Supporting Information

Theoretical study on solvation mechanism of camptothecin in ionic liquids

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1. Details of molecular simulations

The interactions of ILs with the solute molecules were described by the sum of the Lennard-Jones repulsion-dispersion interaction potential and the Coulomb interaction potential:

$$U = U_{L-J} + U_{Coulon} = \sum_{a=1}^{m} \sum_{b=1}^{n} (4\varepsilon_{ij}^{ab} \left[\left(\frac{\sigma_{ij}^{ab}}{r_{ij}^{ab}} \right)^{12} - \left(\frac{\sigma_{ij}^{ab}}{r_{ij}^{ab}} \right)^{6} \right] + \frac{q_i^a q_j^b}{4\pi\varepsilon_0 r_{ij}^{ab}}) \qquad (S1)$$

here the values of the parameters σ_{ij}^{ab}, r_{ij}^{ab} are the LJ parameters at site a in a molecule i and site b in a molecule j, respectively, r_{ij}^{ab} is the distance between sites a and b, q_i^a and q_j^b are the charges at sites a and b, respectively, and ε_0 is the vacuum permittivity. Potential parameters σ_{ij} and ε_{ij} for the interaction between the atoms of the ionic liquid components with the atoms of CPT molecules are calculated using the Lorentz-Berthelot rule. To describe the interaction between the components of the ionic liquid with the site-site interactions, the Buckingham-type models were used:

$$U_{ij}^{exp-6} = \sum_{a=1}^{m} \sum_{b=1}^{n} \left(\frac{\varepsilon_{ij}^{ab}}{1 - \frac{6}{a_{ij}^{ab}}} \left[\frac{6}{a_{ij}^{ab}} \exp \left(a_{ij}^{ab} \left[1 - \frac{r_{ij}^{ab}}{r_{m,i,j}^{ab}} \right] \right) - \left(\frac{r_{m,i,j}^{ab}}{r_{ij}^{ab}} \right)^6 \right] + \frac{q_i^a q_j^b}{4\pi\varepsilon_0 r_{ij}^{ab}} \right) \qquad (S2)$$

Table S1. The Lennard-Jones parameters and partial atomic charges used in this work.

	Atom	σ (Å)	ε (kcal/mol)	q (e)
CPT	CM	3.5500	0.2929	-0.1540
	CM	3.5500	0.2929	-0.1766
	CM	3.5500	0.2929	-0.0904
	CM	3.5500	0.2929	-0.3120
	CT	3.5000	0.3347	0.5232
	CT	3.5000	0.3347	-0.0580
	NT	3.2500	0.7113	-0.6144
	CM	3.5500	0.3180	0.4591
	CM	3.5500	0.2929	-0.1191
	CM	3.5500	0.2929	-0.1987
	CT	3.5000	0.3347	-0.0679
	NT	3.2500	0.7113	-0.0336
	CT	3.5000	0.2761	-0.0427

	CM	3.5500	0.2929	-0.1152
	CM	3.5500	0.2929	-0.2744
	CM	3.5500	0.3180	-0.1254
	CM	3.5500	0.2929	0.4995
	CT	3.5000	0.2761	0.4525
	CM	3.5500	0.2929	0.7231
	O2	2.9000	0.5858	-0.4222
	CT	3.5000	0.2761	0.1337
	O	2.9600	0.8786	-0.5811
	O	2.9600	0.8786	-0.5516
	OH	3.1200	0.7113	-0.5930
	CT	3.5000	0.2761	-0.1654
	CT	3.5000	0.2761	-0.1805
	HC	2.4200	0.1255	0.1439
	HC	2.4200	0.1255	0.1555
	HC	2.4200	0.1255	0.1463
	HC	2.4200	0.1255	0.1817
	HC	2.4200	0.1255	0.1927
	HC	2.5000	0.1255	0.1187
	HC	2.4200	0.1255	0.1658
	HC	2.5000	0.1255	0.0860
	HC	0.0000	0.0000	0.3744
	HC	2.5000	0.1255	0.0704
	HC	2.5000	0.1255	0.0582
[Omim]$^+$	CM	3.5500	0.3180	-0.0720
	CM	3.5500	0.3180	-0.1920
	NT	3.3000	0.7113	0.1760
	CT	3.5000	0.2761	-0.1920
	CT	3.5000	0.2761	-0.2800
	CT	3.5000	0.2761	-0.1360
	CT	3.5000	0.2761	-0.0960
	HC	2.5000	0.1255	0.1680
	HC	2.5000	0.1255	0.2160
	HC	2.5000	0.1255	0.1440
	HC	2.5000	0.1255	0.0480
	HC	2.5000	0.1255	0.0640
[Br]$^-$	Br-	4.6238	0.3766	-0.8000
[BF$_4$]$^-$	B	3.5814	0.3975	0.6620
	F	3.1181	0.2510	-0.3655
[Cl]$^-$	Cl-	4.4172	0.4928	-0.8000
[ClO$_4$]$^-$	Cl	3.5000	0.4928	0.9400
	O	2.9000	0.8786	-0.4350
[HsO$_4$]$^-$	S	3.5500	1.0460	1.3057
	O	2.9600	0.7113	-0.6616
[NO$_3$]$^-$	N	3.1500	0.7113	0.6352

