Short Report

Effect of Polyethyleneglycols (PEG) on Solubility of Co^{III} 5,10,15,20-Tetra(4-carboxyphenyl)porphyrin and Methylimidazolyl Axial Complex at 298.2 K: Experiment and Modeling

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The solubility of Co^{III} 5,10,15,20-tetra(4-carboxyphenyl)porphyrin and axial complex with methylimidazole in the mixtures of triethyleneglycol-water and tetraethyleneglycol-water was measured in the whole range of polyethyleneglycols (PEG) fractions at 298.2 K using the isothermal saturation method. The composition of the mixture at which the maximal solubility was observed has been revealed. The cosolvent force of PEGs was quantified according to the linear logarithmic model proposed by Yalkowsky applied in the ranges (cosolvent volume fraction, f): $0 \le f_{PEG} \le 0.24$ in triethyleneglycol-water and $0 \le f_{PEG} \le 0.3$ in tetraethyleneglycol-water mixtures. A mathematical approach based on the tenets of the molecular association theory and a simple lattice model (ASL = association solution + lattice) was used to estimate the solubility values of the investigated porphyrins in water-PEG solutions. The ASL model appeared to present a simple means of estimating the solubility of Co^{III} 5,10,15,20-tetra(4-carboxyphenyl)porphyrin and axial complex with methylimidazole in polyethyleneglycol-water mixtures using a single variable parameter.

Keywords: solubility, cosolvency, porphyrin, axial ligand

Introduction

Metalloporphyrins are long used as promising agents for photodynamic therapy of cancer.[1] Metalloporphyrins based extracoordinated compounds are useful for the creation of new materials and substrates for the targeted delivery to cellular systems applied in medicine.[2] Numerous information concerning the extracoordination equilibrium processes including such ones in which nitrogen-containing ligands participate have been accumulated by now.[3-5] At that, it have been noted that σ-donor and π-acceptor ligands of a similar electronic nature are superposed in the metalloporphyrin internal coordination sphere to the best advantage.[6]

N-Methylimidazole (MeIm) is an aromatic heterocyclic organic compound with two nitrogen atoms in the structure. Due to its electron-unsaturated nature MeIm reveals sufficiently high reactivity which allows using it as a primary product for pharmaceutical preparations. The inclusion of the methylimidazole fragment in the structure of an organic compound is an important guideline to designing the effective drugs.[7] Both in organic and aqueous media MeIm forms sufficiently stable axial complexes with different cobalt porphyrins by means of donor-acceptor interaction between the coordinatively unsaturated cobalt cation and electron-donating nitrogen atom of the methylimidazole molecule.[4,8] Solubility is a key parameter determining the bioavailability of the pharmaceutical substances. The solubility growth in the presence of the cosolvent might actually reduce the amount of the drug delivered and, thus, lack any undesirable effects of the cosolvent. At that, by disrupting water's self-association, the cosolvents reduce water's ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility.[9]

The solubility of the porphyrin metallocomplexes is determined by many factors, among which the porphyrin molecular structure and physicochemical and structural characteristics of the solvent are of a great importance.[10] The role of the latter factor appears to be of particular importance when the research is carried out in mixed solvents in order to increase the solubility. Fedulova *et al.*[11] showed that the porphyrins with polar groups are effectively incorporated into the micelles with the opposite charge at the expense of electrostatic interactions with the detergent molecules. Miyako *et al.*[12] have shown that adding an organic cosolvent to water makes the solvating environments less

polar, resulting in a more favorable mixing (solvation) of a hydrophobic solute in the liquid phase. Consequently, one of the parameters influencing the solubility is the cosolvent polarity, which can change the polarity of the hydrophobic solute and, as a result, the solubility.[13] As Vinodu and Padmanabhan[14] indicated, polyethyleneglycol (PEG) is a linear and flexible polymer with dipolar character. The geometry of the ether oxygen atoms arrangement plays an important role in the water-ethyleneglycol hydrogen bonds formation.[15] Namely, a special chain conformation is realized in aqueous PEG solution.[16-18] At that, in the solution PEGs were shown to disperse homogeneously the ionic metalloporphyrins and thus facilitate the solubility increase. Numerous information dealing with the solubility of drug compounds[9,19-23] as well as metalloporphyrins[24,25] in mixed solvents have been accumulated by now. However, we found no papers devoted to the experimental and theoretical study of the solubility of metalloporphyrins and their axial complexes in aqueous polyethyleneglycol solutions.

This study is a continuation of our investigations on the porphyrin solubility in mixed solvents by the experimental and calculation methods.[26]

The objective of this study is to measure the solubility of 5,10,15,20-tetra(4-carboxyphenyl)porphyrinate Co[III] and axial complex with *N*-methylimidazole in the mixtures of triethyleneglycol-water and tetraethyleneglycol-water in the whole range of compositions of the mixed solvent; to calculate the solubility of the investigated compounds by means of a simple ASL (associated solution + lattice) model and to assess the predictability of the applied model.

