Predictions of flavonoid solubility in ionic liquids by COSMO-RS: experimental verification, structural elucidation, and solvation characterization†

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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. 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 changes 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 the 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. COSMO sigma-moment 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 donors. The results obtained in this work may be important for achieving an improved understanding of IL solvations and the tailoring of the desired structures of ILs used as the media for efficient enzymatic esterification of flavonoids.

Introduction

The effectiveness and absorption of many drugs are largely controlled by their low solubility, therefore, modification of drugs and producing so-called prodrugs 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 these novel media for a better solution.[12,13]

The characteristics and the state of art of ILs in technology development and applications have been described in a few excellent reviews.[14,15] Among those characteristics of ILs distinguishing them from conventional solvents, the ability to tailor their properties by judicious selection of cation, anion and substituents and an extended family of available structures for selection constitutes the most interesting and attractive features of ionic liquids.[13,16] Actually, from an engineering point of view, it is the above distinct features that qualify ILs as "a designer solvent" and offer a huge potential for practical applications.[13,17] However, screening a desired structure with required properties for a particular task from a large pool of available ILs represents a big challenge facing chemists and engineers.[13,18,19] To establish an efficient IL-based enzymatic reaction system to producce lipophilic derivatives of flavonoids, there exist similar obstacles for the setup of such a reaction system to fulfil the requirement of high productivity and simultaneously being benign for enzyme activity.[20] Solubility estimation approaches could be quite valuable in reducing the time and resources required to identify a good solvent.[8,9,21] Particularly for numerous possible ILs, *a priori*

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screening is needed, because it is impractical to use trial and error methods to find a suitable IL from enormous number of ILs structurally possible for a given function. As reviewed elsewhere,[8,9] Hansen solubility parameters, the group contribution method (UNIFAC) and the quantitative structure–property relationship (QSPR) method *etc.* have been employed for solvent selection for solid solutes. These methods generally need property data to be experimentally available to create reliable training sets, which are currently scarce for ILs, as a group of relatively new compounds.[9,22] As a physically well-founded computational approach and independent of experimental data, COSMO-RS (conductor-like screening model for real solvent) provides a different and feasible alternative for solubility estimation in ILs.[23,24]

As a physically founded model, COSMO-RS integrates dominant interactions (electrostatic (polarity), H-bonding and van der Waals (dispersion)) among IL systems, which adequately summarize multiple solvation interactions of ILs.[23,24] Therefore, this method is able, at least qualitatively, to describe structural variations correctly. Previous publications have also demonstrated the general applicability of COSMO-RS concerning the prediction of solubilities of solids and liquids in ILs.[8,25] Importantly, COSMO-RS introduces the vivid concept of σ-profiles for a qualitative and quantitative comparison of the polarity distribution on molecular surfaces, which integrate the description of electrostatic, hydrogen-bonding and hydrophobicity of a structure. The derived interaction items from COSMO-RS calculation can be conversely used for molecular force field analysis to correlate interaction parameters with structural characteristics qualitatively and quantitatively, which is of general instruction value in the design and development of ILs for specific tasks.[20,26,27] Thus, besides presenting the predicted results of flavonoids in ILs and experimental validation of the COSMO-RS prediction, this work gives more attention to the analysis and assortment of interactions resulting from the specific environment of the ILs applied. These efforts are expected to contribute to an improved understanding of the structure–functionality relationship of ILs and serve later structural optimization of ionic liquids, possibly with high solubilities of flavonoids and benign to enzyme activity as well.

Theoretical basis of COSMO-RS for solubility calculation

Solubility denotes the solute concentration in a solution that is in thermodynamic equilibrium with the solute in the solid state. Therefore, the solubility depends on the difference of the chemical potentials of the solute in the solvent and in pure solute. For a solid solute, the energy change of a compound from the "supercooled" liquid state to the ordered solid state has to be taken into account. The solubility (x_i) at temperature T is thus expressed as a function of pure component properties of the solute (the melting temperature T_m and the free energy difference $(\mu_i^l - \mu_i^l)$ (solid state related to its liquid state) calculated from heat of fusion (ΔH_m^{fus}) and the heat capacity difference of solute in melt state and "hypothetical" "supercooled" melt state) ($C_p^m - C_p^s$) and of the interactions between the solute and solvent in the solution (the activity coefficients, $\ln \gamma_i$):[28]

$$\ln x_i = \frac{1}{RT}\left(\mu_i^i - \mu_i^l\right) - \ln \gamma_i = \frac{1}{R}\left[\Delta H_m^{fus}\left(\frac{1}{T_m} - \frac{1}{T}\right) + \int_{T_m}^{T} \frac{\int_{T_m}^{T}\left(C_p^m - C_p^s\right)dT}{T^2} dT\right] - \ln \gamma_i \quad (1)$$

where R is the gas constant.

The theory of COSMO-RS has been described by Klamt and coworkers.[23,24] Briefly, COSMO-RS is a statistical thermodynamics approach based on the results of quantum chemical-COSMO calculations. Starting from the surface polarization charge densities σ from density functional theory (DFT) COSMO calculations, COSMO-RS considers all interactions, especially electrostatic interaction and H-bonding, in a liquid system as contact interactions of the molecular surfaces, which are written as pair interactions of the respective polarization change densities σ and σ' of the contacting surface. Then, the chemical potential of a surface segment with SCD (screening charge density) σ in an ensemble can be described by the normalized distribution function $p_S(\sigma')$ given by eqn (2).

$$\mu_S(\sigma) = -\frac{RT}{a_{eff}} \ln \left[\int p_S(\sigma') \exp\left\{\frac{a_{aff}}{RT}\left[\mu_S(\sigma') - E_{misfit}(\sigma,\sigma') - E_{HB}(\sigma,\sigma')\right]\right\} d\sigma'\right] \quad (2)$$

where $\mu_S(\sigma)$ is a measure for the affinity of the system S to a surface polarity σ; E_{misfit} represents the electrostatic contact interaction energy; E_{HB} represents the energy contribution from H-bonding interaction; and a_{eff} is the effective contact area between two surface segments. Not being a function of individual surface contacts, E_{vdw} is not included in eqn (2) but added to the reference energy in solution *a posteriori*. The chemical potential of compound X_i in system S is then available from integration of the σ-potential over the surface of X_i. The capability of COSMO-RS to predict the chemical potential μ_S^X of any solute X in any pure or mixed solvent S at variable temperature T enables the calculation of any thermodynamic liquid–liquid equilibrium, which also constitutes the basis of COSMO-RS for solubility estimation. In the current COSMO*therm* program, the free energy of fusion of a solid solute is estimated *via* a QSPR approach and approximated from the following COSMO*therm* descriptors:[25]

$$-\Delta G_{fus}^X = c_1 \mu_i^{(H_2O)} + c_2 N_i^{Ring} + c_3 V_i + c_4 \quad (3)$$