[NTf₂]⁻	O	2.8600	0.8786	-0.4784
	N	3.2500	0.7113	-0.5280
	S	3.5500	0.0460	0.8160
	O	2.9600	0.8786	-0.4240
	CT	3.5000	0.2761	0.2800
	F	2.9500	0.2218	-0.1280
[OAc]⁻	C	3.7500	0.4393	0.5600
	O	2.9600	0.8786	-0.6400
	CT	3.5000	0.2761	-0.2240
	HC	2.5000	0.1255	0.0480
[PF₆]⁻	P	3.7400	0.8700	1.0720
	F	3.1181	0.2522	-0.3120
[TsO]⁻	CM	3.5500	0.2929	-0.4395
	CM	3.5500	0.2929	-0.0501
	CM	3.5500	0.2929	-0.1595
	CM	3.5500	0.2929	-0.0775
	CM	3.5500	0.2929	-0.1630
	CM	3.5500	0.2929	-0.0388
	CT	3.5000	0.2761	-0.1627
	S	3.5500	1.0460	1.2926
	O	2.9600	0.7113	-0.6325
	HC	2.4200	0.1255	0.1524
	HC	2.4200	0.1255	0.1047
	HC	2.4200	0.1255	0.1367
	HC	2.5000	0.1255	0.0658

2. Electrostatic potential (ESP) analysis

Fig. S1 exhibits different potential interaction sites of CPT, cation, and anions by analyzing the ESPs. Where the red and blue colors represent negative and positive ESPs, respectively, and the darker the colors are, the stronger the ESPs are. It can clearly see that the positive and negative areas of CPT are in turn mainly concentrated around the hydroxyl hydrogen and carbonyl oxygen. In terms of cation, the positive regions are dominantly centered on the aromatic ring hydrogen of [Omim]⁺ cation. Similarly, although the negative parts are mainly around the bromine, fluorine, chlorine and oxygen atoms of ten anions, there are large differences in electronegativity between the anions due to different structures. Therefore, the hypothetical interactions of CPT with ions of ILs may include HB, electrostatic, van der
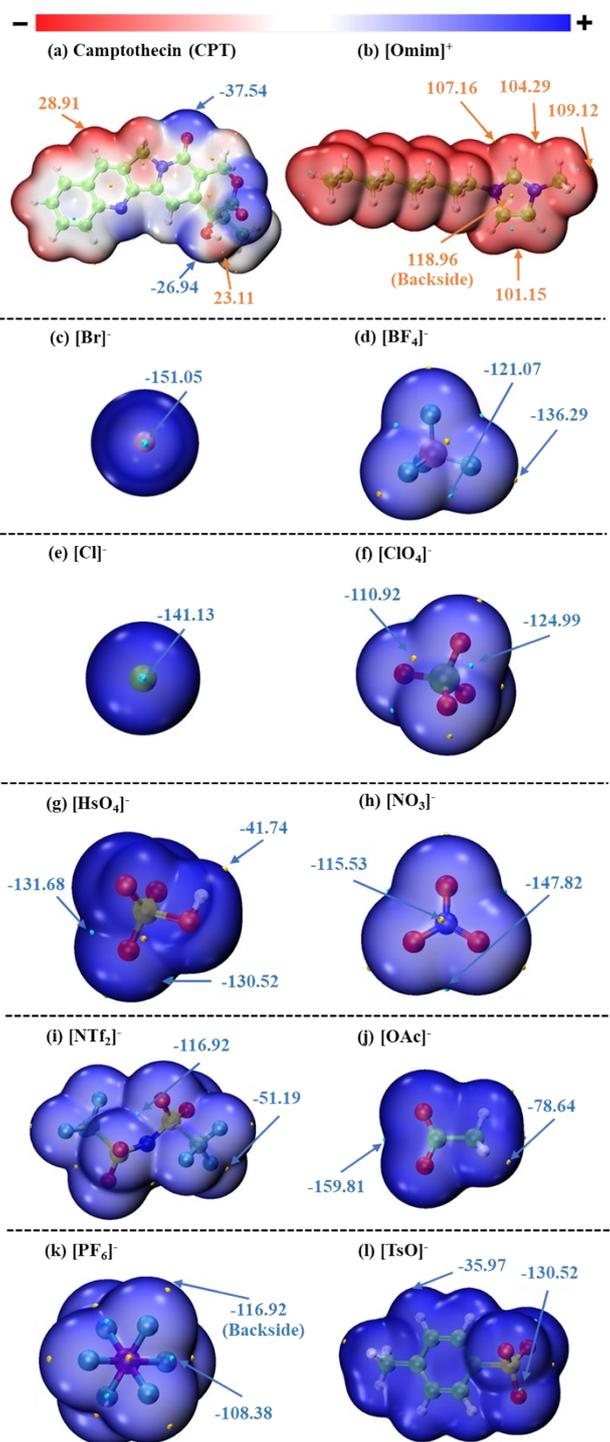
Waals and π−π stacking.

