Prediction of Solubility of Drugs by Conductor-Like Screening Model for Real Solvents

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The solubility of drugs in solvents is fundamentally important for drug development and manufacturing. As the experimental measurements of the solubility are extremely laborious tasks, reliable prediction methods are highly required. We have employed the conductor-like screening model for real solvents (COSMO-RS) in predicting the solubility of drugs and drug-like compounds in various solvent systems. We also evaluated the salt effect on the solubility of caffeine using this method. The present results demonstrated that COSMO-RS has reasonably reproduced the experimental data and have proved that this method is generally available in predicting the solubility of drugs.

Key words solubility; drug; conductor-like screening model for real solvent; mixed solvent; salt effect

The solubility of drugs in various solvents including water is of overwhelming importance for drug development and manufacturing. The information is also very valuable to evaluate the profiles of administration, distribution, metabolism, excretion and toxicity of drugs. Since the solubility of drugs plays a decisive role in the process of drug discovery, it is extremely useful if the solubility can be predicted.

The behavior and the thermodynamic properties of solute–solvent systems must be fully considered in order to predict the solubility of drugs. Due to the lack of rigorous methods to handle the thermodynamic behavior of fluid systems, several phenomenological approaches have been employed. A typical representatives of such methods are UNIFAC[1] and CLOGP.[2] Although these methods are useful, they have serious inherent disadvantages that come from the facts that both methods depend on the experimental data available. The conductor-like screening model for real solvents (COSMO-RS), however, is a more fundamental approach, since the model integrates the concepts of quantum theory, dielectric continuum models, and surface interactions.[3]

In the present study we apply COSMO-RS in predicting the solubility of various drugs in organic solvents and several mixed solvents. The effect of salts to the solubility of drugs is extremely important from the viewpoint of formulation. We have shown that the effect of salts to the solubility of caffeine can be predicted using the conductor-like screening method.

Experimental

Computational Details The calculations of solubility at 25 °C under the ambient pressure were performed roughly in two steps. In the first step, the geometry and polarization charge density on the molecular surface were calculated for solute and solvent molecules. The TURBOMOLE[4] program based on the density functional theory was used for this calculations and the high quality COSMO (conductor-like screening model) parameterization with full geometry optimization at the TZVP basis set was applied. In the second step, the solubility for each solute–solvent system was obtained using the charge densities of the solute and solvent molecules by the COSMO-RS method. COSMO-RS implemented in the COSMO*therm*[5] was used in the present study.

It took 6 h in average to calculate charge density of a molecule by TURBOMOLE with Xenon 2.2 GHz. For a typical calculation of solubility of a solute in a solvent by COSMO-RS, it took about 1 min with Pentium 3 700 MHz. Therefore the resources and time required to perform the calculations are tractable in today's usual chemical laboratories.

Results and Discussion

Prediction of Solubility of Drugs in Single Solvents The number of drugs whose solubilities are quantitatively measured is quite small. As a test set for this study, 15 drugs and drug-like compounds with the experimental solubility data in four common solvents[6] are selected. The solubilities were determined at 25 °C under the ambient pressure. The selected drugs and solvents are shown in Table 1. Water, ethanol, acetone and chloroform were selected as solvents.

The predicted and experimental solubilities are given in Table 1. The solubility of a compound is normally represented as $\log S$, where S is the concentration of the compound in mol/l for a saturated solution in equilibrium with the most stable form of the crystal material. In this study, however, S is defined as the mole fraction of the solute in a saturated solution. The $\log S$ values in Table 1 range from -0.5 to -7.0. The correlation between the predicted and experimental solubilities is reasonably good. A regression equation with a correlation coefficient (r^2) of 0.81 and a root mean square error (rmse) of 0.64 log unit was yielded. Since the solubilities of 15 compounds in four different solvents are compared, the good correlation obtained strongly indicates that the present method is not dependent on the solute and solvent molecules. The rmse values for water, ethanol, acetone and chloroform are 0.51, 0.61, 0.84 and 0.56, respectively. The prediction accuracy does not depend on solvent. The slightly large value of acetone is obviously due to the small number of experimental data used. These results demonstrate that the present method can be applied to the prediction of solubility of any solute in any solvent.

For caffeine, hydrocortisone, and nifedipine, the solubilities in four solvents are available. It is of interest to compare the predicted and experimental solubilities. As given in Table 1, the predicted values reproduce the experimental ones reasonably well.