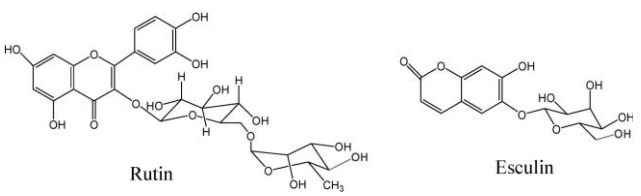
where c_1 to c_4 are the QSPR parameters for the free energy of fusion of the solute. $\mu_i^{(H_2O)}$ is the chemical potential of solute i in water, N_i^{Ring} is the number of ring atoms in compound i and V_i is the molecular volume of the solute. Crystal structure prediction for drugs has to be considered as an unsolved problem. In eqn (3), COSMO-RS treats the quantity size, rigidity, polarity and number of H-bonds as plausible driving forces of crystallization. Molecular size is described by V_i, which is available in the framework of COSMO-RS. The molecular rigidity of drugs largely results from ring structures

and therefore the number of ring atoms N_i^{Ring} is used as descriptor of rigidity. $\mu_i^{(H_2O)}$ is a combined measure of polarity and H-bonding, which can be estimated by COSMO*therm*. Therefore, the chemical potential of a compound in pure water is of special importance in the computation of solubility in COSMO-RS. The parameterizations of the QSPR parameters for fully relaxed Turbomole DFT/COSMO calculations with the larger TZVP basis set (namely BP_TZVP_C21_0106.ctd) used in this calculation includes solubility parameters that are derived from a set of solubility data of 150 aqueous solubilities.[25]

Computational details and calculation sets of flavonoids and ionic liquids

The molecular structures of flavonoids (rutin, esculin, quercetin, isoquercetrin and naringin, *etc.*) (Scheme 1) were sketched as two-dimensional structures and subsequently converted to three-dimensional geometries using Chemdraw Ultra 8.0. To obtain the lowest energy conformations for each flavonoid, special care has been taken into consideration in choosing *cis-trans* and conformational isomerism of the sugar ring structures that are able to build internal hydrogen bonds. The energy of molecular conformations was minimized by MOPAC (Molecular Orbital PACkage) 2000.[26] Using the geometries thus optimized, the computation of the COSMO polarization charge densities σ of the molecular surfaces were performed with the TURBOMOLE 5.7 program package on the density functional theory level, utilizing the BP (B88-VWN-P86) functional with a triple-ζ valence polarized basis set (TZVP).[25] Most of the COSMO files of the cations and anions involved in this work adopt the provision from a latest database of BP-COSMO-IL (COSMO/logic GmbH & Co KG, Leverkusen, Germany). The COSMO files of the cations and anions of ILs excluded in this database but used in this work were generated following a procedure similar to the one we used for flavonoid molecules. All solubility calculations of flavonoids are performed using COSMOthermX_2.1 program (COSMOlogic GmbH & Co KG, Leverkusen, Germany). For flavonoid inputs, only the conformation lowest in energy was used, and for cations and anions of ILs multiple conformers were input with activated conformer treatment in the automatic computation.

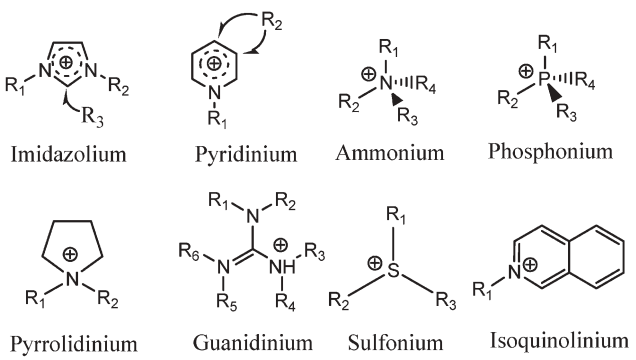
In all calculations of the solubilities of flavonoids in ILs, the cation and anion of an IL are treated as separate molecules with equal molar fractions ($n_{\mathrm{cation}} = n_{\mathrm{anion}} = n_{\mathrm{IL}}$). Thus, the COSMOtherm calculation is based on a ternary mixture (cation, anion and solute), differing from an experimental determination treated as a binary system consisting of IL and solute. Therefore, a transition calculation from the solubility of a ternary system ($x_S^{\mathrm{ternary}} = n_i/(n_i + 2n_{\mathrm{ion}})$) to the solubility of a binary system ($x_S^{\mathrm{binary}} = n_i/(n_i + n_{\mathrm{IL}})$) was done to acquire the comparative datum with the experimental value. The intensive interests of this work are not placed on the discussion of methodology itself but devoted to the revelation of the dominant interactions among IL systems to govern the solubility of flavonoids. For a better comparison of solubilities of flavonoids in different types of ILs under the same conditions, all calculations (regardless of small or large solubility) were performed with a non-iterative mode, which means the solubility computed is a zeroth order approximation.



Scheme 1 Structures of rutin and esculin.

To achieve a comprehensive evaluation on the properties of ILs, the calculation set of cations involved in this work covered the most important types of possible cations, such as imidazolium, pyridinium, pyrrolidinium, ammonium, phosphonium, sulfonium, guanidinium, isoquinolinium, and isouronium, *etc.* (Scheme 2). To investigate the effects of the incorporated substituents on the hydrophobic–hydrophilic property of ILs and the subsequent influence on the solubility of flavonoids, various chain lengths of alkyl groups were appended to the parent structures at different positions, with a total of 59 structures. The anions examined include the often used types (*e.g.* PF_6^-, BF_4^- and tf_2N) and those uncommon groups[29,30] that have properties varying from "non-polar" to moderate and strong polar anions. The number of the anion types involved amounts to 32. Therefore, the calculation set of ILs in this work is 1888 combinations, which covered almost all hitherto known important commercially available ILs (not included are those functionalized ILs developed for special tasks). It should be mentioned that not all combinations lead to ionic liquids, at least some of them do not exist as liquid at room temperature. However, they are perceived as ionic liquids herein for the convenience of model processing.

The common structural nature of flavonoids is a polyphenyl ring with saccharide substituents. Therefore, rutin with a 2-phenylchromone parent structure (three phenolic rings) and disaccharide substituents and esculin with a chromone parent structure (two phenolic rings) and monosaccharide substituents were selected as the representative structures for an extensive investigation of solubility (Scheme 1). Another reason for choosing these two flavonoids is that their lipophilic derivatives have previously been shown to have improved antioxidation properties.[7]



Scheme 2 Basic structures of the cations of ionic liquids evaluated in this study.

The average absolute error (*AAE*) was determined by eqn (4)

$$AAE = \sum|\log S_{\text{predict}} - \log S_{\text{exp}}|/n \quad (4)$$

and root mean square deviations (*RMSD*) from eqn (5)

$$RMSD = \left[\frac{1}{n}\sum\left(|\log S_{\text{predict}} - \log S_{\text{exp}}| - AAE\right)^2\right]^{1/2} \quad (5)$$

where log *S* are the logarithms of the molar percentage of the predicted and experimental solubility (mol%) and *n* is the number of the compounds used.

