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Hydration of Aza-aromatic Aldehydes. II. Solvent Effect on the Equilibrium Constants of the Hydration

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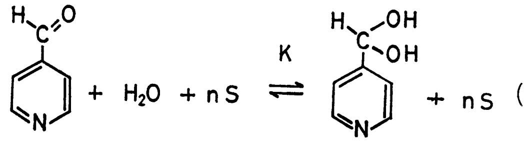
The equilibrium constants for the hydration reaction of 4-pyridinecarbaldehyde were determined in several solvents by ^{1}H-NMR spectroscopic measurements. The hydration reactions were sensitive to the nature of the solvents. In strong donor solvents such as hexamethylphosphoric triamide, pyridine, and dimethyl sulfoxide, formation of the hydrate is far more favorable than in water or other poor donor solvents. Thus the stabilization of the product by hydrogen bond formation is assumed to favor the reaction. Polarity of the solvent alone does not explain the solvent effect, even if it is supposed to affect the equilibria secondarily.

The hydration reaction to form geminal diols is known on several aliphatic aldehydes carrying electronegative groups.[1–5)] The present authors have reported in a previous paper[6)] that the corresponding geminal diols were produced when the six-membered aza-aromatic aldehydes carrying a formyl group at 2 or 4-position were submitted to the reaction with water. The enthalpies of hydration were determined from the temperature dependence of their ^{1}H-NMR spectra. In this report, equilibrium constants (K) of the hydration of 4-pyridinecarbaldehyde (given by Eq. 1) were determined in several organic solvents by means of ^{1}H-NMR spectroscopy.[7)] The advantage of NMR spectroscopy in the determination of free and hydrated species of aldehydes in mixtures has been described by several authors.[8–12)] In the case of 4-pyridinecarbaldehyde, it is possible to observe two sets of resonance lines assigned to the hydrated and the free species in its ^{1}H-NMR spectrum.[6)] The methine proton signal of the hydrated species appears at *ca.* 4 ppm upfield relative to the formyl proton signal of the unhydrated species. Similarly, ring proton signals of the hydrated species shift *ca.* 0.5 ppm upfield relative to those of the unhydrated species.



(1)

The hydration of aza-aromatic aldehydes is an addition reaction initiated by the nucleophilic attack of water molecule on the positively-charged carbonyl carbon atom. In an aldehyde–water–solvent ternary system, the hydration reaction is supposed to be affected considerably by the nature of solvent because of the difference in polarity and in hydrogen-acceptability, or electron-donability, in hydrogen bond formation. Thus the equilibrium constants were determined in various solvents and with various proportions of reactant system in order to study the specific interaction between the solvent and the solute molecules, and to elucidate how the solvent participates in the reaction mechanism.

Experimental

Preparation of Materials. 4-Pyridinecarbaldehyde was distilled prior to use. Deuterium oxide was used as the nucleophilic reagent in place of H_2O in most runs. No remarkable difference in equilibrium constant was observed in comparison with the results using H_2O.[13)] Deuterated solvents were used without further purification. Other solvents were purified by the usual procedures.

Measurement of ^{1}H-NMR Spectra. ^{1}H-NMR experiments were performed with a JEOL JNM C-60H NMR spectrometer. In cases of very dilute solutions, the spectra were measured with a JEOL JNM FX-60 or an FX-100 NMR spectrometer, accumulations carried out hereby in order to get a high signal-to-noise ratios. Equilibrium constants of the hydration in various solvents were determined from the ratios of integrated intensities of the free and the hydrated species of the aldehyde. The relative integrated intensity was obtained as a mean of the observed values by several (at least 3) times of scans in the integration mode. Chemical shifts are given in terms of part per million (ppm) downfield from TMS. The probe temperature was kept at 34.5 °C in all measurements except otherwise stated.

TABLE 1. THE ENTHALPY OF HYDROGEN BOND FORMATION BETWEEN 4-(HYDROXYMETHYL)PYRIDINE AND DIMETHYL SULFOXIDE

$C=4.42\times10^{-3}$ mol/l $H=21.1$ KJ/mol

T/K	ε_f/l mol^{-1} cm^{-1}	ε_h/l mol^{-1} cm^{-1}
292.5	39.5	58.5
297.7	40.6	52.7
303.7	42.5	46.5
309.3	44.8	41.4
316.2	46.1	35.1

