Computational prediction of cellulose solubilities in ionic liquids based on COSMO-RS

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**ABSTRACT**: A computational approach is presented for prediction of cellulose solubilities in ionic liquids (ILs) based on COSMO-RS (Conductor-like Screening Model for Real Solvents). Thermodynamically stable molecular structures were optimized from 2D structures of cellulose and ILs following specific force-field based search of conformation lowest in energy and quantum chemical optimizations of molecular geometry. The thermodynamic property of logarithmic activity coefficient (lnγ) and excess enthalpy (HE) were calculated by COSMO-RS based on the COSMO molecular surfaces of cellulose and ILs to qualitatively predict the ability of ILs for cellulose dissolution. To evaluate the method, four sets of ILs were used to calculate lnγ and HE based on four different cellulose models. The goodness-of-fit of linear regressions between the experimental cellulose solubilities and the calculated lnγ and HE shows that lnγ is more reliable than HE for prediction of the dissolving power of ILs to dissolve cellulose. However, HE is more suitable for prediction of the dissolution ability of halogen-based ILs. Moreover, all the cellulose models gave comparably good prediction results regarding of the dissolving power of ILs based on the calculated lnγ, but the cellobiose model was identified as the optimal model due to the relatively higher prediction ability (R2) across different IL datasets. The approach is time efficient and robust, which provides a novel method for large-scale screening of ILs for cellulose dissolution.

Keywords: Ionic liquids; cellulose solubility; COSMO-RS; activity coefficient; excess enthalpy

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**1. Introduction**

Biomass is an abundant renewable resource on the earth [1]. Growing concerns about sustainability and environmental protection brings large amount of attention to efficient conversion of biomass into valuable products such as biofuels, chemicals and biomaterials, as the concept of biorefinery suggests [2-4]. Plants and plant-based biomass (lignocellulose) contains three major components: cellulose, hemicellulose and lignin [5]. Cellulose, as the largest component of lignocellulose and a sustainable raw material, is widely used in producing paper, fiber, membrane, and other commodity materials and chemicals, meanwhile, it has a high global quantity (~700,000 billion tons) and only a small amount (~0.1 billion tons) is currently used for production, which leaves a large space for wide employment [6, 7]. For the full utilization of cellulose, a prime step is to dissolve cellulose. Cellulose is a type of linear-chain biopolymer consisting of several hundred to over ten thousand β-(1–>4)-linked glucose repeating units [6, 8]. The linear structure enables numerous cellulose strands to be packed into crystalline fibrils through enormous number of intramolecular and intermolecular hydrogen bonds [9], which makes cellulose highly resistant to chemical modification and difficult to dissolve. Ionic liquids (ILs) as a new type of green solvents, provides the possibility to dissolve cellulose [8, 10] and lignocellulosic biomass [5, 11] in a clean process, which has attracted a great deal of academic and industrial interest. These solvents are salts generally composed of a large, low-symmetry and non-reactive organic cation and an organic or inorganic anion that can largely tune their physical and chemical properties [12, 13]. Compared to conventional solvents [14-19], ILs show remarkable properties such as low vapor pressure, high thermal stability, non-flammability, non-volatility and low toxicity. Moreover, by proper selection of cation – anion combinations, ILs can be tailored with desired properties (e.g. viscosity, density and solubility) [20, 21].

Appropriate ILs can be selected as cellulose solvents. In the recent years, more than 60 ILs have been experimentally examined for their solubilities of cellulose [8]. However, there is a vast number of ILs available, and selection of the most appropriate ILs with desired solubilities from a large pool of possible ILs for a specific task requires long time and many experiments, which highlights the advantage of using rapid and accurate *a priori* screening tools to predict the dissolution capacity of ILs. COSMO-RS (Conductor-like Screening Model for Real Solvents) as a physically founded approach combining quantum chemistry and statistical thermodynamics, has recently attracted great attention for calculation of thermodynamic properties [22-27]. COSMO-RS integrates dominant interactions of H-bonds, misfits, and van der Waals forces in the ionic liquid systems to characterize multiple solvation interactions, and can be used for performing mixture calculations at various temperatures [28]. With COSMO molecular surface generated by quantum chemical methods (QM), COSMO-RS calculates the charge distribution (σ-profile) on the molecular surface and chemical potential (μ) of molecule in a liquid solvent or mixture based solely on information concerning the 3D molecular structure. The computed chemical potentials are the basis for prediction of other thermodynamic equilibrium properties such as activity coefficient (γ), excess enthalpy (HE) and solubility. By reducing the thermodynamics of a mixture to the interaction of a number of surface segments, COSMO-RS gains full predictivity from underlying QM calculations, which enables high-speed screening of compounds for desired properties.