Results and discussion

COSMO-RS solubilities of esculin in ILs

The primary objective of this study is to acquire fundamental knowledge regarding what are the dominant interaction parameters that govern the solubilities of flavonoids in ILs and what are the structural characteristics behind these interactions. Therefore, a large pool of ILs (59 cations × 32 anions) was employed for solubility evaluation by COSMO-RS calculation. Fig. 1 shows the predicted solubilities of esculin in the ILs of different cations paired with differing anions (A) and in the ILs of different anions paired with varying cations (B). It is difficult to find any regularity in the plotting of the solubilities of esculin *versus* cation alteration in Fig. 1A. For most of the ILs with same cation, the solubilities of esculin (logarithm of molar fraction) varied over a wide range (from 0 to 10^{-6}) with the change of the anion paired. However, if the same data are plotted as the function of anion variation, a different and interesting observation can be visualized (Fig. 1B). That is, in the same anion interval, apart from some exceptions (examinations of the structures of ILs for the exception cases reveal that these ILs exist as solids at room

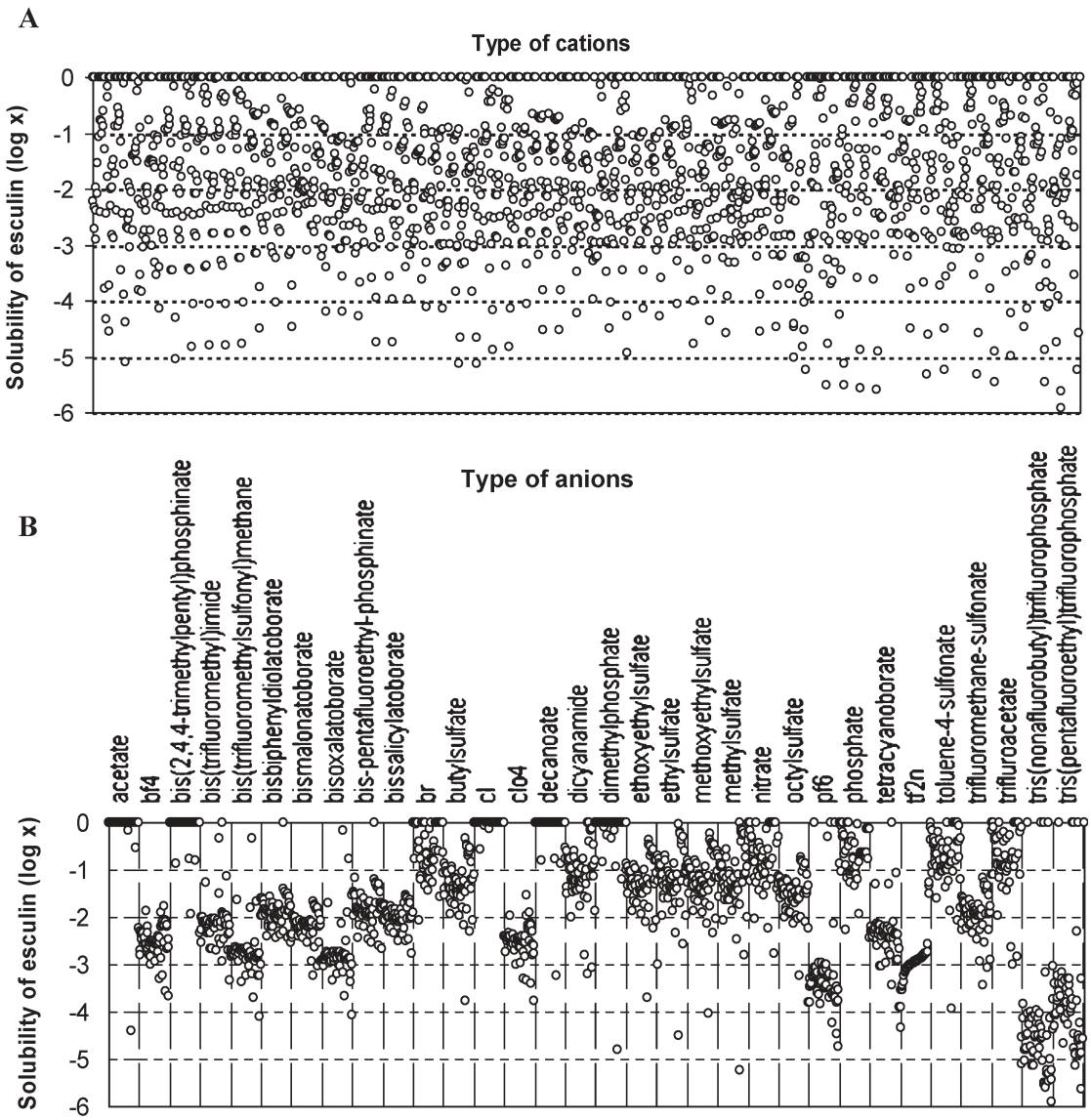


Fig. 1 COSMO-RS predictions of the solubility of esculin in 1888 types of ionic liquids (theoretically possible) created from 59 types of cations and 32 types of anions at 298.15 K. The data shown are categorized by cations (A) and by anions (B), respectively. The 59 cations have basic structures as shown in Scheme 2 but different substituents, which are not shown in this figure. The data in Fig. 1A and 1B are the same data but plotted *versus* cation and anion variation, respectively. See the ESI† for the chemical structures of the anions evaluated.

temperature, but are perceived as liquids in the prediction), the group of ILs with the same anion gave a narrow variation range of the solubilities of esculin. For instance, regardless of the structural variations of cations paired, acetate, deaconate and chlorion *etc.* based ILs generally have very high solubility of esculin (some are even theoretically mutual miscible according to COSMO-RS estimation). For PF_6^- based ILs, the solubilities of esculin varied within 10^{-3}–10^{-5} (log x) and for tris(nonafluorobutyl)trifluorophosphate based ILs the solubilities are generally lower than 10^{-4}. The results suggested that the solubilities of esculin in ILs are determined, to a greater extent, by the anion rather than the cation part of the solvent IL. In other words, the solubilities of esculin in the solvent ILs with different anion and cation combinations are largely anion-dependent. To examine whether other flavonoids have a similar tendency, a similar computation of the solubilities of rutin in a total of 1888 combinations of ILs was carried out, and the solubilities of quercetin, isoquercetrin and naringin were calculated in part of the databases (data not shown). The results demonstrated that the anion-dependency of the solubilities of flavonoids in the solvent ILs with different cation–anion pairings is universal for rutin and other test flavonoids, which indicates that there are some intrinsic interactions between flavonoid molecules and solvent ILs which deserve to be explored.

