The Study of Partition Coefficients. The Prediction of Log *P* Value Based on Molecular Structure

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An effort has been made to determine the partition coefficients from the physical quantities based on the molecular structure. The quantities are representatives of energies which constitute the solvation energy of the solute molecule. The log *P* value is expressed with them as

$$\log P = -1.26 + 3.78\,\phi_{ct} - 0.72\,\mu_1 - 1.28\,\mu_2$$
$$(N{=}244,\ R{=}0.959,\ \text{S.D.}{=}0.54,\ F{=}934).$$

For the practical use, the following equation is recommended:

$$\log P = -1.36 + 3.89\,\phi_{ct} - 1.09\,\mu_2 - 0.085U_H + 0.021U_C - 0.134U_N - 0.198U_O$$
$$(N{=}244,\ R{=}0.976,\ \text{S.D.}{=}0.42,\ F{=}787).$$

Here, ϕ_{ct} is the representative related to the charge-transfer energy and μ_1, μ_2, U_H, U_C, U_N, and U_O are those related to the electrostatic energy. The molecular structure of the solute molecule has been shown to be very important in the determination of the log *P* value. A log *P* value with a higher precision can be obtained by modifying the approximations used.

For almost one hundred years, many investigators have been carrying out studies of partition coefficients in both basic and applied fields.[1] However, the results of their studies were not sufficiently good to satisfy all of the investigators. For example, despite the fact that a partition coefficient is a physicochemical quantity, it still cannot be elucidated theoretically and universally. The difficulties in calculating it are due to the complexity of the phenomena in a liquid; the system is a cluster of many characteristic particles. These particles have a diversity of structures and electronic states. The collective state of molecules in a liquid or a solution shows properties over a wide range, from order to disorder. It is difficult to provide systematic explanations for such complexity. These days, however, progress in computer systems is enabling researchers to directly approach the subject.

The partition coefficients have been explained by a linear free-energy relationship. Under this relationship, the logarithm of the partition coefficient of a molecule, log *P* value, has been determined by the sum of the values given to the molecular fragment, the so-called fragment constants.[2] In recent years, this method has been refined[3] and the fragment constants have been specified as various values.[4] Although this method is convenient to use, the physicochemical and microscopical significance of the fragment constants are not clear. The calculation techniques were inadequate during the initial stage of the physicochemical study.[5] The trials[6,7] which determine the fragment constant using the physicochemical method did not make the essence of the subject clear. Those trials should reveal the inherent limit of the method. There is a method which expresses the log *P* value by using the observed physical quantities;[8] however, it is not useful for the designed molecules.

Thus, it is necessary to formulate a partition coefficient faithfully along the general concept of the free energy. The log *P* value of a solute molecule is derived from the transfer energy which is the difference in the standard free energy between two phases. The standard free energy of a solute in a solvent corresponds to the solvation energy in an infinite dilution.

By modifying the previous studies[9,10] in our present study, the solvation energy could be expressed by the summation of various types of energy in a molecular system which consists of a solute molecule and solvent molecules. The representatives of each of the energies could be obtained by examining each energy type. The solvation energy is represented by a linear combination of these representatives. Some approximations were introduced in order to determine the representatives. As a result, in some cases there may be a disagreement between the observed and the calculated values, since the approximation is not appropriate for these particular molecules. Such results suggest the elimination of the approximation, or at least an improvement in it. Thus, these modifications provided a better understanding of the phenomena. It is therefore important to discuss the applied approximation and its result.

To use alternatively both the molecular dynamics method and the super molecular approach method is desired as a technical method for calculations, but it is difficult on account of the costly computer facilities. The method stated in the report has been worked out, taking into account the first solvation layer and the continuum model.[11]

Method

The partition coefficient P of a non-associated solute molecule is given by the transfer energy $\Delta\mu^\circ_{12}$ per solute molecule between two phases, the solvent 1 and 2,[12]

$$\log P_{12} = -\Delta\mu^\circ_{12}/2.303\,kT, \qquad (1)$$

where k is Boltzmann's constant, and T is the absolute temperature. If solvent 1 and 2 are water and 1-octanol, respectively, $\log P_{12}$ is the so-called $\log P$.