COSMO-RS has a general suitability for prediction of properties of IL systems [27, 29]. Previous publications have also demonstrated the applicability of COSMO-RS in prediction of solubilities of biopolymers [30-32] and drug molecules [28] in ILs based on COSMO surfaces of different molecular models. Given that an appropriate database of QM-COSMO calculations is available, COSMO-RS are well suited for the task of screening large numbers of solvents or solutes. On the other hand, the impact of conformations of cations/anions/solutes on the prediction quality of COSMO-RS is well recognized that even two different conformations with nearly identical energies for same molecule can result in complete different predictions of thermodynamic properties [33, 34]. Thus, it is important to carefully select molecular model and conformation in order to obtain quantitatively and qualitatively correct predictions. Sampling of multiple relevant conformers according to their Boltzmann distribution of free energy can be a good solution [30]. In this work, we were interested in examining the solubilities of cellulose in ILs by the use of a ‘medium’ thermodynamically stable conformational state [35] both for cellulose and IL in COSMO-RS calculation, which may help to rapidly reduce computation time. The thermodynamically stable molecular conformation was obtained through specific force-field based search of lowest-energy conformer and QM-based geometry optimization. The ADF COSMO-RS [36-39] was facilitated to conduct the DFT (density functional theory) optimization of molecular geometry and calculations of thermodynamic properties for prediction of cellulose solubilities in ILs on the availability of convenient scripting tools. In order to evaluate our approach, four different cellulose models (i.e. glucose, cellobiose, cellotriose and cellotetraose) were selected to represent cellulose, and four diverse sets of ILs were used to calculate the lnγ of cellulose in ILs and the HE of mixture at different temperatures. The calculated lnγ and HE were compared with available experimental data of cellulose solubilities by linear regression, and the best cellulose model for prediction of cellulose solubilities in ILs was selected based on the goodness-of-fit of the regressions.

2. **Methods**

**2.1. Theoretical basis for COSMO-RS calculation**

Dissolution of cellulose is a result of disruption of the inter- and intra-molecular hydrogen bonding, and the formation of new hydrogen bonds mainly between the carbohydrate hydroxyl protons and the anions of the ILs [35, 40-42]. The logarithmic activity coefficient (lnγ) of cellulose in ILs at infinite dilution and HE of mixture (0.8:0.1:0.1 in mole fraction for biopolymer, IL cation and anion respectively) which are supposed to have correlations with cellulose solubility were calculated by COSMO-RS to qualitatively measure the dissolution ability of ILs.

The activity coefficients is associated with the affinity of solutes to solvents resulting from differences in the strength and nature between molecules caused by local pairwise interactions of surface segments due to the electrostatic misfit, hydrogen bonding and van der Waals dispersive forces [34]. With the chemical potential (μiS) of a compound in a mixture being calculated, the activity coefficient (γiS) at a given temperature (T) can be derived by the following equation [23]:

, (1)

where μiS and μiX are the potential of compound *i* in the reference state of the mixture and the pure compound, respectively.

HE is a fundamental thermodynamic property (defined as the temperature derivative of the Gibbs free energy), which gives an insight into the behavior of the species in solution and can act as a sensitive measure of the intermolecular interactions within the mixture [33]. In the current version of ADF COSMO-RS, the HE (kJ/mol) is calculated based on Gibbs-Helmholtz equation:

, (2)

where GE is excess Gibbs free energy (kJ/mol), and T is temperature (K).

