

## Supplementary Information

### **A synergistic ‘push and pull’ ionic liquid biphasic system for enhanced extraction separation of cholic acid and deoxycholic acid**

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## Computational Details of COSMO-RS

COSMO-RS (Conductor-like Screening Model for Real Solvents), is a predictive method for thermodynamic equilibria using a statistical thermodynamics approach based on the quantum chemical calculations<sup>1</sup>. In COSMO calculations, the solute molecules, which are CA and DCA molecules in this study, are calculated in a virtual conductor environment to induce a polarization charge density on the interface between the molecule and the conductor<sup>2</sup>.  $\sigma$ -profile ( $p^i(\sigma)$ ) is the relative amount of surface with polarity  $\sigma$  on the surface of molecule. The interaction energy model including electrostatic ( $E_{\text{misfit}}$ ), hydrogen bonding ( $E_{\text{HB}}$ ) and van der Waals ( $E_{\text{vdW}}$ ) can be calculated, and then the chemical potential and infinite dilution activity coefficient  $\gamma^i_S$  of solute ( $i$ ) in solvent ( $S$ ) can be obtained according to Eq (1) - Eq (7). The capacity and selectivity of solute ( $i$  and  $j$ ) in solvent ( $S$ ) can be predicted according to Eq (8), Eq (9) and Eq (10):

$$p_s(\sigma) = \sum_{i \in S} x_i p^i(\sigma) \quad (1)$$

Where  $p_s(\sigma)$  and  $p^i(\sigma)$  refer to  $\sigma$ -profile of the mixture of several compounds and each compound, respectively.

$$E_{\text{misfit}}(\sigma, \sigma') = \alpha' a_{\text{eff}}(\sigma + \sigma')^2 \quad (2)$$

$$E_{\text{HB}} = a_{\text{eff}} c_{\text{HB}} \min(0; \min(0; \sigma' + \sigma_{\text{HB}}) \max(0; \sigma - \sigma_{\text{HB}})) \quad (3)$$

$$E_{\text{vdW}} = a_{\text{eff}}(\tau_{\text{vdW}} + \tau'_{\text{vdW}}) \quad (4)$$

Where  $\alpha'$ ,  $a_{\text{eff}}$ ,  $c_{\text{HB}}$ , and  $\sigma_{\text{HB}}$  refer to an interaction parameter, the effective contact area, the hydrogen bond strength and the threshold for hydrogen bonding respectively, and  $\tau_{\text{vdW}}$  and  $\tau'_{\text{vdW}}$  refer to the element specific vdW interaction parameters.

$$\mu_S(\sigma) = -\frac{RT}{a_{\text{eff}}} \ln \left[ \int p_S(\sigma') \exp \left( \frac{RT}{a_{\text{eff}}} (\mu_S(\sigma') - E_{\text{misfit}}(\sigma, \sigma') - E_{\text{HB}}(\sigma, \sigma')) \right) d\sigma' \right] \quad (5)$$

$$\mu^i_S = \mu^i_{C,S} + \int p^i(\sigma) \mu_S(\sigma) d\sigma \quad (6)$$

$$\gamma^i_S = \exp \left( \frac{\mu^i_S - \mu^i_i}{RT} \right) \quad (7)$$

$$Capacity_i = 1 / \gamma'_S \quad (8)$$

$$Capacity_j = 1 / \gamma'_S \quad (9)$$

$$Selectivity_{ij} = \gamma'_S / \gamma'_S \quad (10)$$

Where  $\mu_S(\sigma)$ ,  $\mu^i_{C,S}$ ,  $\mu^i_S$ ,  $\mu^i_i$  and  $\gamma'_S$  refer to  $\sigma$ -potential measuring the affinity of the system to a surface of polarity  $\sigma$ , the area and volume parameter, the chemical potential in solvent  $S$ , the chemical potential of pure compound  $i$  and infinite dilution activity coefficient of solute ( $i$ ) in solvent ( $S$ ).

