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Report

Solubility Predictions for Solid Nitriles and Tertiary Amides Based on the Mobile Order Theory

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The solubilities of hexadecanenitrile, octadecanenitrile, *N,N*-diphenyl capramide, and *N,N*-diphenyl lauramide are predicted in common organic nonelectrolyte solvents using the solubility equation derived from the mobile order theory. In the framework of this theory, the formation of hydrogen bonds is treated on the basis of stability constants. Two values characterizing the nitrile–alcohol and the tertiary amide–alcohol hydrogen bonds, 175 and 600 cm^3 mol^{-1}, respectively, are determined. Although the formation of solute–solvent specific molecular interactions brings about a net increase in the solubility, the solubilities of the nitriles and amides in alcohols remain lower than those measured in nonassociated solvents because of the large negative hydrophobic effect of the alcohol molecules.

KEY WORDS: Solubility; mobile order theory; hydrogen bond; stability constant; thermodynamics; proton acceptors.

INTRODUCTION

The temporary order introduced in a liquid by the formation of hydrogen bonds (preferential contacts) as well as the labile nature and the perpetually moving character of these bonds (their mobility) constitute the basic foundation of the mobile order thermodynamics of liquids developed by Huyskens and Siegel (1–4). Its quantitative development led to equations describing the effect of solvent–solvent, solute–solute, and solvent–solute interactions on the chemical potential of the solute, from which a universal predictive equation for solubility (in volume fraction) of solid and liquid substances [Eq. (1)] has been derived (5).

$$\mathrm{In}\,\Phi_B = A + B + D + F + O + OH \qquad (1)$$

This equation takes into account all contributions to the free-energy change when a solid solute *B* is dissolved in a solvent *S* and may contain, at most, six terms: the fluidization of the solute (term *A*), the exchange entropy correction resulting from the difference in molar volumes of solute and solvent (term *B*), the change in nonspecific cohesion forces in solution (term *D*), the hydrophobic effect (for self-associated solvents; term *F*), the hydrogen bond formation between proton-acceptor solutes and proton-donor solvents (term O), and the hydrogen bond formation between amphiphilic solutes and proton-acceptor and/or proton-donor solvents as well as the autoassociation of the solute in solution (term OH). The above equation has been successfully applied to predict the solubility of aliphatic and aromatic hydrocarbons and polychlorinated aromatic hydrocarbons in nonpolar, polar, and hydrogen-bonded solvents such as alcohols and water (6–8). Furthermore it has been demonstrated from the analysis of the relative importance of the different terms in Eq. (1) that the aqueous solubility was determined essentially by the magnitude of the hydrophobic effect (9,10). More recently, the present model was used to predict the solubility of crystalline proton-acceptor substances (11), i.e., ketones and esters, able to form hydrogen bonds with alcohols, and to determine the stability constants characterizing these hydrogen bonds. In the same work, it was shown, first, that the formation of such specific molecular interactions brings about a net increase in the solubility without modifying the values of the other contributions relevant to the solution process and, second, that the stability constants so determined were transferable from one solute molecule to another when forming the same type of hydrogen bond with the solvent.

The aim of this paper is to apply this new theoretical approach to predict the solubility of further crystalline proton-acceptor substances, namely, nitriles and tertiary amides, and to determine their stability constants with alcohols. For this purpose, two solid nitriles (hexadecanenitrile and octadecanenitrile) and two solid amides (*N,N*-diphenyl capramide and *N,N*-diphenyl lauramide) have been chosen. Their solubilities are predicted in a series of common organic solvents of differing polarities and are compared to the experimental values taken from the literature.

RESULTS AND DISCUSSION

To predict the solubility of solid proton-acceptor solutes, only three or five terms of Eq. (1) must be considered according to whether the solvent is a proton donor or not.