**2.2. Geometry optimization and COSMO-RS calculations**

The COSMO-RS calculations were based on the ADF COSMO result files [38], which are the results of COSMO quantum mechanical calculation on the basis of information solely concerning the molecular structure. The molecular structure used for COSMO calculation were generated through a computational route including following steps: 1) the molecules of cellulose models and ILs were sketched as 2D structures using Marvinsketch [43]; 2) the structures of cellulose models were subjected to a 3D conversion from 2D by Molconvert [43] and a conformational search at energy minimization based Dreiding force field [44] by Cxcalc [43]; and 3) the obtained lowest-energy conformer of celluloses were optimized with geometry based on PM6 [45] method of MOPAC [46, 47] – and this saves time of DFT optimization at the late stage that the SCF (self-consistent field) gets converged at a smaller amount of geometry cycles. In contrast, the ILs were conducted with searching a lowest-energy conformer based on the universal force field (UFF) [48] implemented in OpenBabel [49]. The PM6 method will deform the structures of some cations thus was not used in optimization of ILs. The obtained geometries of cellulose and ILs were further optimized to obtain the COSMO-RS result files by DFT method using the main parametrization GGA:BP/TZP in ADF [36]. The σ-profiles, σ-potentials, and thermodynamic properties such as lnγ and HE were then calculated at a given temperature by COSMO-RS based on the obtained COSMO result files. A self-developed scripting tool called MoDoop was utilized to automatize the overall computational workflow, which imports the 2D structures of cellulose and ILs and exports the COSMO-RS calculated σ-profiles, σ-potentials and thermodynamic properties. Here, generation of COSMO-RS result files is the most time-consuming step, but it only needs to be conducted once for each molecule. Given that the COSMO result file of a molecule is available, it can be reused in later COSMO-RS calculations. In addition, according to our preliminary results of lnγ calculation by ADF COSMO-RS, the hydrogen bond strengths of ILs that contain halogen elements (e.g. Cl-, Br- and I-) are in overall underestimated compared to those without halogen elements. We thus adjusted the values of the subkey CHB (chb) and SIGMAHBOND (σhb) of the key CRSPARAMETERS respectively to 7400 and 0.014 for the halogen-based ILs based on the discrepancy between the predicted values of our best model and the experimental data of cellulose solubilities in ILs reported in the literature [32]. The default values for the two subkeys are 8850 and 0.00854. The subkey HB\_ALL is also applied for the dataset including halogen-based ILs, otherwise, the default COSMO-RS parameter setting will be used.

**2.3. Cellulose models**

As COSMO-RS is based on time-consuming quantum chemical computation, the computing time increases drastically on the growing size of molecule, which makes it unfeasible for direct calculation of the whole cellulose molecule. A practical way is to choose a representative part of the polymer, which remains the major characteristic features of the molecule for efficient quantum chemical calculations. Even though one monomer (i.e. glucose) is usually enough to carry out studies on understanding crucial solute-solvent interactions responsible for the dissolution of the polymer, including more repeating units can introduce the actual interactions between neighboring monomeric units. In this work, four molecules composed of different numbers of glucose units were used to model the structure of cellulose - they are glucose, cellobiose, cellotriose and cellotetraose, as the respective 2D structure and COSMO molecular surface shown in Fig. 1(a)-(d).



**Fig. 1.**  COSMO molecular surfaces and 2D structures of four cellulose models: (a) glucose, (b) cellobiose, (c) cellotriose, and (d) cellotetraose. On the COSMO surface, the red regions indicate positive COSMO charge density with the underlying molecular charge negative, the blue regions indicate negative COSMO charge density with the underlying molecular charge positive, and the yellow and green regions indicate almost neutral charges.

**2.4. IL datasets**

Four sets of ILs [32, 50-52] were used to calculate lnγ of cellulose at infinite dilution and HE of mixture to estimate the solubilities of cellulose in ILs at different temperatures. The first set of ILs was used as the main set for evaluation of the predictivity of our method based on different cellulose models, and the other three sets were used to validate the reliability of the method. The COSMO result files for all the IL structures were also calculated based on the procedures described in section 2.2.

The first set of ILs consists of 357 ILs extracted from the work of Liu et al. [32] involving 17 potential cations of methylimidazolium+, pyridinium+, ethylmorpholinium+ and methylpyrrolidinium+ with functional groups of ethyl, allyl, 2-hydroxylethyl, 2-methoxyethyl or acryloyloxypropyl, and 21 common anions, as shown in Table 1 and 2 respectively. They have used this set of ILs to evaluate their ability to dissolve cellulose at 90 °C based on COSMO-RS, for which three cellulose models were used to represent cellulose, and the mole fraction of 0.5, 0.25 and 0.25 was set for the cellulose model, IL cations and anions. By comparing the regression fit between COSMO-RS calculated lnγ and experimental solubilities of microcrystalline cellulose (MCC) in seven ILs, the mid-monomer part of cellotriose was selected to be their best cellulose model.

Table 1. Cations of the first set of ILs [32]

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Cation | Structure | R |
| 1 | Emim |  |  |
| 2 | Amim |  |
| 3 | HOEtmim |  |
| 4 | EtOMmim |  |
| 5 | AOPmim |  |
| 6 | Epy |  |  |
| 7 | Apy |  |
| 8 | HOEtpy |  |
| 9 | EtOMpy |  |
| 10 | Eemor |  |  |
| 11 | Aemor |  |
| 12 | HOEtemor |  |
| 13 | EtOMemor |  |
| 14 | Empyrr |  |  |
| 15 | Ampyrr |  |
| 16 | HOEtmpyrr |  |
| 17 | EtOMmpyrr |  |

