Measurement and correlation of solubility of theobromine, theophylline and caffeine in water and organic solvents at various temperatures

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Table S1. Experimental Solubility Data for benzil in acetone and acetonitrile at T = 298.15 K and p = 0.1 MPa[a]

solvent	x_{benzil}	RSDs/%	x^{b}_{benzil}	Deviation/%
acetone	0.159	1.08	0.160	0.63
acetonitrile	0.0645	1.94	0.0635	1.57

[a] $u_r(x)$ = 0.003; $u(p)$ = 5 Kpa; $u(T)$ = 0.01 K; [b] Reference R1

Table S2. RSDs of experimental solubility data for theobromine, theophylline and caffeine in different solvents at T = (288.15 to 328.15) K and p = 0.1 MPa

RSDs/%	T /K	water	methanol	T /K	ethanol	1-propanol
	288.07	0.79	2.61	288.15	0.47	1.78
	298.10	0.71	1.83	298.20	0.17	0.98
	308.93	0.55	0.32	308.19	0.74	0.47
	318.62	2.39	0.40	318.16	1.39	0.42
	328.15	3.32	1.87	328.16	1.09	0.69
theobromine	T /K	ethyl acetate	acetone			
	288.13	0.22	2.91			
	297.99	0.52	1.44			
	308.08	0.43	0.35			
	318.07	0.40	0.34			
	328.17	0.93	1.27			
RSDs/%	T /K	water	methanol	T /K	ethanol	1-propanol
	288.06	0.21	3.50	288.01	2.46	0.80
	298.16	0.62	2.42	297.95	1.70	0.54
	308.16	0.62	1.06	308.01	2.44	0.93
	318.13	2.47	0.92	318.11	2.02	0.10
	328.19	2.03	0.25	328.09	3.00	1.04
theophylline	T /K	ethyl acetate	acetone			
	288.02	0.26	0.15			
	298.15	1.50	0.77			
	308.15	2.70	1.56			
	318.15	2.48	2.47			
	328.10	3.29	0.72			
RSDs/%	T /K	water	ethanol	T /K	methanol	1-propanol
	288.01	0.53	2.20	288.24	0.76	2.03
	298.11	2.80	0.88	298.17	0.80	1.27
	308.09	1.91	0.05	308.17	1.02	0.39
	318.11	2.87	0.48	318.20	0.34	1.64
	328.15	1.96	0.82	328.12	1.63	1.81
caffeine	T /K	ethyl acetate	acetone			
	288.24	1.79	0.93			
	298.09	0.13	2.39			
	308.21	1.20	0.36			
	318.15	3.02	1.46			
	328.18	3.55	1.36			

Table S3. Comparison of experimental solubility data for theobromine in this work and the data from the literature at p = 0.1 MPa

T / K	solubility (mole fraction, $10^5 x_1$)					
	298.10	298.15	308.93	308.15	318.62	318.15
water	4.73[a]	100.87[b]	6.93[a]	102.84[b]	10.01[a]	104.44[b]
T / K	298.20	298.15	308.19	308.15	318.16	318.15
ethanol	2.26[a]	2.33[b]	3.85[a]	3.85[b]	6.31[a]	6.34[b]

[a] experimental solubility data for theobromine in this work; [b] $u_r(x)$ = 0.1; Reference R2

Table S4.1. Comparison of experimental solubility data for theophylline in this work and the data from the literature at p = 0.1 MPa

T / K	solubility (mole fraction, $10^4 x_1$)					
	308.16	308.5	318.13	316.7	328.19	326.2
water	9.91[a]	4[b]	14.10[a]	9[b]	21.64[a]	18[b]
T / K	308.01	309.4	318.11	318.6	328.09	325.2
ethanol	17.30[a]	8[b]	25.41[a]	20[b]	31.92[a]	36[b]

[a] experimental solubility data for theophylline in this work; [b] $u_r(x) = 5$; Reference R2

Table S4.2. Comparison of experimental solubility data for theophylline in this work and the data from the literature at p = 0.1 MPa

T / K	solubility (mole fraction, $10^4 x_1$)			
	297.95	298.15	308.01	309.15
ethanol	11.60[a]	13.57[b]	17.30[a]	18.08[b]
T / K	298.15	298.15	308.15	309.15
ethyl acetate	6.73[a]	5.69[b]	9.01[a]	8.39[b]
T / K	298.15	299.15	308.15	309.15
acetone	9.30[a]	11.03[b]	12.41[a]	11.85[b]

[a] experimental solubility data for theophylline in this work; [b] Reference R3

Table S5.1. Comparison of experimental solubility data for caffeine in this work and the data from the literature at p = 0.1 MPa