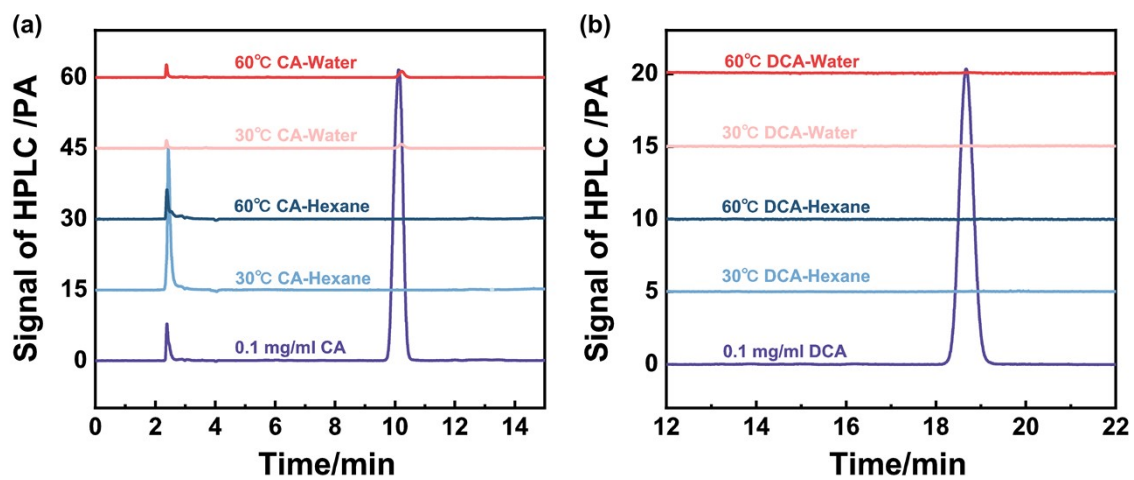
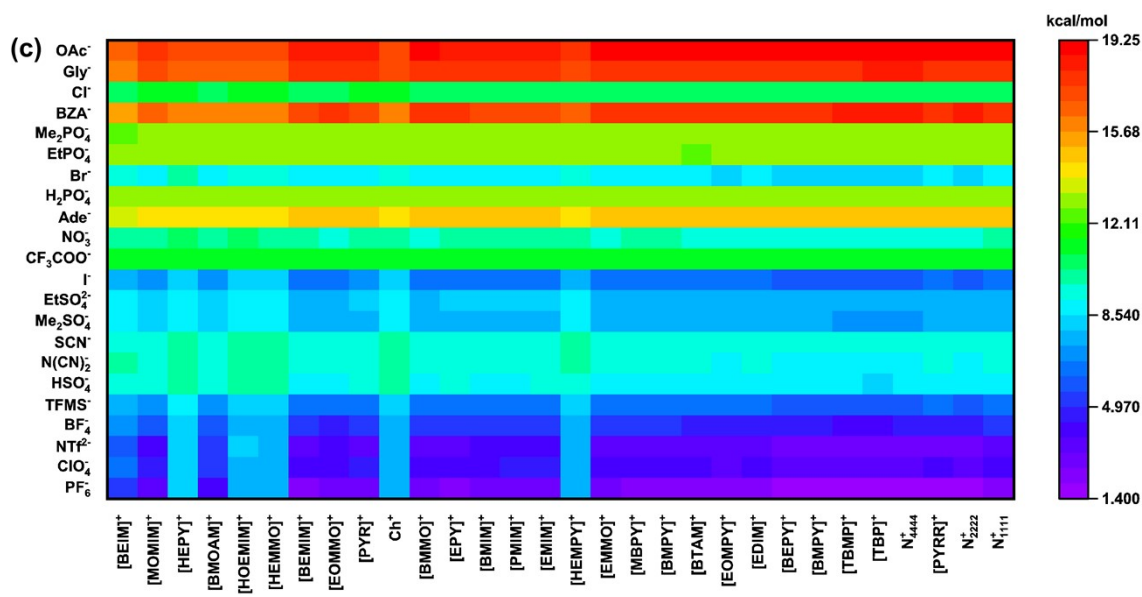
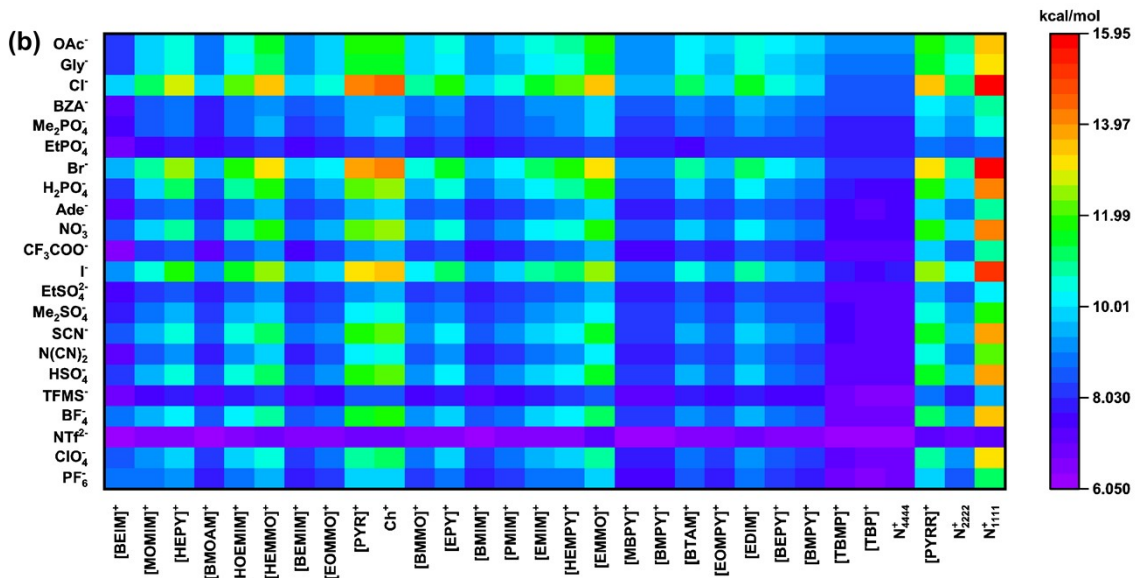
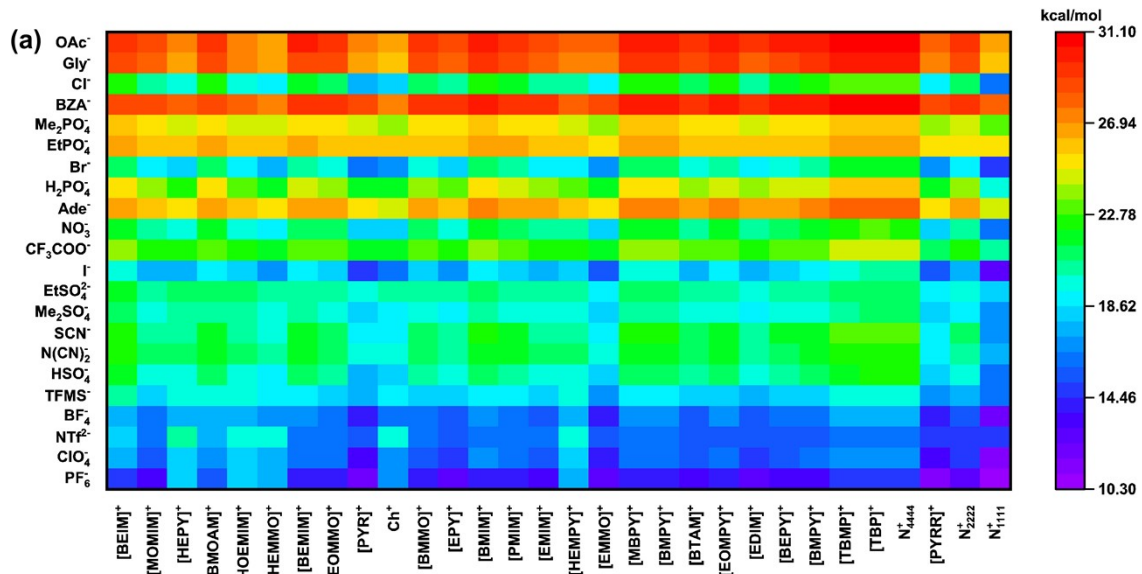