Table 2. Anions of the first set of ILs[32]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| No. | Anion | Structure | No. | Anion | Structure |
| 1 | Ac |  | 12 | HCOO |  |
| 2 | AlCl4 |  | 13 | HSO4 |  |
| 3 | Br |  | 14 | I |  |
| 4 | BF4 |  | 15 | MeOEtSO4 |  |
| 5 | BuSO4 |  | 16 | MeSO4 |  |
| 6 | BEN |  | 17 | N(CN)2 |  |
| 7 | Cl |  | 18 | PF6 |  |
| 8 | ClO4 |  | 19 | TF2N |  |
| 9 | DMP |  | 20 | TOS |  |
| 10 | DEP |  | 21 | DEC |  |
| 11 | DBP |  |  |  |  |

The second IL set includes seven ILs by the combinations of a common cation (C4mim+) (see Table 3) and seven different carboxylate anions (−COO−) (see Table 4). Experimental solubilities of MCC at 70°C were taken from the work of Xu et al. [50].

Table 3 Cations of the second set of ILs[50]

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Cation | Structure | R |
| 1 | C4mim |  |  |

Table 4. Anions of the second set of ILs[50]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| No. | Anion | Structure | No. | Anion | Structure |
| 1 | Ac |  | 5 | HOCH2COO |  |
| 2 | HCOO |  | 6 | HSCH2COO |  |
| 3 | C6H5COO |  | 7 | CH3CHOHCOO |  |
| 4 | H2NCH2COO |  |  |  |  |

The third IL set contains 9 imidazolium cations (C1mim+ - C9mim+) and 7 anions as shown in Table 5 and 6 respectively. The experimental solubilities of Avicel cellulose in some of the ILs at 100°C were taken from the work of Vitz et al. [51].

Table 5. Cations of the third set of ILs [51]

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Cation | Structure | R |
| 1 | C1mim |  |  |
| 2 | C2mim |  |
| 3 | C3mim |  |
| 4 | C4mim |  |
| 5 | C5mim |  |
| 6 | C6mim |  |
| 7 | C7mim |  |
| 8 | C8mim |  |
| 9 | C9mim |  |

Table 6. Anions of the third set of ILs[51]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| No. | Anion | Structure | No. | Anion | Structure |
| 1 | Ac |  | 5 | F |  |
| 2 | Br |  | 6 | I |  |
| 3 | Cl |  | 7 | MeO2PO2 |  |
| 4 | EtO2PO2 |  |  |  |  |

The fourth IL set is composed of 12 cations and 5 anions, as shown in Table 7 and 8 respectively. Most cations in this set are associated with a particular bulky structure or a long alkyl chain. The experimental solubilities of Avicel cellulose at 110°C were given with some of the ILs in this set referring to the work of Zhao et al. [52].

Table 7. Cations of the fourth set of ILs [52]

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Cation | Structure | R |
| 1 | Bu4N |  |  |
| 2 | Bu4P |  |  |
| 3 | C2mim |  |  |
| 4 | C4mim |  |
| 5 | C8mim |  |
| 6 | HOEt2MeIm |  |
| 7 | HOEt3MeIm |  |
| 8 | MeOEt2EtIm |  |  |
| 9 | MeOEt3EtIm |  |
| 10 | MeOEt4EtIm |  |
| 11 | MeOEt2Et3N |  |  |
| 12 | MeOEt3Et3N |  |

Table 8. Anions of the fourth set of ILs [52]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| No. | Anion | Structure | No. | Anion | Structure |
| 1 | Ac |  | 4 | N(CN)2 |  |
| 2 | Cl |  | 5 | TF2N |  |
| 3 | HCOO |  |  |  |  |

**3. Results and discussion**

**3.1. σ-potentials of cellulose models**

The chemical potential of a surface segment μs(σ) with charge density σ in COSMO-RS, which is also called σ-potential, is a measure for the affinity of the system S to a surface of polarity σ. The σ-potential distribution on the molecular surface can approximately be divided into three main regions: the H-bond donor region (σ < −0.0082 e Å-2), the non-polar region (−0.0082 < σ < +0.0082 e Å-2), and the H-bond acceptor region (σ > +0.0082 e Å-2) [33]. As shown in Fig. 2, cellotetraose presents strongest hydrogen bonding acceptor capacity among the four cellulose models, which is reflected by more positive σ-potential in the H-bond acceptor region while more negative σ-potential in the H-bond donor region than the other three models; cellotriose shows strongest hydrogen donor capacity which is reflected by more positive σ-potential in the H-bond donor region; glucose and cellobiose are in between, where the latter contains slightly more hydrogen donor volume than the former. Thus, cellotriose and cellotetraose give the most and least affinity for the H-bond acceptor surface, respectively. The ranking of solubilities of the four cellulose models in IL is found to be cellotriose > cellobiose > glucose > cellotetraose, given that the IL dissolution process is chiefly anion responsible.



**Fig. 2.**  σ-potentials of four cellulose models: glucose, cellobiose, cellotriose and cellotetraose predicted by COSMO-RS.

