Using COSMO-RS to Design Choline Chloride Pharmaceutical Eutectic Solvents

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S1. Tables

Table S1. Name, *CAS number, and melting properties, along with each reference, for the compounds whose solid-liquid phase equilibrium data with choline chloride was taken from the literature.*

Compound	CAS Number	T_m /K	$\Delta_m H$ /(kJ/mol)	Reference
Decanoic Acid	334-48-5	304.8	27.50	[1]
Dodecanoic Acid	143-07-7	317.5	37.83	[1]
Tetradecanoic	544-63-8	327.0	42.39	[1]
Hexadecanoic	57-10-3	336.8	51.02	[1]
Octadecanoic	57-11-4	343.7	61.36	[1]
Tetradecanol	112-72-1	311.0	49.37	[2]
Hexadecanol	36653-82-4	321.6	33.10	[3]
Octadecanol	112-92-5	330.1	40.10	[3]
D(+)-Glucose	2280-44-6	420.7	32.446	[4]
D(-)-Fructose	57-48-7	386.2	27.312	[4]
D(+)-Sucrose	57-50-1	455.9	41.007	[4]
D(+)-Xylose	58-86-6	416.2	31.677	[5]
Choline Acetate	14586-35-7	362.6	8.8817	[6]
[N_{4444}] Cl	1112-67-0	342.8	19.43	[6]
[BzCh] Cl	7221-40-1	351.4	8.73	[6]
[C_4mpyr] Cl	479500-35-1	473.0	30.896	[6]
[C_2mim] Cl	65039-09-0	350.4	8.588	[6]
[C_2OHmim] Cl	61755-34-8	358.9	20.974	[6]
[N_{2222}] Cl	56-34-8	526.8	51.24	[1]
[N_{3333}] Cl	5810-42-4	503.1	66.58	[1]

Table S2. *Experimental (x_1,T) data of the solid-liquid equilibria for eutectic mixtures composed of ChCl + pharmaceutical compounds at atmospheric pressure.*[a,b]

x_1	T / K	x_1	T / K
[Ch]Cl phase		Drug phase	
[Ch]Cl (1) + Acetylsalicylic Acid (2)			
0.286	340.65	0.101	381.52
0.414	382.48	0.206	354.85
0.499	418.25		
0.595	450.78		
0.696	495.55		
0.800	527.48		
0.893	555.58		
[Ch]Cl (1) + Ibuprofen (2)			
0.396	326.05	0.111	344.52

0.513	351.25	0.229	338.62
0.613	395.82	0.303	335.08
0.695	443.15		
0.797	495.92		
0.895	547.62		
[Ch]Cl (1) + Ketoprofen (2)			
0.310	349.75	0.103	361.62
0.398	366.25	0.213	354.72
0.505	390.52		
0.603	418.68		
0.695	465.85		
0.789	500.92		
0.881	541.85		
[Ch]Cl (1) + Paracetamol (2)			
0.504	321.18	0.101	425.82
0.597	339.62	0.207	387.82
0.695	407.92	0.302	371.52
0.794	461.02	0.407	352.08
0.893	537.55		

[a]Melting points device. Standard uncertainties, *u*, are $u(T)$ = 0.4 K and $u_r(x)$ = 0.002. [b]Oil bath method (composition range of 0.5 to 0.7). Standard uncertainties, *u*, are $u(T)$ = 1.0 K and $u_r(x)$ = 0.002.