Figure S1. The HPLC curves of saturated solutions of (a) CA and (b) DCA in hexane and water at 30°C and 60°C compared with the 0.1 mg/ml standard solution. The similar amount of CA and DCA samples from hexane and water were all diluted ten times.



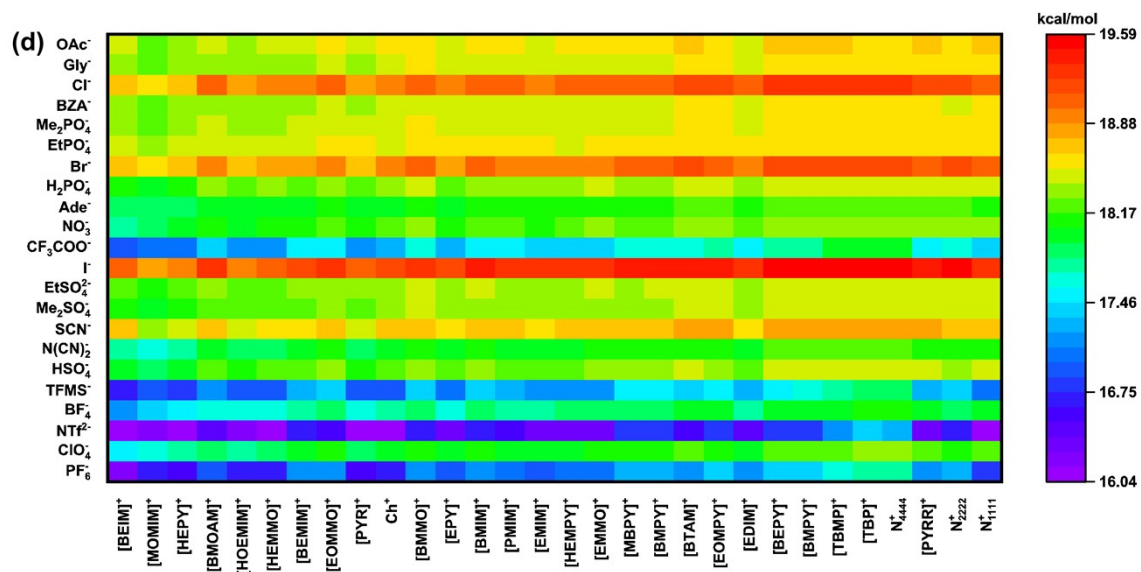
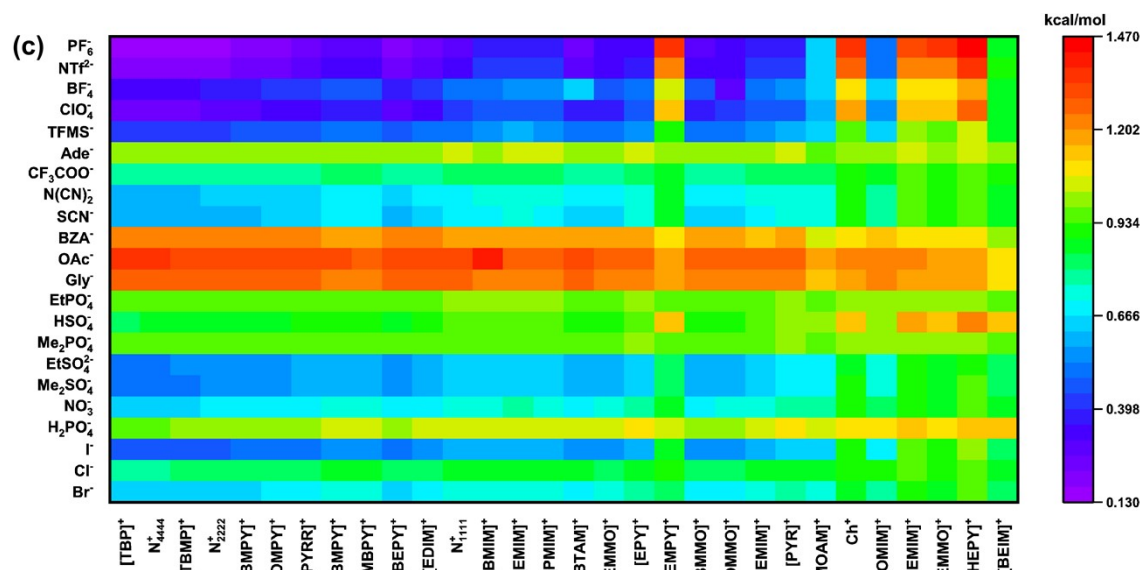
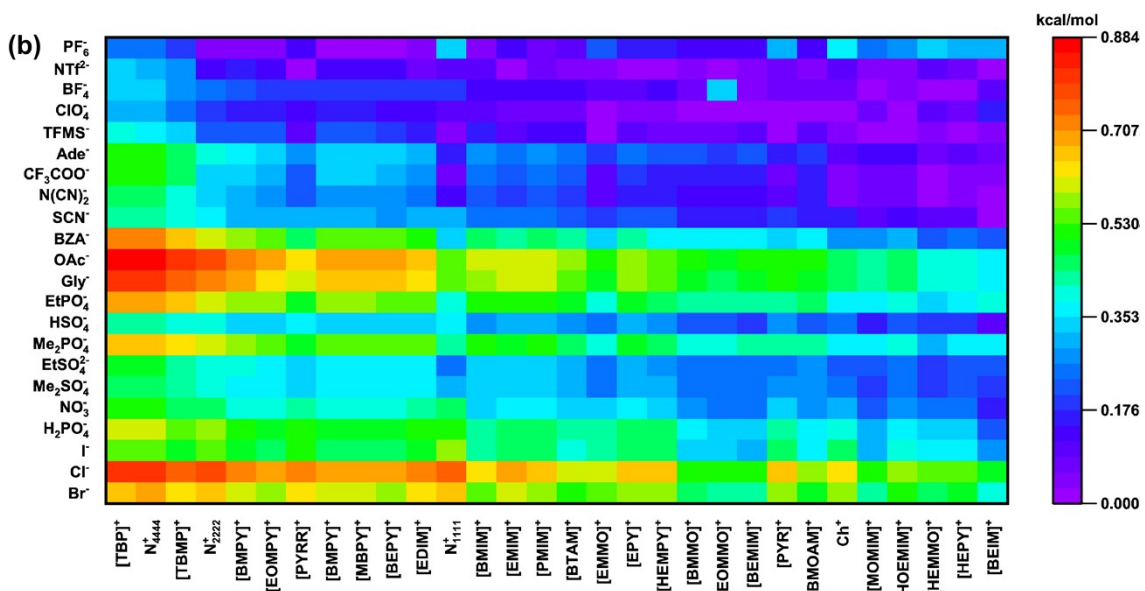