**3.2. lnγ, HE, σ-profiles vs. cellulose solubilities**

The thermodynamic property lnγ and HE calculated based on the four cellulose models by COSMO-RS are listed in Table 9 along with experimental cellulose solubilities at measured temperature of each IL dataset. Linear regressions were conducted between the experimental cellulose solubilities and the calculated lnγ and HE based on selected ILs from each dataset. The goodness-of-fit were measured by the R-squared (R2) and the residual standard error (RSE), and the results are listed in Table 10. The mean absolute error (MAE) is also given. The R2 values of the linear regressions show that lnγ generally gives more stable predictions of cellulose solubilities than that of HE for the first, second and fourth IL dataset. Casas et al. [31] also suggested that γ is a more reliable reference parameter than HE. However, HE gave a better prediction of dissolving power of the halogen ILs based on the third IL dataset. The same testing route on all the IL datasets were repeated using varied 2D structures of ILs with slightly different 3D conformations due to an random search, the similar prediction results were obtained. Thus, our approach is considered to be reliable and the results from one test of each are presented and discussed below.

**Table 9.** Experimental cellulose solubilities along with logarithmic activity coefficient (lnγ) and excess enthalpy (HE in kJ mol-1) of ILs calculated at measured temperature by COSMO-RS based on four cellulose models.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **IL** | **Solubility** | | **T ()** | **glucose** | | **cellobiose** | | **cellotriose** | | **cellotetraose** | |
| (wt%) | (g/mol IL) | **lnγ** | **HE** | **lnγ** | **HE** | **lnγ** | **HE** | **lnγ** | **HE** |
| [Emim]Ac1 | 27 | 46 | 90 | -8.92 | -8.53 | -12.50 | -8.77 | -18.68 | -8.97 | -17.30 | -8.41 |
| [Amim]Cl1 | <17 | <26 | 90 | -5.04 | -5.88 | -7.57 | -5.97 | -10.85 | -6.02 | -11.07 | -5.86 |
| [Emim]DEP1 | 15 | 40 | 90 | -5.36 | -6.23 | -7.73 | -6.47 | -11.86 | -6.71 | -9.96 | -5.98 |
| [Apy]Cl1 | 15 | 23 | 90 | -5.12 | -5.93 | -7.70 | -6.02 | -11.02 | -6.07 | -11.33 | -5.91 |
| [HOEtmim]Br1 | 9.1 | 19 | 90 | -3.49 | -5.44 | -5.26 | -5.49 | -7.62 | -5.53 | -7.33 | -5.37 |
| [HOEtpy]Br1 | 9.1 | 18 | 90 | -3.61 | -5.51 | -5.46 | -5.56 | -7.90 | -5.59 | -7.67 | -5.44 |
| [EtOMmim]Cl1 | 8.3 | 15 | 90 | -4.64 | -5.79 | -6.93 | -5.89 | -9.94 | -5.93 | -9.96 | -5.77 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| [C4mim]Ac2 | 15.5 | 30.7 | 70 | -13.59 | -7.48 | -19.23 | -7.76 | -28.57 | -8.02 | -27.90 | -7.31 |
| [C4mim]HCOO2 | 12.5 | 23.0 | 70 | -12.22 | -7.87 | -17.47 | -8.17 | -26.08 | -8.44 | -25.10 | -7.67 |
| [C4mim]C6H5COO2 | 12 | 31.2 | 70 | -11.33 | -5.65 | -16.10 | -5.89 | -23.90 | -6.11 | -23.04 | -5.46 |
| [C4mim]H2NCH2COO2 | 12 | 25.6 | 70 | -12.46 | -7.03 | -17.66 | -7.30 | -26.33 | -7.53 | -25.49 | -6.88 |
| [C4mim]HOCH2COO2 | 10.5 | 22.5 | 70 | -11.29 | -6.79 | -16.09 | -7.11 | -24.08 | -7.41 | -22.74 | -6.61 |
| [C4mim]CH3CHOHCOO2 | 9.5 | 21.7 | 70 | -9.02 | -5.47 | -13.08 | -5.74 | -19.65 | -6.04 | -18.23 | -5.20 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| [C2mim]Cl3 | 10-14 | 14.7-20.5 | 100 | -4.81 | -5.90 | -7.27 | -5.99 | -10.48 | -6.03 | -10.62 | -5.87 |
| [C6mim]Cl3 | 6 | 12.2 | 100 | -3.35 | -5.43 | -4.87 | -5.51 | -6.97 | -5.55 | -6.68 | -5.40 |
| [C7mim]Cl3 | 5 | 10.8 | 100 | -3.18 | -5.36 | -4.61 | -5.43 | -6.60 | -5.47 | -6.27 | -5.33 |
| [C4mim]Br3 | 2-3 | 4.4-6.6 | 100 | -3.25 | -4.99 | -4.82 | -5.05 | -6.91 | -5.10 | -6.77 | -4.93 |
| [C7mim]Br3 | 1 | 2.6 | 100 | -2.67 | -4.72 | -3.92 | -4.78 | -5.61 | -4.82 | -5.40 | -4.66 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| [C2mim]Ac4 | 15 | 25.5 | 110 | -7.56 | -8.03 | -10.62 | -8.27 | -15.83 | -8.44 | -14.66 | -7.90 |
| [MeOEt2EtIm]Ac4 | 12 | 31.0 | 110 | -9.04 | -7.09 | -12.81 | -7.37 | -19.04 | -7.60 | -18.25 | -6.93 |
| [MeOEt3Et3N]Ac4 | 10 | 30.7 | 110 | -9.52 | -6.96 | -13.51 | -7.30 | -20.00 | -7.60 | -19.42 | -6.78 |
| [MeOEt2Et3N]Ac4 | 10 | 26.3 | 110 | -9.11 | -7.10 | -12.90 | -7.43 | -19.09 | -7.70 | -18.43 | -6.93 |
| [HOEt2MeIm]Ac4 | 5 | 11.5 | 110 | -6.55 | -7.62 | -9.17 | -7.86 | -13.65 | -8.05 | -12.34 | -7.48 |
| [HOEt3MeIm]Ac4 | 2 | 5.5 | 110 | -5.48 | -7.39 | -7.64 | -7.63 | -11.38 | -7.82 | -9.92 | -7.27 |
| [C4mim]HCOO4 | 8 | 14.7 | 110 | -6.63 | -8.15 | -9.35 | -8.38 | -14.06 | -8.58 | -12.71 | -7.98 |
| [Bu4P]HCOO4 | 6 | 18.3 | 110 | -8.31 | -6.95 | -11.88 | -7.22 | -17.80 | -7.46 | -16.83 | -6.74 |
| [MeOEt2EtIm]Cl4 | 2 | 4.7 | 110 | -4.14 | -5.27 | -6.24 | -5.37 | -8.97 | -5.43 | -8.94 | -5.23 |