S2. Figures

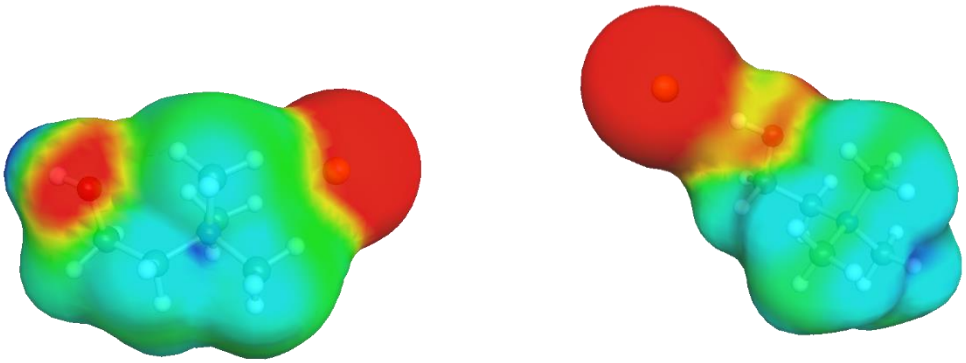
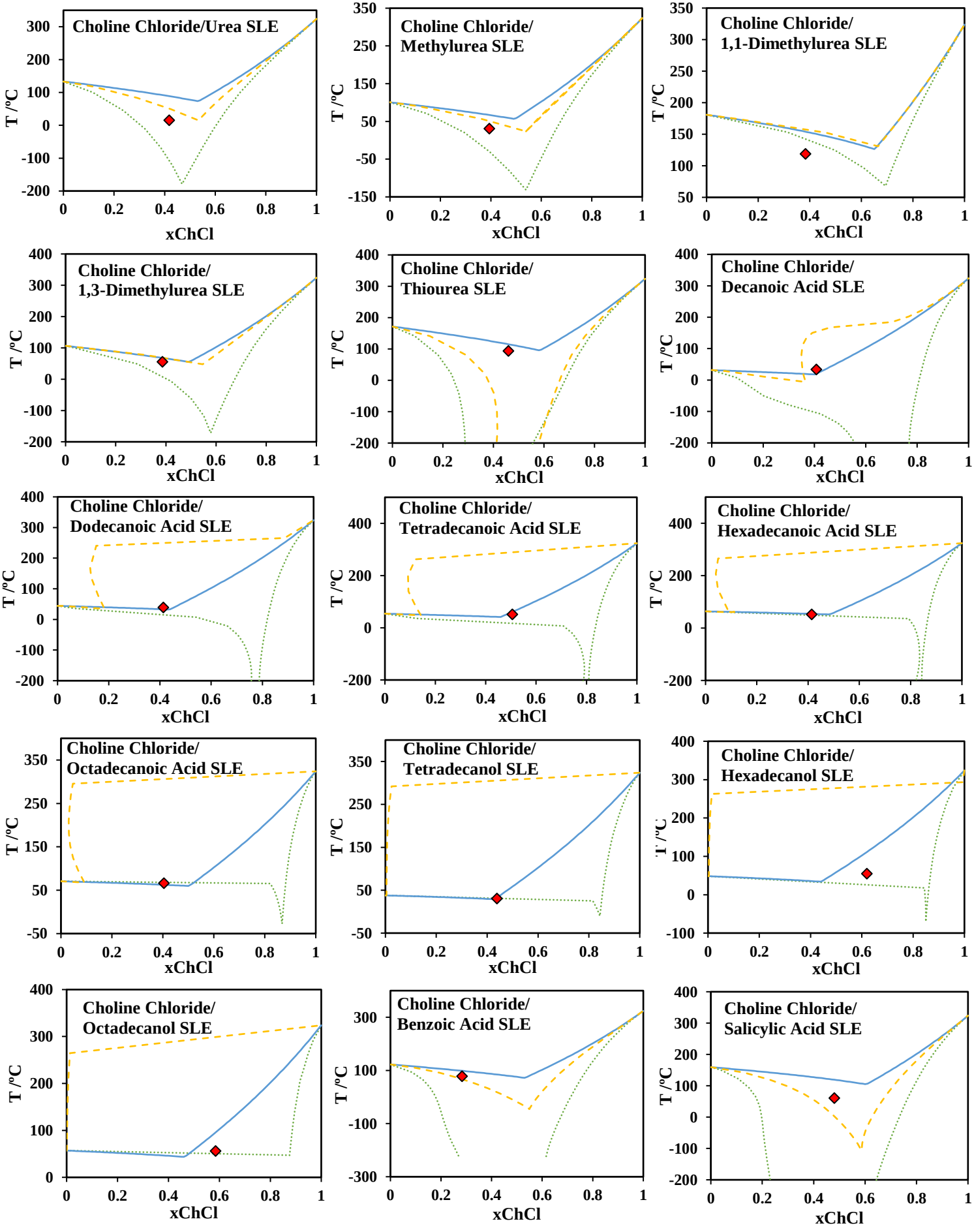
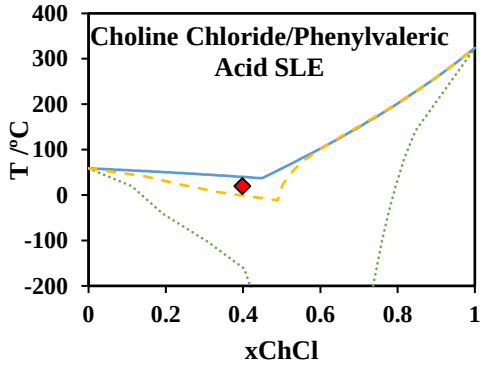
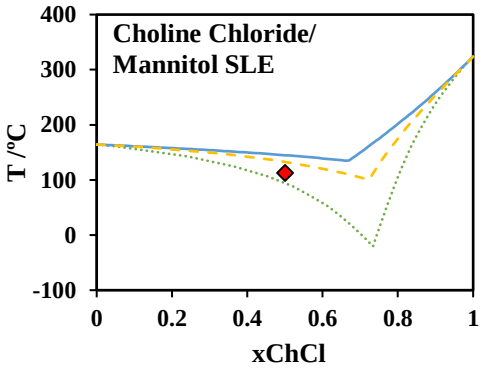