Experimental

Materials

Triethylene glycol 99% ($HO(CH_2CH_2O)_2CH_2CH_2OH$) formula weight 150.17, lot STBC0706V) Sigma-Aldrich (Germany). Tetraethylene glycol 99% ($HO(CH_2CH_2O)_3CH_2CH_2OH$) formula weight 194.23, lot MKBF7880V Aldrich (USA). 5,10,15,20-Tetrakis-(4-carboxyphenyl)porphyrin (molecular mass 790.77 g mol^{-1}, CAS registry No. 14609-54-2) was obtained from Sigma-Aldrich. 1-Methylimidazole 99% (molecular mass 82.10 g mol^{-1}, CAS registry No. 616-47-7) was obtained from Sigma-Aldrich.

Porphyrin preparation

Co[III] 5,10,15,20-Tetrakis-(4-carboxyphenyl)porphyrin was synthesized by the method described in detail elsewhere[27] and identified by UV-Vis spectra, IR (infrared

spectrometry), ^{1}H NMR (nuclear magnetic resonance), and elemental analysis (see Supplementary Information section). Briefly, Co[III] 5,10,15,20-tetrakis-(4-carboxyphenyl) porphyrin was prepared by refluxing 5,10,15,20-tetrakis-(4-carboxyphenyl)porphyrin (1 g) and anhydrous CoCl$_2$ (0.5 g) in dimethylformamide (200 mL) for up to 6 h. The refluxing solution was then evaporated to about 20 mL and cooled in an ice bath. CCl$_4$ (150 mL) was added to the remaining solution and the resulting precipitate filtered, washed with 2 mol L^{-1} HCl followed by CCl$_4$ and dried *in vacuo*. Yield: 64%.

The axial complex of Co[III] tetra(4-carboxyphenyl) porphyrin with *N*-methylimidazole was obtained by the described above procedure where methylimidazole is added in the dimethylformamide with other necessary components. Co[III] Tetra(4-carboxyphenyl)porphyrin complex with *N*-methylimidazole is a final product of spectrophotometric titration of Co[III] 5,10,15,20-tetrakis-(4-carboxyphenyl)porphyrin by methylimidazole (absorption spectra in the Soret region for the titration process is introduced in Figure S1 in the Supplementary Information section). Figure S1 indicates that at lower methylimidazole concentrations (0-2.2 × 10^{-6} mol L^{-1}) the formation of the axial complex with one methylimidazole molecule occurs, next, in the concentration interval (2.2 × 10^{-6}-2.6 × 10^{-5} mol L^{-1}) the axial complex with two methylimidazole molecules is formed.

Buffer preparation

The buffer solution pH 7.4 was prepared by mixing the solutions of the appropriate concentrations of sodium and potassium salts of phosphoric acid (Na$_2$HPO$_4$·12H$_2$O and KH$_2$PO$_4$), as described elsewhere.[28] All chemicals were of analytical grade. The pH values were measured by using Electroanalytical Analyser, Type OP-300, Radelkis (Hungary) standardized with pH 1.68, 6.86 and 9.22 solutions.

Solubility determinations

All the experiments were carried out by the isothermal saturation method at 298.2 ± 0.1 K. The binary solvent mixtures were prepared by mixing the appropriate volume of the solvents with the uncertainty of 0.5-1.5%. The solubility was determined by equilibrating an excess amount of porphyrin in the binary solvent mixtures in glass ampoules placed into an air thermostat with a temperature-control system with the uncertainty of ± 0.1 °C supplied by a stirring device. The point of the solution thermodynamic equilibrium was determined from the solubility kinetic

dependences and averaged 48 hours. After the saturation was achieved, the saturated mixtures were centrifuged at 13000 rpm for 20 min in a centrifuge Biofuge stratus (Germany) under the temperature control. The saturated solutions were diluted to obtain optical densities in the range from 0.15 to 0.9, and then assayed at the appropriate wavelength (Soret band) using spectrophotometer Cary-50 (USA). Concentrations of the diluted solutions were determined from the calibration curves. Each experimental datum is an average of at least three experimental measurements, and the mean relative standard deviation of three repetitive experiments is 2-4%.