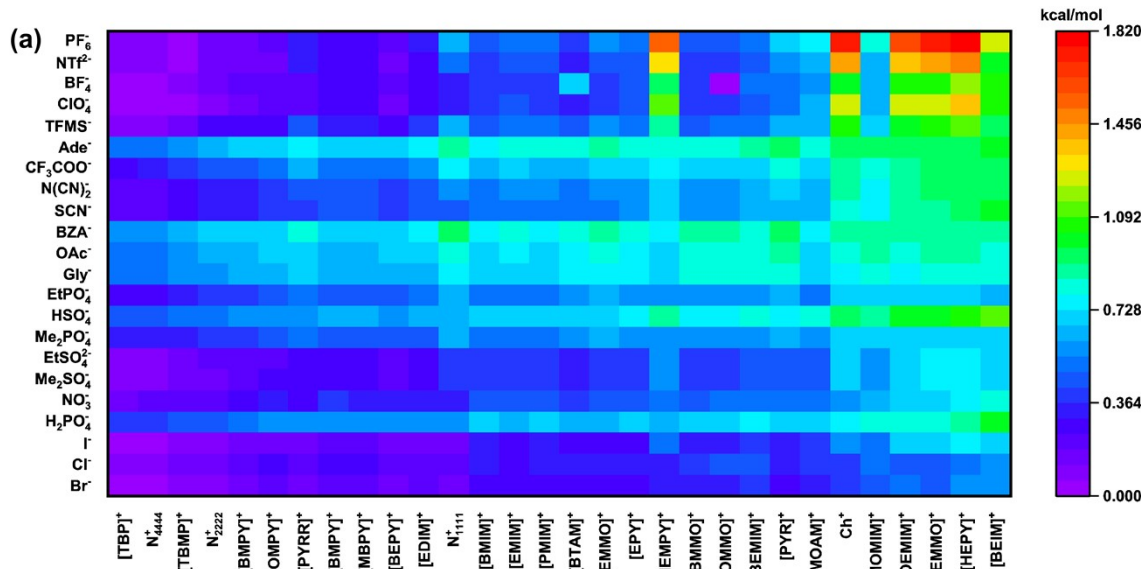


Figure S2. The intermolecular forces of CA and ILs predicted by COSMO-RS: (a) total mean interaction force; (b) misfit interaction force; (c) hydrogen bonding force and (d) van der Waals force between ionic liquids and CA at infinite dilution. The cations and anions were sequenced with the same as the capacity of CA in ionic liquids.



