Prediction and verification of the solubility of flavonoids in ionic liquids
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Prediction and verification of the solubility of flavonoids in ionic liquids

——A priori design of the green routes for efficient enzymatic synthesis of lipophilic flavonoid derivatives

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Abstract

Predictions of the solubility of flavonoids in a large variety of ionic liquids (ILs) with over 1800 available structures were examined based on COSMO-RS computation. The results show that the solubilities of flavonoids are strongly anion-dependent; and the ILs could be classified into 3 groups according to the values of flavonoid solubility. Experimental measurement of the solubilities of esculin and rutin in 12 ILs with varying anions and cations show that predicted and experimental results generally have a good agreement. Based on the sound physical basis of COSMO-RS, the solubility change of flavonoids were quantitatively associated with solvation interactions and structural characteristics of ILs. COSMO-RS derived parameters, i. e. misfit, H-bonding and van der Waals interaction energy, are shown to be capable of characterizing the complicated multiple interactions in IL system effectively. H-bonding interaction is the most dominant interaction for ILs (followed by misfit and van der Waals interactions) to determine the solubility of flavonoids, and the anionic part has greater effect on the overall H-bonding capability of the IL. Based on basicity of anions, ILs were categorized into 3 groups, corresponding to the classification of the solubility of flavonoid. While COSMOment descriptors, which roughly denote the characteristic properties of the ILs, might be of general value to have a fast estimation for the solubilities of flavonoids as well as those compounds with massive moieties as H-bonding donor.

Key words: Ionic liquids (ILs), COSMO-RS (Conductor-like Screening Model for Real Solvent), flavonoid, esculin, prediction, solvation.

1. Introduction

The effectiveness and absorption of many drugs are largely controlled by their low solubility, therefore, modification of drugs and producing so-called prodrug is a useful method to obtain improved properties [1-3]. Flavonoids are such a group of prominent molecules with multiple physiological activities. However, their functions are limited by their low aqua- and lipo- solubility and resultant low bioavailability [4-6]. Lipophilisation of flavonoids into fatty acid esters has been proven to be an efficient way to expand functionalities and applications in human nutrition [5, 7]. The presence of solvents is essential in all steps of pharmaceutical processes (reaction, separation and formulation) [8]. The particular importance of a good choice of solvents for a reaction results from the fact that the medium

often affects the overall reaction rate, selectivity or yield [9, 10]. However, the attempts to establish an efficient enzymatic esterification of flavonoids with fatty acids using conventional solvents have been seriously upset by their low solubility [7, 11]. As neoteric green solvents, the unique properties and tunable physical and chemical characteristics of ionic liquids (ILs) guide one to resort to the novel media for a better solution[12, 13].

Validation of COSMO-RS predictions

To examine the accuracy of COSMO-RS predictions of the solubilities of flavonoids, 12 different types of ILs, representing different anion types and dissolution abilities as categorized above, were selected as solvents and esculin and rutin were chosen as model flavonoid molecules for evaluation (Fig. 2 and 3). Most of the ILs tested have higher viscosity, and 1-ethyl-3-methylimidazolium toluene-4-sulfonate (EMIM.OTs) is even solid at room temperature. Therefore, the measurements were conducted at 40 and 60 °C to accelerate dissolution. This test temperature is far from the boiling points of ILs and the evaporation of ILs can be neglected, thereby the measurements stay in a safe temperature range. The scatter plot of Fig. 2A shows a rather homogeneous error distribution of esculin solubilities at 40 °C, which means the solubilities of esculin in the ILs were not systematically overestimated or underestimated. The predicted and experimental values gave average absolute error (AAE) of 0.29 log-unit and root mean square deviations (RMSD) 0.25 log-unit. These data suggested a better quality of esculin solubility prediction in ILs than a previous report concerning prediction of aqueous solubility of drugs and pesticides with COSMO-RS [24]. The predictions of esculin solubility at the temperature of 60°C achieve the accuracy with the AAE of 0.39 and RMSD 0.22. The accuracy is comparable with that at 40 °C. No systemic deviation is observed, suggesting that 60 °C (the temperature range often used for lipase catalysis) is within the safety interval for COSMO-RS prediction.

Analysis of the multiple solvation interactions between esculin and ILs

It is known that ionic liquids are among the most complex solvents [30]. Clearly, single parameter like "polarity", normally used for the characterization of conventional solvents, is not sufficient to describe the structure and diversity of functionality of ILs. Several approaches have been proposed that allow one to examine and categorize the different solvent-solute interactions [30, 31]. These solvatochromic or chromatographic approaches employ probe molecules to characterize the most dominant interactions of ILs, namely, polarity, hydrogen bond basicity, and dispersion, etc [30, 31]. These efforts are capable of categorizing the types and strength of interactions of an extensive number of ILs that effectively delineate their similarities and differences. However, those descriptions could not or at least have not been associated with the quantification of the thermodynamic properties of ILs, which is just the need for a practical application [25]. As a physically well-founded computation approach, COSMO-RS integrates dominant interactions among IL systems (electrostatic (polarity), H-bonding and van der Waals (dispersion)), which adequately summarize multiple solvation interactions of ILs [30]. Importantly, this methodology provides a direct quantitative scaling of the thermodynamic properties of ILs at a specific solvation environment [25]. Therefore, it is theoretically possible to associate the specific interactions determining the solubility of flavonoids with the cationic and/or anionic part of the ILs through force field analysis of the measures derived from COSMO-RS computation.

