Mechanistic Studies on Hydrotropic Solubilization of Nifedipine in Nicotinamide Solution

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Nicotinamide is a hydrotropic agent that has been demonstrated to solubilize a wide variety of drugs through complexation. Past investigations on the potential interaction of nicotinamide with a solubilized drug have inadequately focused on aliphatic hydrotropes. This study examined the mechanism for the hydrotropic solubilization of nifedipine, a poorly water-soluble drug, in the aqueous solution of nicotinamide using not only nicotinamide analogues but also urea analogues as aliphatic hydrotropes. The values of stability constants, $K_{1:1}$ and $K_{1:2}$, at different temperatures in nicotinamide solution were determined by the phase solubility technique, and were utilized to estimate the thermodynamic parameters of complex formation between nifedipine and nicotinamide. The enthalpy change values suggested the participation of intermolecular forces other than hydrogen bonding in complexation. The aqueous solubility of nifedipine was measured in the presence of nicotinamide, urea and their analogues: *N*-methylnicotinamide, *N*,*N*-diethylnicotinamide, nipecotamide, methylurea, ethylurea and butylurea. The drug solubility increased in proportion to the amount of alkyl substituent on the amide nitrogen, and the solubilizing effect of butylurea was as high as that of nicotinamide. Furthermore, the relationship between the logarithmic drug solubilities in 1.0 M aqueous solutions of nicotinamide or urea analogues *versus* the logarithmic octanol–water partition coefficient values of ligands as an indication of hydrophobicity was found to be linear. The significant contributor to the hydrotropic solubilization of nifedipine with nicotinamide was therefore the ligand hydrophobicity rather than the aromaticity of the pyridine ring.

Key words nifedipine; nicotinamide; hydrotropic solubilization; complex formation; stability constant; hydrophobic interaction

Increasing the water solubility of insoluble and slightly soluble drugs is of major concern. Addition of hydrotropes or hydrotropic agents is one aqueous solubilization technique, and the term hydrotropic agent was first introduced by Neuberg[1] to designate anionic organic salts which, at high concentrations, considerably increase the aqueous solubility of poorly soluble solutes. This is in contrast to "normal" solution behavior since addition of a second compound, especially at high concentrations, generally causes precipitation of the less-soluble solute. Saleh and El-Khordagui[2] extended the definition of the term hydrotropic agent to include cationic and non-ionic organic compounds bearing the essential structural features of Neuberg's hydrotropes.

Nifedipine, a calcium-channel agent, is a poorly water-soluble drug.[3] Jain *et al.*[4] showed the solubilization of nifedipine with sodium benzoate and sodium salicylate in water. The present authors previously demonstrated that nicotinamide had the ability to dramatically increase the aqueous solubility of nifedipine.[5]

Nicotinamide, a nontoxic vitamin B_3, is well known as a hydrotropic agent, and its most commonly proposed solubilization mechanism is complexation.[6–14] The formation of complex species between nicotinamide and certain heteroaromatic drug molecules has been shown by molecular orbital calculation to occur *via* a π-donor π-acceptor mechanism.[7–9] Using nicotinamide and its related compounds, Rasool *et al.*[13] also showed that the aromaticity (π-system) of the pyridine ring which might promote the stacking of molecules through its planarity, was an important factor in complexation because the aromatic amide ligands enhanced the aqueous solubilities of the test drugs to a greater extent than the aliphatic amide ligands. On the other hand, Kenley *et al.*[14] revealed that the hydrophobicity of ligands including nicotinamide was a general determinant of water-soluble complex formation, and donor–acceptor interactions did not control complex formation for the substrate–ligand combinations they considered. However, since aromatic ligands have heretofore been focused on by researchers, further investigation with aliphatic ligands is needed to provide a better contributory understanding to hydrotropic solubilization: aromaticity or hydrophobicity.

Our approach, accordingly, has been to clarify the role of hydrophobicity on the aqueous solubility enhancement of nifedipine by complexation with nicotinamide using not only nicotinamide analogues but also urea analogues as aliphatic hydrotropes. Thermodynamic parameters for the complex formation between nifedipine and nicotinamide were estimated on the basis of the stability constants of such formation determined by phase solubility studies. The solubilizing effects of nicotinamide, urea and their analogues were also examined by molecular orbital and partition coefficient approaches.