Figure S1. Geometrics and electrostatic potential surfaces (ESPs) of (a) CPT, (b) [Omim]⁺, (c) [Br]⁻, (d) [BF₄]⁻, (e) [Cl]⁻, (f) [ClO₄]⁻, (g) [HsO₄]⁻, (h) [NO₃]⁻, (i) [NTf₂]⁻, (j) [OAc]⁻, (k) [PF₆]⁻, and (l) [TsO]⁻ (isodensity contour =0.001 a.u.).

3. Analysis of System Equilibrium

To this end, in the NPT production phase, the density of the process and the root mean square deviation (RMSD) of solute in the system determine whether the system reached equilibrium. Figures S2 and S3 show the changes of system density and RMSD of CPT with time of ten CPT-ILs systems at 298.15 K and 1 atm during the production of MD simulation. As can be seen from Figure S2, in the last 10 ns of MD simulation, the density of ten systems is stable, indicating that each system is stable and in equilibrium. Moreover, it can be seen from Figure S3 that the RMSD of solute in the ten systems reached equilibrium in the first 10 ns of the MD simulation process, that is, the data of production molecular dynamics simulation is reliable for subsequent analysis.
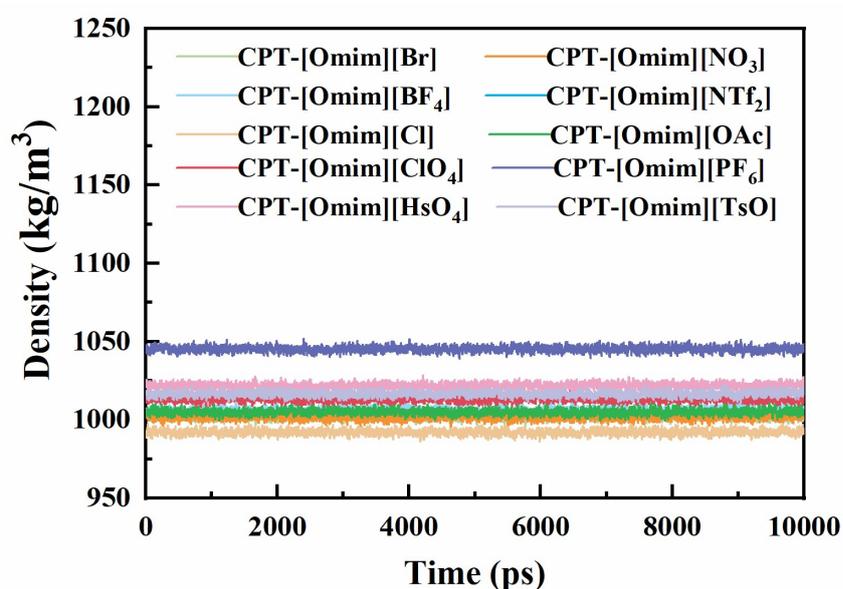