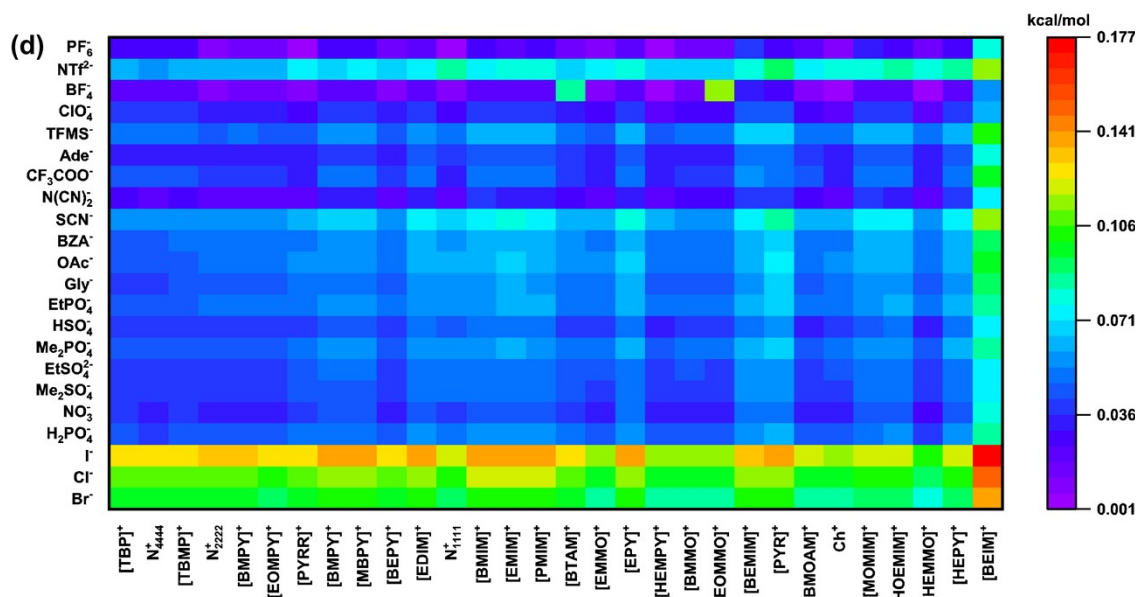


Figure S3. The differences of intermolecular forces between CA-ILs and DCA-ILs predicted by COSMO-RS at infinite dilution: (a) the absolute value differences of the total mean interaction forces; (b) misfit forces; (c) hydrogen bonding forces and (d) Van der Waals forces. The cations and anions were sequenced with the same as the selectivity of CA to DCA in ionic liquids.



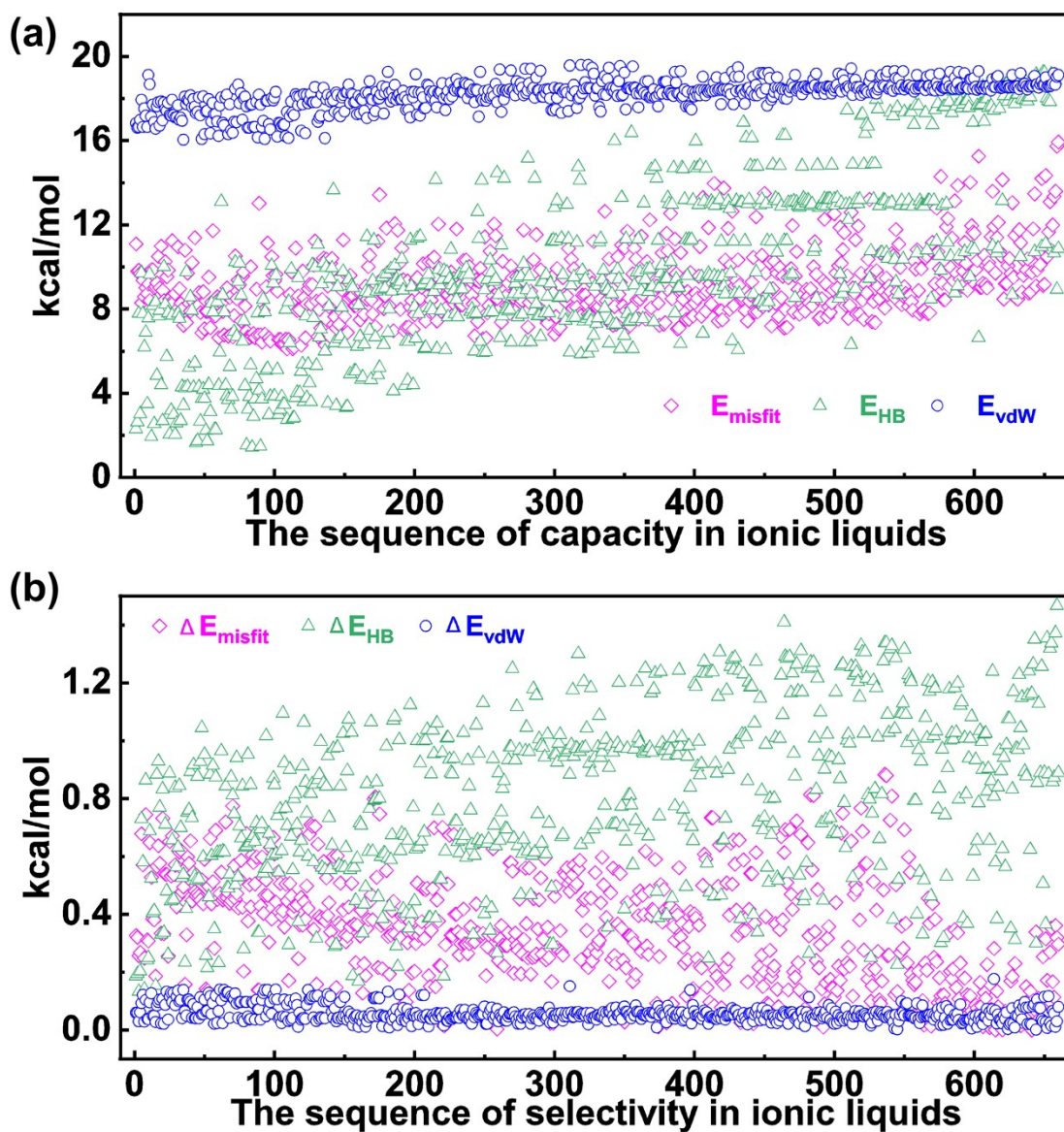


Figure S4. The correlation between capacity prediction of CA and three intermolecular interactions (a) in 660 ILs by COSMO-RS. The correlation between selectivity prediction of CA-DCA and the absolute difference of three intermolecular interactions (b) in 660 ILs by COSMO-RS.