Experimental

Materials Nifedipine, nicotinamide, urea, methylurea, ethylurea and butylurea were obtained from Wako Pure Chemical Industries Co., Ltd., Japan. *N*-Methylnicotinamide, *N*,*N*-diethylnicotinamide and nipecotamide were obtained from Tokyo Kasei Kogyo Co., Ltd., Japan. Chemical structures and molecular weights of these substances are shown in Fig. 1. All other chemicals were of reagent grade. All experiments were carried out under subdued light to prevent light degradation of nifedipine.

Phase Solubility Studies Excess amounts of nifedipine were added to aqueous solutions (5 ml) containing various concentrations of nicotinamide, *N*-methylnicotinamide, *N*,*N*-diethylnicotinamide, nipecotamide, urea, methylurea, ethylurea or butylurea. After shaking for 48 h at 25,

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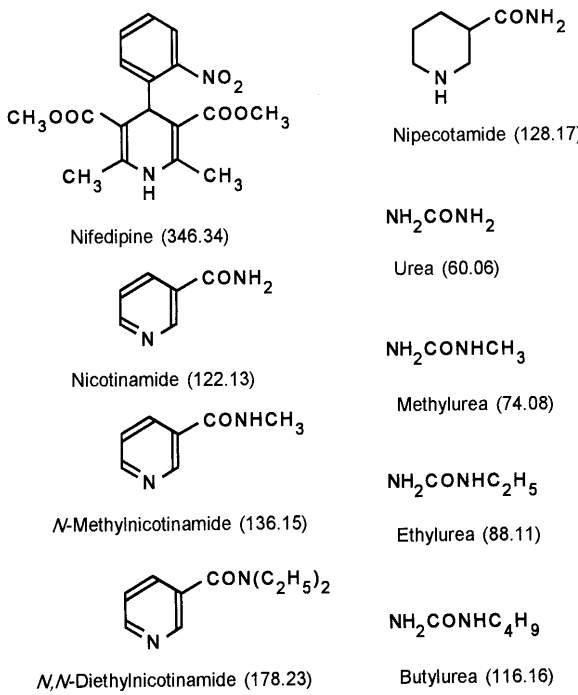

Fig. 1. Chemical Structures of Nifedipine, Nicotinamide and Urea Analogues

Molecular weights are described in parentheses. *N,N*-Diethylnicotinamide is only a liquid substance.

37 or 45±1 °C, samples were withdrawn, filtered (0.2 μm), diluted with methanol and analyzed by HPLC at 237 nm. Similarly, the drug solubility in 1,4-dioxane, methanol, acetonitrile or 1,2-dichloroethane (5 ml) containing various concentrations of *N,N*-diethylnicotinamide was determined at 25±1 °C. The chromatograph operating conditions were as follows: C18 reversed-phase column (YMC-Pack ODS-H80); 0.05 M phosphate buffer (pH 3.0) : methanol : tetrahydrofuran (60 : 32 : 8) eluant; flow rate of 1.3 ml/min; 237 nm detector (Shimadzu Seisakusho Co., Ltd., Japan).

Mathematical Analysis of Phase Solubility Data The interaction of nifedipine with nicotinamide was studied using the standard phase solubility method. The data were analyzed by assuming that both 1 : 1 and 1 : 2 complexes could be formed in accordance with the following relationships:

$$[S_0]+[L]=[SL] \quad (1)$$

$$[S_0]+[2L]=[SL_2] \quad (2)$$

where $[S_0]$ is the equilibrium solubility of nifedipine (drug) in the absence of nicotinamide (ligand), $[L]$ is the molar concentration of the free ligand, $[SL]$ is the molar concentration of the 1 : 1 drug : ligand complex, $[2L]$ is the molar concentration of ligand dimers, and $[SL_2]$ is the molar concentration of the 1 : 2 drug : ligand complex.