T / K	solubility (mole fraction, $10^3 x_1$)					
	298.11	298	308.09	308	318.11	318
water	1.61[a]	2.09[b]	2.27[a]	2.62[b]	2.96[a]	3.08[b]
T / K	298.17	298	308.17	308	318.20	318
methanol	1.89[a]	2.00[b]	2.80[a]	2.68[b]	4.26[a]	3.41[b]
T / K	298.11	298	308.09	308	318.11	318
ethanol	1.32[a]	1.71[b]	2.04[a]	2.05[b]	3.22[a]	2.19[b]
T / K	298.09	298	308.21	308	318.15	318
ethyl acetate	3.54[a]	4.05[b]	4.88[a]	4.46[b]	6.89[a]	4.84[b]

[a] experimental solubility data for caffeine in this work; [b] $u_r(x) = 0.013$; Reference R4

Table S5.2. Comparison of experimental solubility data for caffeine in this work and the data from the literature at p = 0.1 MPa

T / K	solubility (mole fraction, $10^3 x_1$)							
	288.01	287.96	298.11	298.14	308.09	308.06	318.11	318.01
water	1.23[a]	196.5[b]	1.61[a]	202.0[b]	2.27[a]	207.41[b]	2.96[a]	212.6[b]
T / K	288.01	287.76	298.11	298.5	308.09	307.67	318.11	317.92
ethanol	0.78[a]	0.794[b]	1.32[a]	1.319[b]	2.04[a]	2.063[b]	3.22[a]	3.652[b]

[a] experimental solubility data for caffeine in this work; [b] Reference R5

Table S6. Adjustable parameters along with RMSD values of the Apelblat equation

Solute	Solvent	*A*	*B*	*C*	10^5RMSD
theobromine	water	-169.821	4267.465	25.542	$7.31 \cdot 10^{-2}$
	methanol	-105.775	809.411	16.327	$8.05 \cdot 10^{-2}$
	ethanol	-228.589	5868.410	34.790	$2.95 \cdot 10^{-2}$
	1-propanol	-123.743	683.656	19.424	$2.36 \cdot 10^{-2}$
	ethyl acetate	-165.799	4003.716	24.800	$2.30 \cdot 10^{-2}$
	acetone	-259.705	8366.863	38.769	$6.62 \cdot 10^{-2}$
theophylline	water	69.588	-7073.649	-9.351	3.22
	methanol	454.025	-24248.722	-66.570	2.60
	ethanol	288.299	-16370.793	-42.142	4.99
	1-propanol	128.354	-9332.422	-18.188	4.87
	ethyl acetate	27.871	-3641.172	-4.029	1.43
	acetone	203.088	-11541.867	-30.075	2.09
caffeine	water	-87.030	1316.990	13.375	3.06
	methanol	-361.394	13009.408	54.671	0.40
	ethanol	102.134	-8562.021	-14.051	2.52
	1-propanol	-224.154	6272.435	34.539	1.98
	ethyl acetate	-116.681	2545.747	17.993	7.64
	acetone	10.732	-3297.427	-0.921	10.12

Table S7. Adjustable parameters along with RMSD values of the UNIQUAC equation

Solute	Solvent	a_{21}/(J·/mol^{-1})	a_{12}/(J·mol^{-1})	10^4RMSD
theobromine	water	4031.272	-82.595	$2.83 \cdot 10^{-2}$
	methanol	4229.736	-80.457	0.12
	ethanol	3945.447	-31.323	$4.98 \cdot 10^{-2}$
	1-propanol	3742.694	-22.934	$2.04 \cdot 10^{-2}$
	ethyl acetate	3694.805	-7.980	$3.23 \cdot 10^{-2}$
	acetone	3752.516	-18.272	$3.35 \cdot 10^{-2}$
theophylline	water	15725.861	-4254.232	1.14
	methanol	9655.399	-2742.599	3.13
	ethanol	4042.131	-714.437	2.91
	1-propanol	3717.911	-633.780	0.83
	ethyl acetate	3649.172	-129.549	0.24
	acetone	3829.868	-276.135	0.48
caffeine	water	3550.581	-859.968	0.73
	methanol	4235.619	-578.397	0.72
	ethanol	9568.523	-2930.783	8.99
	1-propanol	9600.848	-3017.875	10.81
	ethyl acetate	3636.145	-852.791	9.33
	acetone	6134.524	-2007.571	2.34