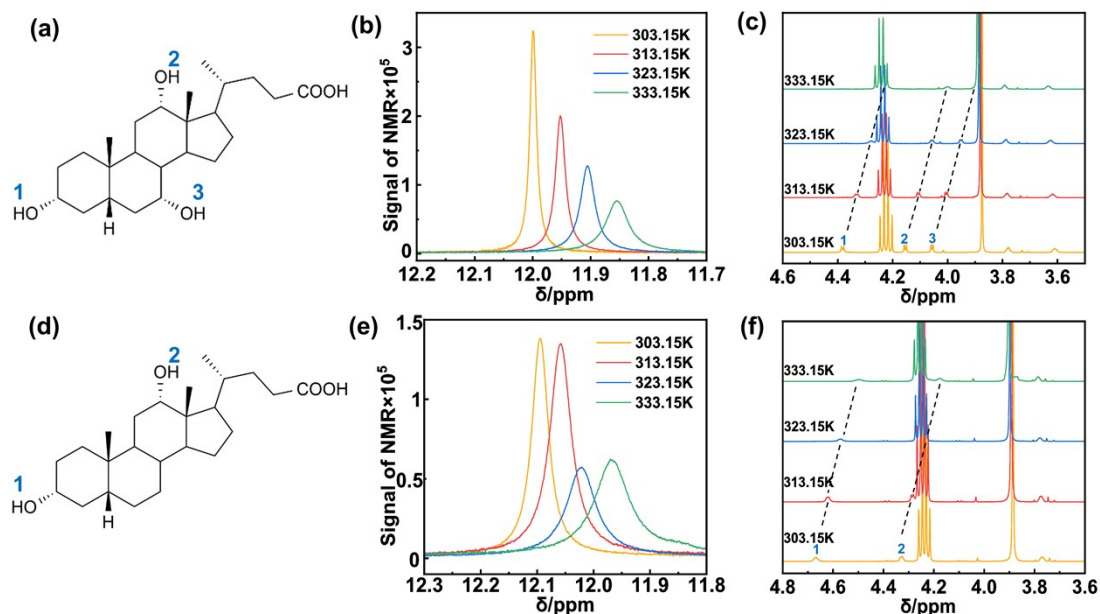


Figure S5. The chemical structure and active hydrogens number of CA (a);  $^1\text{H-NMR}$  chemical shifts of the carboxyl hydrogen of CA in [EMIM]Cl-CA mixture at different temperatures ( $\delta/\text{ppm}$ , relative to  $\text{TMS-}d_6$ ) (b);  $^1\text{H-NMR}$  chemical shifts of three hydroxyl hydrogens of CA in [EMIM]Cl-CA mixture at different temperatures (c); The chemical structure and active hydrogen numbers of DCA (d);  $^1\text{H-NMR}$  chemical shifts of the carboxyl hydrogen of DCA in [EMIM]Cl-DCA mixture at different temperatures (e);  $^1\text{H-NMR}$  chemical shifts of two hydroxyl hydrogens of DCA in [EMIM]Cl-DCA mixture at different temperatures (f).

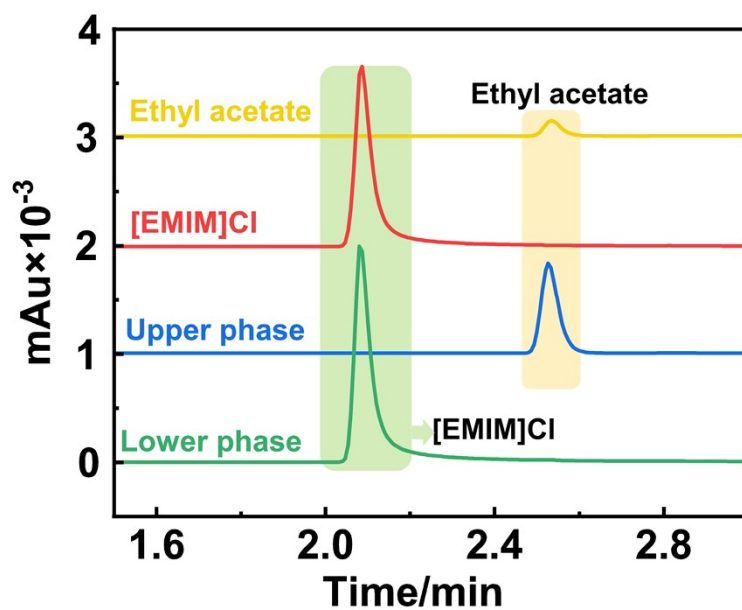


Figure S6. The HPLC chromatograms of samples taken from the upper (blue) and lower (green) phases after liquid-liquid equilibrium at 303.2 K, and those of 10 mg/mL ethyl acetate (yellow) and 5 mg/mL [EMIM]Cl (red) dissolved in methanol were shown as control. The biphasic system was initially composed of 10 mol.% [EMIM]Cl aqueous solution and ethyl acetate of equal volume. Samples from the upper and the lower phases were both diluted by ten times with methanol. The injection volume of all the samples was 1  $\mu$ L.