$K_{1:1}$ and $K_{1:2}$ stability constants are calculated using the following equations[15]:

$$K_{1:1}=\frac{[SL]}{[S_0][L]} \quad (3)$$

$$K_{1:2}=\frac{[SL_2]}{[S_0][L]^2} \quad (4)$$

$$\frac{[S_T]-[S_0]}{[L_T]-2([S_T]-[S_0])}=\alpha+\beta\{[L_T]-2([S_T]-[S_0])\} \quad (5)$$

where $[S_T]$ is the total molar concentration of the drug and $[L_T]$ is the total molar concentration of the ligand, and where:

$$\alpha=\frac{K_{1:1}[S_0]}{1-K_{1:1}[S_0]} \quad (6)$$

$$\beta=\frac{K_{1:2}[S_0]}{(1-K_{1:1}[S_0])^2} \quad (7)$$

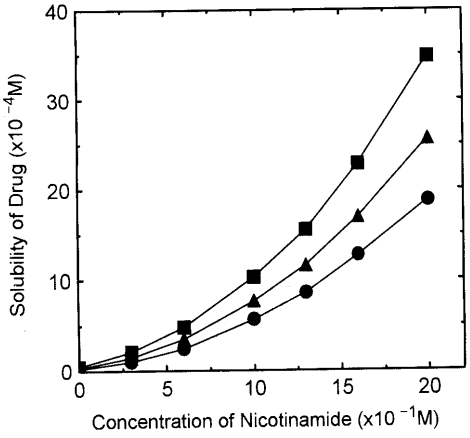

Fig. 2. Aqueous Solubility of Nifedipine as a Function of Nicotinamide Concentration

●, 25 °C; ▲, 37 °C; ■, 45 °C.

A plot of the left side of Eq. 5 *versus* $[L_T]-2([S_T]-[S_0])$ gives a straight line with a slope equal to β and an intercept equal to α. The stability constants, $K_{1:1}$ and $K_{1:2}$, can be calculated from the intercept and slope, respectively.

Estimation of Thermodynamic Parameters for the Stability Constant The free energy change ΔF is determined from the stability constant K by the expression:

$$\Delta F=-2.303\boldsymbol{R}T\log K \quad (8)$$

where $\boldsymbol{R}$ is the gas constant (8.3143 J·mol^{-1}·K^{-1}) and T is the absolute temperature. The enthalpy change ΔH is estimated from the stability constant at several temperatures by the following relationship:

$$\log K=-\frac{\Delta H}{2.303\boldsymbol{R}}\times\frac{1}{T}+const. \quad (9)$$

A linear plot of $\log K$ against $1/T$ (a van't Hoff plot) yields ΔH from slope. The entropy change ΔS is related to ΔF and ΔH as:

$$\Delta S=\frac{\Delta H-\Delta F}{T} \quad (10)$$

Calculation of Logarithmic Octanol–Water Partition Coefficient Semi-empirical molecular orbital calculation by the AM1[16] method with CAChe MOPAC (SONY Tektronix Corp., Japan) was performed to determine the fully optimized structure, dipole moment and π-electron density. Then, based on its optimized structure, the logarithmic octanol–water partition coefficient ($\log P$) was estimated by the CAChe $\log P$ stationery (SONY Tektronix Corp., Japan) which is the technique of Bodor *et al.*[17,18]

Results and Discussion

Stability Constants and Thermodynamic Parameters for Nifedipine–Nicotinamide Interaction Phase solubility diagrams for nifedipine in the aqueous solution of nicotinamide at different temperatures are shown in Fig. 2. It was evident from the data that the drug solubility was significantly enhanced by nicotinamide. Positive curvature indicated a greater solubilizing power at higher concentrations of nicotinamide; this is characteristic of hydrotropic solubilization, and probably is due to the formation of higher order water-soluble complexes of nifedipine with nicotinamide.