Figure S2. The changes of ten mixed system density during the production of MD simulation.
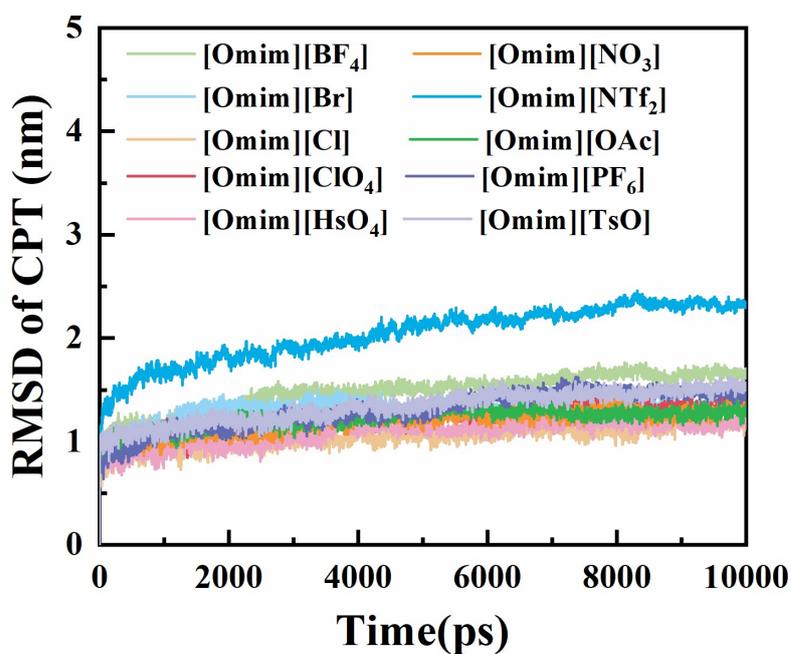
Figure S3. The RMSD of solute in the system during the production of MD simulation.

4. Definition of the first solvation shell

Table S2. The definition of the first solvation shell used in this work.

ILs	r(Å)
[Omim][Br]	5.35
[Omim][BF$_4$]	6.02
[Omim][Cl]	5.86
[Omim][ClO$_4$]	5.73
[Omim][HsO$_4$]	5.44
[Omim][NO$_3$]	6.11
[Omim][NTf$_2$]	6.06
[Omim][OAc]	5.87
[Omim][PF$_6$]	5.47
[Omim][TsO]	6.01

5. Definition and results of the intermittent time correlation function (TCF) of hydrogen bond (HB), $C_{HB}(t)$.

The HB dynamics are characterized by the intermittent TCF, $C_{HB}(t)$, which is calculated according to eqn (S3):

$$C_{HB}(t) = \frac{\langle h(0)h(t)\rangle}{\langle h(0)h(0)\rangle}$$

(S3)

where h(t) is variable of HBs. h(t) corresponds to 1 if the HB exist at time t otherwise it is equal to zero. Therefore, the intermittent TCF $C_{HB}(t)$ can better reflect the process of the formation, breaking, reformation, and the rebreaking of HBs. Namely, $C_{HB}(t)$ reports the structural relaxation time of HBs (τ_C^{HB}). Fig. S2 represents plots of the intermittent TCF $C_{HB}(t)$ between the anions or cations and CPT for the ten studied mixtures.
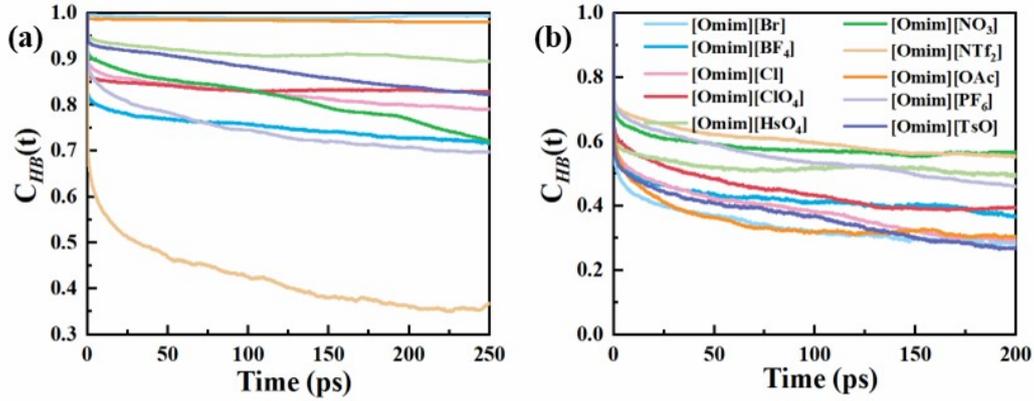

Figure S4. The intermittent time correlation function (TCF) for all HBs in CPT-ILs mixtures: (a) camptothecin-anion (CPT-A), and (b) camptothecin-cation (CPT-C).