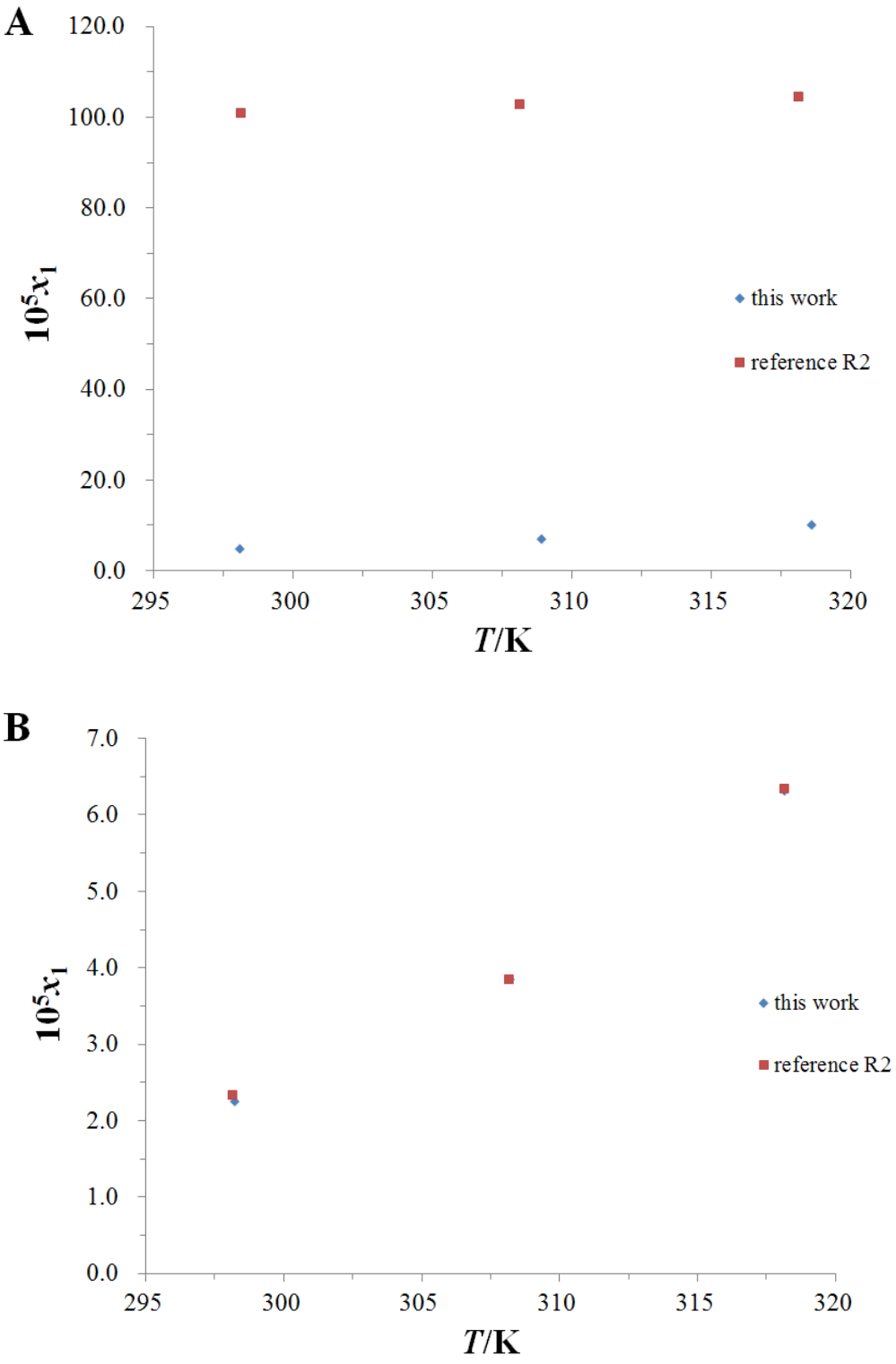

Figure S1. Graphical comparison of solubility values of theobromine in water (A) and ethanol (B).