It has been shown that higher order complexes are formed as the result of different types of interactions. One type of interaction may involve the formation of dimers or aggregates containing two or more molecules of the ligand,[15] but higher order complexes can also form *via* a stepwise interaction involving the substrate and two

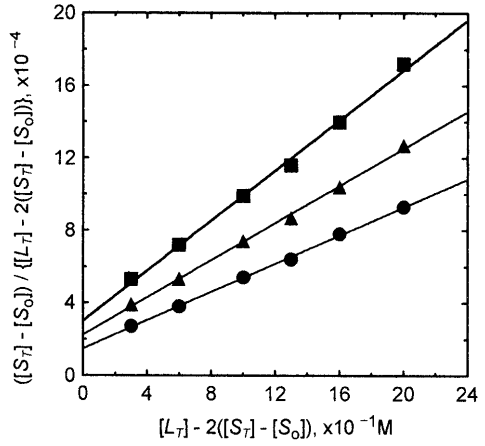

Fig. 3. Plots for the Determination of Stability Constants for Nifedipine–Nicotinamide Interaction

●, 25 °C; ▲, 37 °C; ■, 45 °C.

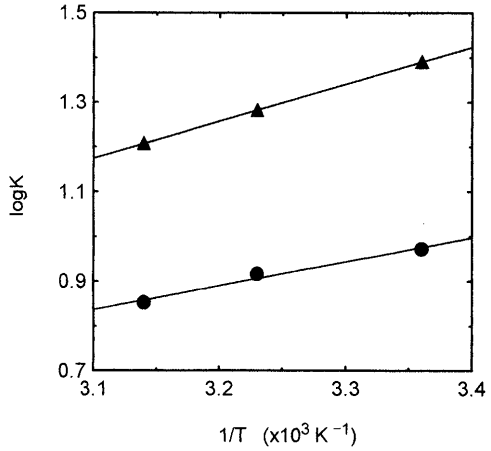

Fig. 4. Van't Hoff Plots of Stability Constants for Nifedipine–Nicotinamide Interaction

●, $K_{1:1}$; ▲, $K_{1:2}$.

Table 1. Stability Constants for Nifedipine–Nicotinamide Interaction

Temp. (°C)	S_0 ($\times 10^{-4}$ M)	$K_{1:1}$(M^{-1})	$K_{1:2}$ (M^{-2})
25	0.16	9.4	24.6
37	0.27	8.3	19.1
45	0.43	7.1	16.1

Table 2. Thermodynamic Parameters for Nifedipine–Nicotinamide Interaction

Stability constant	Temp. (°C)	ΔF (kJ·mol^{-1})	ΔH (kJ·mol^{-1})	ΔS (J·mol^{-1}·K^{-1})
$K_{1:1}$(M^{-1})	25	−5.545	−10.55	−16.80
	37	−5.441		−16.49
	45	−5.193		−16.85
$K_{1:2}$ (M^{-2})	25	−7.935	−16.52	−28.82
	37	−7.610		−28.75
	45	−7.356		−28.83

molecules of the ligand.[19] A characteristic that many hydrotropic agents share is the ability to self-associate in aqueous solutions at hydrotropic concentrations (*i.e.*, > 1 M).[2,4] Similarly, nicotinamide is found to self-associate in aqueous solution primarily as dimers and trimers using light-scattering.[20] The mechanism of solubilization by nicotinamide in this study was described with Eq. 1 and 2 by assuming that the higher order complexes could be formed by direct reaction between the drug and nicotinamide dimers. Figure 3 shows that the increase in the solubility of nifedipine as a function of nicotinamide concentration is consistent with the predicted relationship based on Eq. 5. The values of stability constants, $K_{1:1}$ and $K_{1:2}$, for this system are exhibited in Table 1. These values, which indicate the solubilizing capability of nicotinamide, decreased as temperature increased. These results are in accord with a view of the effect of temperature on the riboflavin–nicotinamide hydrotropic system discussed by Coffman and Kildsig[21]: they proposed that the self-association of nicotinamide impacted on the hydrotropic solubilization since nicotinamide self-associated to a lesser extent at higher temperature.