Solvation Energy and Transfer Energy. The solvation energy $\Psi(\mathrm{M})$ of a solute molecule is given by

$$\Psi(\mathrm{M}) = \psi_{\mathrm{M}}(\mathrm{M}) + \psi_{\mathrm{S}}(\mathrm{M}) + \psi_{\mathrm{MS}}(\mathrm{M}), \qquad (2)$$

where M represents the state of the solute in the solvent S. $\psi_{\mathrm{M}}(\mathrm{M})$ is the intramolecular free energy of the solute in state M. $\psi_{\mathrm{S}}(\mathrm{M})$ is the free energy of cavity formation of the solute in the solution.[13] $\psi_{\mathrm{MS}}(\mathrm{M})$ is the sum of the interaction energies between the solute and the solvent molecules. The transfer energy is given by

$$\begin{aligned} \Delta\mu^\circ_{12} &= \Psi_2(\mathrm{M2}) - \Psi_1(\mathrm{M1}), && (3\text{-}1)\\ &= \phi_{\mathrm{solute}} + \phi_{\mathrm{solution}} + \phi_{\mathrm{inter}}. && (3\text{-}2) \end{aligned}$$

The energies expressed in Eq. 3-2 are given by following equations:

$$\begin{aligned} \phi_{\mathrm{solute}} &= \psi_{\mathrm{M}}(\mathrm{M2}) - \psi_{\mathrm{M}}(\mathrm{M1}), && (4\text{-}1)\\ \phi_{\mathrm{solution}} &= \psi_{\mathrm{S}_2}(\mathrm{M2}) - \psi_{\mathrm{S}_1}(\mathrm{M1}), && (4\text{-}2) \end{aligned}$$

and

$$\phi_{\mathrm{inter}} = \psi_{\mathrm{MS}_2}(\mathrm{M2}) - \psi_{\mathrm{MS}_1}(\mathrm{M1}), \qquad (4\text{-}3)$$

where subscripts 1 snd 2 denote solvents 1 and 2, respectively.

Linear Free Energy Relationship. The linear free energy relationship from Eqs. 1 and 3-2 are obtained as follows:

$$\log P = \sum_i f(i)/2.303\,kT, \qquad (5)$$

where $f(i)$ is the energy of the i-th element. The additivity of the $\log P$ value is attributed to the property of the energy. If the energy, $f(i)$, is a linear combination of a physicochemical quantity, Q_{ij}, which itself corresponds to each of the energies, then the value of $\log P$ is given as

$$\log P = \sum_i \sum_j \alpha_{ij} \cdot Q_{ij}, \qquad (6)$$

where α_{ij} is the coefficient of Q_{ij}. α_{ij} is determined deductively by the physical meaning or inductively by the least squares method when the $\log P$ values are observed.

Analysis

Approximations. Calculations of the $\log P$ values are almost impossible without using approximations. A water-methane system can be considered in place of a water-1-octanol system (approx. 1), since the dielectric properties of methane resemble that of 1-octanol, compared to water. The size and shape of methane gives merit to the calculation, and leaves no problem in the theory. Water and methane are hereinafter considered to be the two solvents, 1 and 2, respectively.