Solubility in non-proton-donor solvents:

$$\mathrm{In}\,\Phi_B = A + B + D \qquad (2)$$

Solubility in proton-donor solvents (alcohol):

$$\mathrm{In}\,\Phi_B = A + B + D + F + O \qquad (3)$$

Representing single physical phenomena related to the solubilization process, each term involved in Eqs. (2) and (3) has a well-defined expression and contributes favorably or unfavorably to the solubility.

$$A = -\Delta_{\mathrm{melt}}H[(1/T) - (1/T_m)]/R \qquad (4)$$

$$B = 0.5\Phi_S[(V_B/V_S) - 1] + 0.5\ln(\Phi_B + \Phi_S V_B/V_S) \qquad (5)$$

$$D = -\Phi_S{}^2 V_B(\delta_B' - \delta_S')^2/(RT) \qquad (6)$$

$$F = -r_S\Phi_S(V_B/V_S) \qquad (7)$$

$$O = \ln\{1.0 + K_O[(\Phi_S/V_S) - (\Phi_B/V_B)]\} \qquad (8)$$

In these expressions, $\Delta_{\mathrm{melt}}H$ and T_m represent the molar heat and the temperature of fusion; V_B, δ_B', Φ_B, V_S, δ_S', and Φ_S stand for the molar volume, the modified nonspecific solubility parameter, and the volume fraction, respectively, of the solute *B* and of the solvent *S;* r_S represents the "structuration" or "mobile order" factor of the solvent, amounting

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Table I. Physical Properties of the Solutes

Solute	V_B (cm^3/mol)^a	δ_B' (J$^{1/2}$cm$^{-3/2}$)	$\Delta_{melt}H$ (kJ/mol)	T_m (°C)
Hexadecanenitrile	283.6	17.24	56.804	31.4^b
Octadecanenitrile	316.6	17.68	65.808	41.0^b
N,N-Diphenyl capramide	334.0	17.93	35.157	47.5^c
N,N-Diphenyl lauramide	367.0	17.54	40.776	57.0^c

[a] Calculated from group contributions (5).

[b] From Ref. 12.

[c] From Ref. 13.

to 0 for the nonassociated solvents and approximately 1 for the alcohols; and K_O is the stability constant, which characterizes the hydrogen bond formed between the proton-acceptor solute and the proton-donor solvent.

All these physicochemical properties, except K_O, needed for the solubility predictions are reported in Table I for the solid nitriles and amides and can be found in Ref. 11 for the solvents in which solubilities are calculated. However, as no experimental value of the molar heat of fusion and of the modified nonspecific solubility parameter of the considered solutes could be found in the literature, an alternative procedure is proposed to calculate them simultaneously from experimental solubilities. Given a solute and its experimental solubility, Φ_B^{exp}, in some nonassociated solvents, we determine its modified nonspecific solubility parameter, δ_B', as the value for which the fluidization constant, A, calculated from Eq. (2) for each solvent shows the best constancy defined by the minimum of the standard deviation, σ. An example of such determinations is presented in Table II for octadecanenitrile. From these calculations, we conclude that the values of the modified nonspecific solubility parameters, δ_B', of hexadecanenitrile, octadecanenitrile, *N,N*-diphenyl capramide, and *N,N*-diphenyl lauramide amount to 17.24, 17.68, 17.93, and 17.54 J$^{1/2}$cm$^{-3/2}$, respectively, whereas their fluidization constants amount to -0.8724, -1.8048, -0.7612, and -1.3230, respectively. Using these results together with the experimental melting temperatures, T_m, one easily obtains the values of the molar heat of fusion, $\Delta_{melt}H$ (Table 1) by means of the expression of the fluidization constant, A [Eq. (4)].

On the basis of the data reported in Table I, it is then possible by using Eq. (2) to predict the solubilities of the nitrile and amide solutes in any nonassociated solvent the modified nonspecific solubility parameter of which is known. The results are compared to the experimental values in Table III, and the quality of the predictions is estimated by the solubility ratios, $\Phi_B^{pred}/\Phi_B^{exp}$, between the predicted and the experimental values. Of the 40 solubilities predicted in nonassociated solvents, 35 have a solubility ratio in the range of 0.86 to 1.09, the worst ratio of the five remaining results amounting to only 2.46 for octadecanenitrile in acetonitrile. Such results clearly demonstrate the power and the validity of the solubility model to predict the solubility of polar proton-acceptor substances in a wide range of nonassociated organic solvents.