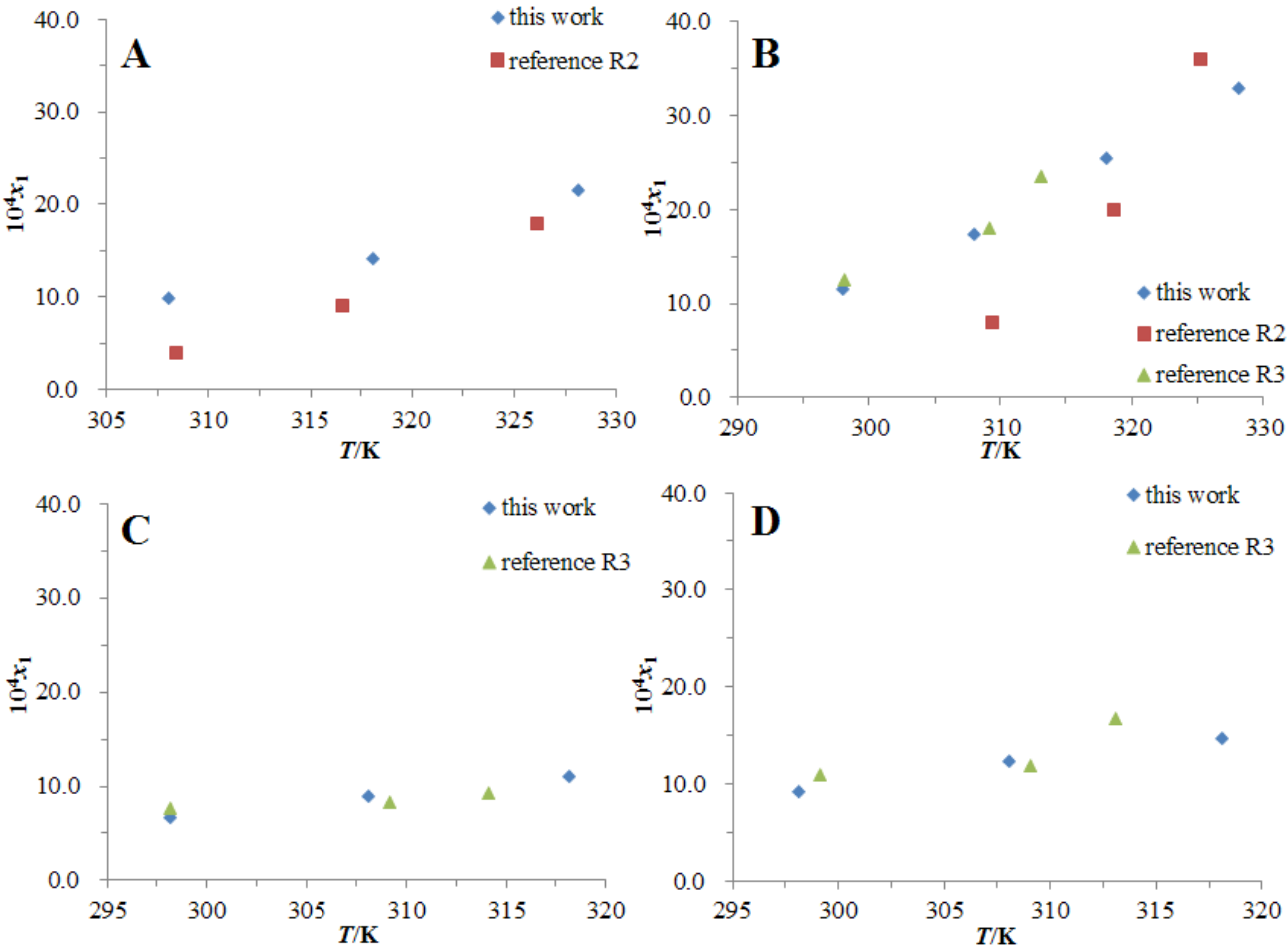

Figure S2. Graphical comparison of solubility values of theophylline in water (A), ethanol (B), ethyl acetate (C) and acetone (D).