Theory and calculations

ASL calculations

The calculation of the solubility of a poorly soluble substance S requires the determination of the activity coefficient at infinite dilution γ_S^∞. According to the ASL model the logarithm of the activity coefficient of a substance S in infinitely diluted solution $\ln \gamma_S^\infty$ is a sum of three contributions: chemical $(\ln \gamma_S^\infty)_{chem}$, combinatorial $(\ln \gamma_S^\infty)_{comb}$, and residual $(\ln \gamma_S^\infty)_{res}$.[29] The chemical contribution in $\ln \gamma_S^\infty$ value is determined by the association processes and in the general case is expressed by the equation 1:

$$\left(\ln \gamma_S^\infty\right)_{chem} = \ln\left(\frac{\varphi_{S_1}}{\varphi_S}\right)^\infty + \frac{r_S}{\bar{r}} - \frac{r_S}{\bar{r}\chi} \qquad (1)$$

where $\bar{r} = \sum_i r_i x_i$, r_i is the volume parameter of the molecules of the ith component in the solution ($i = A$ (the main solvent), B (cosolvent) and S), x_i is the molar fraction of the ith component in solution, $\varphi_S = r_S x_S/\bar{r}$ and $\varphi_{S_1} = r_S x_{S_1}/\bar{r}$ are the segment fractions of the solute S and of the monomers S_1 in solution, respectively, χ is the average association degree, which is calculated by solving a set of equations including the equations of material balance and the mass action law. The combinatorial contribution $(\ln \gamma_S^\infty)_{comb}$ is determined by the difference between the molecular sizes of the components. Guggenheim-Staverman approximation is the equation 2:

$$\left(\ln \gamma_S^\infty\right)_{comb} = \ln\left(\frac{r_S}{\bar{r}}\right) + 1 - \frac{r_S}{\bar{r}} - q_S \frac{z}{2}\left[\ln\left(\frac{r_S \bar{q}}{q_S \bar{r}}\right) + 1 - \frac{r_S \bar{q}}{q_S \bar{r}}\right] \quad (2)$$

where z is the coordination number of the lattice, $\bar{q} = \sum_i q_i x_i$, q_i, is the surface parameter of the molecules of the ith component in solution. The residual contribution $(\ln \gamma_S^\infty)_{res}$ is determined by the universal intermolecular interactions and can be calculated on the basis of a simple lattice model, equation 3:

$$\left(\ln \gamma_S^\infty\right)_{res} = \left(\frac{z}{RT}\right)\left[\theta_A q_S \omega_{AS} + \theta_B q_S \omega_{BS} - \theta_A \theta_B q_S \omega_{AB}\right] \quad (3)$$

where ω_{ij} is the interchange energy, $\theta_i = q_i x_i/\bar{q}$ is the surface fraction of the ith component in solution. In order to calculate the solubility x_S in ASL model it is reasonable to consider $\Delta_\theta \ln(x_S)$ value defined as equation 4:

$$\Delta_\theta \ln(x_S) = \ln(x_S) - \theta_A \ln(x_S) - \theta_B \ln(x_{S,B}) \qquad (4)$$

Equation 4 is a deviation from additivity, $\ln(x_S)$, $\ln(x_{S,A})$, and $\ln(x_{S,B})$ are the respective values of $\ln(x_S)$ in pure solvents A and B. Using the surface fractions for the expression of the deviation from additivity allows us to leave out of account not only the constants connected with the choice of the standard conditions but also the solute-solvent interchange energies ω_{AS} and ω_{BS}.[29] The resultant equation to calculating the solubility x_S of a poorly soluble substance S in a binary solvent A + B is the equation 5.

$$\Delta_\theta \ln(x_S) = -\Delta_\theta(\ln \gamma_S^\infty)_{chem} - \Delta_\theta(\ln \gamma_S^\infty)_{comb} - \Delta_\theta(\ln \gamma_S^\infty)_{res} \quad (5)$$

The individual contributions $\Delta_\theta(\ln \gamma_S^\infty)_k = (\ln \gamma_S^\infty)_k - \theta_A(\ln \gamma_S^\infty)_k - \theta_B(\ln \gamma_S^\infty)_k$ (k = chemical, combinatorial and residual ones) can be calculated using equations 1-3.

Results and Discussion

The structures of the investigated Co^{III} 5,10,15,20-tetra(4-carboxyphenyl)porphyrin (**1**), axial complex with methylimidazole (**2**) and polyethyleneglycols are summarized in Figure 1.
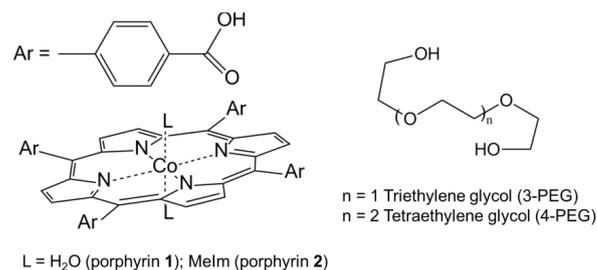

n = 1 Triethylene glycol (3-PEG)
n = 2 Tetraethylene glycol (4-PEG)

L = H₂O (porphyrin **1**); MeIm (porphyrin **2**)

Figure 1. Schematic of the investigated objects.

Experimental solubility

A series of the solubility experiments for 5,10,15,20-tetra(4-carboxyphenyl)porphyrin Co^{III} (**1**) and axial complex with methylimidazole (**2**) in the whole range of the compositions of the mixed solvent: aqueous phosphate buffer pH 7.4, 3-PEG/4-PEG were performed at

T = 298.2 K and atmospheric pressure. The results of the experiments are given in Table S1.