Although the solubility values in nonassociated solvents are relatively close to each other, some general rules regarding the evolution of the solubility values can be drawn from the analysis of the relative importance of the three different terms contributing to the solubility (Table III). For most solvents, the fluidization of the solute constitutes the dominating term and always represents a hindrance to the solubility. Accordingly, among solutes belonging to the same class of organic compounds, the one with the lowest fluidization term will show the highest solubility. Furthermore, with respect to a given solute, the solvents can be classified into two groups: one having a modified nonspecific solubility parameter close to that of the solute, such that the difference $\|\delta_B' - \delta_S'\|$ is lower than 1.5, and the others above 1.5. In the first group of solvents, the solute will in general be more soluble, and its highest solubility will be observed in the solvent with the lowest molar volume. This trend is confirmed, for instance, in observing the following series of octadecanenitrile solubilities: $CHCl_3$ (80.7 cm^3/mol) > benzene (89.4 cm^3/mol) > CCl_4 (97.1 cm^3/mol) > diethyl ether (104.8 cm^3/mol). In the second group of solvents, the solubilities will be lower and will vary according to the balance of two opposite effects, B and D. As a result, the classification of these solvents with regard to the solute solubility is a priori much more difficult to establish.

Table II. The Fluidization Constant, A, of Octadecanenitrile at 20°C for Different Values of Its Modified Nonspecific Solubility Parameter, δ_B'

		δ_B' (J$^{1/2}$ cm$^{-3/2}$)				
Solvent	Φ_B^{exp}	17.40	17.50	17.68	17.80	17.90
Hexane	0.1757	−1.9912	−1.9402	−1.8439	−1.7765	−1.7581
Cyclohexane	0.3367	−1.7508	−1.7207	−1.6637	−1.6237	−1.5890
Benzene	0.5200	−1.5906	−1.5996	−1.6142	−1.6229	−1.6295
CCl_4	0.4377	−1.8666	−1.8632	−1.8551	−1.8482	−1.8415
Diethyl ether	0.3207	−2.1414	−2.1573	−2.1830	−2.1979	−2.2091
Ethyl acetate	0.3006	−1.7138	−1.7562	−1.8294	−1.8759	−1.9133
Butyl acetate	0.2886	−1.7447	−1.7737	−1.8227	−1.8530	−1.8768
Acetone	0.3316	−1.5992	−1.6510	−1.7412	−1.7993	−1.8464
Methyl ethyl ketone	0.3826	−1.5971	−1.6313	−1.6903	−1.7278	−1.7581
$\langle A \rangle$		−1.7772	−1.7881	−1.8048	−1.8139	−1.8202
σ^a		0.1907	0.1767	0.1663	0.1716	0.1831

[a] Standard deviation: $\sigma = \{[n\Sigma x^2 - (\Sigma x)^2]/[n(n-1)]\}^{0.5}$.

Table III. Experimental, Φ_B^{exp}, and Predicted, Φ_B^{pred}, Solubilities of the Nitriles and Tertiary Amides in Various Solvents and the Contributions A, B, D, F, and O