6. Definition and calculation scheme for the interaction energy

In this work, the interaction energies between CPT and ILs were calculated by the sum of contributions from the van der Waals and the electrostatic interactions, which were defined by the following expressions:[1–4]

$$E_{\text{ele}} = \sum_{i=1}^{N} \sum_{j=i+1}^{N} \frac{q_i q_j}{r_{ij}}$$

(S4)

$$E_{vdW} = \sum_{i=1}^{N} \sum_{j=i+1}^{N} \left(4\varepsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] \right)$$

(S5)

where parameters q, ε and σ are the atomic charges, well-depths and collision diameter, respectively, while r_{ij} was the distance between atoms i and j. As reported, these two terms can be used to r_{ij} less than a cutoff value.[3] Based on this, van der Waals energy and

electrostatic interaction energy contributions were computed by averaging the energies in every time step of the simulation, where the average interaction energies were calculated by employing a cutoff of 12 Å. Accordingly, E_{vdW} were calculated by the sum of van der Waals energies of CPT with cations and anions, i.e., $E_{vdW} = E_{vdW}^{C\text{-}CPT} + E_{vdW}^{A\text{-}CPT}$. Similarly, E_{ele} are defined as the sum of electrostatic energies of CPT with cations and anions, e.g., $E_{ele} = E_{ele}^{C\text{-}CPT} + E_{ele}^{A\text{-}CPT}$. Then, the van der Waals and electrostatic energies contribute to the total intermolecular interaction energy between CPT and ILs, i.e., $E_{IL\text{-}CPT} = E_{vdW} + E_{ele}$.

7. Definition and calculation scheme for the self-diffusion coefficients

Self-diffusion coefficients (D) for systems were calculated from last the 10 ns of MD trajectory using the slope of mean square displacement (MSD), based on the Einstein relation as expressed in eqn (S6):

$$D_i = \frac{1}{6}\lim_{t \to \infty} \frac{d}{dt}\langle[\vec{r}_i(t) - \vec{r}_i(0)]^2\rangle = \frac{1}{6}\lim_{t \to \infty} \frac{d\Delta r_i^2}{dt} \tag{S6}$$

where $\vec{r}_i(t)$ and $\vec{r}_i(0)$ represent the position of the ion i at time t and 0, respectively. The quantity in braces is the ensemble-averaged MSD of the corresponding molecule, and 1/6 indicates that the system is three-dimensional.

In this work, the estimate self-diffusion coefficient of ILs was obtained by eqn (S7) approximately

$$D = 0.5(D_+ + D_-) \tag{S7}$$

where D_+ and D_- are self-diffusion coefficients calculated by eqn (6) of cation and anion, respectively.

8. Method and detail for viscosity calculation

For viscosity calculation, some researchers obtained the viscosity by Green–Kubo (GK)[5]

formula via equilibrium MD trajectories, however, it requires a larger calculation to support the simulation results. Another method is the correlation of the self-coefficient based on the Stokes-Einstein equation,[6] but the result dependents on the reference viscosity. In this work, viscosities of systems were obtained by the nonequilibrium molecule dynamics (NEMD) simulation. In the simulation process, we added perturbation to the systems and it resulted in a velocity gradient according to the following eqn (S8):

$$a_x(z) + \frac{\eta}{\rho} \frac{\partial^2 v_x(z)}{\partial z^2} = 0 \tag{S8}$$

where

$$a_x(z) = A cos\left(\frac{2\pi z}{l_z}\right) \tag{S9}$$

$$v_x = V cos\left(\frac{2\pi z}{l_z}\right) \tag{S10}$$

$$V = \frac{\sum_{i=1}^{N} m_i v_{i,x} cos\left(\frac{2\pi z}{l_z}\right)}{\sum_{i=1}^{N} m_i} \tag{S11}$$

An acceleration $a_x(z)$ was applied in the x direction, which is a function of the z coordinate, v_x is the velocity, l_z is the height of the box, and the viscosity can be calculated from A and V

$$\eta = \frac{A}{V}\rho\left(\frac{l_z}{2\pi}\right)^2 \tag{S12}$$

and the values of NEMD parameters are presented in the section Simulation Details.