Based on the anion-dependent solubilities of esculin, the ILs examined could be classified into 3 groups (Fig. 1B). The first group dissolves flavonoids at very high concentration (log x, 0–−1), which includes the ILs with the anions of Cl^-, Br^-, decanoate, dimethylphosphate, dihydricphosphate, acetate, trifluoroacetate, bis(2,4,4-trimethylpentyl)phosphinate, and toluene-4-sulfonate *etc*. The second group of ILs have moderate solubilities (log x, −1–−2.5) and includes the anions of dicyanamide, bisbiphenyldiolatoborate, bis-pentafluoroethyl-phosphinate, bissalicylatoborate, ethoxyethylsulfate, methoxyethylsulfate, alkylsulfate (methyl-, ethyl-, butyl-, and octyl-), trifluoromethane-sulfonate, bis(trifluoromethyl)imide, bis(trifluoromethylsulfonyl)methane, *etc*. The third group of ILs, with the anions of BF_4^-, PF_6^-, bismalonatoborate, bisoxalatoborate, ClO_4^-, tetracyanoborate, tf_2N (bis(trifluoromethylsulfonyl)imide), tris(nonafluorobutyl)trifluorophosphate, tris(pentafluoroethyl) trifluorophosphate, *etc.*, have solubilities of esculin (log x) are generally less than −2 regardless of whatever cations are paired (Fig. 1B). Interestingly, the above categorization of ILs for esculin is also seen to be validated for rutin, with a few exceptions, according to our calculation (data not shown), indicating, in some way, a similar solvation behaviour between ILs with esculin and rutin. This categorization of ILs is apparently useful to quantify solute–solvent interactions and thus deserves to be further examined and investigated.

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

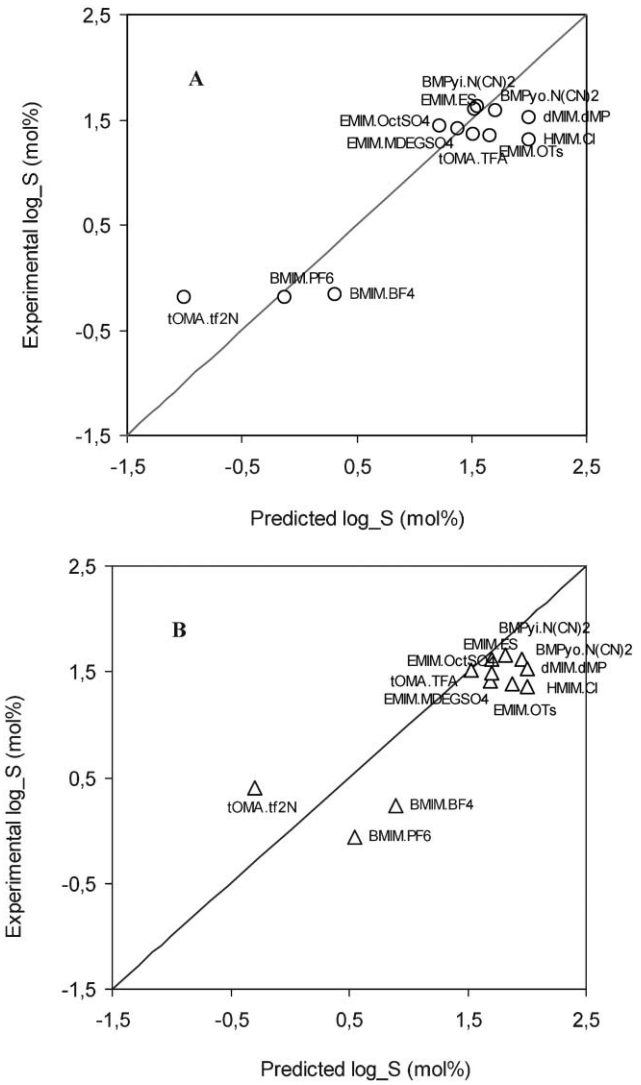


Fig. 2 COSMO-RS predictions plotted *versus* experimental values of the solubility of esculin in 12 types of ILs at 313.15 K (A) and 333.15 K (B). For abbreviations for ILs see Experimental.

(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 °C 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-units and root mean square deviations (*RMSD*) of 0.25 log-units. 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.[25] The predictions of esculin solubility at the temperature of 60 °C achieve an accuracy of an *AAE* of 0.39 and *RMSD* of 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.

Predicted and experimental data for the solubilities of rutin in 12 types of ILs at 40 and 60 °C are depicted in Fig. 3A and 3B, respectively. It is clear that for solvents BMIM.PF_6, BMIM.BF_4 and tOMA.tf_2N at either 40 or 60 °C, the experimental values are significantly higher than the predicted data. These significant differences lead to a bigger error for the total test set of 12 ILs. The average absolute error for the solubility of rutin at 40 °C is 1.41 log-units and the root mean square deviations is 1.51; while the AAE for 60 °C is 1.16 and RMSD amounts to 1.10 log-units. This result is still acceptable compared to the prediction of solid solute by other methods.[28] Inspection of the data in Fig. 3 reveals that the major errors come from the greater deviations of the predicted solubilities of rutin in BMIM.PF6, BMIM.BF4 and tOMA.tf_2N from the corresponding experimental data, which cover over 50% of the total absolute error. Interestingly, even for the solubility of esculin in tOMA.tf_2N, the predicted value also seriously deviates from the experimental datum in the same direction. This result seems to suggest that COSMO-RS did not give a sufficient and accurate description of the interaction between tOMA.tf_2N and flavonoid molecules.

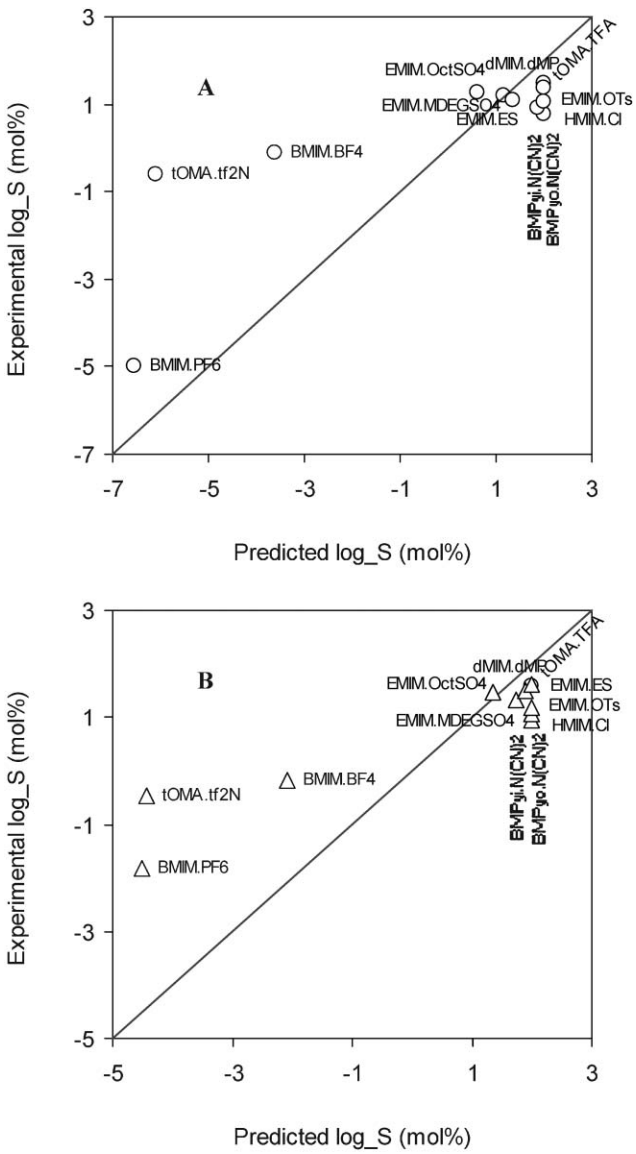


Fig. 3 COSMO-RS predictions plotted *versus* experimental values of the solubility of rutin in 12 types of ILs at 313.15 K (A) and 333.15 K (B). For abbreviations for ILs see Experimental.