Solvent	$\Phi_B^{\mathrm{exp}a}$	Φ_B^{pred}	$\Phi_B^{\mathrm{pred}}/\Phi_B^{\mathrm{exp}}$	B	D	F	O
Hexadecanenitrile (20°C): $A = -0.872$							
Nonassociated solvents							
$CHCl_3$	0.790	0.736	0.93	0.585	−0.019	·	·
Benzene	0.723	0.710	0.98	0.559	−0.029	·	·
CCl_4	0.694	0.700	1.01	0.516	−0.000	·	·
Acetone	0.637	0.694	1.09	0.745	−0.237	·	·
Nitroethane	0.613	0.677	1.10	0.810	−0.328	·	·
Diethyl ether	0.540	0.671	1.24	0.503	−0.030	·	·
Methyl ethyl ketone	0.662	0.661	1.00	0.637	−0.180	·	·
Cyclohexane	0.647	0.641	0.99	0.516	−0.088	·	·
Ethyl acetate	0.635	0.637	1.00	0.602	−0.181	·	·
Butyl acetate	0.567	0.574	1.01	0.441	−0.124	·	·
Hexane	0.517	0.563	1.09	0.457	−0.160	·	·
Alcohols							
Methanol ($K_O = 0$)	0.136	0.0136	0.10	3.908	−0.457	−6.873	·
Methanol ($K_O = 175$)	0.136	0.0942	0.69	3.631	−0.386	−6.311	1.576
Isopropanol ($K_O = 0$)	0.276	0.0901	0.38	1.841	−0.019	−3.355	·
Isopropanol ($K_O = 175$)	0.276	0.335	1.21	1.406	−0.010	2.451	0.835
Butanol ($K_O = 0$)	0.358	0.116	0.32	1.443	−0.001	−2.726	·
Butanol ($K_O = 175$)	0.358	0.343	0.95	1.116	−0.000	−2.026	0.712
Octadecanenitrile (20°C): $A = -1.805$							
Nonassociated solvents							
$CHCl_3$	0.643	0.508	0.79	1.165	−0.037	·	·
Benzene	0.520	0.468	0.90	1.104	−0.059	·	·
CCl_4	0.438	0.451	1.03	1.024	−0.016	·	·
Diethyl ether	0.321	0.416	1.30	0.980	−0.054	·	·
Methyl ethyl ketone	0.383	0.341	0.89	1.314	−0.584	·	·
Ethyl acetate	0.301	0.323	1.07	1.207	−0.532	·	·
Acetone	0.332	0.302	0.91	1.740	−1.133	·	·
Butyl acetate	0.289	0.293	1.02	0.833	−0.254	·	·
Cyclohexane	0.337	0.291	0.86	1.105	−0.534	·	·
Hexane	0.176	0.184	1.05	0.955	−0.841	·	·
Nitroethane	0.182	0.179	0.98	2.068	−1.986	·	·
Acetonitrile	0.0323	0.0793	2.46	3.155	−3.885	·	·
Alcohols							
Methanol ($K_O = 0$)	0.0148	0.00419	0.28	4.399	−0.317	−7.746	·
Methanol ($K_O = 175$)	0.0148	0.0239	1.61	4.324	−0.305	−7.593	1.646
Isopropanol ($K_O = 0$)	0.0742	0.0247	0.33	2.218	−0.096	−4.015	·
Isopropanol ($K_O = 175$)	0.0742	0.0869	1.17	2.097	−0.084	−3.759	1.109
Butanol ($K_O = 0$)	0.135	0.0340	0.25	1.785	−0.033	−3.324	·
Butanol ($K_O = 175$)	0.135	0.103	0.76	1.674	−0.028	−3.086	0.974
***N,N*-Diphenyl capramide (30°C): $A = -0.761$**							
Nonassociated solvents							
Acetonitrile	0.669	0.849	1.27	0.695	−0.098	·	·
Acetone	0.856	0.799	0.93	0.621	−0.085	·	·
Nitroethane	0.770	0.798	1.04	0.646	−0.110	·	·
Benzene	0.748	0.785	1.05	0.526	−0.006	·	·
CCl_4	0.835	0.769	0.92	0.505	−0.006	·	·
Methyl ethyl ketone	0.736	0.767	1.04	0.559	−0.064	·	·
Ethyl acetate	0.736	0.749	1.02	0.535	−0.063	·	·
Cyclohexane	0.671	0.714	1.06	0.529	−0.105	·	·
Butyl acetate	0.667	0.690	1.04	0.429	−0.038	·	·
Alcohols							
Methanol ($K_O = 0$)	0.619	0.0112	0.02	4.610	−0.226	−8.114	·
Methanol ($K_O = 600$)	0.619	0.775	1.25	1.291	−0.012	−1.843	1.071
Isopropanol ($K_O = 0$)	0.644	0.0675	0.10	2.266	−0.147	−4.049	·
Isopropanol ($K_O = 600$)	0.644	0.663	1.03	0.942	−0.019	−1.465	0.893