Figure S1. *Sigma surfaces of alternative geometries for the choline chloride ion pair, as calculated using TURBOMOLE.*


Choline Chloride/Urea SLE
Choline Chloride/ Methylurea SLE
Choline Chloride/ 1,1-Dimethylurea SLE
Choline Chloride/ 1,3-Dimethylurea SLE
Choline Chloride/ Thiourea SLE
Choline Chloride/ Decanoic Acid SLE
Choline Chloride/ Dodecanoic Acid SLE
Choline Chloride/ Tetradecanoic Acid SLE
Choline Chloride/ Hexadecanoic Acid SLE
Choline Chloride/ Octadecanoic Acid SLE
Choline Chloride/ Tetradecanol SLE
Choline Chloride/ Hexadecanol SLE
Choline Chloride/ Octadecanol SLE
Choline Chloride/ Benzoic Acid SLE
Choline Chloride/ Salicylic Acid SLE
T /°C
xChCl


Choline Chloride/Phenylvaleric Acid SLE
T /°C
xChCl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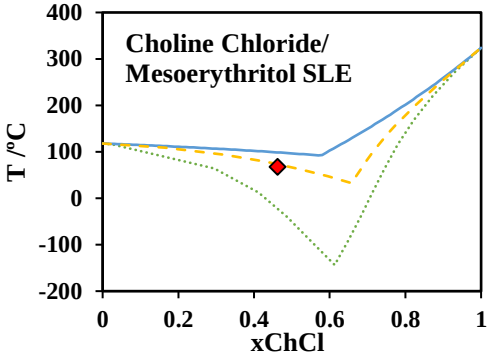
T /°C
xChCl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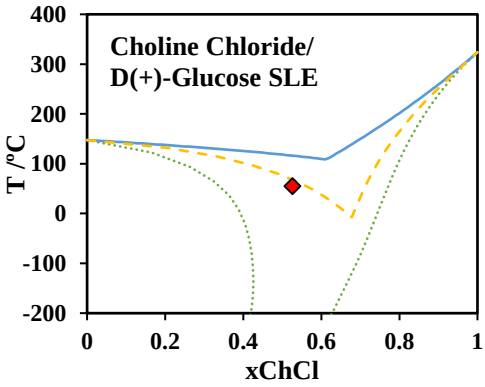
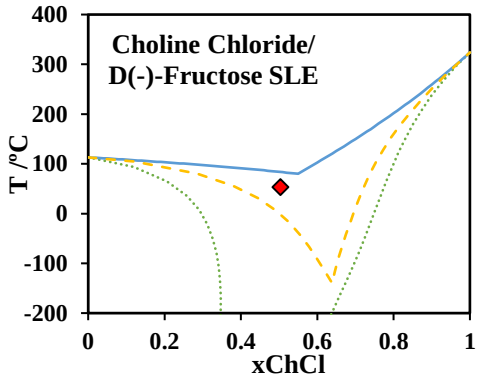
T /°C
xChCl


