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Solubilities of Sulfadiazine, Sulfamethazine, Sulfadimethoxine, Sulfamethoxydiazine, Sulfamonomethoxine, Sulfamethoxazole, and Sulfachloropyrazine in Water from (298.15 to 333.15) K

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Using a static equilibrium method, the solubilities of sulfadiazine, sulfamethazine, sulfadimethoxine, sulfamethoxydiazine, sulfamonomethoxine, sulfamethoxazole, and sulfachloropyrazine in water have been determined experimentally from (298.15 to 333.15) K. The experimental data were correlated with the modified Apelblat equation. The calculated results show good agreement with the experimental data.

Introduction

Sulfonamides are a group of synthetic organic drugs, derived chiefly from sulfanilamide, that are chemically similar to *para*-aminobenzoic acid (PABA) and capable of inhibiting bacterial growth and activity by interfering with the metabolic processes in bacteria that require PABA. They are extensively used in agriculture to prevent diseases in livestock and treat illness. The potential exists for quantities of these drugs to be excreted as the parent compound and/or metabolites and enter the environment due to the spreading of manure and its slurry on agricultural land or direct deposition by grazing livestock.[1] Solubility is one of the most important physicochemical properties of drugs. In determining the transport of sulfonamides in the environment and assessing their risk to terrestrial and aquatic ecosystems, it is necessary to know their solubility. However, only a limited amount of solubility data for sulfonamides have been reported from (298.15 to 313.15) K.[2−4] In this study, solubilities of sulfonamides in water have been measured from (298.15 to 333.15) K. The experimental data were correlated with the modified Apelblat equation.[5−8]

Experimental Section

Materials. Sulfonamides: sulfadiazine, sulfamethazine, sulfadimethoxine, sulfamethoxydiazine, sulfamonomethoxine, sulfamethoxazole, and sulfachloropyrazine, obtained from Daming Biotech. Co. Ltd., were further purified by recrystallization from aqueous solutions. After filtration and drying, their purities were determined by UV spectrometry (type UV-2401PC, Shimadzu Co. Ltd.) to be 0.996 in mass fraction. Water used in the experiments was doubly distilled.

Apparatus and Procedure. The solubility was measured by a static equilibrium method.[3] Nearly 100 mg of each sulfonamide was added separately to 50 mL of water in glass flasks. The mixtures were then stirred in a mechanical shaker for 1 h. Samples were then allowed to stand in water baths (type 501, Shanghai Laboratory Instrument Works Co. Ltd.) kept at the appropriate temperature (± 0.02 K). The equilibration of other sulfonamides has been reported to be achieved after 30 h.[2] Therefore, in this work, the initial equilibrium time of the saturated solution was 72 h; then it was analyzed once for 5 h until the analyzing results were replicated three consecutive times. After this time, the supernatant solutions were filtered to ensure that they were free of particulate matter before sampling. Concentrations were determined by measuring UV absorbances after appropriate dilution and interpolation from previously constructed calibration curves for each sulfonamide. To permit conversion between molarity and mole fraction concentration scales, the density of the saturated solutions was determined with a digital density meter. All the solubility experiments were repeated at least three times, and the mean values were considered as the measured results. The uncertainty of temperature measurements was ± 0.05 K. The reproducibility of measurements was 0.1 K, which corresponds to a relative deviation in composition smaller than 1 %. The result showed that the deviations of the measured solubility from the literature values[2,9] were less than 2 %.

Table 1. Comparison of Values of Measurement and References for Mole Fraction Solubilities (x) of Some Sulfonamides in Water at Different Temperatures

system	T/K	$10^5 x_{\mathrm{exptl}}$	$10^5 x_{\mathrm{ref}}$	rel dev/%
sulfadiazine + water	298.15	0.4819	0.4870[9]	−1.06
sulfamethazine + water	298.15	2.919	2.896[2]	0.79
	303.15	3.565	3.613[2]	−1.35
	308.15	4.188	4.244[2]	−1.34
sulfamethoxazole + water	298.15	2.698	2.664[2]	1.26

Results and Discussion

The solubilities of sulfadiazine, sulfamethazine, and sulfamethoxazole in water listed in Table 1 are measured, respectively, to complete the data reported in the literature.[2,9]

The temperature dependence of sulfonamide solubility in water has been described by the modified Apelblat equation[5−8]

$$\ln x = A + \frac{B}{T} + C \ln T \tag{1}$$

where x is the mole fraction of sulfonamide; T is the absolute temperature; and A, B, and C are constants determined by least-squares analysis. The values of these parameters are listed in Table 3. The relative deviations between the experimental and calculated values are also listed in Table 2.