As it follows from the data in Table S1, the coordination of the methylimidazole molecule facilitates the aqueous solubility. As Gamboa *et al.*[30] clearly demonstrated for Co^{III} 5,10,15,20-tetraphenylporphine, an evident feature in the porphyrin crystalline phase is a successive layer arrangement, which follows a macrocycle surface which is completely planar. The substitution of the water molecule coordinated at the central Co-cation by the axial ligand promotes more friable packing, possibly changing the planarity[31] and, as a consequence, can decrease the energy required for the dissolution of the porphyrins. Moreover, being a polar ionizable substance *N*-methylimidazole forms a stable axial complex thus increasing the polarizability of the conjugated ϖ-system of the porphyrin fragment promoting dipole-dipole and disperse interactions with the solvent.

According to the aqueous solubility the studied porphyrins **1** and **2** can be classified as very slightly soluble substances (United States Pharmacopeia, USP 23).[32] Therefore techniques aimed to improving the solubility of the investigated objects are of particular interest. The experimental data show the porphyrins to be barely soluble in pure water and in either *n*-ethylene glycol, but the solubility reaches a maximum for a certain proportion between both solvents (Figure 2).
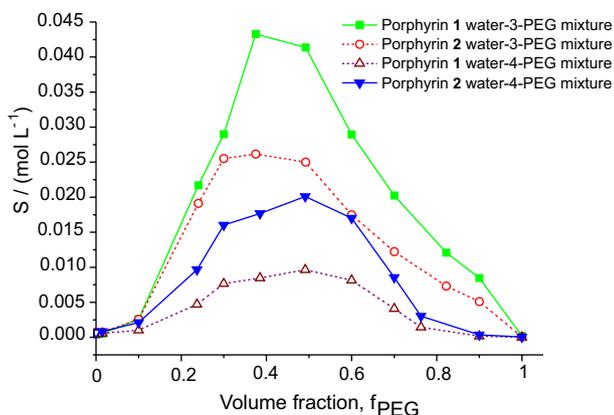

Figure 2. Effect of 3-PEG and 4-PEG on the solubility of porphyrins **1** and **2** at 298.2 K and pressure p = 0.1 MPa.

The maximal solubilities at cosolvent volume fraction, f, for $f_{3-PEG} = 0.375$ and $f_{4-PEG} = 0.491$ are observed (Figure 2). It should be noted, that the investigated porphyrins **1** and **2** with four carboxyl groups at pH 7.4 have the "peripheral charge" to be equal zero (uncharged state).[33,34] Due to this fact the dissociation of the carboxyl groups at pH 7.4 is not observed, only hydrogen bonding but not ion-dipole interactions can occur. At that, in the mixed solvent the

heterosolvation can takes place due to the amphiprotic nature of the PEG molecule and the presence of large hydrophobic part in the porphyrin molecule and small hydrophilic carboxyl-groups.[35] Moreover, different polyethyleneglycol additions to aqueous solutions can cause the stabilization of the water structure,[36,37] the universal solvation by means of dipole-dipole and disperse interactions between alkyl H-atoms of the alcohol-group of the PEG and the π-electrons of the conjugated porphyrin system[38] as well as the destruction of a *quasi*-crystalline water structure.[39] The prevalence of one or several of the above factors determines the solubility of the investigated porphyrins **1** and **2** at different water-polyethyleneglycol proportions in the mixed solvent.

Log-linear cosolvency model

The addition of the cosolvent is manifested in a higher solubility of non-polar compounds in cosolvent-water mixture.[40,41] Yalkowsky[18] proposed that the cosolvency phenomenon involves the treatment of the empiric-analytical log-linear model. The equation allowed to correlate and to explain the cosolvent effect on the solubility of the compounds that are slightly soluble in aqueous media is the equation 6:[18]

$$\log S_{mix} = \log S_w + \sigma f_c \qquad (6)$$

where S_{mix} and S_w are the total solute solubilities in the cosolvent-water mixture and in water, respectively, σ is the cosolvent solubilization power for the particular cosolvent-solute system, and f_c is the volume fraction of the cosolvent in the aqueous mixture. The individual sigma (σ) terms can be derived from the slope of the log (S_{mix}/S_w) *vs.* cosolvent volume fraction (f_c) profile by regression analysis. Using the solubilities of the investigated porphyrins in water-PEG mixture we have drawn log-linear solubilization plots presented in Figure 3 for all porphyrin-water-PEG systems up to $f_{PEG} = 0.3$.