The transfer energy $\Delta\mu^\circ_{12}$ can be explained by three terms: ϕ_{solute}, ϕ_{solution}, and ϕ_{inter}. If the structure of a solute molecule in methane is assumed to be the same as that in water, then $\phi_{\mathrm{solute}}=0$ (approx. 2). The contribution of ϕ_{solution} is neglected, since there is insufficient information regarding the configuration and the orientation of solvent molecules on the solute surface (approx. 3). As for ϕ_{inter}, the attractive forces are generally the main interactions in the liquid state. They are the induction energy, dispersion energy, charge-transfer energy, and electrostatic energy. The induction energy can be neglected, since it is usually small.[14] The dispersion energy can also be neglected because of the difficulty in its estimation. The charge-transfer energy, which is a short-range interaction, and the electrostatic energy, which is a long-range interaction, are denoted by Ect and Ecoul, respectively. Thus, the interaction energy is given by

$$E = E_{\mathrm{ct}} + E_{\mathrm{coul}} \quad \text{(approx. 4)}. \qquad (7)$$

This is known as the Klopman-Hudson equation.[15]

$\psi_{\mathrm{MS}}(\mathrm{M})$ in Eq. 2 is given by the summation of all interactions among the solute molecule and all of the solvent molecules surrounding it:

$$\psi_{\mathrm{MS}}(\mathrm{M}) = \sum_j \sum_k E_{jk} \cdot \Delta\tau_j \cdot \Delta\tau_k, \qquad (8)$$

where $\Delta\tau_j$ and $\Delta\tau_k$ are the volume elements, and E_{jk} is the interaction energy between the volume elements. Generally speaking, the contribution of the solvent outside the solvation layer is negligible. In order to simplify the calculation, solvent molecules are estimated only in the first layer (approx. 5). If the thickness of the layer is fixed, the summation in Eq. 8 is replaced by that on the surface of the solute. The solvent accessible surface (SAS)[16] is adopted as the molecular surface.

Representatives of Charge-Transfer Energy. In order to simplify the calculation, the orientation of a solvent molecule is assumed to be such that an atom in the solvent molecule faces the solute molecule in proportion to its ratio, R_k, covering the surface of the solvent one. The total charge-transfer energy, ψ_{ct}, then, is given as follows according to Eq. 8:

$$\psi_{\mathrm{ct}} = \sum_j \sum_k \sum_p \sum_q [E_{\mathrm{ct}}]_{pq} \cdot \delta_{pj} \cdot \delta_{qk} \cdot \Delta s_j \cdot R_k, \qquad (9\text{-}1)$$

where

$$R_k = \Delta s_k / S_{\mathrm{slv}}, \qquad (9\text{-}2)$$

and δ_{pj} and δ_{qk} are Kronecker's δ; thus, $\delta_{pj}=1$ if the

p-th STO of the solute molecule belongs to the j-th atom of the same molecule, and $\delta_{pj}=0$ otherwise. The existing probability of a solvent molecule in the volume element $\Delta\tau_j$ is proportional to the surface area element Δs_j if the thickness of the layer is fixed. $\sum_j$ corresponds to the sum of all the solvent molecules in the first solvation layer. $\delta_{qk}=1$ if the q-th STO of the solvent molecule belongs to the atom in the volume element $\Delta\tau_k$, and $\delta_{qk}=0$ otherwise. $\sum_k$ indicates the sum for taking the average of the orientation of the solvent. S_{slv} is the total surface area of the solvent molecule, and Δs_k is the surface area element. $[E_{\mathrm{ct}}]_{pq}$ is given as follows:[15]

$$[E_{\mathrm{ct}}]_{pq} = -2\left(\sum_m^{Oc.}\sum_n^{Un.} - \sum_m^{Un.}\sum_n^{Oc.}\right)\frac{C_{mp}^2 \cdot C_{nq}^2}{\varepsilon_n - \varepsilon_m}\beta_{pq}^2 \qquad (10)$$

The resonance integral β_{pq} is strongly dependent on the interatomic distance. Therefore, it is sufficient to take only the atoms exposed to the molecular surface, as the object of the calculation of β_{pq}. The sum of two van der Waals radii[17] of atoms, which face each other across the solute surface, is used as the interatomic distance in the calculation.