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Table 2. Solubilities of Sulfadiazine, Sulfamethazine, Sulfadimethoxine, Sulfamethoxydiazine, Sulfamonomethoxine, Sulfamethoxazole, and Sulfachloropyrazine in Water at Various Temperatures

T/K	10^5x	rel dev/%	T/K	10^5x	rel dev/%
		Sulfadiazine + Water			
298.15	0.4819	0.64	318.15	1.334	−0.30
303.15	0.6198	−1.4	323.15	1.697	0.52
308.15	0.8230	0.73	328.15	2.102	−0.45
313.15	1.053	0.22	333.15	2.621	0.087
		Sulfamethazine + Water			
298.15	2.919	−0.82	318.15	5.814	0.13
303.15	3.565	1.3	323.15	6.786	0.059
308.15	4.188	0.18	328.15	7.873	−0.36
313.15	4.903	−0.75	333.15	9.186	0.36
		Sulfadimethoxine + Water			
298.15	0.3068	0.073	318.15	0.7253	0.82
303.15	0.3830	−0.15	323.15	0.8756	0.0066
308.15	0.4775	0.25	328.15	1.054	−0.48
313.15	0.5832	−0.71	333.15	1.276	0.19
		Sulfamethoxydiazine + Water			
298.15	0.5518	−0.36	318.15	1.481	−0.36
303.15	0.7190	0.37	323.15	1.878	0.36
308.15	0.9259	0.65	328.15	2.338	−0.15
313.15	1.166	−0.61	333.15	2.916	0.099
		Sulfamonomethoxine + Water			
298.15	0.3882	0.18	318.15	0.9628	0.93
303.15	0.4899	−0.0017	323.15	1.173	−0.39
308.15	0.6134	−0.33	328.15	1.452	−0.42
313.15	0.7646	−0.51	333.15	1.761	−0.30
		Sulfamethoxazole + Water			
298.15	2.698	−0.59	318.15	5.426	−0.31
303.15	3.266	0.37	323.15	6.327	−1.2
308.15	3.916	0.89	328.15	7.533	0.48
313.15	4.610	0.065	333.15	8.768	0.27
		Sulfachloropyrazine + Water			
298.15	1.124	0.22	318.15	2.300	0.64
303.15	1.350	0.49	323.15	2.748	0.77
308.15	1.592	−1.0	328.15	3.280	0.42
313.15	1.908	−0.83	333.15	3.912	−0.70

Table 3. Parameters of Equation 1 for Sulfadiazine, Sulfamethazine, Sulfadimethoxine, Sulfamethoxydiazine, Sulfamonomethoxine, Sulfamethoxazole, and Sulfachloropyrazine + Water Systems

system	A	B	C	ard/%
sulfadiazine + water	53.232	−7121.6	−7.3005	0.55
sulfamethazine + water	3.0938	−3347.2	−0.40382	0.50
sulfadimethoxine + water	4.7649	−4223.6	−0.57816	0.33
sulfamethoxydiazine + water	−24.053	−3417.3	4.1089	0.37
sulfamonomethoxine + water	−28.683	−2875.0	4.5397	0.38
sulfamethoxazole + water	−18.409	−2432.8	2.8177	0.52
sulfachloropyrazine + water	−132.34	2649.3	19.667	0.64

The relative deviations (rel dev values) are calculated according to

$$\text{rel dev (\%)} = \left(\frac{x - x_c}{x}\right)\cdot 100 \tag{2}$$

The average relative deviations for each system in this study are also listed in Table 3. The average relative deviations (ard values) are calculated according to

$$\text{ard (\%)} = \frac{100}{N}\sum_{i=1}^{N}\left|\frac{x_i - x_{ci}}{x_i}\right| \tag{3}$$