Analysis of the multiple solvation interactions of rutin and ILs

Compared to esculin, rutin has 1 more phenolic ring and a disaccharide substituent. To examine the similarities and differences of the solvation behaviours of ILs between rutin and esculin, a similar computation has been conducted for solute rutin as done for esculin (Fig. 6). Fig. 6 displays that rutin has a wider varying range of solubility, and the minimum solubility (molar fraction) is around the magnitude of 10^{-13}. The classification of solubility by the orders of magnitude of the values appears to be very clear (Fig. 6). In the high solubility zone the solubility of rutin is zero (Group 1'); in the low solubility zone the solubility is less than 10^{-4} (Group 3') and the solubility varies within the range of 10^{-1} – 10^{-4} in the second group. Comparison of Fig. 4 and 6 reveals that the solubility of rutin decrease against anion type in a generally similar but not totally the same order like esculin, indicating a similar but different solvation behaviour between rutin and esculin. Similar to esculin, the van der Waals

interactions for rutin are nearly constant, but the absolute values (about 25 kcal/mol) are markedly higher than those for esculin (around 15 kcal/mol). This strong interaction results from bigger molecular size and mass of rutin. Different from esculin, the misfit interaction for rutin with anion alteration shows a smaller variability, indicating that in the same solvent environment different solutes behave different solvations or induce solvents to exhibit different polarities, as reported elsewhere [25, 30]. The data in Fig. 6 show that there are strong H-bonding interactions between rutin and anions of ILs in the high soluble zone to stabilize the dissolved molecules, and this interaction is generally greater than van der Waals interaction for the ILs in this zone except for the cases of Br^- and toluene-4-sulfonate. This result suggests that the additional saccharide ring of rutin adds much to the H-bonding interaction with ILs. However, this structural characteristic does not always generate a desirable effect for the dissolution of rutin; because more saccharide rings will result in a bigger molecular misfit or increase the molecular dissimilarity with hydrophobic ILs, thus, lead to a significant lower solubility of rutin in those ILs with weak H-bonding capability (Group 3' in Fig. 6).

Concluding remark and outlook

The primary interest of this study is not only to validate COSMO-RS predictions, but also to achieve a better understanding of the functionality of structural moiety of ILs through the powerful force field analysis function of COSMO-RS methodology based on its sound physical basis. It turns out that COSMO-RS predictions generally have a good agreement with the experimental data, compared to the predictions of the solubilities of solid solute by other approaches [24, 26]. Considering that the predictions of this model cover vast structural diversity of ILs and the calculations are performed without any specific parameter adjustment, the results and accuracy are encouraging and acceptable. The physically founded basis of COSMO-RS and validation of this work proved that the predicted results are reliable, and thus the necessary experimental efforts for quantitative determination of the solubilities of flavonoids in ILs could be reduced. The results of this work also revealed a reasonable anion-dependency of the solubility of flavonoids in ILs, and accordingly presented a first systemic categorization of anions based on flavonoid solubility. With this interesting finding, we anticipate that the grouping for anions of ILs might be generally applicable to those solutes with massive moieties as H-bonding donor. We note the reports so far concerning the ILs that are capable of dissolving cellulose [33], carbohydrate [34], and protein, [35] etc, the anions of which (Cl^-, Br^-, $H_2PO_4^-$ and $(CN)_2N^-$, etc) are exclusively included in the first group of the categorization in this study ($(CN)_2N^-$ on the border) (Fig. 4 and 6). To confirm this interesting finding, we calculated the solubility of two repetitive units of cellulose, carbohydrate and protein (used in place of macromolecular structures) in BMIM-based ILs with the anion spectrum as in Fig. 6. The predictions give surprisingly good agreement with the categorization of anions for rutin (data not shown). The results strengthened the experimental basis of COSMO-RS, and further identified the general applicability of this physically founded model, as well as the reasonability of a logical extension of some conclusions in this work.

Experimental

analysis.

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Tables and Figures

Table 1 COSMO-RS descriptor of HB_acc3 (hydrogen bonding acceptor moment indicates hydrogen bond basicity) for 32 anions of ionic liquids and classification of solvation interactions. For structural formulae, see supplementary information.

Group I		**Group II**		**Group III**	
Anion types	HB_acc3	Anion types	HB_acc3	Anion types	HB_acc3
acetate	39,0533	ethylsulfate	19,2952	bis(trifluoromethyl)imide	4,0642
decanoate	38,2772	octylsulfate	19,1774	bis(trifluoromethyl sulfonyl)methane	3,8915
bis(2,4,4-trimethyl pentyl) phosphinate	37,8887	butylsulfate	19,1238	clo4	3,7574
cl	36,6278	methylsulfate	18,5006	tetracyanoborate	3,4554
phosphate	35,9622	dicyanamide	15,5327	bisoxalatoborate	3,0140
dimethylphosphate	35,1611	Bisbiphenyl diolatoborate	12,7544	bf4	2,4740
br	29,6444	bis-pentafluoroethyl phosphinate	12,6559	tf2n	2,3089
toluene-4-sulfonate	25,9431	bissalicylatoborate	12,6200	tris(nonafluorobutyl) trifluorophosphate	0,0747
ethoxyethylsulfate	20,6579	bismalonatoborate	10,8007	tris(pentafluoroethyl) trifluorophosphate	0,0108
methoxyethylsulfate	20,5119	trifluoromethane-sulfonate	10,6147	pf6	0.0000
trifluoroacetate	20,3944				
nitrate	19,4858				

Captions to Figures

Fig. 4 COSMO-RS derived descriptors used to characterize the solvation interactions of esculin and BMIM-based ionic liquids with different anions. (○) predicted solubility. (◇) misfit interaction energy, (□) H-bonding interaction energy and (△) van der Waals interaction energy in respective ILs at 298.15 K.