Thus, the contribution of the charge-transfer energy in the water-methane system is given by

$$\phi_{\mathrm{ct}} = \psi_{2,\mathrm{ct}} - \psi_{1,\mathrm{ct}}, \qquad (11)$$

where $\psi_{1,\mathrm{ct}}$ and $\psi_{2,\mathrm{ct}}$ are the charge-transfer energy in the water and methane solvent, respectively.

Representatives of Electrostatic Energy. Since a methane molecule is minimally polarized in such a mild field as the solution, the electrostatic energy between the solute and the solvent molecules in the methane solvent is negligible for any solutes:

$$\psi_{2,\mathrm{coul}} = 0.$$

The contribution of the electrostatic energy is given by

$$\begin{aligned}\phi_{\mathrm{coul}} &= \psi_{2,\mathrm{coul}} - \psi_{1,\mathrm{coul}} \\ &= -\psi_{1,\mathrm{coul}},\end{aligned} \qquad (12)$$

where $\psi_{1,\mathrm{coul}}$ is the electrostatic energy in water. The simplest form of $\psi_{1,\mathrm{coul}}$ is given as

$$\psi_{1,\mathrm{coul}} = -\boldsymbol{\mu}\cdot\boldsymbol{E}, \qquad (13)$$

where $\boldsymbol{\mu}$ is the molecular dipole moment of the solute and $\boldsymbol{E}$ is the electric field applied to the solute. If $\boldsymbol{E}$ is fixed over any solute molecules, $\psi_{1,\mathrm{coul}}$ depends on $\boldsymbol{\mu}$. The molecular dipole moment is calculated as the sum of two terms,[18]

$$\boldsymbol{\mu} = \boldsymbol{\mu}_1 + \boldsymbol{\mu}_2, \qquad (14)$$

where the first contribution term $\boldsymbol{\mu}_1$ is obtained from the net charges located at the nuclear position and the second contribution term $\boldsymbol{\mu}_2$ is essentially a hybridization term. Thus, the absolute values of $\boldsymbol{\mu}_1$ and $\boldsymbol{\mu}_2$ are adopted as the representatives of $\phi_{1,\mathrm{coul}}$.

$$\mu_1 = |\boldsymbol{\mu}_1|, \quad \mu_2 = |\boldsymbol{\mu}_2|. \qquad (15)$$

Multiple Linear Regression. Thus, ϕ_{ct}, μ_1, and μ_2 are representatives of the energies based on the molecular structure. These are not on the same level as the approximations. According to Eq. 6, the $\log P$ value is given by a linear combination of these representatives. The relationship is obtained by applying a multiple linear regression analysis.

Observed Log *P* Values and Molecular Structures. The observed $\log P$ values used in the analysis are those of 265 molecules. These were selected according to the order of the molecular size with the following atomic types of H, C, N, and O atoms on the Hansch-Leo data base.[19]

All of the structures of the 265 molecules were geometrically optimized by using the MNDO method.[20] The analyses on the conformation were carried out for 26 molecules, and there was a wide gap between the observed value and the calculated one in the preliminary work. One of the criteria used in the conformational analysis was the total energy for the optimized structure; another one was the stabilization owing to the solvation. The former was obtained directly by a MNDO calculation, but the latter was not so easily obtained. Some conformers, ranging from the lowest energy to one about 3 kcal mol^{-1} higher, are the objects of investigations. As for tautomers, the structures generally considered were fully optimized by the MNDO calculation.

A solvent molecule with a radius of 1.50 Å was used in order to calculate the area of the SAS. The molecular volume was defined as that of the space surrounded by SAS. The other molecular properties were obtained by NNDO calculations.