It should be pointed out that an accurate measurement of flavonoids in those ILs with high viscosity is methodologically difficult. For instance, HMIM.Cl (7985 mPa s at 25 °C), EMIM.OTs (solid at 25 °C) and dMIM.dMP (391.1 mPa s at 25 °C) have high viscosity, in which both rutin and esculin have higher solubility according to COSMO-RS estimation. However, both flavonoids have bigger molecular weight and are structurally cohesive compounds. With more solute added to the solvents, the viscosity of the system becomes much greater (like semi-solid). In this case, agitation to promote dissolution is impossible and prolonging equilibrating time (over 2 months) doesn't help much for diffusion. This fact demonstrated that the presented experimental data for HMIM.Cl, EMIM.OTs and dMIM.dMP in Fig. 2 and 3 are far less than real solubilities in these solvents due to methodological impossibility, which means that the model estimation for the ILs with high solubility is actually more accurate than the shown data. This probably may explain a better agreement of experimental solubility of rutin with the predicted value at 60 °C, because the dissolution of rutin at 60 °C is observed faster than at 40 °C in high-viscosity ILs and enables the measured value to be closer to its real solubility. However, this doesn't represent the reasons accounting for greater deviation of the predictions for the solubilities of rutin in BMIM.PF_6, BMIM.BF_4 and tOMA.tf_2N, because of their relatively lower viscosity and lower solubility of flavonoids. Most likely, the solubilities of rutin in these three types of ILs could be systematically underestimated by COSMO-RS. More studies are needed to look into the issue more thoroughly.

Overall, COSMO-RS essentially gave a good prediction of the solubilities of representative flavonoid molecules in the ILs with varied cation structures and different anions, as experimentally validated. The predicted results at 60 °C give almost the same accuracy as at 40 °C, which indicates that the temperature range tested in this work is within the safety and effective prediction range of COSMO-RS prediction for ILs with high upper limit of liquidus. The prediction quality for the case of esculin is better than that for rutin (Fig. 2 and 3). The model shows a better estimation for strong solvation ionic liquids than those ILs with lower solubility (paired anions of BF_4^-, PF_6^- and tf_2N) (Fig. 2 and 3). The results demonstrated that the model is capable of producing a reasonable prediction of the solubilities in almost arbitrary cation–anion combinations existing as liquid at the test temperature range.[22,25,31] This is perhaps of particular interest to serve as a first guide in the selection of solvents from a large pool. Most importantly, being a sound physical founded model, COSMO-RS could give reasonable force field analysis in a complicated system and therefore is able to quantify the function property of the structural moiety. This function of the COSMO-RS approach is particularly useful for IL structural design for a specific task, as demonstrated in a recent work,[26] by provision of a

molecular level understanding of the structure–function relationship of ILs, which constitutes intensive contents in the following section.

Analysis of the multiple solvation interactions between esculin and ILs

It is known that ionic liquids are among the most complex solvents.[32] Clearly, single parameters like "polarity", normally used for the characterization of conventional solvents, are 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.[32,33] These solvatochromic or chromatographic approaches employ probe molecules to characterize the most dominant interactions of ILs, namely, polarity, hydrogen bond basicity, and dispersion, *etc*.[32,33] 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.[26] 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.[32] Importantly, this methodology provides a direct quantitative scaling of the thermodynamic properties of ILs in a specific solvation environment.[26] 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.

Fig. 4 shows the predicted solubilities of esculin in BMIM-based ILs with varying anions and the corresponding solvation interaction energies. According to the solubility of esculin, the ILs (in terms of the anions paired) could be classified into 3 groups: $\log_{10}$(solu_S) of 0–1, 1–2 and >2 (Fig. 4). Among the 3 descriptor parameters (Fig. 4), van der Waals interaction is strongly negative for all ILs and varies within a narrow range of value. Misfit interaction could be regarded as a disguised form of polarity, and in COSMO-RS it is defined as electrostatic interaction between the two contacting ensembles. Actually this term integrates the molecular shape, size and charge density and distribution,[34] which reflects, to some extent, the dissimilarity and mismatching property of the two interacting molecules. Its positive value indicates the ionic nature of ILs is thermodynamically unfavourable for the dissolution of a neutral molecule (herein esculin). The declining values with the anions paired denote a decreasing polarity of the anions and corresponding ILs, and also indicates that a less polar IL favours the dissolution of esculin if judged only by this parameter. However, the decrease of