1,2,3,4: no. of IL dataset

**Table 10.** Goodness-of-fit of linear regressions between experimental cellulose solubilities and thermodynamic properties (lnγ and HE) calculated based on different cellulose models by COSMO-RS associated with different IL datasets.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **IL**  **set** | **Property** | **glucose** | | | **cellobiose** | | | **cellotriose** | | | **cellotetraose** | | |
| **R2** | **RSE** | **(MAE)** | **R2** | **RSE** | **(MAE)** | **R2** | **RSE** | **(MAE)** | **R2** | **RSE** | **(MAE)** |
| **1** | **lnγ** | 0.87 | 2.39 | 1.28 | **0.87** | **2.33** | **1.26** | 0.87 | 2.35 | 1.35 | 0.86 | 2.50 | 1.53 |
| **HE** | 0.81 | 2.89 | 1.96 | 0.81 | 2.89 | 1.90 | 0.80 | 2.92 | 1.97 | 0.81 | 2.90 | 2.06 |
| **2** | **lnγ** | 0.76 | 1.01 | 0.74 | 0.76 | 1.00 | 0.75 | 0.75 | 1.03 | 0.77 | **0.78** | **0.97** | **0.72** |
| **HE** | 0.24 | 1.78 | 1.30 | 0.22 | 1.80 | 1.31 | 0.20 | 1.83 | 1.33 | 0.26 | 1.76 | 1.29 |
| **3** | **lnγ** | 0.77 | 1.70 | 1.16 | 0.73 | 1.86 | 1.28 | 0.72 | 1.87 | 1.29 | 0.68 | 2.02 | 1.39 |
| **HE** | 0.98 | 0.55 | 0.38 | **0.98** | **0.53** | **0.36** | 0.98 | 0.55 | 0.37 | 0.97 | 0.57 | 0.40 |
| **4** | **lnγ** | 0.86 | 3.88 | 2.91 | 0.86 | 3.81 | 2.72 | 0.85 | 3.94 | 2.86 | **0.86** | **3.76** | **2.41** |
| **HE** | 0.12 | 4.16 | 3.26 | 0.15 | 4.10 | 3.15 | 0.16 | 4.06 | 3.07 | 0.11 | 4.19 | 3.29 |

The first set of ILs [32] was conducted with COSMO-RS calculation at 90°C. Cations and anions are sorted based on the scaled lnγ values with respect to each cellulose model as shown in Fig. 3, where the ILs with high dissolving power (strongly negative values of lnγ) appear in the lower left corner (blue area), while ILs with low dissolving power (positive values of lnγ) appear in the upper right corner (red area). The cations in Fig. 3(a) - (d) appear in same orders in the high (HOEtmim - HOEtemor) and low dissolving power area (Aemor - Empyrr) and slightly different order in the medium area. The main difference in the order of the anions is associated with the halogen ILs.