Choline Chloride/ D(+)-Glucose SLE
T /°C
xChCl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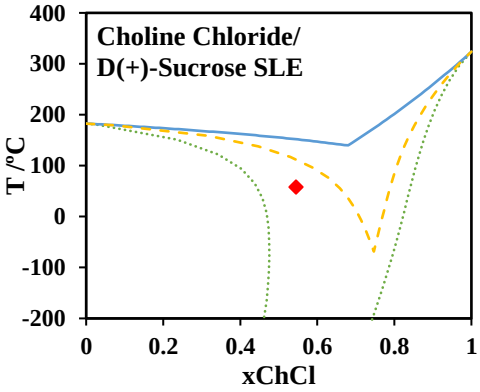
xChCl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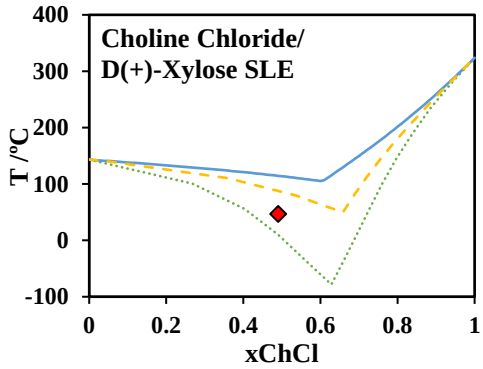
Choline Chloride/ D(+)-Xylose SLE
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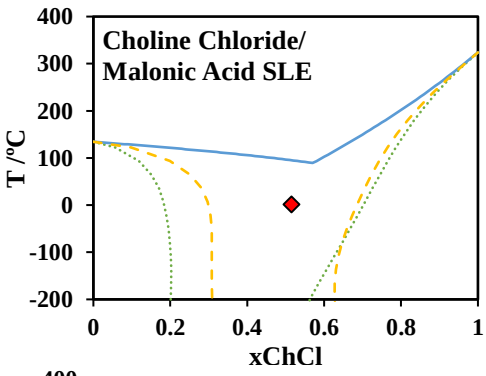
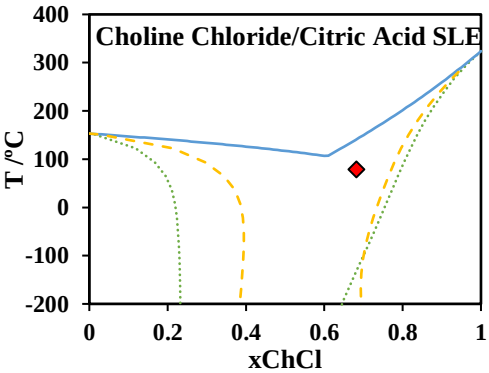
xChCl