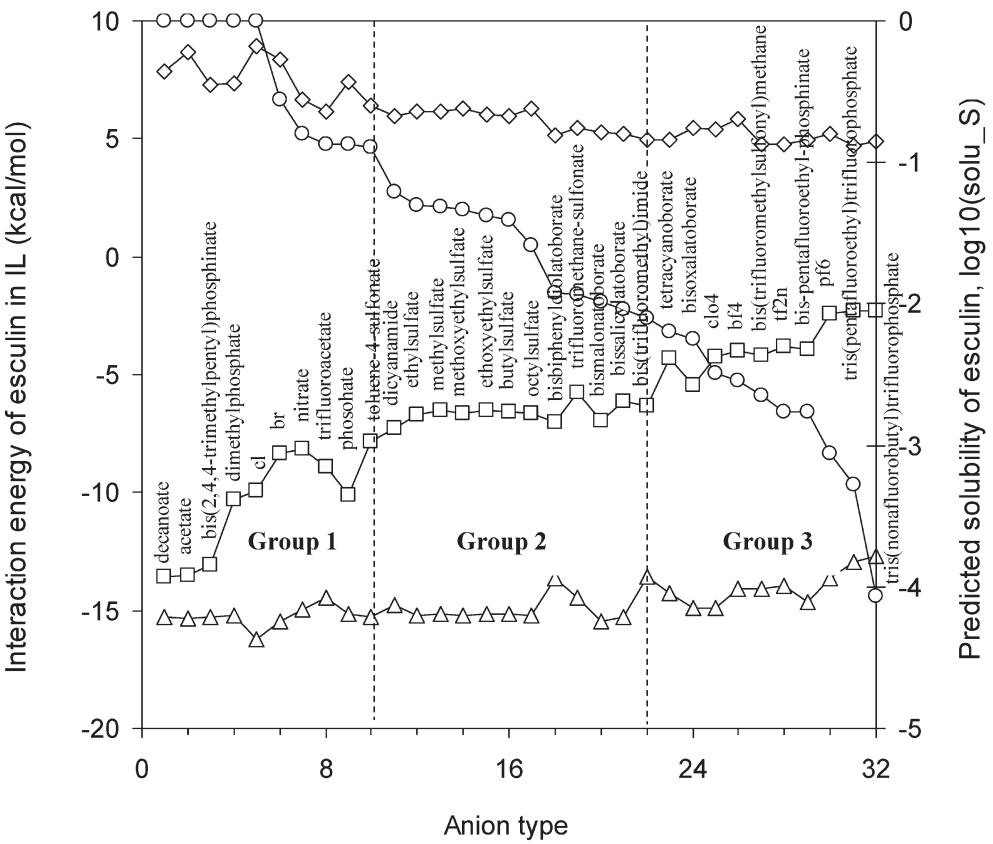


Fig. 4 COSMO-RS derived descriptors used to characterize the solvation interactions of esculin and BMIM-based ionic liquids with different anions. (○) Predicted solubility, (◇) misfit interaction energy, (□) H-bonding interaction energy and (△) van der Waals interaction energy in respective ILs at 298.15 K. All interactions are calculated at indefinite dilution. See the ESI† for the chemical structures of the anions evaluated.

misfit interaction energy is apparently not enough to compensate for the continuous reduction of the H-bonding power of ILs to stabilize the dissolved esculin (Fig. 4). Clearly, the decrease of solubility has shown a pronounced dependency of the increase of H-bonding interaction energy (Fig. 4). In the first group of ILs the dissolved esculin is stabilized by the strong H-bonding between anion and solute, yielding a very high solubility; while for the anions in the third group, like PF_6^-, the H-bonding capability attenuates seriously (H-bonding interaction energy close to 0), leading to a lower solubility of esculin. The results suggested that, for a solute with the presence of a structure (herein saccharide rings) being a good H-bonding donor, the anion part of ILs or the H-bonding capability of the anion plays a decisive role in the determination of solute solubility.

To have a close look into the effects of the structural variation of cations on the solubility of esculin, the prediction was carried out on the ionic liquids of the 4 basic structures of imidazolium, pyridinium, ammonium and phosphonium with variable substituents (Fig. 5). Acetate (A), methylsulfate (B) and PF_6^-, representing three different groups (Fig. 4), were selected as the paired anions to examine how structural changes of the cationic part influence the solvation behaviours of the ILs with different anionic properties. In agreement with the results in Fig. 1B, $\log_{10}$(solu_S) is zero no matter what substituent is incorporated into the 4 basic cation structures of the ILs when the anion is acetate (Fig. 5A); in the ILs with the anion of PF_6^- the esculin solubilities vary between −3–−4 (Fig. 5C); and in the ILs with the anion of methylsulfate the solubility has a wider fluctuating range (−0.5–−2) (Fig. 5B). As depicted in Fig. 5, for the same solute molecule of esculin, the structural variation in the cation part results in little change of the van der Waals interaction and different anions also have comparable values (around −15 kcal mol^{-1}). The strongly negative values for acetate (Fig. 5A) and less negative value for PF_6^- (Fig. 5C) of the H-bonding interaction could explain the high and low solubility of esculin in respective ILs. The case for the ILs with the anion of methylsulfate is in between that of acetate and PF_6^-, and the absolute values of the H-bonding and misfit interaction energies are very close. This probably may explain a slightly wide variation range of esculin solubility. Briefly, the results presented in Fig. 5 further demonstrate that the solubility of esculin in an ionic liquid is largely governed by the H-bonding capability of its anionic part (great difference in the orders of magnitude), and the change of the cationic part generally results in small variation of solubility (within 1 order of magnitude).

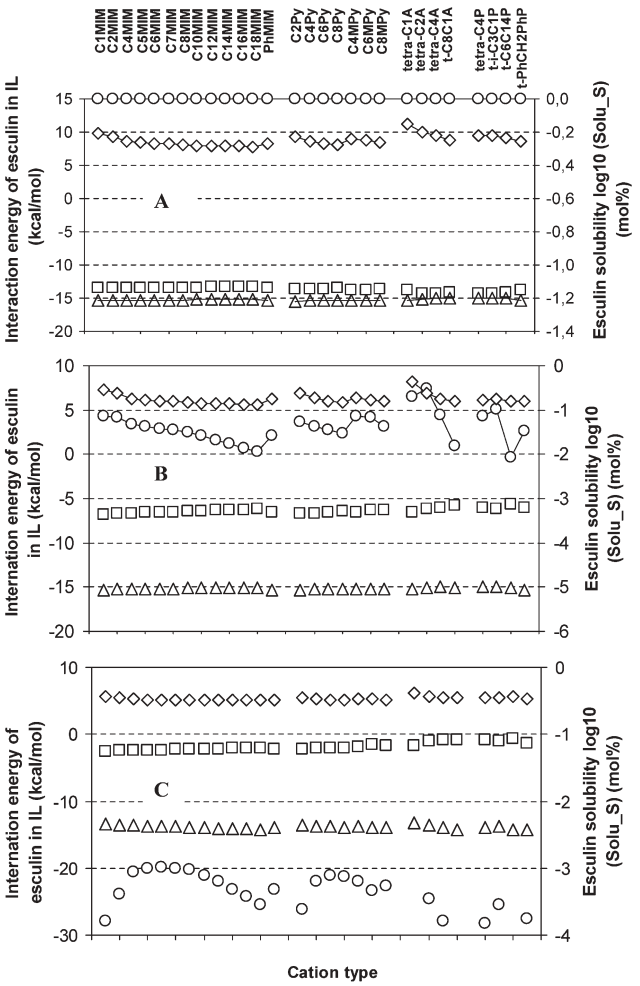


Fig. 5 Solvation interactions of esculin and acetate- (A), methylsulfate- (B) and hexaflurophosphate- (PF_6) based ionic liquids with different cations characterized by COSMO-RS derived descriptive parameters. (○) Predicted solubility, (◇) misfit interaction energy, (□) H-bonding interaction energy and (△) van der Waals interaction energy in respective ILs at 298.15 K. All interactions are calculated at indefinite dilution. Abbreviations: C1MIM to C18MIM represents 1-methyl- to octadecyl-3-methylimizadolium, respectively. PhMIM is 1-benzyl-3-methyl-imidazolium. C2Py to C8Py stand for 1-ethyl- to octyl-pyridinium, respectively, and C4MPy, C6MPy and C8MPy corresponds to 1-butyl-, hexyl- and octyl-3-methylpyridinium. Other abbreviations: Tetra-methylammonium (tetra-C1A), tetra-ethylammonium (tetra-C2A), tetra-*n*-butylammonium (tetra-C4A) and methyl-trioctyl-ammonium (t-C8C1A or tOMA). tetrabutyl-phosphonium (tetra-C4P), triisobutyl-methyl-phosphonium (t-*i*-C4C1P), trihexyl-tetradecyl-phosphonium (t-C6C14P) and benzyl-triphenyl-phosphonium (t-$PhCH_2PhP$).