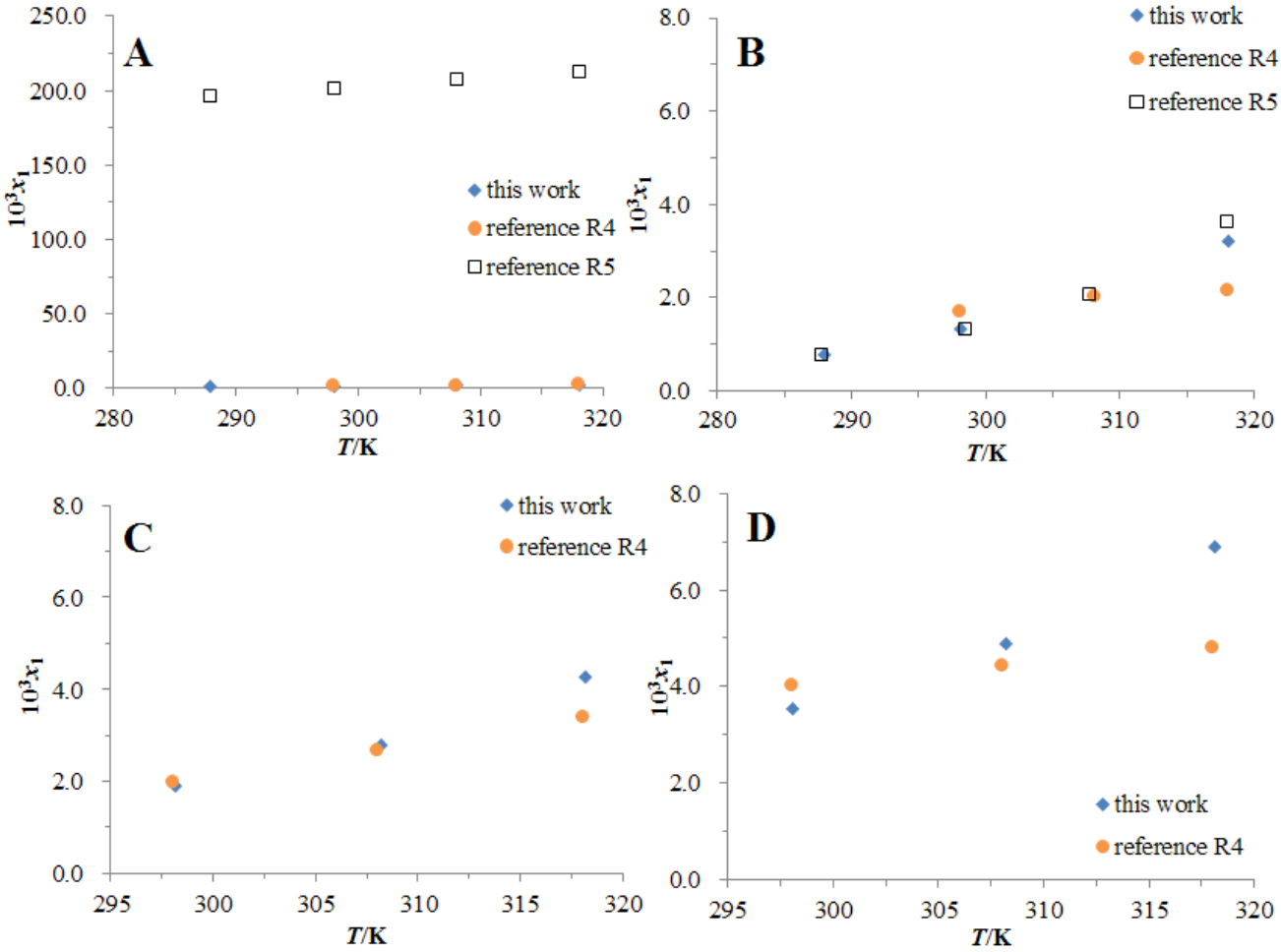

Figure S3. Graphical comparison of solubility values of caffeine in water (A), ethanol (B), methanol (C) and ethyl acetate (D).