Table III. Continued

Solvent	$\Phi_B^{\mathrm{exp}a}$	Φ_B^{pred}	$\Phi_B^{\mathrm{pred}}/\Phi_B^{\mathrm{exp}}$	B	D	F	O
Butanol (K_O = 0)	0.653	0.0998	0.15	1.791	−0.064	−3.267	·
Butanol (K_O = 600)	0.653	0.629	0.96	0.828	−0.011	−1.345	0.827
	N,N-Diphenyl lauramide (30°C): $A = -1.323$						
	Nonassociated solvents						
Benzene	0.620	0.645	1.04	0.922	−0.036	·	·
CCl_4	0.709	0.631	0.89	0.867	−0.005	·	·
Acetone	0.611	0.604	0.99	1.255	−0.435	·	·
Methyl ethyl ketone	0.575	0.576	1.00	1.067	−0.295	·	·
Nitroethane	0.563	0.561	1.00	1.419	−0.675	·	·
Ethyl acetate	0.539	0.550	1.02	1.014	−0.289	·	·
Cyclohexane	0.490	0.532	1.09	0.928	−0.236	·	·
Butyl acetate	0.457	0.487	1.07	0.776	−0.172	·	·
	Alcohols						
Methanol (K_O = 0)	0.400	0.00355	0.01	5.092	−0.423	−8.985	·
Methanol (K_O = 600)	0.400	0.0761	0.19	4.768	−0.363	−8.331	2.674
Isopropanol (K_O = 0)	0.386	0.0326	0.08	2.593	−0.075	−4.617	·
Isopropanol (K_O = 600)	0.386	0.420	1.09	1.674	−0.027	−2.768	1.577
Butanol (K_O = 0)	0.414	0.0475	0.11	2.097	−0.019	−3.799	·
Butanol (K_O = 600)	0.414	0.421	1.02	1.367	−0.007	−2.308	1.407

[a] From Refs. 12–14.

Experimentally, the formation of a hydrogen bond in solution between a proton-acceptor solute and a proton-donor solvent increases the solute solubility by decreasing the free energy of the system. This additional positive contribution to the solubility is treated in the frame of the mobile order theory by the O term [included in Eq. (3)], which is based on stability constants, K_O, and on the concentration of the active sites of the solvent, Φ_S/V_S. This approach allows consideration of the important entropy effects accompanying the formation of specific molecular complexes. However, the positive effect generated by the H-bond formation between an acceptor solute and an amphiphilic solvent such as alcohol is counterbalanced by the negative hydrophobic effect resulting from the self-association of the solvent, which is taken into account by the F term in Eq. (3). For this reason, it must be expected that the solubilities will remain lower in alcohols than in the nonassociated solvents.

To make solubility predictions in alcohols by means of Eq. (3), one needs to know the magnitude of the stability constants, K_O, characterizing the hydrogen bonds formed between the OH groups of the alcohols and the nitrile or amide groups of the solutes. However, the stability constants appearing in Eq. (8) are those corresponding to a high concentration of the alcohol and hence are influenced by the self-association of the alcohol molecules. They may thus differ from the values determined, for instance, by IR spectroscopy, from solutions of both the solvent and the solute in an inert solvent such as CCl_4, in a concentration range where self-association is negligible. Moreover, as these stability constants depend in principle both on solute and on solvent, different values should be used for each particular system, thus preventing any prediction. Fortunately, it has been shown (5,11) that the values of K_O did not vary much for a given type of hydrogen bond. To simplify the problem, two values, i.e., 175 and 600 $cm^3\ mol^{-1}$, corresponding to the averages of the particular stability constants (Table IV) de-