** Fig. 3.** The logarithmic activity coefficients (lnγ) of cellulose at infinite dilution in 357 ILs calculated by COSMO-RS at 90°C based on four cellulose models: (a) glucose, (b) cellobiose, (c) cellotriose, and (d) cellotetraose. The lnγ values were scaled.

The linear regressions between experimental solubilities (in wt%) of microcrystalline cellulose (MCC) at 90°C and the calculated lnγ and HE were conducted based on seven ILs, good correlations were obtained with all the four cellulose models, and the cellobiose model (see Fig. 4) was identified as the best model (R2=0.87, RSE=2.33) for prediction of the lnγ.



**Fig. 4.** Linear regression between experimental cellulose solubility at 90°C and COSMO-RS calculated lnγ based on the cellobiose model and seven ILs from the first dataset.

The lnγ values predicted from the four cellulose models show high correlation (R2>=0.95) with the ones predicted by the mid-monomer of cellotriose of Liu et al. [32], and the cellobiose model was identified to have the most predictive power (R2=0.87, RSE=2.33). Moreover, the four models provided good prediction of dissolution ability of HOEtmimBr and HOEtpyBr, but slightly underestimated the dissolution capacity of AmimCl compared to the experimental data. It was also found that the dissolution power of EtOMmimCl was overestimated by the models, which was also reported in the literature [31, 32]. Kahlen et al. [30] stated that the ability of chloride to form hydrogen bonds was not fully taken into account in COSMO-RS, which may result in the disagreements between the experimental and predicted results of chloride ILs. Nevertheless, the four models used in this work provided good predictions of cellulose solubilities in non-halogen ILs. According to the σ-profile analysis by Liu et al. [32], the BEN- anion should generally have more dissolution capacity than the DEP- anion, and this order is in good agreement with the lnγ prediction results of all the four cellulose models as shown in Fig. 3. The σ-profiles of cellobiose, BEN- and DEP- anion also show that BEN- is more complementary than DEP- with cellulose within the non-polar and H-bond acceptor region (see Fig. 5), which further confirms that BEN- has more cellulose dissolution power than DEP-.



**Fig. 5.** σ-profile of cellobiose, BEN- and DEP-.

The second set of ILs [50] was conducted with COSMO-RS calculation at 70°C. Linear regressions were conducted between the experimental solubilities (in wt%) of microcrystalline cellulose (MCC) and the calculated values of lnγ and HE with respect to each cellulose model. The cellotetraose model gave highest goodness-of-fit with lnγ (R2=0.78, RSE=0.97) based on all the carboxylate anions excluding HSCH2COO- as shown in Fig. 6. The cellobiose model (Fig. 6 right) predicts the most similar results with the cellotetraose model, which can be used as an alternative model when considering the time cost of COSMO-RS calculation. Moreover, Zhao et al. [53, 54] suggested the following aspects attribute to better dissolution (i) ions with less steric hindrance, and (ii) anions with high electronegativity and without any electron-withdrawing group, which was well proved by the experimental values of this dataset. The suggested attributes related to size and electronegativity were confirmed by some of the anions in the lnγ prediction of cellulose solubilities. For instance, HCOO- has higher solubility than C6H5COO- due to less steric hindrance; H2NCH2COO- has higher solubility than HOCH2COO- due to weaker electron-withdrawing group; and CH3CHOHCOO- has lowest solubility due to the bulky structure and the strong electron-withdrawing group. However, some conflicts are still remaining, for instance, the predicted solubility of HCOO- is slightly lower than H2NCH2COO-, and the solubility of HSCH2COO- was not properly predicted.



**Fig. 6.** Linear regression between experimental cellulose solubilities at 70°C and COSMO-RS calculated lnγ based on the cellotetraose (left) and cellobiose (right) model and six ILs from the second dataset.

