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Theoretical Analysis of Phase Diagrams and Mixing Heats of Systems of Ketone/1-Alcohol

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Theoretical treatment of phase diagrams and mixing heats based on hydrogen-bond configuration has been expanded to hydrogen-bonded solutions containing molecules with proton acceptors but without proton donors. The crystal–liquid phase diagrams and the mixing heats of systems of ketone/1-alcohol were reproduced by the theory. Parameters determined from fitting enabled us to estimate the ratio of the number of acceptors associated with donors in the total number of acceptors and the relative contribution of association between molecules of different kinds.

Ketones are very useful solvents to mediate hydrophobic and hydrophilic agents. The compatibility with hydrophobic agents may be attributed to the carbonyl group, which plays a role in the solution as a proton acceptor and forms hydrogen bonds with proton donors in hydrophobic agents such as alcohol and amine. The hydrogen bond is an important interaction in biological reactions and drug designs in medicinal chemistry.[1] The hydrogen-bond characteristics of ketone may be a key to understanding the hydrogen-bond properties of complex molecules such as acids and proteins, which contain carbonyl groups.

Largely positive mixing heats have been observed in systems of ketone/1-alcohol.[2–9] However, they have been hardly used to clarify the hydrogen-bond characteristics of ketone. The simultaneous analysis of the mixing heats and crystal–liquid phase diagrams of the systems should give us the knowledge of the phenomenological free energy, but only a few studies has been reported. In our previous work,[10] we have reproduced a number of phase diagrams and mixing heats of systems of alcohol/alcohol by using a theory based on hydrogen-bond configuration, and fittings to the theory revealed the hydrogen-bond characteristics of each system of alcohol/alcohol.

In this paper, the theory has been expanded to reproduce experimental data for systems containing molecules with proton acceptors but without proton donors and to reveal the hydrogen-bond characteristics of systems of ketone/1-alcohol.

Ketones are proton acceptors but not donors and do not form hydrogen bond in the pure state. Alcohols, however, are both donors and acceptors and do form hydrogen bonds in the pure state. When alcohol is dissolved in ketone, the proton donors of alcohol can approach not only the proton acceptors of alcohol but also those of ketone. This increase of hydrogen-bond configurations available to alcohol produces a large mixing entropy as shown in our previous work.[10] In solution, ketone can use not only the space occupied by ketone but also that occupied by alcohol. This increase of space configurations available to ketone also produces the large mixing entropy. If we assume Flory–Huggins mixing entropy,[11] we can derive the mixing entropy of ketone (component-1) and alcohol (component-2) as

$$\begin{aligned}\Delta S_{\mathrm{mix}}/R = -n_1 \ln \varphi_1 + n_2 \ln[(n_{10} s_1 \gamma_{12} + n_{1\mathrm{c}} \gamma_{1\mathrm{c}} s_{1\mathrm{c}} \gamma_{12} \\ + n_{2\mathrm{c}} \gamma_{2\mathrm{c}} s_{2\mathrm{c}} + n_{20} s_2)/n_2 s_2]\end{aligned} \quad (1)$$

where R is the gas constant, n_i is the number of moles of component-i, and φ_i is its volume fraction. s_1 is defined as the average number of the hydrogen bond-free proton acceptors of component-1. s_2 is defined as the average number of the hydrogen bond-free proton acceptors of component-2, when the component-2 is not associated with component-1. $s_{i\mathrm{c}}$ is defined as the average number of hydrogen bond-free proton acceptors of component-i, when the component-1 is associated with component-2. $\gamma_{i\mathrm{c}}$ is the correction parameter to the intramolecular geometric factor of the proton acceptor of component-i due to the hydrogen bonding between component-1 and component-2. γ_{12} is the geometric factor of proton acceptor of component-1 against proton donor of component-2. n_{10} is the number of moles of component-1 without hydrogen bonding. $n_{1\mathrm{c}}$ is the number of moles of component-1 with hydrogen bonding between component-1 and component-2. n_{20} and $n_{2\mathrm{c}}$ are the number of moles of component-2 with hydrogen bonding between components-2 and components-2, and between components-1 and components-2, respectively. The method of calculation of n_{i0} and $n_{i\mathrm{c}}$ were presented in our previous work.[10] In eq 1, the first and second terms contribute to the space configuration available to components-1 (ketone) and the hydrogen-bond configuration available to components-2 (alcohol), respectively.