Results

The following equation was obtained by using the representatives of ϕ_{ct}, μ_1, and μ_2:

$$\begin{aligned}\log P = &-1.26(\pm0.17) + 3.78(\pm0.15)\phi_{\mathrm{ct}} \\ &-0.72(\pm0.03)\mu_1 - 1.28(\pm0.07)\mu_2 \\ &(N{=}244,\ R{=}0.959,\ \mathrm{S.D.}{=}0.54).\end{aligned} \qquad (16)$$

In addition, an equation for more practical use than Eq. 16 is

$$\begin{aligned}\log P = &-1.36(\pm0.17) + 3.89(\pm0.19)\phi_{\mathrm{ct}} \\ &-0.085(\pm0.014)U_{\mathrm{H}} + 0.021(\pm0.008)U_{\mathrm{C}} \\ &-0.134(\pm0.017)U_{\mathrm{N}} - 0.198(\pm0.018)U_{\mathrm{O}} \\ &-1.09(\pm0.06)\mu_2 \\ &(N{=}244,\ R{=}0.976,\ \mathrm{S.D.}{=}0.42),\end{aligned} \qquad (17)$$

where U_{H}, U_{C}, U_{N}, and U_{O} are the representatives instead of μ_1. Figure 1 shows the relationship between the observed $\log P$ value and the calculated one through Eq. 17.

Derivations of U_{H}, U_{C}, U_{N}, and U_{O}, and the values of each parameter in Eqs. 16 and 17 are deposited as Document No. 8808 at the Office of the Editor of Bull. Chem. Soc. Jpn.

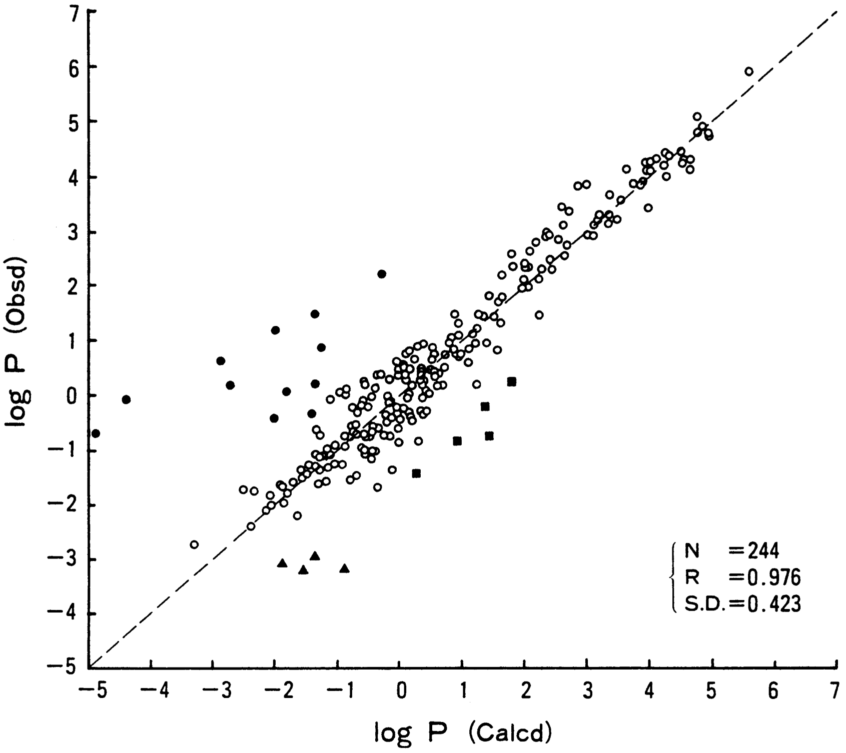

Fig. 1. Observed log$P$ values plotted against values calculated through Eq. 17. ○: Molecules in the group A, B, C, D, and E, ●: Nitro compounds (Group F), ▲: Amino acids (Group G), ■: Symmetrical molecules (Group H). For details of the groups, Document should be referred to.

Discussion

The results showed excellent agreement between the observed and calculated log$P$ values for 244 molecules among 265. The remaining 21 molecules could not be the objects of the analysis.