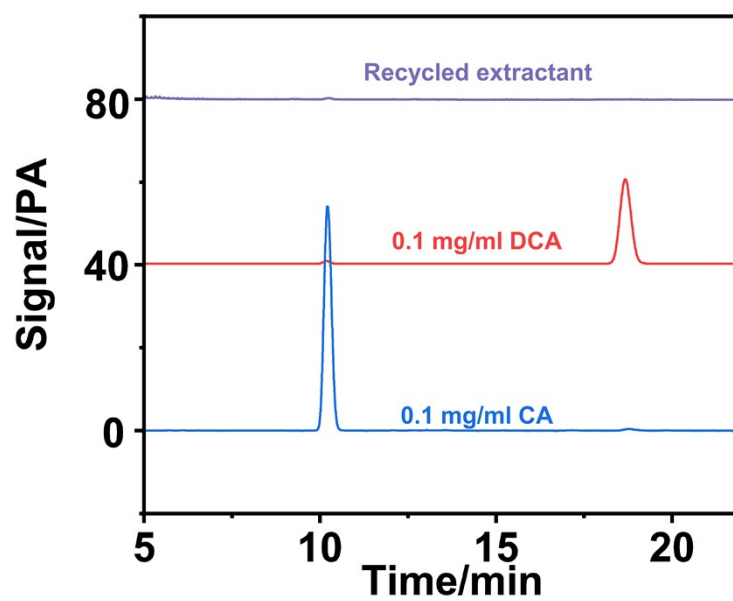


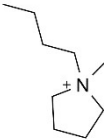

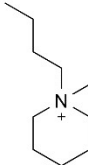

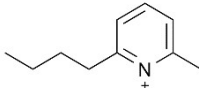

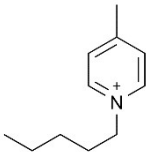
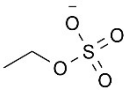
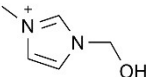
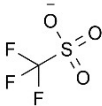
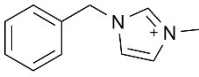
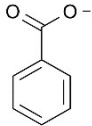
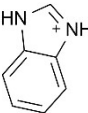

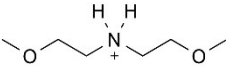



Figure S7. HPLC chromatograms of the recycled extractant solution (purple), 0.1 mg/mL CA (red) and DCA (blue) solutions, respectively. The sample from the recycled extractant was diluted by five times and the injection volume was all 10  $\mu$ L. The concentration of CA in the diluted recycled extractant was determined to be 0.002 mg/mL.

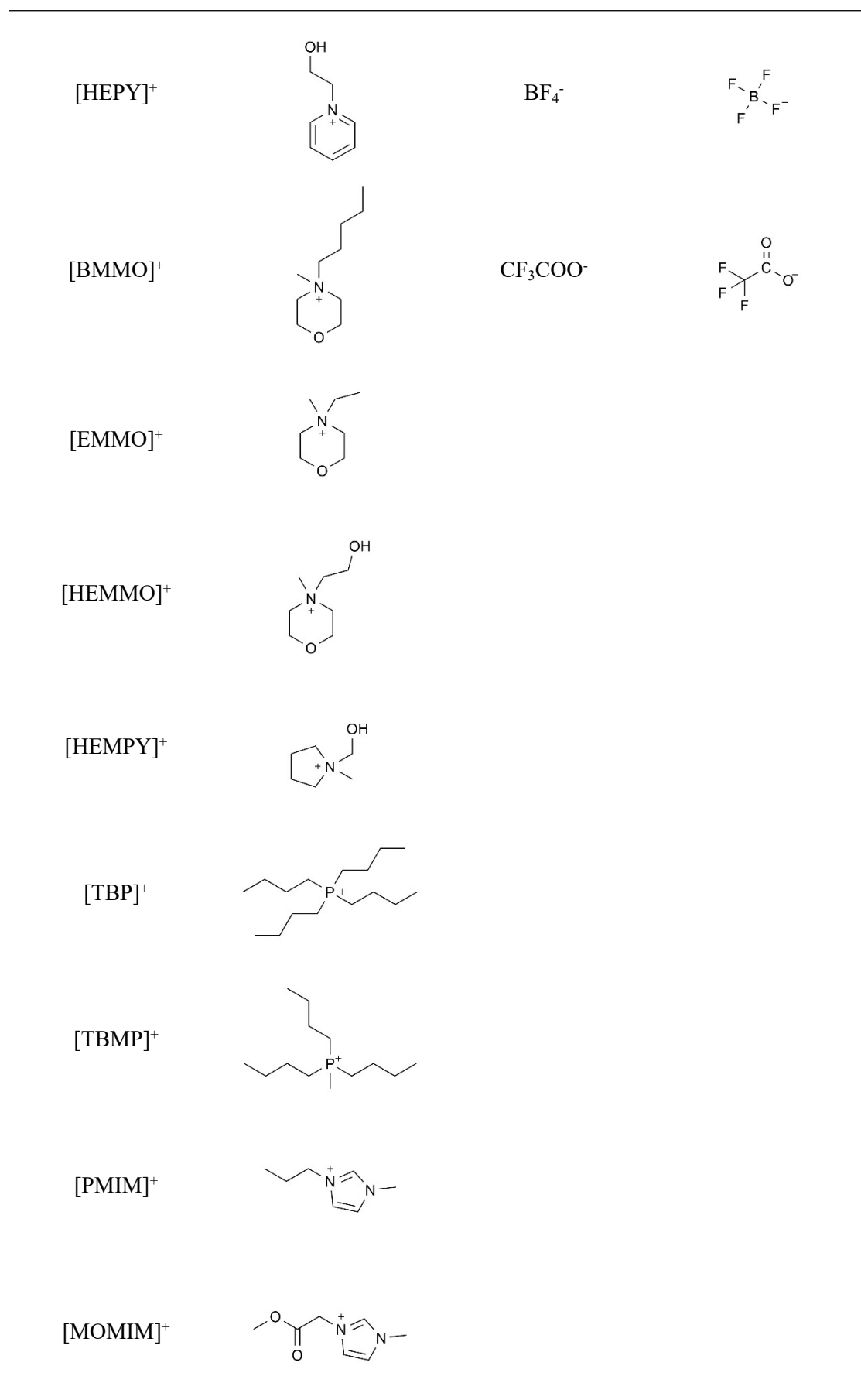
Table S1. The cations and anions of ionic liquids