Table IV. Stability Constants, K_O, of Solute–Alcohol H Bonds Derived from the Experimental Solubilities, Φ_B^{exp}, by Means of Eq. (3)

Solute	Solvent	Φ_B^{exp}	K_O (cm^3/mol)
Hexadecanitrile (20°C)	Methanol	0.1363	232.92
	Isopropanol	0.2758	133.11
	Butanol	0.3581	188.78
Octadecanenitrile (20°C)	Methanol	0.01478	96.93
	Isopropanol	0.07421	141.03
	Butanol	0.1346	251.01
N,N-Diphenyl capramide (30°C)	Methanol	0.6191	411.66
	Isopropanol	0.6438	541.33
	Butanol	0.6528	702.78
N,N-Diphenyl lauramide (30°C)	Methanol	0.3997	1001.00
	Isopropanol	0.3858	551.52
	Butanol	0.4140	586.07

duced from experimental solubilities, are therefore determined to characterize, respectively, the nitrile–alcohol and tertiary amide–alcohol H-bond formation in solution.

Using these two values, the solubilities of the four solid solutes in alcohols have been calculated by means of Eq. (3), and the results as well as the contributions stemming from the different terms involved are reported in Table III. As expected, the solubility values in alcohols are in most cases lower than those observed or calculated in the nonassociated solvents.

The analysis of the relative importance of the different terms reveals that in alcohols, the solubility is determined mainly by the hydrophobic effect (F term), which varies according to the following relationship: The smaller the size of the alcohol, the larger the hydrophobic effect and the lower the solubility, i.e., the solubility is lower in methanol than in isopropanol or in butanol. Finally, to assess the particular effect of the intermolecular H-bond formation, we have also reported in Table III the values of the predicted solubilities (and the contributions of the individual terms) obtained by assuming that no hydrogen bond could be formed between the solutes and the alcohols ($K_O = 0$ cm^3 mol^{-1}). Comparison of these results with those obtained when K_O's differ from zero shows that the presence of the O term increases the solubility of the solute. This enhancement originates, first, from the stabilizing effect associated to the solute–solvent intermolecular H-bond formation, which is accounted for by the O term, itself, and, second, from the net positive resulting effect of the modifications of the other contributions. In contrast to what has been observed in our previous work (11), the O term is not always simply added to the other contributions without modifying their values. In fact, the O term does not significantly modify the values of the other contributions only when the volume fraction, Φ_S, of the solvent remains close to one. For instance, in the case of *N,N*-diphenyl capramide, the hydrophobic F term is hardly reduced when the O term is introduced. This result demonstrates that the loss of freedom of the alcohol molecules caused by the introduction of a foreign substance (entropy decrease) is diminished when alcohol molecules can form hydrogen bonds with those foreign molecules.

CONCLUSION

The solubility equation derived from the thermodynamics of the mobile order is used to predict the solubility of four proton-acceptor substances, i.e., two solid nitriles and two tertiary amides, in nonelectrolyte solvents including alcohols. In contrast to apolar substances, the present solutes are able to interact in solution with alcohols by forming hydrogen bonds. The effect of these intermolecular bonds on the solubility is taken into account by the O term in the solubility equation, the treatment of which is based mainly on stability constants, K_O. Determined from experimental solubilities, two mean standard stability constants, i.e., 175 and 600 cm^3 mol^{-1}, are used to characterize, respectively, the nitrile–alcohol and tertiary amide–alcohol hydrogen bonds.

Although the solute–alcohol H-bond formation has a positive influence on the solubility by increasing its value, the solubility of the proton-acceptor solutes studied remains lower in alcohols than in nonassociated solvents due to the negative hydrophobic effect resulting from the self-association of the alcohol molecules.

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