the basic elements for understanding the behavior of porphyrins in an environment similar to the physiological one.

2. Methods

2.1. PORPHYRIN PARAMETERIZATION

Porphyrin geometry and charge distribution, used in MD simulations, were obtained by means of ab initio calculations. Parameterization of both $TPPS^{4-}$ and $Fe(II)TPPS^{4-}$ was performed using the PRODRG server [5] for the Gromos96 force field, with redefinition of groups and modification in charge distribution. The conformation of each porphyrin used as input for the PRODRG was obtained from a preliminary quantum mechanics (QM) calculation of geometry optimization. The level of the theory used in the QM calculations was DFT/B3LYP [6, 7] with pseudopotential SBJKC [8] and basis SBKJC. All the QM calculations were performed with the GAMESS program [9]. No solvent effects were considered at this stage.

The porphyrins under study have a total charge -4 (in electronic charge units) at pH 7, as the SO_3^- group in each side-chain contributes with charge -1. The charge distributions used for the parameterization of Coulombian interactions for each porphyrin are shown in Table I. It was obtained by means of the following steps: (i) a QM geometry optimization, to obtain the conformation corresponding to the energy minimum, (ii) a QM single point energy calculation (SPE), to obtain the electrostatic surface potential, using the last frame of step (i), and (iii) the restrained electrostatic potential (RESP) method [10] applied to the output of step (ii), to obtain the charge

distribution. This method was selected due to the presence of buried atoms (atoms in the porphyrin ring).

The N and H atoms in the central ring of the $TPPS^{4-}$ molecule have a total charge of -0.59. This profile changes when the $TPPS^{4-}$ is complexed with the ion Fe^{2+}. The total charge of the N and Fe in the $Fe(II)TPPS^{4-}$ is about -0.17, but the Fe maintains a positive charge of 0.517. Besides, its first neighbors (N22, N24, N25, and N26), the Fe has a local influence on the second neighbors (C16, C21, C48, and C53) too: they have an average charge of 0.19 in the $TPPS^{4-}$ but 0.038 in the complexed form. The effect of the Fe beyond first and second neighbors is not significant.

2.2. MOLECULAR DYNAMICS SIMULATIONS

Each porphyrin was solvated with about 1500 water molecules (SCP water model) [11] in a periodic dodecahedric box such that 1.0 nm is the minimal distance from the solute to the walls. The solution was electrostatically neutralized by the addition of four Na^+ counterions. Electrostatic interactions were treated using the particle mesh Ewald method, and the cut-off for both Coulombian and Van der Waals interactions was 1 nm. Systems were coupled to a thermal bath at 310 K with a coupling pressure of 1 bar. All the MD simulations were performed with the GROMACS 4.0 package [12]. The simulation step was 2 fs.

The preparation of the systems previous to MD simulations was made according to the same standard protocol previously used for protoporphyrin IX (PPIX) and heme [4]. For self-containedness, let us summarize the steps.

Systems were equilibrated with successive energy minimizations (EM): (i) EM with solute position restriction, using steepest descent method, (ii) EM without solute position restriction, using steepest descent method, and (iii) EM without solute position retriction, using LBFGS method [13].

Before collecting the useful MD data, two steps of MD were performed: (i) MD (500 ps) with porphyrin position restriction to avoid the overlapping of the Van der Waals radii of the water molecules and to allow orientation of hydration shells, (ii) MD (500 ps) for thermalization.

Finally, MD simulations (10 ns) were carried out to obtain the useful trajectories.

2.3. DATA ANALYSIS

The solvation properties were studied based on the computation and analysis of the RDF $g(r)$ of

TABLE I

Charge values (in electronic charge units) for each atom of TPPS^{4-} and Fe(II)TPPS^{4-}, obtained via RESP on B3LYP/SBJKC quantum calculations. Numeric labels identify each atom according to Figure 1.