The data in Tables 2 and 3 indicate that the calculated solubilities show good agreement with the experimental data, which demonstrates that the modified Apelblat equation can be used to correlate the solubility data of sulfadiazine, sulfamethazine, sulfadimethoxine, sulfamethoxydiazine, sulfamonomethoxine, sulfamethoxazole, and sulfachloropyrazine in water. The relative deviations among all these 56 data points for sulfadiazine, sulfamethazine, sulfadimethoxine, sulfamethoxydiazine, sulfamonomethoxine, sulfamethoxazole, and sulfachloropyrazine + water systems do not exceed 1.4 %, and the total average relative deviation is 0.47 %. The experimental solubility and correlation equation in this work can be used as essential data and models to serve in the process of environmental risk assessment.

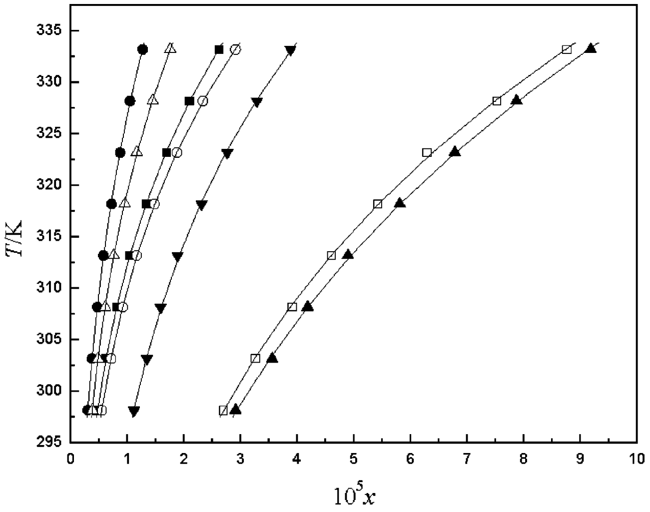


Figure 1. Solubilities of sulfonamides in water: ■, sulfadiazine + water; ▲, sulfamethazine + water; ●, sulfadimethoxine + water; ○, sulfamethoxydiazine + water; △, sulfamonomethoxine + water; □, sulfamethoxazole + water; ▼, sulfachloropyrazine + water; —, calculated from eq 1.

By using the data shown in Table 2, T∼x curves for sulfadiazine, sulfamethazine, sulfadimethoxine, sulfamethoxydiazine, sulfamonomethoxine, sulfamethoxazole, and sulfachloropyrazine + water systems were plotted. From Figure 1, it is evident that the solubility of each sulfonamide in water is low.

According to Scatchard−Hildebrand's theory,[10] the solubility of a solute in a solvent is largest when the solubility parameters of the solute and the solvent are the same, which means that the larger the difference in the solubility parameter value between the solute and the solvent, the lower the solubility of the solute in the solvent will be. The solubility parameter values of sulfadiazine (δ = 27.9 $\text{MPa}^{1/2}$), sulfamethazine (δ = 26.8 $\text{MPa}^{1/2}$), sulfadimethoxine (δ = 26.9 $\text{MPa}^{1/2}$), sulfamethoxydiazine (δ = 27.3 $\text{MPa}^{1/2}$), sulfamonomethoxine (δ = 27.3 $\text{MPa}^{1/2}$), sulfamethoxazole (δ = 27.2 $\text{MPa}^{1/2}$), and sulfachloropyrazine (δ = 27.9 $\text{MPa}^{1/2}$) were calculated by the Fedors group contribution method.[11] The solubility parameter for water is 47.9 $\text{MPa}^{1/2}$, which comes from the CRC handbook.[11] The values of the solubility parameter of sulfadiazine, sulfamethazine, and sulfamethoxazole determined in the present study agree with those values reported in the literature.[4,12] From the solubility parameter values, it is clear that the difference of the solubility parameter value between each sulfonamide and water is large, explaining why the solubility of each sulfonamide in water at constant temperature is low.[13]