The third set of ILs [51] was conducted with COSMO-RS calculation at 100°C. Five halogen-based ILs (three Cl- and two Br-) associated with a common cation of C4mim+ that have experimental solubilities of Avicel cellulose (>0 wt%) mutually consistent with available rules (such as, the higher the hydrogen bond basicity and polarity of the anion, the more efficient of the IL to dissolve cellulose [50, 55]) were selected for validation of the cellulose solubility prediction by COSMO-RS. The glucose model turned out to give the best prediction of experimental cellulose solubility by lnγ (R2=0.77, RSE=0.11) as shown in Fig. 7. However, according to the regression analysis, two chloride ILs were underestimated and two bromide ILs were overestimated with their dissolution ability. In contrast, the excess enthalpy (HE) gave much better predictions based on the cellobiose model (R2=0.98, RSE=0.53) as indicated in Fig. 7, where the tendency of the calculated HE were in good agreement with the experimental cellulose solubilities. Thus, HE is considered as a better indicator of cellulose solubilities in halogen contained ILs particularly associated with same cations.



**Fig. 7.** Linear regression between experimental cellulose solubility at 100°C and COSMO-RS calculated lnγ (left) and HE (right) respectively based on the glucose (left) and cellobiose (right) model and five ILs from the third dataset.

The fourth set of ILs [52] was conducted with COSMO-RS calculation at 110°C. Most ILs in this set are associated with a bulky or long-chain cation. 9 ILs available with experimental solubility of Avicel cellulose (>=2 wt%) that were mutually consistent with the available knowledge (e.g., the ability of the ILs to dissolve cellulose decreases with increased alkyl chain length of the cations [53, 56]) were selected for validation of the COSMO-RS predictions. As a result, all the cellulose models gave stably high prediction of experimental cellulose solubility (in g mol-1 IL) by lnγ, and the best prediction results was found from the cellotetraose model (R2=0.86, RSE=3.76) as shown in Fig. 8. In the presence of some large-size cations, the measured cellulose solubilities can be dominated by the molecular weights of ILs, which could be the reason why the solubility data in g mol-1 IL rather than in wt% has better regression fit with the calculated property data. Among the remaining models, the cellobiose model (Fig. 8) presents the second best prediction of the experimental cellulose solubility by lnγ (R2=0.86, RSE=3.81), which can be considered as an alternative model.



**Fig. 8.** Linear regression between experimental cellulose solubility at 110°C and COSMO-RS calculated lnγ based on the cellotetraose (left) and cellobiose (right) model and 9 ILs from the fourth dataset.

Based on the above evaluation, it is verified that lnγ as a more reliable reference property can be well applied to predict cellulose solubilities in different ILs, especially non-halogen ILs, while HE is more suitable for prediction of the dissolving power of halogen-based ILs. With the lnγ calculation, the four cellulose models gave comparably good predictions of the dissolution ability of ILs. Although the glucose model gave best predictions for halogen-based ILs and the cellotetraose model presented best predictions for homogenous non-halogen ILs, the cellobiose model always give best or second best predictions regarding the goodness-of-fit values measured by R2 and RSE for all type of ILs. Cellobiose is also a comprehensive and economic model which introduces actual interactions between neighboring monomeric units by inclusion of repeating units in minimum, therefore it can be considered as the optimal model for screening of different types of ILs related to cellulose dissolution. The key factors of cellulose dissolution in selected ILs are the dominant interactions of H-bonds, misfits, and van der Waals forces in IL systems, which summarize multiple solvation interactions between cellulose and ILs, and are characterized as a whole by the COSMO-RS calculated thermodynamic properties.

**4. Conclusions**

A computational approach was developed for prediction of cellulose solubilities in ILs based on COSMO-RS. The COSMO-RS calculations were based on COSMO molecular surfaces of cellulose and ILs optimized from their 2D structures following specific route of force-field based searching of conformation lowest in energy and geometry optimizations by quantum chemical methods. The structure optimization method is time efficient and uses single thermodynamically stable conformer for representation of cellulose and IL, thus enables large-scale *in silico* screening of ILs. Four cellulose models were evaluated in our approach based on four sets of ILs with experimental cellulose solubilities measured at different temperatures. The lnγ at infinite dilution and HE, as sensitive indicators of molecular interactions, were calculated by COSMO-RS. lnγ has generally good predictions of cellulose solubility across all the IL datasets and is thus considered as a reliable reference property for qualitative prediction of cellulose solubility. In addition, the high goodness-of-fit of the linear regression between the experimental cellulose solubility and lnγ also made it possible for quantitative prediction of cellulose solubilities in ILs. The HE provides relatively poor prediction for each IL dataset, however, it gave good prediction of the dissolving power of the halogen-based ILs. By comparing the prediction results, the cellobiose model was selected as the best model among all the four models for screening of different types of ILs for cellulose dissolution. Nevertheless, it is worth noting that COSMO-RS are conformational sensitive, and the conformational states searched by different approaches (force fields, geometry optimization methods, etc.) may lead to different thermodynamic estimations of COSMO-RS. In other words, the best cellulose model is highly dependent on the approaches applied on the structure optimization, which highlights the significance of our optimization method.

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