Choline Chloride/ Malonic Acid SLE
T /°C
xChCl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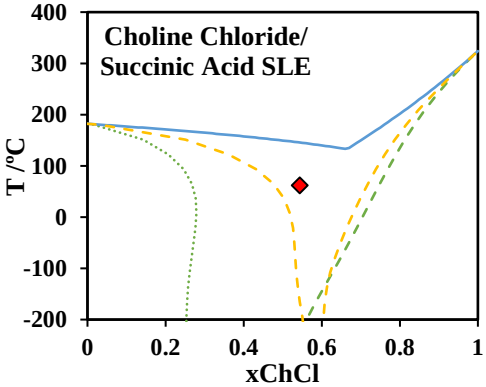
xChCl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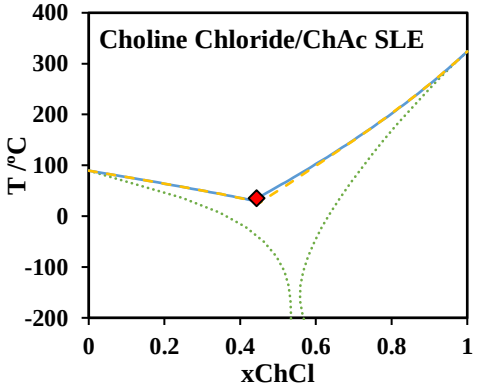
T /°C
xChCl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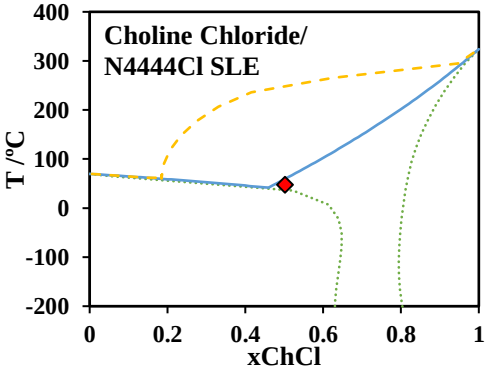
xChCl