According to a pseudochemical reaction process,[14−16] the dissolution process of solid (S) in liquid (W) can be expressed as S + W = SW; the relationship of its dissolution equilibrium constants and activities can be expressed as

$$K_i = \frac{a_i}{a_z a_w} \tag{4}$$

Table 4. ΔH_s and ΔS_s for Different Sulfonamides in Water at Different Temperatures

T/K		298.15	303.15	308.15	313.15	318.15	323.15	328.15	333.15
sulfadiazine	ΔH_s/kJ·mol^{-1}	41.11	40.80	40.51	40.20	39.90	39.59	39.29	38.99
	ΔS_s/kJ·mol^{-1}·K^{-1}	137.9	134.6	131.4	128.4	125.4	122.5	119.7	117.0
sulfamethazine	ΔH_s/kJ·mol^{-1}	26.83	26.81	26.79	26.78	26.76	26.74	26.73	26.71
	ΔS_s/kJ·mol^{-1}·K^{-1}	89.98	88.44	86.95	85.51	84.11	82.76	81.45	80.17
sulfadimethoxine	ΔH_s/kJ·mol^{-1}	33.68	33.66	33.63	33.61	33.59	33.56	33.54	33.51
	ΔS_s/kJ·mol^{-1}·K^{-1}	113.0	111.0	109.1	107.3	105.6	103.9	102.2	100.6
sulfamethoxydiazine	ΔH_s/kJ·mol^{-1}	38.60	38.77	38.94	39.11	39.28	39.45	39.62	39.79
	ΔS_s/kJ·mol^{-1}·K^{-1}	129.5	127.9	126.4	124.9	123.5	122.1	120.7	119.4
sulfamonomethoxine	ΔH_s/kJ·mol^{-1}	35.16	35.34	35.53	35.72	35.91	36.10	36.29	36.48
	ΔS_s/kJ·mol^{-1}·K^{-1}	117.9	116.6	115.3	114.1	112.9	111.7	110.6	109.5
sulfamethoxazole	ΔH_s/kJ·mol^{-1}	27.21	27.33	27.45	27.56	27.68	27.80	27.91	28.03
	ΔS_s/kJ·mol^{-1}·K^{-1}	91.27	90.15	89.06	88.02	87.00	86.02	85.06	84.14
sulfachloropyrazine	ΔH_s/kJ·mol^{-1}	26.72	27.54	28.36	29.18	29.99	30.81	31.63	32.45
	ΔS_s/kJ·mol^{-1}·K^{-1}	89.64	90.85	92.03	93.17	94.27	95.35	96.39	97.40

Due to the relatively small solubility of each sulfonamide in water, it is believed that a_s and a_w almost keep constant in the experimental range, each of which is considered as a constant.

$$J' = a_z a_w \tag{5}$$

So, eq 4 can be written as

$$K_i = \frac{\gamma_i x_i}{J'} \tag{6}$$

where r_i is the activity coefficient of sulfonamide i in the solution and x_i is the mole fraction of sulfonamide i in the solution.

On the basis of the assumption used in the inferential process for the modified Apelblat equation that the activity coefficient is invariable during a certain temperature range,[17] r_i in eq 6 can be merged into J'. Equation 7 can be obtained from eq 6 by logarithmic treatment.

$$\ln K_i = \ln x_i + J \tag{7}$$

where J is a temperature-independent constant.

On the basis of the Gibbs equation and the modified Van't Hoff method,[18−21] the equation for calculating the molar enthalpies of dissolution, ΔH_s, could be obtained.

$$\Delta H_s = R\frac{d \ln K_i}{dT^{-1}} \tag{8}$$

Substituting the differential of eq 7 into eq 8 yields

$$\Delta H_s = R\frac{d \ln x_i}{dT^{-1}} \tag{9}$$

Using eq 1 to obtain the derivative of ln x_i to T^{-1} and substituting it into eq 9, we obtain

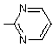
$$\Delta H_s = RT(C - B/T) \tag{10}$$

According to the fundamental thermodynamic relation,[10] the equition for calculating the molar entropies of dissolution, ΔS_s, could be obtained accordingly.

$$\Delta S_s = R(C - B/T) \tag{11}$$

According to the parameters of the modified Apelblat equation listed in Table 3, ΔH_s and ΔS_s listed in Table 4 can be calculated from eq 10 and eq 11, respectively.