Figure 3 shows the segments of the solubility profiles for porphyrins **1** and **2**, which are log-linear and follow equation 6. At that, a distinct downward curvature is noticed in the profiles in the range of larger f_{PEG}. With high positive deviations from the log-linear model. In the range $0 \leq f_{3-PEG} \leq 0.24$ in the systems **1/2** (water-3-PEG) log S follows a linear function with a good correlations $r^2 = 0.9987/0.9985$. The slope σ is resulted in $7.1486 \pm 0.2584/6.1258 \pm 0.2414$ for porphyrins **1** and **2**, respectively. Whereas, in the systems **1/2** (water-4-PEG) a linear function with $r^2 = 0.9969/0.9991$ is observed in the range $0 \leq f_{4-PEG} \leq 0.3$. The slope is resulted in
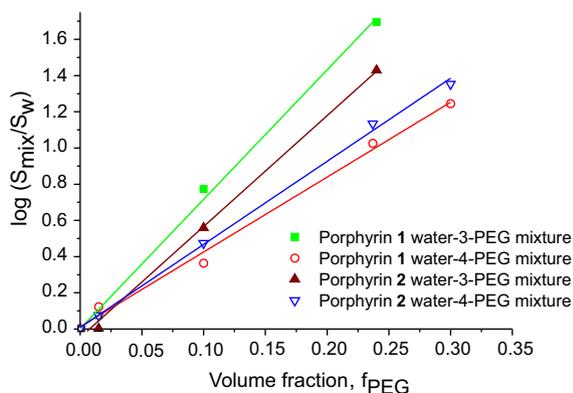
Figure 3. Solubilization profiles of porphyrins **1** and **2** in water-PEG mixtures (f_{PEG} = 0-0.3).

$4.1363 \pm 0.1874/4.5880 \pm 0.1103$ for porphyrins **1** and **2**, respectively. As the slope values means an excellent cosolvent force of both 3-PEG and 4-PEG, it can be concluded that Yalkowsky's theory can be applied for the considered systems in the stated ranges of f_{PEG} since the solubility increases significantly. Namely, the solubility of porphyrins **1/2** for $f_{3\text{-}PEG}$ = 0.24 is 49.6/26.9 times higher than in water, whereas for $f_{4\text{-}PEG}$ = 0.24 the solubility growth is appeared to be 10.7/13.6 times higher than in water, respectively. The results clearly indicate that 3-PEG is a more powerful solubilizer than 4-PEG for the porphyrins studied.

It is interesting to consider the desolubilization effect observed in the investigated mixed solvents at large volume fractions of the cosolvent. At that, the log linear functions with good correlations ($r^2 \geq 0.9979$) are observed for porphyrins: **1** in the range $0.5 \leq f_{3\text{-}PEG} \leq 0.9$ and **2** $0.7 \leq f_{4\text{-}PEG} \leq 0.9$ (Figure S2 in the Supplementary Information section). The negative slopes are resulted in $-1.6914 \pm 0.0633/-6.9183 \pm 0.0780$ for porphyrins **1** and **2** in water-3-PEG/4-PEG, respectively. It is interesting to note that for the porphyrins studied the desolubilization force of 3-PEG is lower than that of 4-PEG as opposed to solubilization one. The change in polarity of the solvent brought about by cosolvent may contribute whether and to what extent a solute is solubilized or desolubilized.[9]

Hydrogen bond donor densities

In order to understand the possible reasons of the obtained results we calculated a parameter that reflects the ability of cosolvent (PEG) to donate a proton in a hydrogen bond, hydrogen bond densities (HBD) for the neat PEGs from the density of the PEG and the number of proton donor groups on the molecule. HBD are considered as the polarity indexes, show good correlation with solubilization power of the cosolvent and can be determined by the following equation 7.[13]

(No. of proton donor groups) × (density of cosolvent) × 1000/molecular weight of cosolvent   (7)

The density of the PEG and the number of proton donor groups on the molecule have been calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2015 ACD/Labs). As expected, 3-PEG (HBD = 14.77) exhibited better solubilization power in comparison with 4-PEG (HBD = 12.73). But it should be noted that this regularity is observed only in the ranges of $0 \leq f_{3\text{-}PEG} \leq 0.24$ and $0 \leq f_{4\text{-}PEG} \leq 0.3$.

Excess properties correlations

Solutions with quite different properties are obtained when different amounts of the cosolvent are added to water. The effect of the medium on equilibria of chemical phenomenon is an important subject and one of great scope and difficulty.[19] Sometimes a solute shows a condition of maximum solubility that appears when the mentioned parameter is similar to that of the solvent medium.[42,43] The information on such properties as excess volumes can be useful in the development and testing of correlations with the macroscopic properties, leading to better understanding the intermolecular interactions and the association processes in the solution.[44] In the present work we analyzed the dependence of the excess solubility values of porphyrins **1** and **2** (log (S_{mix}/S_{calc})) on the excess volumes (V^E) of the mixed solvent (Figure S3 in the Supplementary Information section). Excess volumes of the mixtures water-tri-/tetraethyleneglycol were collected from the literature[39] and the excess solubilities were calculated in this study by the following equation 8.