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 10^{-13}. The classification of solubility by order of magnitude of the values appears to be very clear (Fig. 6). In the high solubility zone, the logarithmic 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 decreases against anion type in a generally similar, but not totally the same order, as 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

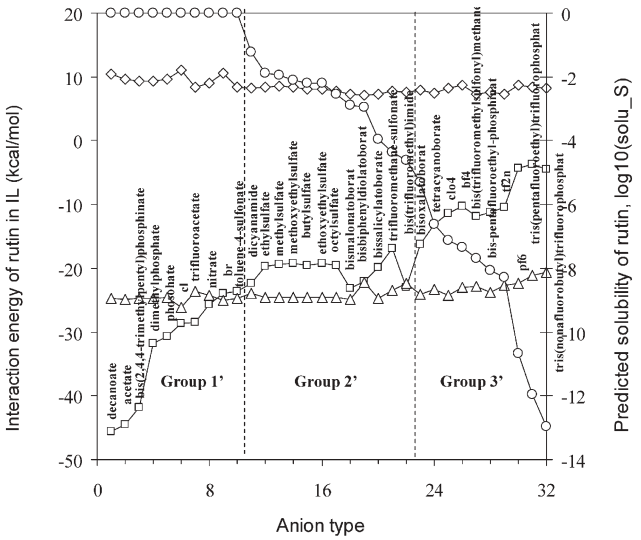


Fig. 6 COSMO-RS derived descriptors used to characterize the solvation interactions of rutin and BMIM-based ionic liquids with different anions. (○) Predicted solubility, (◇) misfit interaction energy, (□) H-bonding interaction energy and (△) van der Waals interaction energy in respective ILs at 298.15 K. All interactions are calculated at indefinite dilution. See the ESI† for the chemical structures of the anions evaluated.

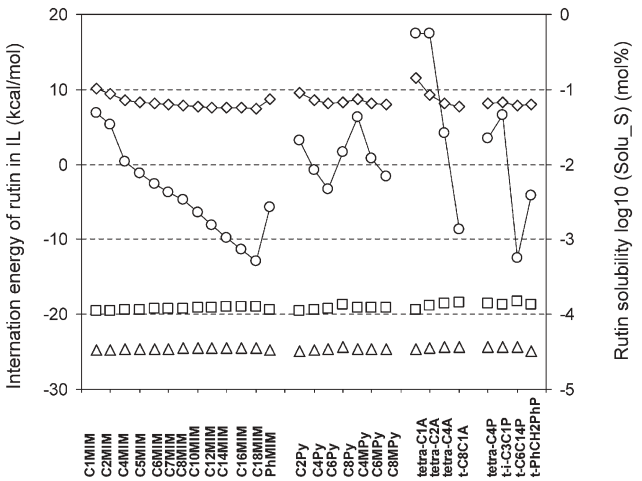


Fig. 7 Solvation interactions of rutin and methylsulfate based ionic liquids with different cations characterized by COSMO-RS derived descriptive parameters. (○) Predicted solubility, (◇) misfit interaction energy, (□) H-bonding interaction energy and (△) van der Waals interaction energy in respective ILs at 298.15 K. All interactions are calculated at indefinite dilution. The abbreviations are the same as in Fig. 5.

25 kcal mol^{-1}) are markedly higher than those for esculin (around 15 kcal mol^{-1}). This strong interaction results from the bigger molecular size and mass of rutin. Differently from esculin, the misfit interaction for rutin with anion alteration shows a smaller variability, indicating that in the same solvent environment, different solutes have different solvation or induce solvents to exhibit different polarities, as reported elsewhere.[26,32] The data in Fig. 6 show that there are strong H-bonding interactions between rutin and anions of ILs in the high solubility 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, and thus, lead to a significantly lower solubility of rutin in those ILs with weak H-bonding capability (Group 3′ in Fig. 6).

As we did for esculin, we also calculated the rutin solubility in the ILs having cations with varying substituents. Similar to the observations for esculin, the rutin solubility in the ILs with acetate anion is zero and in the ILs with PF_6^- anion is less than 10^{-6} (logarithm of molar fraction) regardless of substituent variation in the cation (details not shown). A greater variation range of the rutin solubility in the ILs containing methylsulfate as anion but with the alteration of substituents in the cation can be seen in Fig. 7. This change plausibly corresponds to the change of misfit interaction, indicating that rutin appears to be more sensitive to the incorporation of hydrophobic substituents due to the massive occurrence of polar saccharide rings. The increasing hydrophobicity of the cation may enhance the repulsion between IL and rutin, and counteract the H-bonding interaction that facilitates dissolution of rutin. This interaction may thus exert a more significant effect for those ILs with moderate H-bonding capability (*e.g.* methylsulfate), and leads to an evident decrease of the solubility of rutin (Fig. 7).

Concluding remarks 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 moieties 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.[25,28] Considering that the predictions of this model cover the 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,[35] carbohydrate,[36] and protein,[37] *etc*, the anions of which (Cl^-, Br^-, $H_2PO_4^-$ and

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 ESI

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	ClO_4	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	BF_4	2.4740
Br	29.6444	Bis-pentafluoroethyl phosphinate	12.6559	tf_2N	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	PF_6	0.0000
Trifluoroacetate	20.3944				
Nitrate	19.4858				

$(CN)_2N^-$, *etc*) are exclusively included in the first group of the categorization in this study ($(CN)_2N^-$ is 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 reasonableness of a logical extension of some conclusions in this work.

Importantly, the descriptors derived from COSMO-RS are also shown to give a different, but surprisingly equivalent description of the physics of molecules and a similar quantitative scaling in the corresponding terms of another experimental based solvation model—the Abraham equation.[32,38] The overlap of chemical content of the molecular descriptors between COSMO sigma-moments of COSMO-RS and experimental descriptors in the Abraham equation has been demonstrated elsewhere.[38] COSMO sigma-moments (total 5 parameters) are molecular descriptors derived from COSMO-RS calculation, among which the second and third sigma moment (Sig2 and Sig3) and the hydrogen bond moments (HB_acc3 and HB_don3), are chemically corresponding to the measures of polarity/polarizability, H-bonding basicity and H-bonding acidity, respectively.[38] The zeroth sigma-moment is identical with the molecular surface.[38] Table 1 lists the HB_acc3 of the anions evaluated in this work. Anions are good H-bonding acceptors but negligible donors (HB_don3 is generally zero, data not shown). This parameter could be used to classify ILs into 3 groups based on basicity (Table 1). Clearly, the categorization of anions in Table 1 is similar but not the same as in Fig. 4 and 6. For example, ethoxyethylsulfate and methoxyethylsulfate (Group I) belong to Group 2 in Fig. 4 or Group 2′ in Fig. 6. The reason is that HB_acc3 is an intrinsic property of the solvent and does not change with specific solute. However, the specific interactions between IL and different solutes can be different due to varying molecular size, surface charge density and distribution, symmetry, *etc* of the solute. Therefore, misfit, H-bonding and van der Waals interaction energies employed in this work could theoretically give a more correct and accurate description for the solvation behaviour of flavonoids in ILs. Our results show a comparable visualization of the solvation behaviours of ILs in the characterization of ionic liquids as described by Anderson *et al.*[32] Namely, the anion has a greater influence on the overall H-bond basicity of ILs; hydrogen bond basicity varies significantly with anions but vary little for cation alternation; and the dispersion forces show only a slight variability for the ILs evaluated. However, as a first rough selection of ILs for flavonoid dissolution, HB_acc3 is very useful to evaluate the H-bonding capability of anions (Table 1 and Fig. 4 and 6). Based on the changes of measures from COSMO-RS *versus* cationic variation depicted in Table 2, it is also easy to reason why misfit interaction energy decreases, H-bonding changes little and the corresponding decrease of solubility of flavonoids at the small scale follows the changes of cationic substituents (Fig. 5). In brief, the results in this study demonstrated that, as an experimentally independent approach, COSMO-RS is capable of producing a high-quality characterization of multiple solvation interactions of ILs comparable to that obtained from other experimental models. The knowledge and understanding of the relationships of properties with interactions and characteristic moieties of ILs can thereby serve molecular design and structural optimization for constructing a desirable structure with high solubility of flavonoids. However, the establishment of an efficient