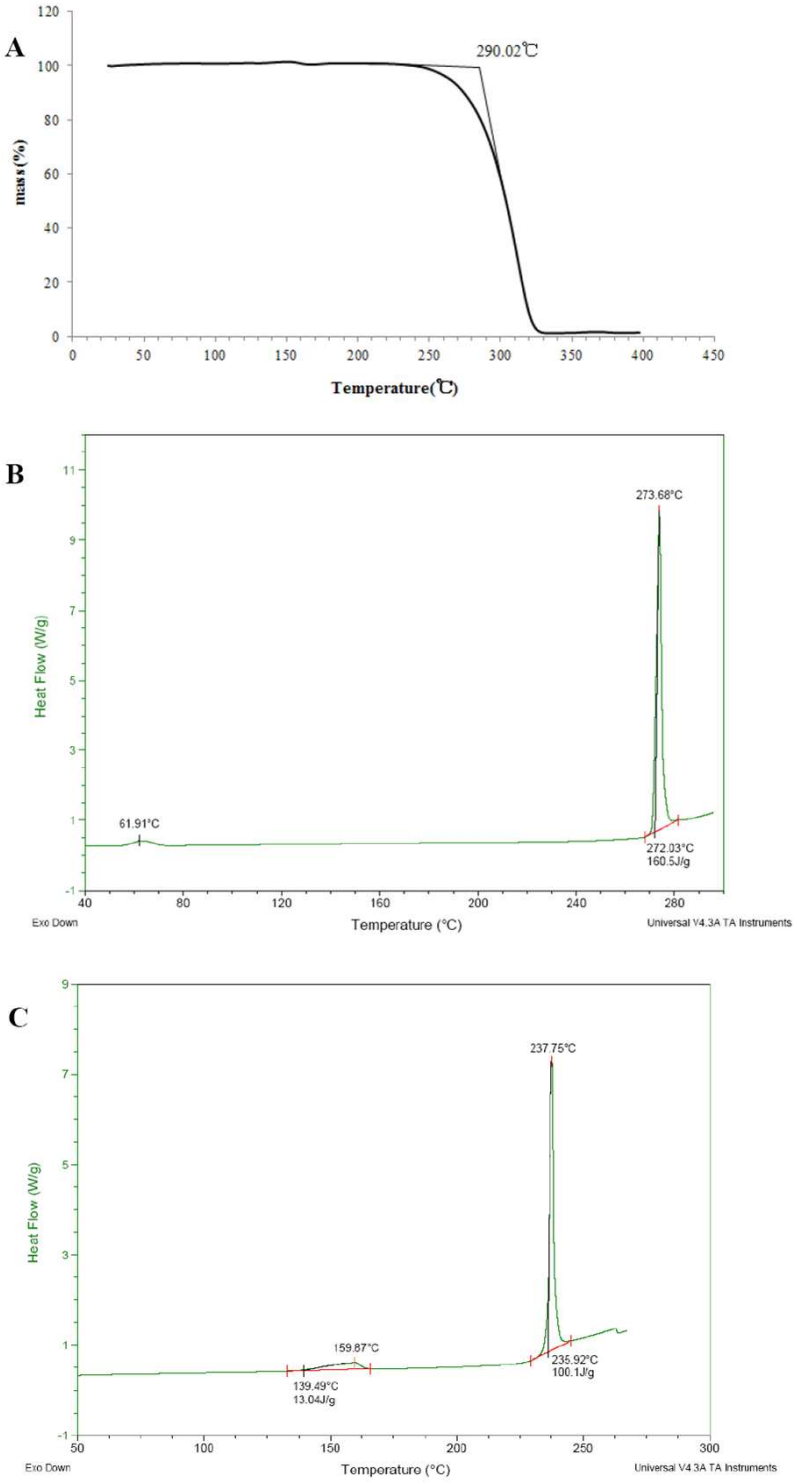

Figure S4. Experimental TGA measurement of theobromine (A) and DSC measurement of theophylline (B) and caffeine (C)