$$\log (S_{mix}/S_{calc}) = \log S_{mix} - f_c \log S_c + (1 - f_c) \log S_w \quad (8)$$

Equation 8 is a measure of interactions taking place in the porphyrin-water-PEG mixed solvent not occurring in the mixtures of the porphyrin with the individual water and PEG. Positive deviations from the log-linear model, particularly large at the intermediate points of PEG concentrations, are observed (Figure S3), means the non-ideality of the system. The excess volumes are negative and the curves tend to be somewhat skewed, indicating an increase in the order of the systems partially due to the formation of hydrogen bonds or structured liquids. The maximums of the excess volumes for the systems water-3-PEG/4-PEG are revealed at f_{PEG} = 0.6. The points of maximal log (S_{mix}/S_{calc}) and V^E at $f_{4\text{-}PEG}$ = 0.6 is observed for porphyrins **1-2**. In the system water-3-PEG the maximum of the excess solubility of both porphyrins is

shifted concerning the maximum of the excess volume and appear to be at $f_{3\text{-PEG}} = 0.5$. Similarities in the shapes of the $\log(S_{mix}/S_{calc})$ *vs.* f plots for both porphyrins suggested PEG-water interactions as the primary reason for their deviations. At that in water-4-PEG solutions the deviation of the solubility of both porphyrins from ideality correlates better with the volume properties of the mixed solvent in comparison with water-3-PEG system.

As the design of cosolvent formulations is a slow and costly process the predictive models for cosolvent solubilization are of a great importance. In this study we use a simple ASL (associated solution + lattice) model to calculate the solubility of porphyrins **1** and **2** in the mixed solvents 3-PEG-water and 4-PEG-water in the whole range of PEG fractions. The chemical contribution was calculated using equation 1 assuming that the affinity to hydrogen bonds formation of the neat water and neat PEG molecules as well as in their mixture is so high that for a middle association degree χ it can be assumed that $\chi \to \infty$ and, correspondingly, $1/\chi \to 0$. Really, the results of molecular dynamics modeling show the size of the cluster formed by the water molecules by means of H-bonds to coincide practically with the size of the modeling cell.[45] Due to the fact that PEG molecules as well as water molecules contain a sufficient quantity of active centers to form H-bonds O–H⋯O a condition $1/\chi \to 0$ is met in PEG-water mixture. The geometrical parameters r and q for the molecules of the components of PEG-water mixture were calculated traditionally using Bondi tables[46] excluding the volume parameters of PEG molecules (r_{PEG}). The r_{PEG} values were slightly adjusted in the manner to coincide the volume fraction of the components $\phi_{PEG} = r_{PEG}x_{PEG}/(r_{H_2O}x_{H_2O} + r_{PEG}x_{PEG})$ of the water-PEG mixture with the analytical volume fraction of the prepared samples. The geometrical parameters r and q for the molecules of the components of PEG-water mixture are collected in Table S2 (in the Supplementary Information section). The interchange energy was estimated considering the best agreement with the solubility experiment for the investigated porphyrins. The differences of the ω_{AB} values were shown to be insignificant, and naturally, were determined as: 262 and 249 J mol^{-1} for 3-PEG-water and 4-PEG-water systems, respectively. The results of the solubility calculations for porphyrins **1** and **2** in the mixed solvents are presented in Figure S4 (in the Supplementary Information section). Figure S4 demonstrates the comparison of the solubility profile for the experimental and predicted results. The position of the solubility maximum is determined by the relation of the sizes of the molecules in the mixed water-PEG solvent and the height of the maximum-mainly by the interchange energy ω_{AB}.

It was interesting to evaluate individual contributions in the solubility. As an example, the concentration dependence of chemical, combinatorial and residual contributions in the solubility of porphyrin **1** in 4-PEG-water system is presented in Figure 4.
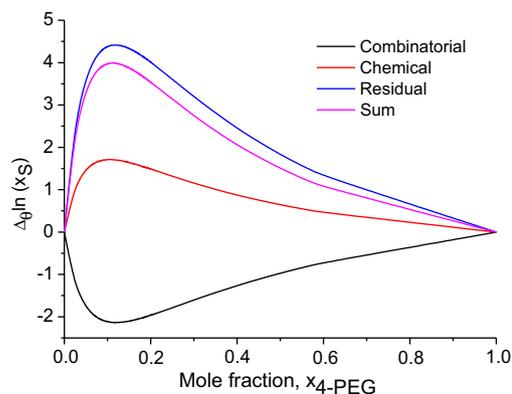

Figure 4. Dependence of chemical, combinatorial and residual contributions in $\Delta_\theta \ln (x_S)$ for porphyrin **1** on the composition of the 4-PEG-water mixture (sum = total contribution equal to $\Delta_\theta \ln (x_S)$-value).