Prediction of Solubility of Drugs in Mixed Solvent Mix solvents are often used in processes of separation, isola-

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Table 1. Calculated and Experimental Solubilities (log *S*) of Drugs in Pure Solvents[a)]

Compounds	Solvents			
	Water	Ethanol	Acetone	Chloroform
Aspirin	−3.449 (−3.478)	−0.670 (−1.215)	0 (n/a)	−1.354 (−1.592)
Atropine	−4.457 (−3.864)	−1.853 (−1.037)	−1.498 (n/a)	−1.011 (−0.662)
Barbital	−2.645 (−3.124)	−1.028 (−1.654)	−1.237 (n/a)	−2.901 (−2.237)
Benzocaine	−3.597 (−4.361)	−0.798 (−1.180)	0 (n/a)	−1.394 (−0.708)
Caffeine	−2.342 (−2.697)	−1.628 (−2.343)	−1.341 (−2.243)	0 (−1.155)
Cocaine	−4.499 (−4.005)	−1.825 (−1.541)	−1.158 (n/a)	−1.115 (−0.561)
Hydrocortisone	−5.168 (−4.857)	−2.729 (−2.617)	−2.508 (−2.844)	−2.686 (−3.450)
Lorazepam	−5.943 (−5.348)	−2.927 (−2.595)	−2.464 (n/a)	−4.552 (−3.124)
Mannitol	−2.619 (−1.753)	−3.211 (−2.414)	−4.516 (n/a)	−7.944 (n/a)
Nifedipine	−5.657 (−6.505)	−1.657 (−2.543)	−1.004 (−1.412)	−1.251 (−1.502)
Perphenazine	−5.870 (−5.905)	−2.843 (−1.664)	−2.102 (−1.950)	−3.461 (n/a)
Phenacetin	−3.871 (−4.115)	−0.991 (−1.672)	−0.711 (n/a)	−0.889 (−1.508)
Phenobarbital	−4.006 (−4.111)	−1.232 (−1.515)	−2.017 (n/a)	−3.483 (−2.066)
Salicylic acid	−3.517 (−3.583)	−0.976 (−0.820)	0 (−0.665)	−2.159 (n/a)
Theophylline	−2.603 (−3.080)	−2.145 (−2.394)	−2.036 (n/a)	−3.223 (−2.393)
rmse	0.50	0.61	0.84	0.56

a) The experimental value in parentheses.

tion or crystallization of drugs. The selection of a suitable mixing ratio for a particular mix solvent system in order to dissolve a solute has been a matter of trial and error. It will be extremely useful if an appropriate mixing rate of the solvent system that dissolves the drug can be predicted based on the chemical structures of the solute and solvents alone. The experimental data on the solubilities of drugs in the mixed solvent with different composition is sparse. Fortunately, excellent experimental data are available for oxolinic acid in water–ethanol system[7)] and sulfadiazine in water–1,4-dioxane system.[8)] The solubilities were determined at 25 °C under the ambient pressure. We used these data to validate the predicted results.

Plots of the predicted *versus* experimental results for the two compounds are shown in Fig. 1. The shapes of the curves of the predicted and experimental results are markedly similar. The absolute values of the predicted solubilities, however, are systematically smaller than the experimental ones. The differences for oxolinic acid and sulfadiazine are roughly 2.0 and 1.6 log unit, respectively. The reason of these shifts is not clear at present. Although the absolute value of solubility cannot be predicted, we can quantitatively determine a relevant composition of solvents that gives a reasonably high solubility of the drug. Since measuring solubility of a drug in mixed solvents with different composition is highly laborious task, it will be extremely helpful if we could predict a semi-quantitative image about the solubility *versus* composition plot. From this viewpoint, the solubility prediction in mixed solvents based on the COSMO-RS method can be very useful.

Prediction of Salt Effects on Drug Solubility Since many processes pertaining to drug formulation or application take place in the presence of varying concentrations of different salts, salt effects on solubility of drug is particularly important. Measuring solubilities of a drug by adding different salts is also an exacting task. Therefore the prediction of the solubilities is a great help. Recently a detailed study about the salt effects on caffeine solubilities in water has been reported.[9)] The solubilities were determined at 25 °C under the ambient pressure. Prediction of the salt effects on the same

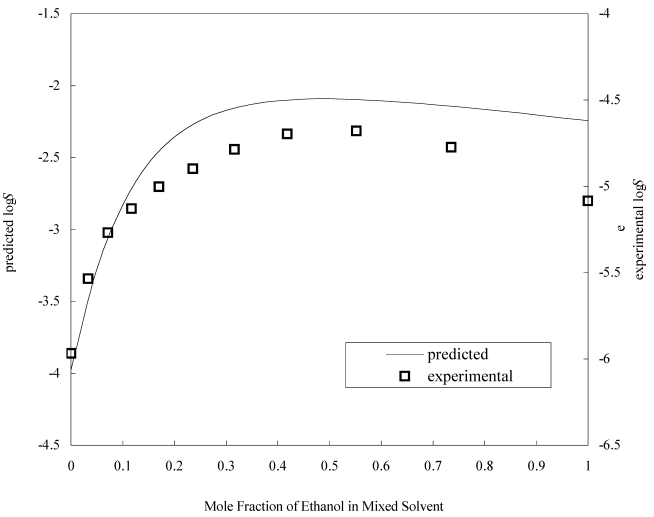

Fig. 1. Comparison between Predicted and Experimental Solubilities in Mixed Solvents

(a) Oxolinic acid in water–ethanol system; (b) sulfadiazine in water–dioxane system.