Thermodynamic parameters for the 1 : 1 and 1 : 2 complex formations were estimated from van't Hoff plot of the temperature dependence of the stability constants (Fig. 4). The values obtained by regression analyses provided information regarding the complex formation of the nifedipine–nicotinamide system (Table 2). The values of the entropy change ΔS (disordering or bond breaking) were negative, revealing the possibility of an increased ordering of the species by complexation. Both values of the free energy change ΔF and the enthalpy change ΔH (bonding strength) were negative, indicating the spontaneity and exothermic nature of the hydrotropic solubilization of nifedipine based on complexation with nicotinamide. Moreover, the ΔH values were similar to the results by Samejima[22] who implied the possibility of hydrogen bonds in interactions between some solubilizates and nicotinamide (< 0.5 M aqueous solution of nicotinamide). However, considering that hydrogen bonds are designated as weak (< 13 kJ·mol^{-1}), normal (13 to 42 kJ·mol^{-1}) or strong (> 42 kJ·mol^{-1}),[23] the strength of those estimated from the ΔH values in Table 2 is not strong; hence it can be speculated that intermolecular forces other than hydrogen bonding are required to explain the aqueous solubility enhancement of nifedipine by complexation with nicotinamide.

Effect of Nicotinamide, Urea and Their Analogues on Nifedipine Solubility To obtain further evidence on the interaction between nifedipine and nicotinamide in water, the solubility of nifedipine was studied in the presence of the following structural analogues (Fig. 5): *N*-methylnicotinamide, *N*,*N*-diethylnicotinamide and nipecotamide. As with nicotinamide, the phase solubility diagram of nifedipine in *N*-methylnicotinamide or *N*,*N*-diethylnicotinamide solution showed the positive curvature. Especially at high concentrations, *N*,*N*-diethylnicotinamide solubilized the drug to a greater extent than nicotinamide. For the aliphatic ligand nipecotamide, on the other hand, the positive curvature of the drug solubility was not apparent within the concentration range studied (< 2.0 M).

To examine the solubilizing effect of aliphatic amides in water, the solubility of nifedipine was also determined in the presence of urea and its related compounds (Fig.

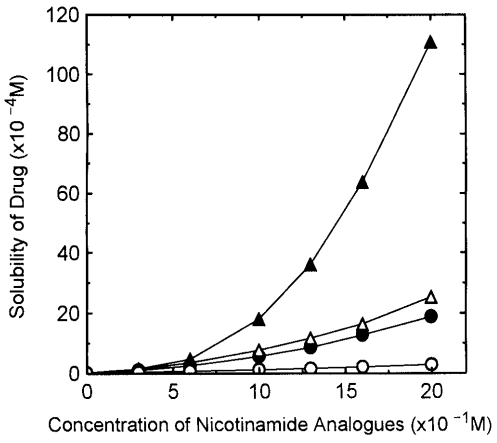

Fig. 5. Aqueous Solubility of Nifedipine as a Function of Nicotinamide Analogue Concentration at 25 °C

○, nipecotamide; ●, nicotinamide; △, *N*-methylnicotinamide; ▲, *N*,*N*-diethylnicotinamide.

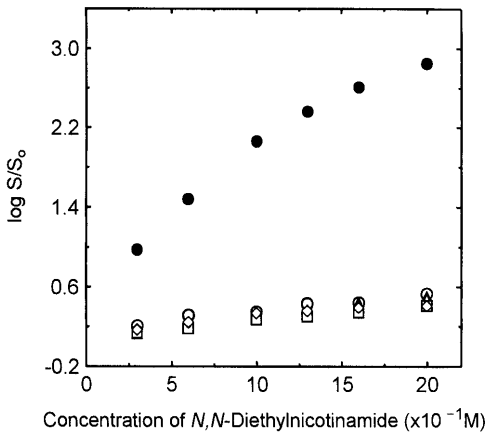

Fig. 7. Logarithmic Solubility Factor of Nifedipine as a Function of *N*,*N*-Diethylnicotinamide Concentration at 25 °C

○, 1,4-dioxane; △, methanol; □, acetonitrile; ◇, 1,2-dichloroethane; ●, water.

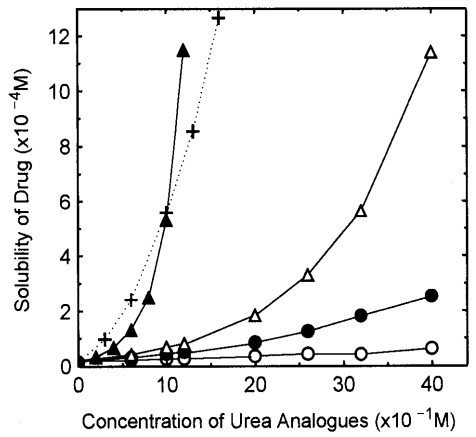

Fig. 6. Aqueous Solubility of Nifedipine as a Function of Urea Analogue Concentration at 25 °C

+, nicotinamide; ○, urea; ●, methylurea; △, ethylurea; ▲, butylurea.