9. Verify the suitability of the basis set

Table S3. The single point energy of anion and cation in the studied drug and IL was calculated using the combination of B3LYP/6-311++G (d, p) and M062X/6-311G (d, p) base groups

Hartree	B3LYP/6-311++G (d, p)	M062X/6-311G (d, p)
CPT	-1182.543654	-1182.049165

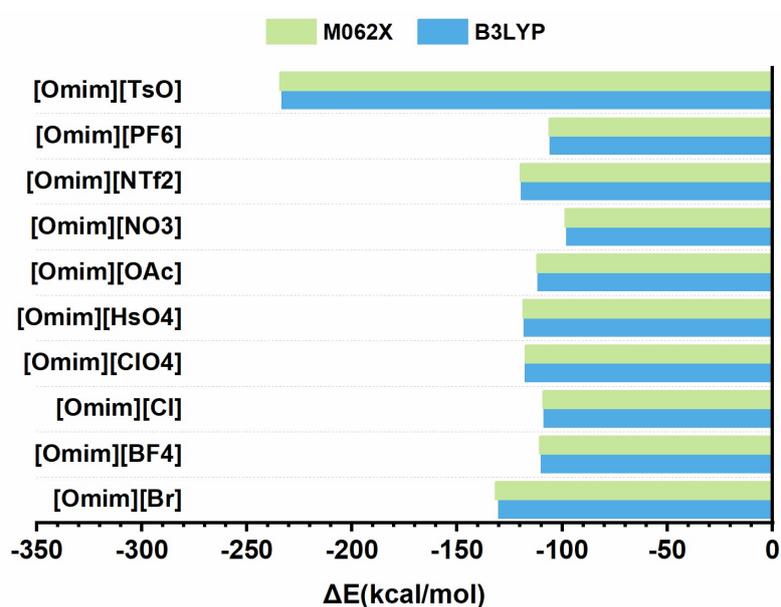|		
Omim	-580.746523	-580.428092
BF$_4$	-424.648901	-424.231926
Br	-24.611361	-24.647785
Cl	-460.30071	-460.131649
ClO$_4$	-760.913067	-760.560007
HsO$_4$	-699.818308	-699.494791
OAc	-280.425517	-280.167074
NO$_3$	-1827.587373	-1826.927344
NTf$_2$	-228.578313	-228.367624
PF$_6$	-940.869297	-940.326637
TsO	-895.012269	-894.595686

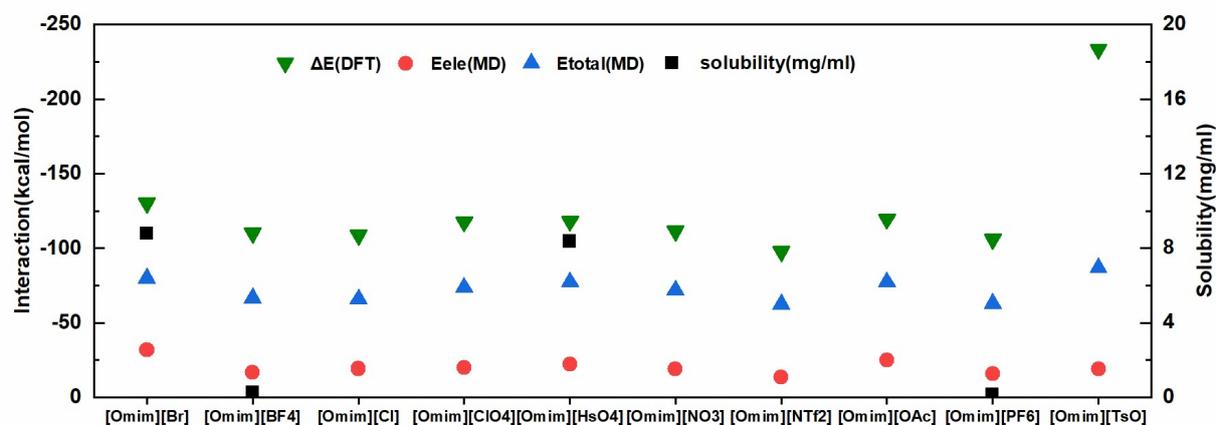**Figure S5.** The binding energy of each system is calculated by different base groups.

Figure S6. The Change trends between CPT and ILs in different IL systems of binding energy ΔE calculated by DFT, electrostatic and total interactions simulated by MD, and experimental solubility data.

References

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