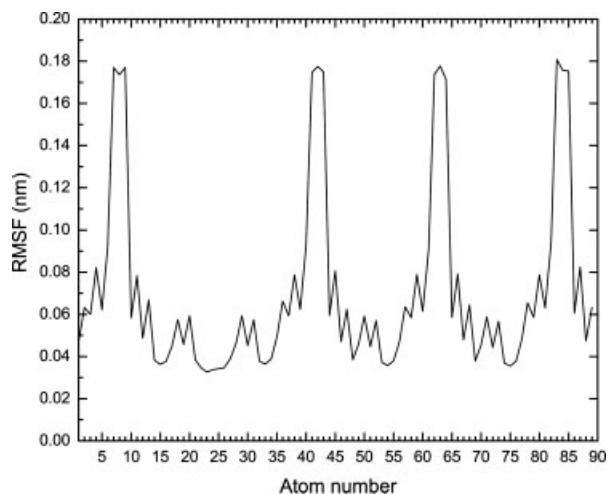|	TPPS				Fe(II)TPPS		
Atom	Charge	Atom	Charge	Atom	Charge	Atom	Charge
C 1	−0.153	C 46	−0.162	C 1	−0.157	C 46	−0.166
H 2	0.099	H 47	0.103	H 2	0.100	H 47	0.104
C 3	−0.048	C 48	0.211	C 3	−0.051	C 48	0.039
H 4	0.100	C 49	−0.204	H 4	0.101	C 49	−0.164
C 5	0.040	H 50	0.137	C 5	0.042	H 50	0.136
S 6	0.437	C 51	−0.204	S 6	0.443	C 51	−0.174
O 7	−0.490	H 52	0.140	O 7	−0.492	H 52	0.140
O 8	−0.492	C 53	0.163	O 8	−0.492	C 53	0.024
O 9	−0.490	C 54	−0.004	O 9	−0.493	C 54	−0.024
C 10	−0.066	C 55	0.046	C 10	−0.074	C 55	0.081
H 11	0.108	C 56	−0.168	H 11	0.110	C 56	−0.169
C 12	−0.145	H 57	0.107	C 12	−0.147	H 57	0.108
H 13	0.100	C 58	−0.046	H 13	0.099	C 58	−0.054
C 14	0.022	H 59	0.102	C 14	0.057	H 59	0.104
C 15	−0.040	C 60	0.035	C 15	−0.045	C 60	0.041
C 16	0.225	S 61	0.439	C 16	0.064	S 61	0.442
C 17	−0.213	O 62	−0.490	C 17	−0.172	O 62	−0.492
H 18	0.138	O 63	−0.490	H 18	0.136	O 63	−0.490
C 19	−0.197	O 64	−0.491	C 19	−0.168	O 64	−0.492
H 20	0.139	C 65	−0.062	H 20	0.139	C 65	−0.078
C 21	0.153	H 66	0.108	C 21	0.023	H 66	0.110
N 22	−0.374	C 67	−0.149	N 22	−0.149	C 67	−0.143
H 23	0.038	H 68	0.100	Fe 23	0.517	H 68	0.099
N 24	−0.073	C 69	0.038	N 24	−0.155	C 69	0.027
N 25	−0.371	C 70	−0.176	N 25	−0.127	C 70	−0.180
N 26	0.008	H 71	0.143	N 26	−0.262	H 71	0.130
C 27	0.052	C 72	−0.189	C 27	0.086	C 72	−0.187
C 28	−0.168	H 73	0.146	C 28	−0.155	H 73	0.132
H 29	0.146	C 74	0.042	H 29	0.123	C 74	0.028
C 30	−0.175	C 75	0.001	C 30	−0.163	C 75	−0.019
H 31	0.147	C 76	0.044	H 31	0.123	C 76	0.079
C 32	0.057	C 77	−0.157	C 32	0.095	C 77	−0.156
C 33	−0.037	H 78	0.106	C 33	−0.046	H 78	0.107
C 34	0.029	C 79	−0.071	C 34	0.065	C 79	−0.082
C 35	−0.148	H 80	0.109	C 35	−0.149	H 80	0.111
H 36	0.097	C 81	0.050	H 36	0.098	C 81	0.059
C 37	−0.057	S 82	0.453	C 37	−0.062	S 82	0.453
H 38	0.107	O 83	−0.496	H 38	0.107	O 83	−0.496
C 39	0.024	O 84	−0.495	C 39	0.028	O 84	−0.495
S 40	0.449	O 85	−0.494	S 40	0.449	O 85	−0.496
O 41	−0.493	C 86	−0.063	O 41	−0.493	C 86	−0.078
O 42	−0.495	H 87	0.106	O 42	−0.494	H 87	0.108
O 43	−0.491	C 88	−0.155	O 43	−0.493	C 88	−0.151
C 44	−0.042	H 89	0.102	C 44	−0.048	H 89	0.102
H 45	0.102	H 90	0.179	H 45	0.103		

FIGURE 2. RMSF of the Fe(II)TPPS^{4-}. Atom numbers correspond to the labels in Table I.

water molecules around given atoms or groups of atoms in the solute. The RDF $g(r)$ describes the density of surrounding particles as a function of the distance r from a given point, such that the number of particles in a spherical shell comprised between r_1 and r_2 is obtained by $\int_{r_1}^{r_2} 4\pi\rho r^2 g(r)dr$, where ρ is the density. The RDF reflects the correlations in the distribution of molecules. The evaluation of the RDF of water molecules (or atoms in water molecules) furnishes the location of the water coordination shells around a given point in the porphyrin, allowing us to assess the hydropathic pattern on each portion of the molecule, as well as on the porphyrin as a whole.