6): methylurea, ethylurea and butylurea. The concentration range of urea, methylurea or ethylurea was up to 4.0 M, whereas that of butylurea was up to 1.2 M because of its aqueous solubility limit. Although the linear solubility behavior of nifedipine was observed in the presence of urea, the obvious positive curvature was recognized in the presence of methylurea, ethylurea or butylurea. Rank order of the solubilizing effect of urea analogues was butylurea > ethylurea > methylurea > urea, indicating that the amount of hydrophobic alkyl substituent was closely related to the solubility of nifedipine. Such substitution on the amide nitrogen of aliphatic amides has been shown to enhance their abilities to solubilize drugs in water.[24] Moreover, it was interesting to note that the solubilizing effect of butylurea for nifedipine was comparable to that of nicotinamide. This finding suggested that the significant contributor to the hydrotropic solubilization of nifedipine with nicotinamide was the ligand hydrophobicity rather than the aromaticity of the pyridine ring which could allow a plane-to-plane stacking.

It has been reported that if the hydrophobic effect makes a major contribution to the stability of a complex in water, the incorporation of an organic solvent into the medium will decrease the complex stability.[25] The effect of *N*,*N*-diethylnicotinamide on the solubility of nifedipine was thus investigated in organic solvents. *N*,*N*-Diethylnicotinamide was chosen because the other hydrotropic agents used in this study tended to dissolve with difficulty in organic solvents. The organic solvents used were 1,4-dioxane, methanol, acetonitrile and 1,2-dichloroethane. Figure 7 depicts the logarithmic solubility factor (log S/S_0) of nifedipine as a function of *N*,*N*-diethylnicotinamide concentration in water or each organic solvent, where the solubility factor represented the drug solubility in a ligand solution of a given concentration (S) divided by the intrinsic drug solubility in an original solvent (S_0). The solubility factor normalizes solubility data with respect to intrinsic solubility.[26] The solvents used have different hydrogen bonding and electrostatic properties; nevertheless, no difference in solubilizing effects of *N*,*N*-diethylnicotinamide was detected in any of the organic solvents, and the prominent increase in drug solubility was seen only in water. This implied that the hydrophobic interaction between nifedipine and the ligand controlled the hydrotropic solubilization of the drug as mentioned above. When two dissolved solute molecules come into contact, some of the "structured" water surrounding them must be released into the bulk medium, resulting in an increase in entropy, which is thought to be the main driving force in the hydrophobic interaction of nonpolar molecules in water. Therefore, water can be regarded as an important component of the hydrotropic system.

Factors Controlling Hydrotropic Solubilization of Nifedipine Some literature subdivides the forces controlling water-soluble complex formation into five categories[14,19]: charge–transfer interactions, electrostatic forces, induction forces, hydrogen bonding and hydrophobic interactions. Both charge–transfer interactions, called electron donor–acceptor interactions, and hydrophobic interactions are frequently large in magnitude, and their forces have been reported to be controlling factors in water-soluble complex formation.[7–9,14,25]

Relative donor–acceptor strengths can be estimated by the calculation of molecular orbital energies; a high energy level of the highest occupied molecular orbital (HOMO)