Characteristics of the 21 Molecules. There were 12 nitro compounds, 4 amino acids, and 5 molecules with a high structure symmetry. In the nitro compounds, the molecular structures optimized by the MNDO method were geometrically unnatural; the C-NO_2 bond is too long (e.g. MNDO; 1.546 Å, 6-31G; 1.479 Å). Therefore, the representatives calculated from the molecular structure may be inappropriate for applications to the analysis. Amino acids are not appropriate for approx.2; the conformations in two solvents are considered to be different. In molecules with high symmetry, the contribution due to the dipole moment is of no value.

Limitation of Fragment Constant Method. If $f(i)$ in Eq. 5 is the energy of the i-th fragment in a molecule, and all fragments are independent of one another, the fragment constant method is valid. This method is, however, invalid if the procedure for dividing the molecule into fragments is inappropriate, and/or if the intra- and the intermolecular interactions involve long-range interactions. For example, though the hydrocarbons are satisfied with the additivity in the log$P$ values, it is difficult to validate the additivity in molecules, having hetero atoms like nitrogen and oxygen atoms.

Correlations of S, V, and ϕ_{ct}. There is a close correlation between the molecular surface area S and the volume V (e.g. R=0.998, N=244). There is also a close correlation between ϕ_{ct} and V (e.g. R=0.984, N=244). The former fact is the reason that the radius of each atom in the molecule is almost the same. As for the latter, if E_{ct} in Eq. 9-1 is fixed, ϕ_{ct} is directly proportional to S, so that ϕ_{ct} has a close correlation with V. Thus, S. V, and ϕ_{ct} have close correlations to one another in a molecule without any long-range interaction, such as the electrostatic interaction.

The interactions of the saturated hydrocarbons, except for the dispersion energy, must be negligible. The log$P$ values in these molecules also seem to depend on ϕ_{ct} in Eqs. 16 and 17. The dependency is considered to be derived from the energies represented by S and/or V. The energies may be the dispersion energy and/or the energy of the cavity formation. Although these energies are not taken up here, the dependency suggests that they are significant for the saturated hydrocarbons.

Log P Value and Molecular Structure. The strength of the intra- and the intermolecular interaction depends upon the molecular structure, so thst a molecular property like the log$P$ value is also changed.

i) Conformer: Table 1 shows the value of the intramolecular energy, the magnitude of the dipole moment, and the observed and the calculated log *P* values of various conformers of three molecules: urea, dioxane, and cyclohexane.

The typical conformers of urea are shown in Fig. 2. Although conformer A1 has the lowest energy in the planar forms, the calculated log *P* value does not agree with the observed value. The calculated log *P* value of conformer A2 is the nearest to the observed one. Dioxane has two typical conformers: a chair form and a boat form. The energy of the chair form is lower than that of the boat form, but the observed value of log *P* shows better agreement with the calculated value of the boat form than that of the chair form. In cyclohexane, the calculated log *P* values are similar to both the chair and the boat forms, but the energy of the chair form is clearly lower than that of the boat form.

ii) Tautomer: Table 2 and Fig. 3 show an example of the tautomer in tetrazole. The observed log *P* value is closer to the calculated one of the 2*H*-type than that of the 1*H*-type. On the other hand, the results of the 6-31G**, calculated by Mazurek and Osman21) reverse the evaluation of the energy in comparison with the MNDO calculations.

Table 1. Conformers

No.	Molecule	Structure		Heat of form.	Total energy	Dipole moment	log P	
				kcal mol^{-1}	hartree	debye	Obsd	Calcd
39	Urea	Planar form	A_1	−44.4	−223.4561a)	3.04	−2.11	−0.857
			A_2	−42.6		3.98		−2.132
			A_3	−39.6		3.92		−2.360
		Non-planar form	B	−36.1	−223.4010a)	2.57		−1.610
			C	−33.7	−223.3984a)	0.42		−1.686
			D	−31.2	−223.3944a)	4.44		−2.924
291	Dioxane	Chair form		−88.5		0.42	−0.27	0.944
		Boat form		−87.5		1.23		0.381
815	Cyclohexane	Chair form		−34.7		0.00	3.44	2.608
		Boat form		−32.2		0.00		2.609

a) 4-21G: C. A. Alsenoy, J. O. Williams, and L. Schafer, *J. Mol. St.*, **78**, 179 (1981).