From Table 4, it is found that the course of each sulfonamide dissolving in water in the experimental temperature range was endothermic, $\Delta H_s > 0$, and ΔS_s for each sulfonamide dissolving in water was relatively large. The positive ΔH_s and ΔS_s for each sulfonamide revealed that each sulfonamide being dissolved in water was an entropy driving process. This phenomenon is likely a result of the different molecular structure and space conformation between solute and solvent. Water molecules as solvent are strong association complexes with a small molecular dimension.[22,23] Owing to the solute sulfonamide molecules containing basic groups such as $-NH_2$, acidic groups such as $>SO_2$, and complicated groups with different characteristics such as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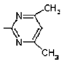
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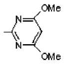
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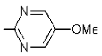
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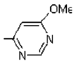
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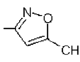
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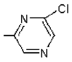
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sulfonamides perhaps involve various forces such as electrostatic force, hydrogen bond, hydrophobic interaction, and stereoscopic effects in the dissolving process.[10] The reason for the entropy increase in the dissolving process is that sulfonamides disrupted the alignment of water molecules, therefore reducing the degree of order of the system while they were dissolved in water. The endothermic effect in the dissolving process ($\Delta H_s > 0$) is perhaps due to the fact that the interactions between sulfonamide molecules and water molecules are more powerful than those between water molecules; the newly formed bond energy with the sulfonamide molecule and the water molecule is not powerful enough to compensate the energy needed for breaking the original association bond in water.

Conclusion

Using a static equilibrium method, the solubilities of sulfadiazine, sulfamethazine, sulfadimethoxine, sulfamethoxydiazine, sulfamonomethoxine, sulfamethoxazole, and sulfachloropyrazine in water have been determined experimentally from (298.15 to 333.15) K. The experimental data were correlated with the modified Apelblat equation. The calculated results show good agreement with the experimental data.

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Literature Cited

(1) Kay, P.; Blackwell, P. A.; Boxall, A. B. A. A lysimeter experiment to investigate the leaching of veterinary antibiotics through a clay soil and comparison with field data. *Environ. Pollut.* **2005**, *134*, 333−341.

(2) Martinez, F.; Gomez, A. Thermodynamic study of the solubility of some sulfonamides in octanol, water, and the mutually saturated solvents. *J. Solution Chem.* **2001**, *30*, 909−923.

(3) Martinez, F.; Avila, C. M.; Gomez, A. Thermodynamic study of the solubility of some sulfonamides in cyclohexane. *J. Braz. Chem. Soc.* **2003**, *14*, 803−808.

(4) Hanaee, J.; Jouyban, A.; Dastmalchi, S.; Adibkia, K.; Mirzazadeh, A.; Barzegarjalali, M. Solubility prediction of sulfonamides at various temperatures using a single determination. *DARU* **2005**, *13*, 37−45.

(5) Apelblat, A.; Manzurola, E. Solubility of oxalic, malonic, succinic, adipic, maleic, malic, citric, and tartaric acids in water from 278.15 to 338.15 K. *J. Chem. Thermodyn.* **1987**, *19*, 317−320.

(6) Wang, L. C.; Wang, F. A. Solubilities of niacin in 3-picoline + water from (287.65 to 359.15) K. *J. Chem. Eng. Data* **2004**, *49*, 155−156.

(7) Wang, F. A.; Wang, L. C.; Song, J. C.; Wang, L.; Chen, H. S. Solubilities of bis(2,2,6,6-tetramethyl-4-piperidinyl) maleate in hexane, heptane, octane, *m*-xylene, and tetrahyrofuran from (253.15 to 310.15) K. *J. Chem. Eng. Data* **2004**, *49*, 1539−1541.

(8) Zhao, J. H.; Wang, L. C.; Wang, F. A. Solubilities of *p*-aminophenol in sulfuric acid + water + (methanol, ethanol, 1-propanol, 2-propanol, 1,2-propanediol and glycerin, respectively) from (292.35 to 348.10) K. *J. Chem. Eng. Data* **2006**, *51*, 376−381.