Table 3. Physicochemical Data for Nicotinamide and Urea Analogues

Ligand	$\log S_{1.0}$[a] (M)	HOMO[b] (eV)	LUMO[c] (eV)	Dipole moment (debye)	Electron density on oxygen atom	$\log P$[d]
Nicotinamide	−3.25	−10.267	−0.583	1.80	6.395	−0.403
N-Methylnicotinamide	−3.11	−10.104	−0.487	2.28	6.381	0.058
N,*N*-Diethylnicotinamide	−2.74	−9.489	−0.429	1.85	6.395	0.982
Nipecotamide	−3.92	−9.702	1.432	3.11	6.389	−0.534
Urea	−4.59	−10.517	1.540	4.09	6.416	−1.893
Methylurea	−4.35	−9.999	1.758	4.08	6.427	−1.386
Ethylurea	−4.16	−9.950	1.745	3.95	6.425	−1.036
Butylurea	−3.27	−10.012	1.609	3.87	6.410	−0.374

a) Logarithmic solubility of nifedipine in 1.0 M aqueous solution of ligand. *b*) Energy level of the highest occupied molecular orbital. *c*) Energy level of the lowest unoccupied molecular orbital. *d*) Logarithmic octanol–water partition coefficient calculated by the technique of Bodor *et al.*[17,18]

Table 4. Linear Regression Analyses of $\log S_{1.0}$ *versus* Physicochemical Parameters

Physicochemical parameter[a]	Slope[b]	Intercept[b]	r^2[c]
HOMO	0.962	5.95	0.209
LUMO	−0.479	−3.28	0.625
Dipole moment	−0.536	−2.00	0.663
Electron density on oxygen atom	−26.838	168.22	0.481
$\log P$	0.713	−3.27	0.901

a) See Table 3. *b*) For the expression: $\log S_{1.0}$ = intercept + slope × (physicochemical parameter). *c*) Squared correlation coefficient.

correlates with a low ionization potential and a high electron donor strength, while a low energy level of the lowest unoccupied molecular orbital (LUMO) correlates with a high electronic affinity and a high electron acceptor strength. Hydrophobicity, on the other hand, can be estimated on the basis of octanol–water partition coefficient, *i.e.*, $\log P$ value; the partition coefficient depends upon the polarity and the size of molecule, and a positive $\log P$ value is assigned to compounds that preferentially partition into octanol.

Electrostatic forces are generated among ions and molecules possessing permanent dipole moments, and induction forces arise as a result of the interaction of an ion or a polar molecule with a neighboring molecule. Since all the compounds used in this study are essentially unionized under the conditions investigated, the dipole moment of ligand should be noted for electrostatic and induction forces. Interactions through hydrogen bonding may also be important in water. A π-electron density on the oxygen atom in the acid amide group of ligand is often given as an indication of the possibility of hydrogen bonding.[8] Consequently, we focused on HOMO energy, LUMO energy, dipolar moment, electron density on oxygen atom and log P as factors that could contribute to complex formation.

Table 3 summarizes the comparison of these physicochemical parameters with the logarithmic solubilities of nifedipine in 1.0 M aqueous solutions of nicotinamide or urea analogues ($\log S_{1.0}$). The reason for using $\log S_{1.0}$ values instead of stability constants is that as the positive curvature of the drug solubility curve becomes larger (*e.g.*, *N*,*N*-diethylnicotinamide and butylurea), the linear regression based on Eq. 5 for the determination of the stability constants becomes worse. The correlation between $\log S_{1.0}$ values and physicochemical parameters of ligands was evaluated by linear regression analyses (Table 4). The $\log S_{1.0}$ values *versus* the $\log P$ values of ligands clearly showed a good correlation (the squared correlation coefficient = 0.901). The degree to which the hydrophobicity accounts for complex formation was unexpectedly great. This result strongly supports the assumption that ligand hydrophobicity is directly related to the degree of hydrotropic solubilization. A possible explanation is that the aggregation of hydrotropic molecules is enhanced by the hydrophobicity of a hydrotrope, thereby leading to the inclusion of nifedipine in these aggregates. Our investigation may be the first to successfully show the importance of hydrophobicity on the hydrotropic solubilization with nicotinamide by paying more attention to urea analogues as aliphatic ligands. Other researchers[8,13,14,26] have insufficiently examined the solubilizing effect of aliphatic hydrotropes.

In conclusion, it was understood that the ligand hydrophobicity rather than the aromaticity of the pyridine ring was mechanistically important to the hydrotropic solubilization of nifedipine with nicotinamide because of the high solubilizing effect of butylurea for the drug, the need of water for the hydrotropic system and the good correlation between $\log S_{1.0}$ values of the drug and $\log P$ values of ligands.

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