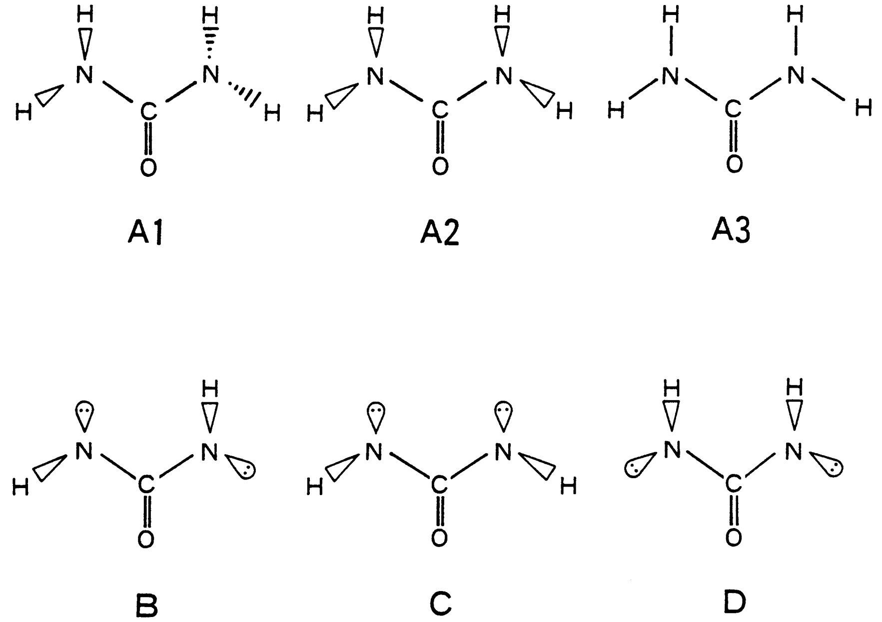

Fig. 2. Conformers of urea. A1, A2, A3: Planar form, B, C, D: Nonplanar form.

Table 2. Tautomers

No.	Molecule	Structure	Heat of form. / kcal mol^{-1}	Total energy / hartree	Dipole moment / debye	log P	
						Obsd	Calcd
28	tetrazole	1H-type	54.0		5.10	−0.60	−2.614
				−256.7573$^{a)}$	5.63$^{a)}$		
		2H-type	58.3		1.89		−0.023
				−256.7601$^{a)}$	2.24$^{a)}$		

a) 6-31G**: A. P. Mazurek and R. Osman, *J. Phys. Chem.*, **89**, 460 (1985).

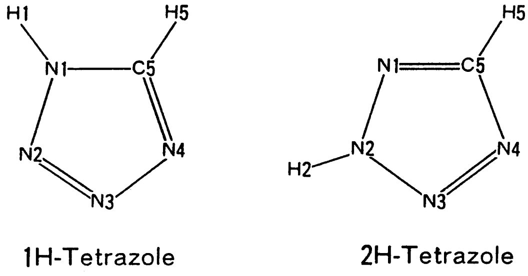

Fig. 3. Tautomers of tetrazole.

Conclusion

The partition coefficient of the solute molecule is determined by the transfer energy which is the difference of the standard free energy between two phases. The standard free energy consists of the intramolecular free energy of the solute molecule, the free energy of the cavity formation, and the interaction energy between the solute molecule and the solvent ones. These energies depend on the molecular structure of the solute. The log P values are represented by linear combination of the representatives of each energy.

This method has a characteristic of being applicable to the molecules, regardless of their types. In the analysis for instance, the log P value was investigated over the wide range of about −3 to 6, where 38% of the molecules were found to have a negative log P value.

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