Choline Chloride/ N4444Cl SLE
T /°C
xChCl

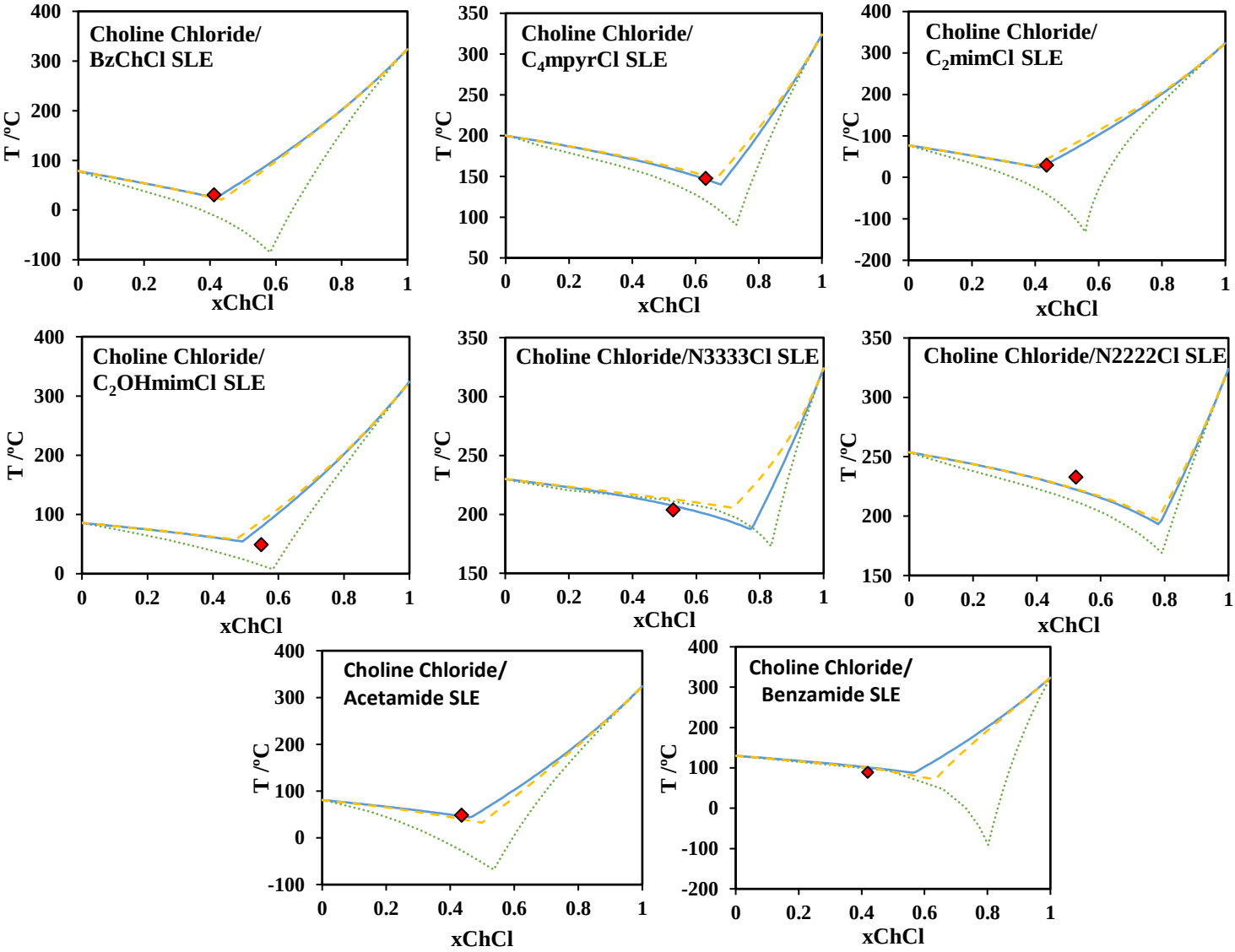


Figure S2. *Solid-liquid equilibria diagrams for thirty-five based choline chloride binary mixtures. In each plot is included the experimental eutectic point, the ideal solid-liquid equilibrium diagram, the solid-liquid equilibrium diagram predicted by COSMO-RS with model A+B and the solid-liquid equilibrium diagram predicted by COSMO-RS with model AB. Legend: ◆ experimental eutectic point; ····· A+B model; - - - - AB model; —— ideal diagram.*

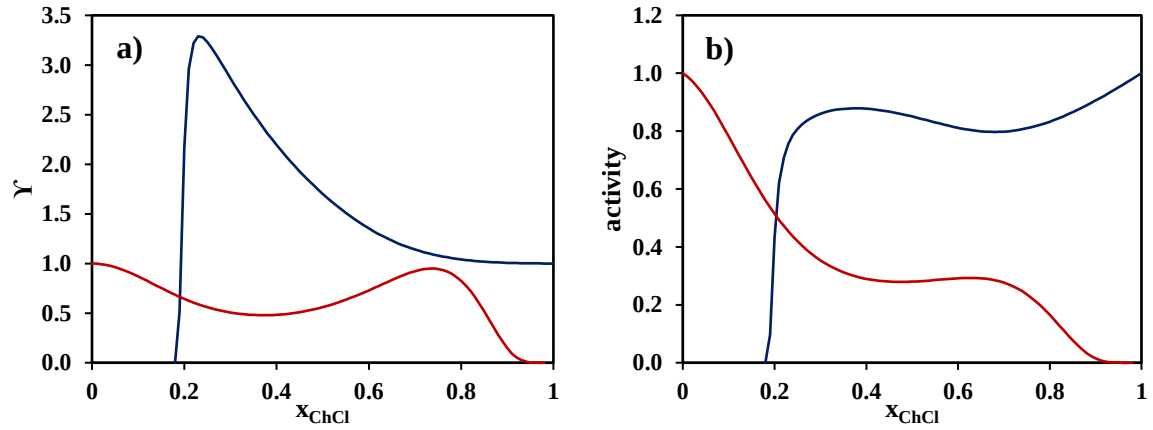


Figure S3. *Activity coefficients (a) and activities (b) of choline chloride and ibuprofen in the choline chloride/ibuprofen binary system, obtained using COSMO-RS. Each data point is calculated at the predicted equilibrium temperature of the system. Legend:* — *choline chloride;* — *ibuprofen.*