Table 2 COSMO-RS descriptors of molecular surface area, the second sigma moment 2 (Sig 2 indicates polarity/polarizability) and HB_don3 (hydrogen bonding donor moment indicates hydrogen bond acidity) for the cations of 1-alkyl-3-methylimidalizium (alkylMIM)

Cations	Area/Å^2	Sig 2	HB_don3
MethylMIM	143.6001	88.0259	2.0735
EthylMIM	161.7652	85.3777	2.0727
ButylMIM	201.9685	84.7111	2.0647
PentylMIM	221.9982	85.2520	2.0537
HexylMIM	241.7418	86.0083	2.0371
HeptylMIM	261.8546	86.6088	1.9864
OctylMIM	281.5146	87.3381	2.0014
DecylMIM	321.5566	88.7644	1.9834
DodecylMIM	361.3977	90.2467	1.9988
TetradecylMIM	401.0784	91.7587	1.9814
HexadecylMIM	441.0983	93.3169	1.9932
OctadecylMIM	480.4567	94.8666	1.9960

enzymatic reaction system involves some unpredictable parameters, such as enzyme activity. Fortunately, COSMO-RS can also aid our effort in some way, because our results show that some parameters, such as water activity and activity coefficients in ILs relevant to enzyme activity, could be accurately estimated by COSMO-RS. The molecular design of ILs assisted by COSMO-RS is in progress in our group.

Experimental

Esculin and rutin hydrate (with purity >99%) were purchased from Sigma–Aldrich Co. (St. Louis, USA). Dimethylsulfonate (DMSO), methanol, acetic acid and triethylamine were from Sigma–Aldrich Co. (St. Louis, USA) and of HPLC grade. 1-Hexyl-3-methylimidazolium (HMIM.Cl), 1-butyl-3-methylpyridinium dicyanamide (BMPyi.N(CN)$_2$), 1-ethyl-3-methylimidazolium toluene-4-sulfonate (EMIM.OTs), 1,3-dimethylimidazolium dimethylphosphate (dMIM.dMP), 1-ethyl-3-methylimidazolium *n*-octylsulfate (EMIM.OctSO$_4$), 1-ethyl-3-methylimidazolium 2(2-methoxyethoxy)ethylsulfate (EMIM.MDEGSO$_4$), 1-ethyl-3-methylimidazolium ethylsulfate (EMIM.ES), methyltrioctylammonium bis(trifluoromethylsulfonyl)imide (tOMA.tf$_2$N), 1-butyl-3-methylimidazolium tetrafluoroborate (BMIM.BF$_4$) and 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM.PF$_6$) were procured from Solvent Innovation GmbH (Köln, Germany) and of minimum 98% purity. Methyltrioctylammonium trifluoroacetate (tOMA.TFA) is from Merck KGaA (Darmstadt, Germany) and with a purity >99.7%. 1-Butyl-1-methylpyrrolidinium dicyanamide (BMPyo.N(CN)$_2$) was purchased from IoLiTec Ionic Liquids Tchnologies GmbH & Co KG and of >98% purity (Denzlingen, Germany). The dissolution and equilibration of esculin or rutin in the solvent ILs were performed in a thermostat oven at 40 or 60 °C with ±0.1 °C accuracy. Typically, 2 mL of ionic liquid were accurately added in a 10 mL capped bottle fixed on a Variomag Telesystem with multiple magnetic stirrers (H+P Labortechnik AG, Oberschleissheim, Germany). The batchwise added esculin or rutin was dissolved with continuous magnetic stirring and the dissolution lasted over 2 months to allow sufficient equilibration. For the case of EMIM.OTs, ultrasonication was employed to assist the dissolution of rutin. The undissolved solid was removed by pressure filtration with a syringe filter (with 0.45 μm PTFE membrane) (Pall Life Science, Ann Arbor, MI, USA) at the same temperature. The resulting IL solution was immediately dissolved in DMSO for HPLC analysis.

The standard curves of esculin, rutin and different ILs were established, respectively. A series of sample concentrations of 0.05, 0.1, 0.2, 0.5, 1, 2, 3, 5 and 10 mg mL^{-1} in DMSO were used and the means of triplicate determinations were adopted. Based on the property of ILs, two elution systems were used for the HPLC analysis of esculin (rutin) dissolved in ILs. The solubility of flavonoids in BMIM.PF$_6$, BMIM.BF$_4$, tOMA.tf$_2$N and tOMA.TFA were eluted with methanol–water (containing 0.1% acetic acid); while other types of ILs use methanol–acetate-triethylamine (TEA) buffer (20 mM; pH, 4.0) elution system. The HPLC analysis was performed on a Hitachi-Merck HPLC Series 7000 (Hitachi-Merck, Japan), conjugated with a PL-ELS 2100 evaporative light scattering detector (ELSD) (Polymer Laboratories, Shropshire, UK). The reverse phase column employed was a Supelcosil LC-18 (250 mm × 4.6 mm) (Supelcosil Inc., Bellefonte, PA). The ELSD was operated at an evaporating temperature of 100 °C and a nebulizing temperature of 50 °C with air as the nebulizing gas at 1.2 SLM. For either methanol–water or methanol–buffer, the elution gradient follows the same program: starts with 30% methanol phase and increase to 100% methanol phase in 10 min; and holds for 6 min and then reduces to 30% methanol phase in 3 min, and keeps at this phase ratio for another 10 min. The mobile phase flow rate was 1.0 mL min^{-1}.

Area percentage was used as mass for solubility calculation. The measured values of the IL and flavonoid were calibrated using standard curves. All HPLC analyses were determined in triplicate and the means were used for evaluation.

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