Name of cation	Structure	Name of anion	Structure
[EMIM] <sup>+</sup>		Cl <sup>-</sup>	-
[BMIM] <sup>+</sup>		Br <sup>-</sup>	-
[EDIM] <sup>+</sup>		I <sup>-</sup>	-
[EPy] <sup>+</sup>		OAc <sup>-</sup>	
N <sub>2222</sub> <sup>+</sup>		SCN <sup>-</sup>	N≡C-S <sup>-</sup>
N <sub>4444</sub> <sup>+</sup>		N(CN) <sub>2</sub> <sup>-</sup>	
Ch <sup>+</sup>		NO <sub>3</sub> <sup>-</sup>	
[PYRR] <sup>+</sup>		EtPO <sub>4</sub> <sup>-</sup>	

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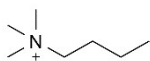
[PYR] <sup>+</sup>		MePO <sub>4</sub> <sup>-</sup>	
[BEPY] <sup>+</sup>		H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	
[BMPI] <sup>+</sup>		HSO <sub>4</sub> <sup>-</sup>	
[BMPY] <sup>+</sup>		MeSO <sub>4</sub> <sup>-</sup>	
[MBPY] <sup>+</sup>		EtSO <sub>4</sub> <sup>-</sup>	
[HOEMIM] <sup>+</sup>		TFMS <sup>-</sup>	
[BEMIM] <sup>+</sup>		BZA <sup>-</sup>	
[BEIM] <sup>+</sup>		Gly <sup>-</sup>	
[BMOAM] <sup>+</sup>		PF <sub>6</sub> <sup>-</sup>	

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[BTAM]<sup>+</sup>



[EOMMO]<sup>+</sup>

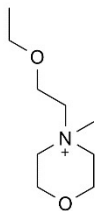




Table S2. Statistical analysis results of interaction energies between CA and IL at infinite dilution

Interaction energy (kcal/mol)	Pearson Correlations	Mean	Standard deviation	Median	Minimum	Maximum
$E_{\text{HB}}$	0.7828	10.139	4.2780	9.5163	1.4297	19.236
$E_{\text{vdW}}$	0.6460	18.199	0.6656	18.360	16.045	19.590
$E_{\text{misfit}}$	0.3563	9.1689	1.6258	8.9023	6.0869	15.933

Table S3. Statistical analysis of the interaction energy differences between CA-IL and DCA-IL at infinite dilution

Interaction energy (kcal/mol)	Pearson Correlations	Mean	Standard deviation	Median	Minimum	Maximum
$\Delta E_{\text{HB}}$	0.4160	0.8148	0.8148	0.8440	0.1335	1.4667
$\Delta E_{\text{vdW}}$	-0.3261	0.0562	0.0563	0.0499	0.0015	0.1766
$\Delta E_{\text{misfit}}$	-0.4344	0.3390	0.3390	0.3351	$2 \times 10^{-5}$	0.8824

Table S4 Parameters of the modified Apelblat equation model of CA, DCA in EA and NBA.

Solvents		Modified Apelblat equation				
		A	B	C	R <sup>2</sup>	10 <sup>3</sup> RMSE
EA	CA	442.86	-23681.30	-65.21	0.998	1.86
	DCA	387.62	-21725.60	-56.63	0.994	4.42
NBA	CA	-108.52	3784.538	15.77	0.995	0.20
	DCA	20.15	-2622.01	-3.10	0.986	1.49

Table S5  $^1\text{H}$  NMR chemical shifts of active hydrogen atoms on CA and DCA with [EMIM]Cl, ethyl acetate(EA) and *n*-butanol(NBA).

NMR sample	Active hydrogen atoms			
	-COOH	-OH <sub>1</sub>	-OH <sub>2</sub>	-OH <sub>3</sub>
CA	11.9388	4.3211	4.1184	4.0131
CA-EA	11.9327	4.3148	4.1176	4.0110
CA-NBA	11.9245	4.334	4.1285	4.0249
CA-IL	12.055	4.4493	4.2195	4.1205
DCA	11.9372	4.4612	4.2046	-
DCA-EA	11.9344	4.4581	4.2015	-
DCA-NBA	11.8805	4.4777	4.2145	-
DCA-IL	11.9821	4.5306	4.2409	-

## Reference

1. A. Klamt, V. Jonas, T. Bürger and J. C. W. Lohrenz, *The Journal of Physical Chemistry A*, 1998, 102, 5074-5085.
2. F. Eckert and A. Klamt, *Aiche Journal*, 2002, 48, 369-385.