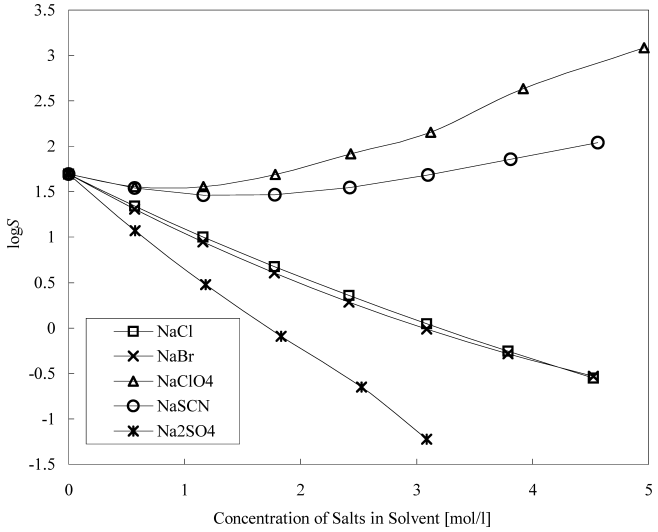

Fig. 2. Predicted Salt Effects on Solubility of Caffeine

system has been performed by COSMO-RS and the results were compared with the experimental ones. The predicted salt effects are shown in Fig. 2.

Solubilities of caffeine decrease with the increasing of the concentration of NaCl, NaBr and Na_2SO_4, whereas the solubilities increase with added NaSCN and $NaClO_4$. The predicted patterns of solubility changes generally agree with these experimental results. The major discrepancy between the predicted and experimental results is observed in the concentration of salts that is required to produce the same amount of solubility change. Experimental results showed that the solubility change occurs at low concentrations of salts, 0.1—1.0 mol/l. In the prediction, much higher concentrations, 2.5—5.0 mol/l, were required to produce the corresponding amount of solubility change. This discrepancy is inherently due to the treatment of intermolecular interactions by the COSMO-RS method. The method ignores the electrostatic interactions between molecules beyond the nearest neighbors. In the ionic solution, however, these interactions are significant and cannot be ignored. Although the absolute values of the concentrations of salts cannot be accurately predicted, the present result demonstrates that the prediction by the COSMO-RS method is practically useful in the processes of drug discovery and manufacturing.

Conclusion

COSMO-RS method is a fundamental approach and not dependent on the experimentally available data. Therefore the solubility prediction by this method is, in principle, applicable any solute and any solvent. The results obtained in this study are extremely satisfactory and have proved that this method is highly valuable in the drug discovery and manufacturing processes.

The major drawback of the method of this sort has been the computation time. As far as the problems treated in the present study concerned, the computation barrier has been practically overcome and the method is entirely feasible.

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References and Notes

1) Fredenslund A., Gmehling J., Rasmussen P., "Vapor Liquid Equilibria Using UNIFAC," Elsevier, Amsterdam, 1977.
2) Hansch C., Leo A. J., "Substituent Parameters for Correlation Analysis in Chemistry and Biology," Wiley, New York, 1979.
3) Klamt A., Eckert F., Hornig M., *J. Comp.-Aided Mol. Design*, **15**, 355—365 (2001).
4) Ahlrichs R., Bär M., Häser M., Horn H., Kölmel C., *Chem. Phys. Lett.*, **162**, 165—169 (1989).
5) Klamt A., Eckert F., "COSMO*therm*," Version C1.2-Revision 07.02, COSMO*logic* GmbH & Co. KG, Leverkusen, Germany, 2002.
6) "The Merk Index," 13th ed., Merck & Co., Inc., New Jersey, 2001.
7) Jouyban A., Romero S., Chan H. K., Clark B. J., Bustamante P., *Chem. Pharm. Bull.*, **50**, 594—599 (2002).
8) Bustamante P., Escalera B., Martin A., Selles E., *J. Pharm. Pharmacol.*, **45**, 253—257 (1993).
9) Al-Maaieh A., Flanagan D. R., *J. Pharm. Sci.*, **91**, 1000—1008 (2002).