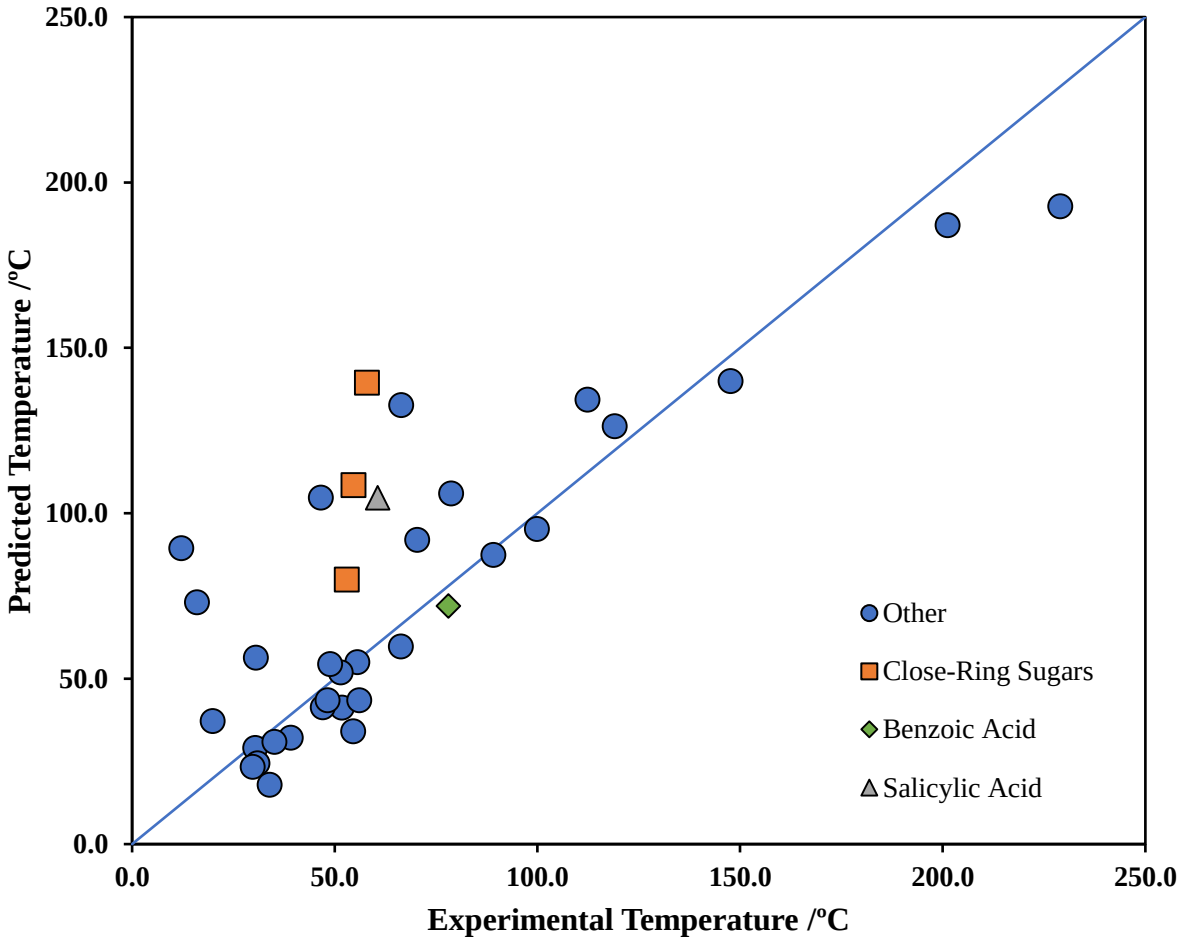


Figure S4. *Predicted vs experimental eutectic temperatures considering the liquid phase as ideal. Benzoic acid, salicylic acid and close-ring sugars are highlighted. The full line represents the equality between predicted and experimental temperatures.*