Moreover, the RDF allows to estimate thermodynamical quantities. In particular, the hydropathicity can be quantified through the potential of mean force defined as $W(r) = -kT \ln g(r)$, where k is the Boltzmann constant and T is the temperature. If $W(r) < 0$ (hence, $g(r) > 1$), the potential is attractive (hydrophilic behavior), otherwise ($g(r) < 1$), it is repulsive (hydrophobic behavior).

3. Results and Discussion

3.1. SIDE-CHAINS FLEXIBILITY

The flexibility of different parts of the porphyrins gives us information on how the molecule interacts with the medium. The root mean square fluctuation (RMSF) plot displayed in Figure 2 manifests the mobility of the side chains. This mobility is very similar for both porphyrins, for this reason, only the RMSF of the Fe(II)TPPS^{4-} is shown in

Figure 2. The four pronounced peaks correspond to each one of the four side chains, where the SO_3^- oxygens achieve the maximal fluctuations. Experimental results show that these side chains can exhibit strong intermolecular interactions with the central part of neighbor protonated porphyrin molecules neutralizing the positive charge and favoring the formation of J-aggregates [14].

3.2. RDF FOR TPPS^{4-} AND FE(II)TPPS^{4-}

The TPPS^{4-} and Fe(II)TPPS^{4-} are well known hydrosoluble porphyrins but $g(r)$ displays a hydrophobic profile (Fig. 3). Despite the strong anionic character with charge -4, the profile is very similar to that of the heme porphyrin [4], with charge -2. The hydrophobic character is responsible for porphyrin H-aggregation processes [15].

Four hydration shells are observed in Figure 3, the first one, at 0.18 nm, corresponds to one hydrogen bond with water and only one water molecule is present in this shell. The second solvation shell is formed at about 0.27 nm, with two water molecules. The third one, at about 0.40 nm, is occupied by eight water molecules and the forth shell, at about 0.71 nm, has 90 water molecules. In total, ~101 water molecules are present in the first four solvation shells.

The $g(r)$ profile indicates that hydrophilicity must reside in well localized regions, as we will see next.
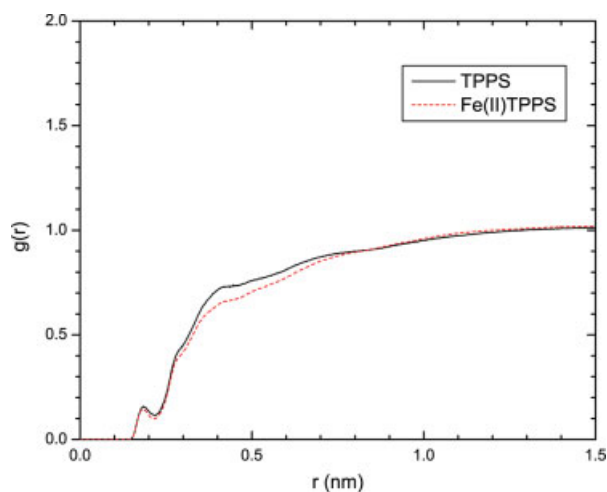

FIGURE 3. RDF of water molecules (center of mass) for TPPS^{4-} and Fe(II)TPPS^{4-}. The distance is relative to the center of mass of each solute. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
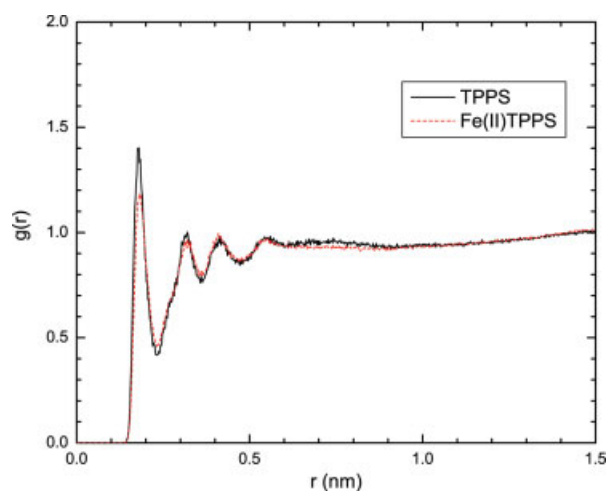
FIGURE 4. RDF of hydrogen atoms of water with respect to the SO_3^- groups in Fe(II)TPPS^{4-} and TPPS^{4-}. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