When component-1 and -2 are mixed, the contribution from the molecular contacts[12] is approximated as

$$\Delta E_{\mathrm{mix}}^{\mathrm{mol}} = (n_1 r_1 + n_2 r_2)\varphi_1 \varphi_2 v_{\mathrm{lattice}}(\delta_{11} - \delta_{22})^2 \quad (2)$$

where v_{lattice} is the volume of one lattice site, r_i is the number of the lattice sites that one component-i molecule occupies, and δ_{ii} is the hydrogen bond-free solubility parameter,[10] which is the contribution from only the molecular contact and does not contain the contribution from hydrogen-bond energy.

The mixing hydrogen-bond energy is expressed as

$$\begin{aligned}\Delta E_{\mathrm{mix}}^{\mathrm{HB}} = -n_{1\mathrm{c}} \varepsilon_{12}^{\mathrm{HB}}(m_1 - s_{1\mathrm{c}}) + n_{2\mathrm{c}} \varepsilon_{22}^{\mathrm{HB}}(s_{2\mathrm{c}} - s_2) \\ - [(n_{10} s_1 + n_{1\mathrm{c}} \gamma_{1\mathrm{c}} s_{1\mathrm{c}})\gamma_{12} \varepsilon_{12}^{\mathrm{HB}} \\ + (n_{2\mathrm{c}} \gamma_{2\mathrm{c}} s_{2\mathrm{c}} + n_{20} s_2)\varepsilon_{22}^{\mathrm{HB}}] x_2 + n_2 s_2 \varepsilon_{22}^{\mathrm{HB}}\end{aligned} \quad (3)$$

where $\varepsilon_{ij}^{\mathrm{HB}}$ is the molar hydrogen-bond energy between proton acceptor of component-i and proton donor of component-j. m_1 is the effective number of proton acceptors of component-1 (ketone). In eq 3, the first and second terms are the energy to maintain the association due to the hydrogen bonds between alcohol and alcohol and between ketone and alcohol, and the third and fourth terms are the energy to break the association due to the hydrogen bonds and to make the hydrogen bonds free in proportional to the number of the hydrogen bond-free proton acceptors.[10]

Table 1. The parameters for systems of acetone/1-alcohol

Component-2	γ_{12}	s_{1c}	s_{2c}	γ_{1c}	γ_{2c}
Methanol	0.858	1.758	1.266	0.946	1.039
Ethanol	0.840	1.769	1.239	0.937	1.039
Propanol	0.810	1.790	1.182	0.922	1.041
Butanol	0.825	1.780	1.172	0.922	1.043
Hexanol	0.870	1.750	1.171	0.922	1.046
Decanol	0.850	1.763	1.167	0.922	1.046

Table 2. The parameters for systems of butanone/1-alcohol

Component-2	γ_{12}	s_{1c}	s_{2c}	γ_{1c}	γ_{2c}
Methanol	0.870	1.750	1.272	0.949	1.039
Ethanol	0.848	1.764	1.240	0.937	1.039
Propanol	0.829	1.777	1.187	0.922	1.042
Butanol	0.840	1.770	1.175	0.922	1.043
Hexanol	0.890	1.736	1.174	0.922	1.046
Octanol	0.870	1.750	1.171	0.922	1.046
Decanol	0.860	1.756	1.169	0.922	1.046

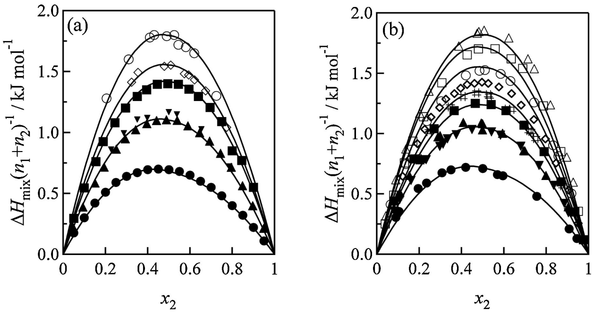

Figure 1. Mixing heats at 298.15 K for ketone/1-alcohol solutions. (a) The solutions are acetone/methanol (●),[3] acetone/ethanol (▲, ▼),[2,4] acetone/propanol (■),[5] acetone/butanol (◇),[2] and acetone/hexanol (○).[2] (b) The solutions are butanone/methanol (●),[6] butanone/ethanol (▲, ▼),[7,9] butanone/propanol (■),[8] butanone/butanol (#, ◇),[7,9] butanone/hexanol (○),[7] butanone/octanol (□),[7] and butanone/decanol (△).[7] The solid curves are the calculated using eqs 2 and 3 together with values in Table 1 and 2.