S3. Experimental Uncertainty

Each straight line, obtained by the method of least squares for the solid-liquid equilibrium data for each compound, may be defined as:

$$T = (m_i \pm sm_i) \cdot x_{ChCl} + (b_i \pm sb_i) \quad \text{(S1)}$$

where T is the solid-liquid equilibrium temperature, m_i is the slope of component's i line with sm_i as its standard error, x_{ChCl} is the molar fraction of choline chloride and b_i is the y intercept of component's i line with sb_i as its standard error. Both the eutectic temperature (T_{eut}) and the eutectic composition can be calculated from the intercept between the lines of both components (denoted below as 1 and 2):

$$T_{eut} = \frac{m_2 \cdot b_1 - m_1 \cdot b_2}{m_2 - m_1} \quad \text{(S2)}$$

$$x_{eut} = \frac{b_2 - b_1}{m_1 - m_2} \quad \text{(S3)}$$

Considering that the standard error sm_i is small when compared to m_i and that the standard error sb_i is small when compared to b_i, for all lines in all systems, a good approximation for the standard uncertainty of the eutectic temperatures calculated (sT_{eut}) is given by a simplified equation for the propagation of uncertainty [7]:

$$sT_{eut} = \sqrt{\left(\frac{\partial T_{eut}}{\partial m_1}\right)^2 \cdot {sm_1}^2 + \left(\frac{\partial T_{eut}}{\partial m_2}\right)^2 \cdot {sm_2}^2 + \left(\frac{\partial T_{eut}}{\partial b_1}\right)^2 \cdot {sb_1}^2 + \left(\frac{\partial T_{eut}}{\partial b_2}\right)^2 \cdot {sb_2}^2} \quad \text{(S4)}$$

Likewise, the standard uncertainty of the eutectic composition (sx_{eut}) can be estimated using:

$$sx_{eut} = \sqrt{\left(\frac{\partial x_{eut}}{\partial m_1}\right)^2 \cdot {sm_1}^2 + \left(\frac{\partial x_{eut}}{\partial m_2}\right)^2 \cdot {sm_2}^2 + \left(\frac{\partial x_{eut}}{\partial b_1}\right)^2 \cdot {sb_1}^2 + \left(\frac{\partial x_{eut}}{\partial b_2}\right)^2 \cdot {sb_2}^2} \quad \text{(S5)}$$

Evaluating the partial derivatives of equations S2 and S3 and substituting back on equations S4 and S5, the resulting final expressions, which are used in this work to estimate each mixture's eutectic temperature and eutectic composition standard errors, are:

$$sT_{eut} = \frac{\sqrt{({m_1}^2 \cdot {sm_2}^2 + {m_2}^2 \cdot {sm_1}^2) \cdot (b_1 - b_2)^2 + (m_1 - m_2)^2 \cdot ({m_1}^2 \cdot {sb_2}^2 + {m_2}^2 \cdot {sb_1}^2)}}{(m_1 - m_2)^2} \quad \text{(S6)}$$

$$sx_{eut} = \frac{\sqrt{({sm_1}^2 + {sm_2}^2) \cdot (b_1 - b_2)^2 + (m_1 - m_2)^2 \cdot ({sb_1}^2 + \cdot {sb_2}^2)}}{(m_1 - m_2)^2} \quad \text{(S7)}$$

S4. References

[1] P.V.A. Pontes, E.A. Crespo, M.A.R. Martins, L.P. Silva, C.M.S.S. Neves, G.J. Maximo, M.D. Hubinger, E.A.C. Batista, S.P. Pinho, J.A.P. Coutinho, G. Sadowski, C. Held, Measurement and PC-SAFT modeling of solid-liquid equilibrium of deep eutectic solvents of quaternary ammonium chlorides and carboxylic acids, Fluid Phase Equilib. 448 (2017) 69–80. doi:10.1016/j.fluid.2017.04.007.

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