(9) Martinez, F.; Gomez, A. Estimation of the solubility of sulfonamides in aqueous media from partition coefficients and entropies of fusion. *Phys. Chem. Liq.* **2002**, *40*, 411−420.

(10) Prausnitz, J. M.; Lichtenthaler, R. N.; Azevedo, E. G. *Molecular Thermodynamics of Fluid-Phase Equilibria*, 3rd ed.; Prentice Hall: Upper Saddle River, NJ, 1999; pp 645−647.

(11) Barton, A. F. M. *CRC Handbook of Solubility Parameters and Other Cohesion Parameters*, 2nd ed.; CRC Press: Boca Raton, FL, 1991; pp 99−148.

(12) Hancock, B. C.; York, P.; Rowe, R. C. The use of solubility parameters in pharmaceutical dosage form design. *Int. J. Pharm.* **1997**, *148*, 1−21.

(13) Wang, L. C.; Wang, F. A. Solubilities of niacin in sulfuric acid + water and 3-picoline + sulfuric acid + water from (292.65−361.35) K. *Fluid Phase Equilib.* **2004**, *226*, 289−293.

(14) Wang, F. A. *Molecular Thermdynamics and Chromatographic Retention*; Meteorology Press: Beijing, 2001; pp 172−176.

(15) Wang, F. A.; Wang, W. C.; Jiang, Y. L. A new model of dielectric constant for binary solutions. *Chem. Eng. Technol.* **2000**, *23*, 623−627.

(16) Wang, F. A.; Chen, H. S.; Zhu, J. Q.; Song, J. C.; Wang, Z. J. Estimation of excess enthalpy for binary systems. *Chem. Eng. J.* **2002**, *85*, 235−243.

(17) Wang, F. A.; Wang, L. C.; Song, J. C.; Wang, L.; Chen, H. S. Solubilities of bis(2,2,6,6-tetramethyl-4-piperdinyl) maleate in hexane, heptane, octane, *m*-xylene, and tetrahydrofuran from (253.15 to 310.15) K. *J. Chem. Eng. Data* **2004**, *49*, 1539−1541.

(18) Bourgois, D.; Thomas, D.; Fanlo, J. L.; Vanderschuren, J. Solubilities at high dilution of toluene, ethylbenzene, 1,2,4-trimethylbenzene, and hexane in di-2-ethylhexyl, diisoheptyl, and diisononyl phthalates. *J. Chem. Eng. Data* **2006**, *51*, 1212−1215.

(19) Saboury, A. A.; Bordbar, A. K.; Moosavi-Movahedi, A. A. The enthalpy of unfolding for jack bean urease with interaction of *n*-alkyl trimethylammonium bromides. *J. Chem. Thermodyn.* **1996**, *28*, 1077−1082.

(20) Lerchner, J.; Kirchner, R.; Seidel, J.; Wahlisch, D.; Wolf, G.; Konig, W. A.; Lucklum, R. Determination of molar heats of absorption of enantiomers into thin chiral coatings by combined IC-calorimetric and microgravimetric (QMB) measurements. 2. Thermodynamics of enantioselectivity in modified cyclodextrins. *Thermochim. Acta* **2006**, *445*, 98−103.

(21) Nazari, K.; Golchin, A. R.; Moosavi-Movahedi, A. A.; Saboury, A. A.; Hakimelahi, G. H.; Shockravi, A.; Tangestani-Nejad, S. Microcalorimetry and binding studies of DNA upon interaction with [pyridine diamine]$_2$[Co(phenanthroline dicarboxylate)$_2$]. *Thermochim. Acta* **2005**, *428*, 157−163.

(22) Nagata, I.; Gotoh, K.; Tamura, K. Association model of fluids. Phase equilibria and excess enthalpies in acid mixtures. *Fluid Phase Equilib.* **1996**, *124*, 31−54.

(23) Nath, A.; Bender, E. On the thermodynamics of associated solutions. I. An analytical method for determining the enthalpy and entropy of association and equilibrium constant for pure liquid substances. *Fluid Phase Equilib.* **1981**, *7*, 275−287.

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