FIGURE 5. RDF of hydrogen atoms of water with respect to the oxygens of Fe(II)TPPS^{4-} and TPPS^{4-}. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

3.3. RDF FOR SO_3^-

It is in SO_3^- groups where the hydrophilic behaviors of the porphyrin reside, making it possible hydrosolubility. Four hydration shells are clearly formed (Fig. 4). The first shell corresponds to one hydrogen bound distance (0.18 nm). The following shells are localized at 0.31, 0.41, and 0.54 nm around each SO_3^- group. Despite, hydration shells are better defined than for the caboxyl groups of the PPIX and heme [4], the degree of local hydrophilicity is not larger, according to the height of the first peak (hydration shell).

The hydrophilic profile is ruled by the oxygen of the SO_3^- group, forming four hydration shells (Fig. 5), with a first peak more pronounced than for the SO_3^- group as a whole. Similarly, in heme porphyrins [4], hydrophilicity is concentrated on the oxygens of CO_2^- groups. The first peak is higher in the latter case because of the favorable ratio of water hydrogens per carboxyl oxygen.

As in the case of PPIX and heme, the presence of iron does not affect the $g(r)$ profile around the side groups.

3.4. RDF FOR FE

Well defined shells are observed around the locus of iron, although shielded by the hydrophobic ring, as shown in Figure 6. Notice that shells are displaced beyond 0.5 nm. Complexation with Fe$^+$ displaces
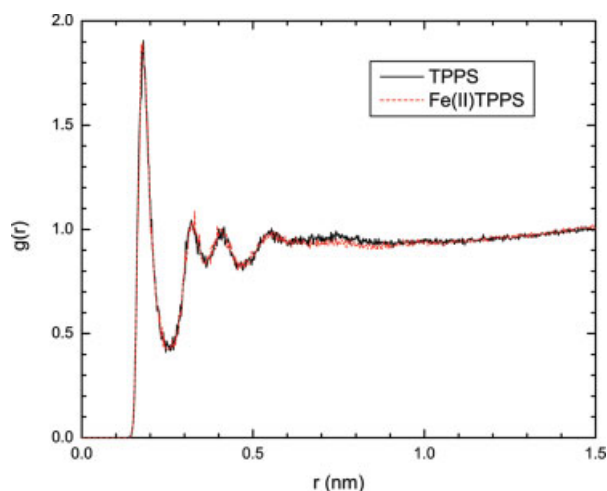
one water molecule, which is responsible for the first maximum, at 0.32 nm, in the $g(r)$ profile.

4. Conclusions

TPPS^{4-} and Fe(II)TPPS^{4-} are well known water-soluble porphyrins. We observe that they are completely solvated with ~100 water molecules.
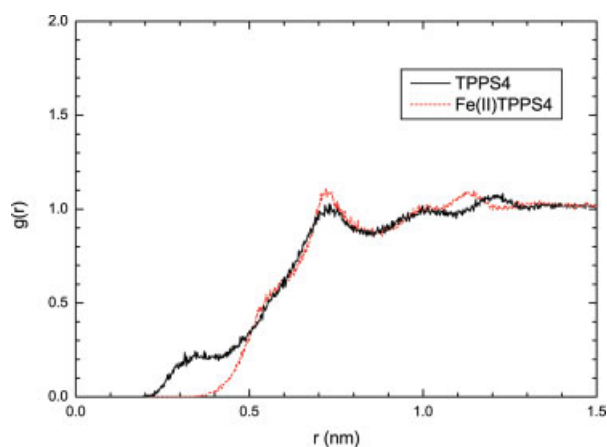

FIGURE 6. RDF of oxygen atoms of water with respect to the locus of iron. In the case of TPPS^{4-}, $g(r)$ was obtained with respect to a virtual point in the geometric center of the ring. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Based on the RDFs of water molecules around each group of atoms in the porphyrins, the non-homogeneous hydropathycity was characterized. The side chains, especially the oxygens of the SO_3^- groups, furnish the local hydrophilic character, while the hydrophobic nature resides in the central ring.

When TPPS^{4-} is complexed with the Fe^{2+}, the iron keeps a significant charge of 0.515, allowing electrostatic interaction with the environment. Although the charge distribution in the porphyrins is altered by complexation with the ion Fe^{2+}, the impact is significant up to second neighbors only. Then, the hydration profile is not noticeably affected by the iron, except by the displacement of one water molecule. In comparison with the PPIX and heme, the side chains of TPPS affect only locally the whole profile.

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