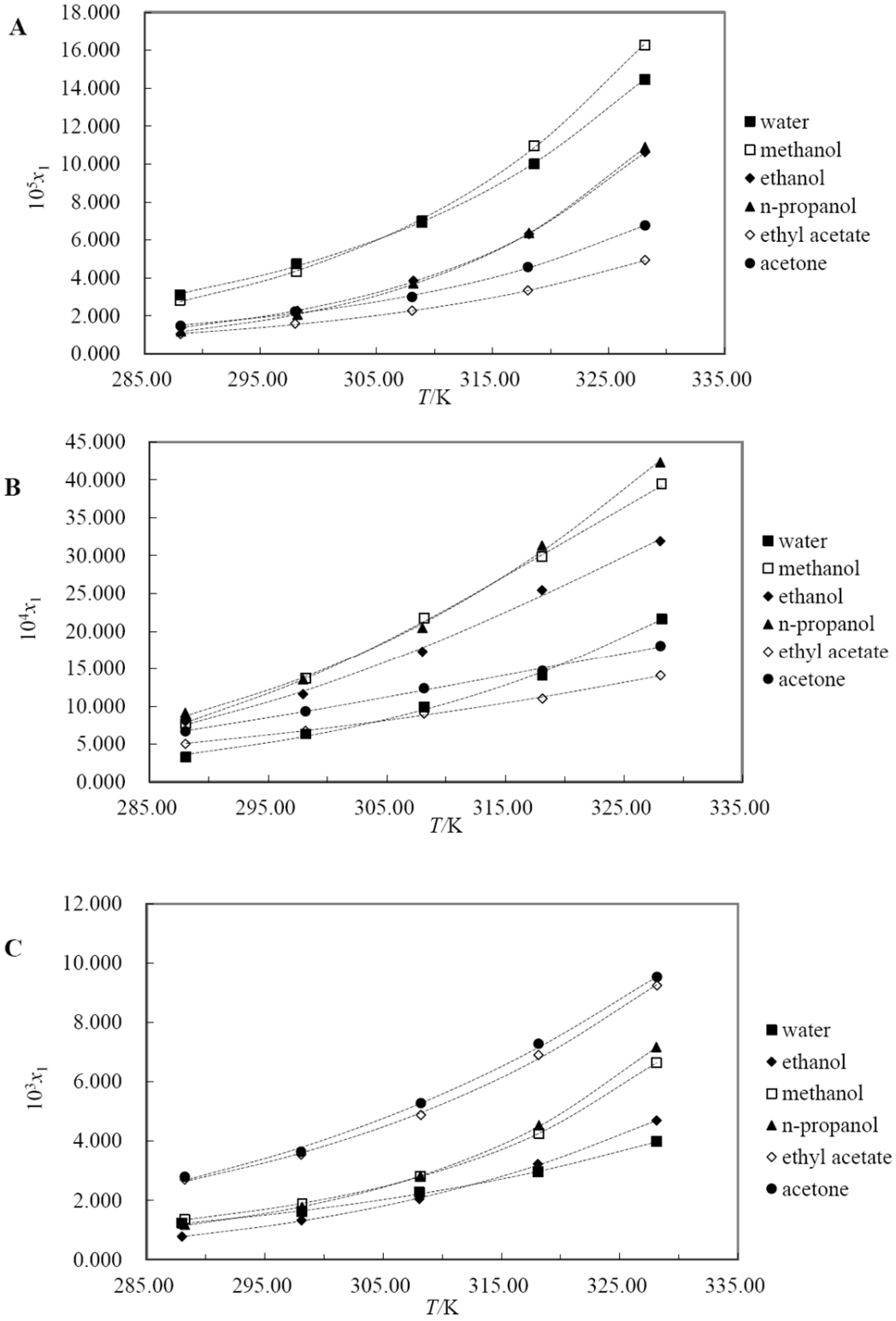

Figure S5. Theobromine (A), theophylline (B) and caffeine (C) solubility values in selected solvents; dashed lines, calculated by the empirical Apelblat equation.

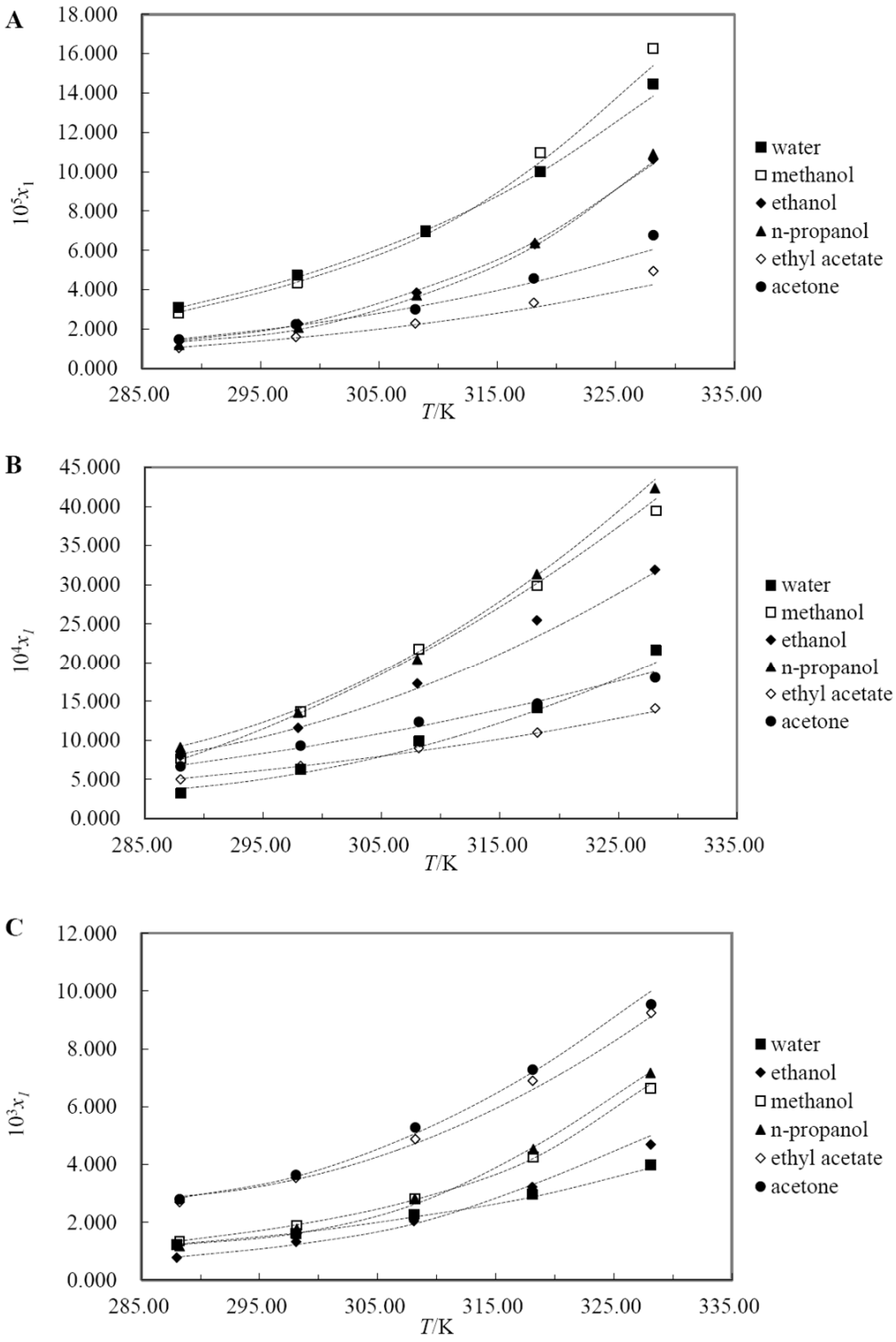

Figure S6. Theobromine (A), theophylline (B) and caffeine (C) solubility values in selected solvents; dashed lines, calculated by UNIQUAC equation.