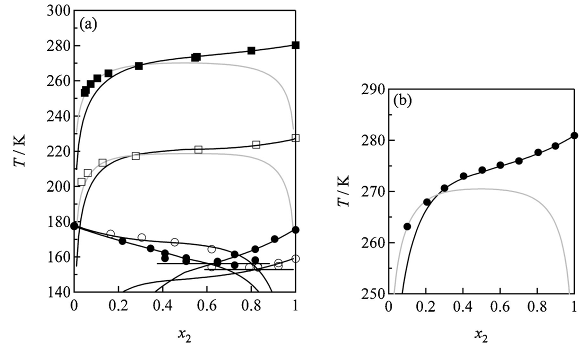

Figure 2. The crystal–liquid phase diagrams of ketone/1-alcohol solutions. (a) The solutions are acetone/methanol (●),[13] acetone/ethanol (○),[13] acetone/hexanol (□),[14] and acetone/decanol (■).[13] (b) The solution is butanone/decanol (●). The solid curves are the calculated using eqs 1–4 together with values in Table 1 and 2. The black and gray lines reproduce the T_m depression of pure crystal and cocrystal, respectively.

In analogy with the analysis of the systems of alcohol/alcohol,[10] the melting temperature (T_m) depression of a cocrystal is used for the fitting to crystal–liquid phase diagram of the systems of ketone/1-alcohol. It is expressed as

$$T_m = T_{mc}\{1 - [c_1(\Delta\mu_1^c - \Delta\mu_1) + c_2(\Delta\mu_2^c - \Delta\mu_2)]/\Delta H_{mc}\} \tag{4}$$

where T_{mc} is the maximum of the melting temperature of the cocrystal, c_i is the mole fraction of component-i in the cocrystal, the superscript c indicates the chemical potential in the mixture with the composition of c_1/c_2 and ΔH_{mc} is the melting heat of the cocrystal. According to the definition, the value of c_i is defined as the mole fraction of component-i at the maximum of the melting temperature of the cocrystal.

s_2 and ε_{22}^{HB} for each alcohol were determined from analysis of the systems of alcohol/alcohol.[10] m_1 for each ketone was set as 2. s_1 for each ketone was also set as 2, because of no hydrogen bonding in the pure state.

We determined the parameters for the systems of ketone/1-alcohol[2–9] by using eqs 1–4 from simultaneous fittings to the mixing heats and crystal–liquid phase diagrams, as shown in the figures of acetone/1-alcohol (a) and butanone/1-alcohol (b). The solid lines are the fitting curves. The parameters used for the fittings are listed in Tables 1 and 2. The six parameters, ε_{12}^{HB}, γ_{12}, s_{1c}, s_{2c}, γ_{1c}, and γ_{2c} were used for fittings in the present theory. γ_{12} mainly depends on ε_{12}^{HB}, and s_{2c}, γ_{1c}, and γ_{2c} depend on s_{1c}. We assumed that the number of hydrogen bonds between ketone and alcohol is proportional to the probability of hydrogen bond between ketone and alcohol; that is, γ_{12} is inversely proportional to s_{1c}.

As shown in Figure 1, the mixing heats of the systems of ketone/1-alcohol are strongly positive and those of acetone/hexanol and butanone/decanol reach about 1.8 kJ mol^{-1}, which exceeds the maximum contribution from the ideal gas mixing entropy ca. 1.72 kJ mol^{-1} at 300 K. This suggests that these solutions should be phase-separated, but actually they are not. We have measured the T_m depression of the system of butanone/decanol. Figure 2 shows the crystal–liquid phase diagrams of the systems of acetone/1-alcohol (a) and butanone/1-alcohol (b). In Figure 2, the T_m depressions of the pure crystal were reproduced by the black lines but cannot be completely reproduced in the ketone-rich region of the systems of acetone/hexanol, acetone/decanol, and butanone/decanol. Because cocrystals are frequently observed in systems of ketone/aromatic alcohol,[13] the melting of 1/1 ratio cocrystals, i.e., $x_2 = c_2 = 0.5$ have been used for fitting to them. The calculated values using the parameters in Tables 1 and 2 are given by the gray lines in Figure 2. The melting heat of the cocrystal used for the fitting is about 25 kJ mol^{-1} for each system. Eutectic melting was observed for acetone/methanol and acetone/ethanol systems, which are reproduced by a straight line in Figure 2a.