The dependences for the other studied systems are similar to the presented in Figure 4. So, the regularities of the contributions in $\Delta_\theta \ln (x_S)$ are analogous in all investigated systems. The residual contribution has the maximal value among others means the contribution from the universal intermolecular interactions to be maximal and positive. The chemical (from the molecular association) and combinatorial (from the differences in the sizes of the molecules) contributions are approximately equal by the absolute value and have the opposite sign. It is interesting to note that in our previous study[9] dealing with the porphyrin solubility in the system associated component-inert component (methanol-tetrachloromethane) the result was different, namely, the contributions can be placed in the following order: chemical > residual > combinatorial. Such a difference of the present and previous results is determined, firstly, by the specific features of the molecular association in the PEG-water mixed solvent ($\chi \to \infty$ in the whole range of the compositions), and, secondly, by considerable differences in the size of the molecules which lead to the increase of the combinatorial contribution in accordance with equations 2 and 6. Thus, it can be concluded that the solubility of the porphyrins in PEG-water mixtures can be assessed by the combination of the contributions from molecular association, differences in the sizes of the molecules, and universal intermolecular interactions.

Conclusions

The solubility of Co^{III} 5,10,15,20-tetra(4-carboxyphenyl) porphyrin and axial complex with methylimidazol in the

mixtures of triethyleneglycol-water and tetraethyleneglycol-water were measured in the whole range of PEG fractions. From the results of this study it can be concluded that the use of low molecular weight polyethyleneglycols is an effective means of solubilizing the investigated porphyrins. The compositions of the mixtures with the maximal solubility were revealed to be $f_{3\text{-PEG}} = 0.375$ and $f_{4\text{-PEG}} = 0.491$ for both investigated compounds. The cosolvent force of PEGs quantified according to the linear logarithmic model proposed by Yalkowsky appeared to be higher in 3-PEG-water mixture in comparison with 4-PEG-water mixtures by a factor of 1.7 for Co^{III} 5,10,15,20-tetra(4-carboxyphenyl)porphyrin and by a factor of 1.3 for axial complex with methylimidazole. The comparative analysis of the excess solubility-values and the excess volumes of the PEG-water solutions was done. It was shown that in 4-PEG-water solutions the deviation of the solubility of both porphyrins from ideality correlates better with the volume properties of the mixed solvent in comparison with 3-PEG-water system. A mathematical approach based on the tenets of the molecular association theory and a simple lattice model (ASL = association solution + lattice) was used to estimate the solubility values of the investigated porphyrins in PEG-water solutions. The ASL model appeared to present a simple approach using a single variable parameter for assessing the solubility of Co^{III} 5,10,15,20-tetra(4-carboxyphenyl)porphyrin and axial complex with methylimidazole in polyethyleneglycol-water mixtures.

Supplementary Information

Supplementary data (NMR, IR, UV-Vis spectra; Figure S1; Figure S2; Figure S3; Figure S4; Table S1; Table S2) are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

References

1. Pandey, R. K.; Zhangin, G. In *Porphyrin Handbook*; Kadish, K. M.; Smith, K. M.; Guilard, R., eds.; Academic Press: New York, 2000, ch. 43.

2. Zenkevich, E. I.; Shulga, A. M.; Sagun, E. I.; von Borczyskowski, C.; Rempel, U.; Chernook, A. V. In *Successes in Porphyrin Chemistry*; Golubchikov, O. A., ed.; St. Petersburg Pubs: St. Petersburg, Russia, 1997, ch. 12.

3. Worksand, C. F.; Ford, P. C.; *J. Am. Chem. Soc.* **2000**, *122*, 7592.

4. D'Souza, F.; Deviprasad, G. R.; Zandler, M. E.; *J. Chem. Soc., Dalton Trans.* **1997**, 3699.

5. Vashurin, A. S.; Pukhovskaya, S. G.; Voronina, A. A.; Semeikin, A. S.; Golubchikov, O. A.; *Macroheterocycles* **2013**, *6*, 257.

6. Koifman, O. I.; Ageeva, T. A.; *Russ. Chem. J.* **2004**, *83*, 140.

7. Kumari, S.; Pramod, K. S.; Nitin, K.; *Chem. Sin.* **2010**, *1*, 36.

8. Mamardashvili, G. M.; Kulikova, O. M.; Chizhova, N. V.; Mamardashvili, N. Z.; Koifman, O. I.; *Macroheterocycles* **2013**, *6*, 323.