■ The approaches of the Apelblat equation and the UNIQUAC model

The empirical Apelblat equation has been widely applied in the correlation of solubility data at different temperatures. The mole fraction solubility of theobromine, theophylline and caffeine can be calculated through eq S1:

$$\ln x_1 = A + \frac{B}{T/\mathrm{K}} + \mathrm{C}\ln T/\mathrm{K} \tag{S1}$$

where x_1 is mole fraction solubility of the solute and T is the absolute temperature. A, B, and C are the adjustable equation parameters which can be obtained by using a non-linear regression method. Estimated parameters along with the corresponding root-mean-square deviations (RMSD) values are listed in Table S6. The root-mean-square deviations (RMSD) were defined by eq S2:

$$\mathrm{RMSD} = [\frac{1}{n}\sum_{i=1}^{n}(x_{1,i}^{\mathrm{cal}} - x_{1,i}^{\mathrm{exp}})^2]^{1/2} \tag{S2}$$

where n is the number of experimental points, $x_{1,i}^{\mathrm{cal}}$ and $x_{1,i}^{\mathrm{exp}}$ are the calculated and experimental solubility values.

According to the solid−liquid equilibrium theory, the experimental data of theobromine, theophylline and caffeine can be expressed as eq S3:

$$\ln(\frac{1}{\gamma_1 x_1}) = \frac{\Delta_{\mathrm{fus}}H}{RT_t}(\frac{T_t}{T} - 1) - \frac{\Delta C_p}{R}(\frac{T_t}{T} - 1) + \frac{\Delta C_p}{R}\ln\frac{T_t}{T} \tag{S3}$$

Where γ_1 is the activity coefficient of solute, x_1 is the mole fraction solubility of the solute, $\Delta_{fus}H$ is the enthalpy of fusion of solute, ΔC_p is the change of the heat capacity, T is the absolute temperature, T_t is the tripe-point temperature of solute, and R is the gas constant.

As the differences between the heat capacities for the solid and liquid phases of the solute can be ignored compared with the enthalpy of fusion ($\Delta_{fus}H$), and the triple-point temperature (T_t) is close to the melting temperature (T_m), eq S3 could be expressed by eq S4:

$$\ln(\frac{1}{\gamma_1 x_1}) = \frac{\Delta_{fus}H}{RT_m}(\frac{T_m}{T} - 1) \tag{S4}$$

The values of x_1, $\Delta_{fus}H$, T_m, and T were known. The activity coefficient of solute in eq 4 can be calculated using the UNIQUAC eq S5:

$$\ln \gamma_i = \ln \frac{\phi_i}{x_i} + \frac{z}{2} q_i \ln \frac{\theta_i}{\phi_i} + l_i - \frac{\phi_i}{x_i} \sum_j x_i l_j + q_i [1 - \ln(\sum_j \theta_j \tau_{ji}) - \sum_j \frac{\theta_j \tau_{ij}}{\sum_k \theta_k \tau_{kj}}] \tag{S5}$$

where

$$\phi_i = \frac{r_i x_i}{\sum_j r_j x_j} \quad , \quad \theta_i = \frac{q_i x_i}{\sum_j q_j x_j} \tag{S6}$$

$$l_i = \frac{z}{2}(r_i - q_i) - (r_i - 1) \tag{S7}$$

The coordination number z is set to 10. r_i and q_i are the structural parameters of pure solvent i. The structural parameters of theobromine, theophylline and caffeine were calculated by the functional group approach.

$$r_i = \sum_{i=1}^{m} n_i R_i , \qquad q_i = \sum_{i=1}^{m} n_i Q_i \tag{S8}$$

where m is the number of functional groups and n is the repeating number of each function group in the molecule. The structural parameters, R_i and Q_i of function group i, were obtained from Dortmund Data Bank (DDBST GmbH, Germany). Parameters τ_{ij} and τ_{ji} are expressed by

$$\tau_{ij} = \exp(-\frac{a_{ij}}{RT}) , \quad \tau_{ji} = \exp(-\frac{a_{ji}}{RT}) \tag{S9}$$

a_{ij} and a_{ji} are the interaction parameters. The solvent-solute interaction parameters were tabulated in Table S7 along with RMSD values. The experimental data and the data correlated by the empirical Apelblat equation and UNIQUAC equation were further shown in Figure S5-6. The dashed lines were calculated by the empirical Apelblat equation and UNIQUAC equation.

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