The mixing heats of systems of ketone/1-alcohol are strongly positive, but Figure 2 shows that the systems are still miscible. The reason these solutions are still homogenous is that the mixing entropy, which is the sum of two contributions of the space configuration and the hydrogen-bond configuration, exceeds the mixing heats.

From the fitting, the hydrogen-bond energy between ketone and 1-alcohol was determined to be 13 kJ mol^{-1}. In our previous work,[10] we estimated the hydrogen-bond energy from the shift of OH stretching in Raman or IR spectroscopy. Using the same method, the value estimated from IR spectroscopy by Becker[15] was about 11 kJ mo1^{-1}, which is close to that estimated in the present work. This agrees with the hydrogen-bond energy between ketone and 1-alcohol being much weaker than that between 1-alcohol and 1-alcohol, which was reported from ab initio calculation.[1] The large differences in the hydrogen-bond energies between ketone/1-alcohol and 1-alcohol/1-alcohol (23–28 kJ mol^{-1})[10] may mainly contribute to these strongly positive mixing heats.

In Tables 1 and 2, the intermolecular geometric factor γ_{12} is a measure of the conformity of alcohol proton donor with ketone proton acceptor. γ_{12} slightly decreases with the length of the alkyl group of 1-alcohol from methanol to propanol in each system, because of the increase in the interference of hydrogen bonding by the alkyl group. However, those for butanol and hexanol are slightly larger than that for propanol and again decrease with the length of the alkyl group of 1-alcohol from hexanol to decanol in each system. The increase of γ_{12} for butanol suggests that the probability of hydrogen bonding between ketone and alcohol slightly increases, which might suggest that hydrophilic groups form an aggregate and that the interference of hydrogen bonding by the alkyl group slightly decreases, when ketone is dissolved in 1-alcohol with longer alkyl groups.

s_{1c} is slightly smaller than s_1 (=2),[10] which means that the number of hydrogen bonds between ketone and 1-alcohol is low. s_{2c} is slightly larger than s_2 (=1.05–1.12),[10] which means that there is little change in the number of hydrogen bonds between the proton acceptor and the proton donor of 1-alcohol, when the pure liquid state of 1-alcohol is compared with the solution state of ketone/1-alcohol.

The ratio of the number of accepters associated with donors in the total number of acceptors is defined by $\xi = (m_i - s_i)/m_{i\max}$, where $m_{i\max}$ is the number of proton acceptors of component-i and equal to 2. m_2 was determined in our previous work[10] to be 1.88. The values ξ for ketone and 1-alcohol in each ketone/1-alcohol solution estimated using s_{1c} and s_{2c} are 0.11–0.13 and 0.30–0.36, respectively. No significant dependence of the length of the alkyl group was observed in ξ for ketone, whereas slight dependence was observed for 1-alcohol; ξ for methanol, ethanol, and propanol–decanol are 0.3, 0.32, and 0.35–0.36, respectively. The value of ξ for large length of the alkyl group approaches that for 1-alcohol in the pure state,[10] 0.38–0.41 calculated using s_2.

Parameters γ_{1c} and γ_{2c} slightly deviate from unity, which is related to the relative contribution of the interaction between molecules of different kinds. The value of γ_{1c} less than unity by about 8% suggests that the hydrogen bonds to the acceptors of ketone are slightly interfered by associated 1-alcohol. In contrast, the value of γ_{2c} larger than unity by about 5% suggests that the hydrogen bonds to the acceptors of 1-alcohol are promoted with associated ketone relatively to associated 1-alcohol.

In conclusion, the expanded theory based on the hydrogen-bond configuration simultaneously reproduced the crystal–liquid phase diagrams and the mixing heats of systems of ketone/1-alcohol using common parameters. The analysis revealed the hydrogen-bond characteristics of ketone and the systems of ketone/1-alcohol, and the origin of the largely positive mixing heats were discussed with the parameters determined from the theoretical analysis.

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