9. Millard, J. W.; Alvarez-Nunez, F. A.; Yalkowsky, S. H.; *Int. J. Pharm.* **2002**, *245*, 153.

10. Mamardashvili, G. M.; Berezin, B. D.; *Russ. Usp. Chem. Porphyrins* **2001**, *3*, 130.

11. Fedulova, I. N.; Bragin, N. A.; Mironov, A. F.; *Bioorg. Chem.* **2007**, *33*, 1.

12. Miyako, Y.; Khalef, N.; Matsuzaki, K.; Pinal, R.; *Int. J. Pharm.* **2010**, *393*, 48.

13. Rubino, J. T.; Yalkowsky, S. H.; *Pharm. Res.* **1987**, *4*, 220.

14. Vinodu, M. V.; Padmanabhan, M.; *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 326.

15. Toryanik, A. I.; *Russ. J. Struct. Chem.* **1984**, *25*, 49.

16. Zinchenko, V. D.; Mank, V. V.; Moiseev, V. A.; Ovcharenko, F. D.; *Russ. Colloid J.* **1976**, *38*, 44.

17. Wessling, E.; Stockhausen, M.; Schuts, G.; *J. Mol. Liq.* **1991**, *49*, 105.

18. Yalkowsky, S. H.; *Solubility and Solubilization in Aqueous Media*; American Chemical Society and Oxford University Press: New York, USA, 1999.

19. Khossravi, D.; Connors, K. B. A.; *J. Pharm. Sci.* **1992**, *81*, 371.

20. Jouyban, A.; *Chem. Pharm. Bull.* **2006**, *54*, 1561.

21. Jouyban, A.; Soltanpour, S.; Acree, W. E.; *J. Chem. Eng. Data* **2010**, *55*, 5252.

22. Kawakami, K.; Oda, N.; Miyoshi, K.; Funaki, T.; Ida, Y.; *Eur. J. Pharm. Sci.* **2006**, *28*, 7.

23. Ruether, F.; Sadowski, G.; *J. Pharm. Sci.* **2009**, *98*, 4205.

24. Li, C.; Wang, Q.; Shen, B.; Xiong, Z.; Chen, C.; *Fluid Phase Equilib.* **2015**, *389*, 41.

25. Li, C.; Wang, Q.; Shen, B.; Xiong, Z.; Chen, C.; *Fluid Phase Equilib.* **2015**, *396*, 58.

26. Nikiforov, M. Y.; Golubev, V. A.; Mamardashvili, G. M.; Alper, G. A.; *Russ. J. Struct. Chem.* **2011**, *52*, 314.

27. Pasternack, R. F.; Parr, G. R.; *Inorg. Chem.* **1976**, *15*, 3087.

28. Simanova, C. A.; *Manual Chemist and Technologist*; Professional: St. Petersburg, Russia, 2004.

29. Nikiforov, M. Y.; Totchasov, E. D.; Alper, G. A.; *Russ. J. Phys. Chem.* **2007**, *81*, 1820.

30. Gamboa, M.; Campos, M.; Torres, L. A.; *J. Chem. Thermodyn.* **2010**, *42*, 666.

31. Li, Z.-S.; Chai, J.-S.; *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2007**, *63*, 1533.

32. The United States Pharmacopeia, USP 23, The United States Pharmacopeial Convention: Rockville, 1990.

33. Williams, G. N.; Hasmbright, P.; *Inorg. Chem.* **1978**, *17*, 2687.

34. Sandanayaka, A. S. D.; Araki, Y.; Wada, T.; Hasobe, T.; *J. Phys. Chem. C* **2008**, *112*, 19209.

35. Goga, S. T.; Glazkova, S. N.; Mchedlov-Petrosyan, N. O.; *Russ. J. Phys. Chem.* **2008**, *82*, 633.

36. Topicheva, I. N.; *Russ. Usp. Chem.* **1980**, *49*, 494.

37. Kiselev, M. G.; Pukhovsky, Y. P.; Alper, G. A.; *Structural Self-Organization in Solutions and on The Border of Phases*; LKI: Moscow, Russia, 2008.

38. Tomoshige, N.; Takoshi, K.; *J. Chem. Eng. Jpn.* **1975**, *8*, 175.

39. Muller, E. A.; Rasmussen, P.; *J. Chem. Eng. Data* **1991**, *36*, 214.

40. Nayak, A. K.; Panigrahi, P. P.; *ISRN Phys. Chem.* **2012**, 1.

41. Sanghvi, R.; Narazaki, R.; Machatha, S. G.; Yalkowsky, S. H.; *AAPS PharmSciTech* **2008**, *9*, 366.

42. Yurquina, A.; Manzur, M. E.; Brito, P.; Manzo, R.; Molina, M. A. A.; *J. Mol. Liq.* **2007**, *133*, 47.

43. Martin, A.; Bustamante, P.; Chun, A. H. C.; *Physical Chemical Principles in the Pharmaceutical Sciences*, 4th ed.; Lea & Febiger: Philadelphia, USA, 1993.

44. Afanasjev, V. N.; *Russ. J. Phys. Chem.* **2003**, *77*, 1206.

45. Nilsson, A.; Pettersson, L. G. M.; *Russ. J. Phys. Chem.* **2011**, *389*, 1.

46. Bondi, A.; *J. Phys. Chem.* **1964**, *68*, 441.