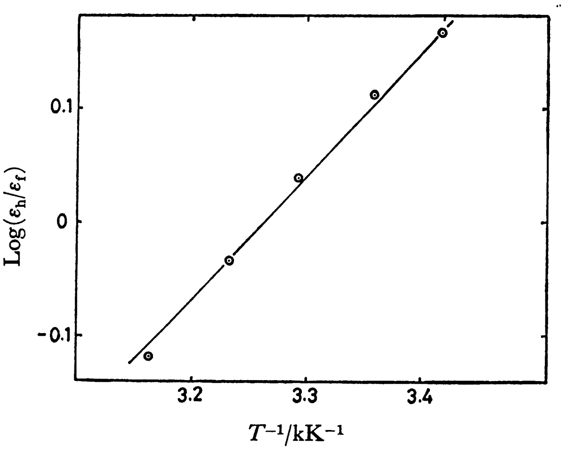


Fig. 1. The log ($\varepsilon_h/\varepsilon_f$) *vs.* $1/T$ of 4-(hydroxymethyl)-pyridine–dimethyl sulfoxide hydrogen bond system.

Determination of $\Delta\nu_{OD}$ and the Enthalpy of Hydrogen Bond Formation by Infrared Spectroscopic Measurements. Infrared O–D stretching absorptions of methanol-*d* were measured with a Hitachi Model 225 grating infrared spectrometer. The reference O–D absorption in benzene was also measured under the same conditions.

The enthalpy of hydrogen bond formation of 4-(hydroxymethyl)pyridine was obtained by measuring the O–H absorption intensities of free and hydrogen-bonded species (ε_f and ε_h, respectively) at several temperatures. The slope and the abscissa of the $(\varepsilon_h/\varepsilon_f)$ *vs.* $1/T$ plot gave the enthalpy and the entropy, respectively. The results are given in Table 1 and Fig. 1.

Results and Discussion

Formation Constants of the Hydrate in Several Organic Solvents. Equilibrium constants of the hydration in various solvents are given together with some indices for the solvent polarity and the hydrogen acceptability in Table 2. The $\Delta\nu_D$ value is defined as the solvent induced shift (in cm^{-1}) of the O–D stretching band of methanol-*d* (CH_3OD) in a solvent with reference to that in benzene (2688 cm^{-1}) and used as a measure for the electron donating power of solvent. Most $\Delta\nu_D$ values were cited from reference,[14] some of them being determined in the present investigation. From the above definition, the $\Delta\nu_D$ value increases with the increasing order of the electron donating power in the hydrogen bond formation. The log K *vs.* $\Delta\nu_D$ plot gives a straight line with $r=0.982$ representing a very good linear relation. A good correlation is also observed between ln K and the donor number (Dn) defined by Gutaman ($r=0.984$).[15] From the results, it is supposed that strong donor solvents facilitate hydrogen bond formation of the produced geminal diol with water, playing an important role in the hydration reaction.

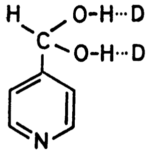
In the reactant system (consisting of the aldehyde, water, and solvent), water molecules form hydrogen bonds with solvent molecules preferably when the solvent is a stronger donor than water. This is estimated from the hydrogen bond energies obtained by NMR and infrared spectroscopic measurements.[16,17] Thus the energy of formation of water–dimethyl sulfoxide hydrogen bond (4.6 kcal/mol) is shown to be larger than that for the self-association of water (4.4 kcal/mol). The water–solvent hydrogen bond stabilizes the aldehyde, disfavoring the formation of geminal diol in the equilibrium. The strong hydrogen bond between the solvent and water molecules tends to destroy the cluster structure of liquid water by breaking the O–H⋯O hydrogen bond constructing the structure. The destruction of the cluster is especially remarkable in the range of larger mole fractions of the strongly donable solvents, being proved by the measurement of neutron inelastic scattering and X-ray diffraction studies.[18] Hydrogen bond formation between the carbonyl oxygen atom and water is also possible in the reactant system. However the hydrogen bond of this type is supposed to be a little weaker than the O–H⋯O hydrogen bond in water-donable solvent and the O–H⋯N hydrogen bond in water–aza-aromatic aldehyde pairs, the difference in the enthaplies of hydrogen bond formations being very small in these two cases. Hence this interaction might affect less remarkably the equilibrium of the hydration reaction.

Similar stabilization may occur in the product system consisting of the geminal diol, water, and the solvent. Contrary to the case of reactant system, the stabilization by forming hydrogen bonds will favor the hydration reaction. As the geminal diol has two O–H functions, it can attain considerably large stabilization in strong donor solvents. In order to estimate the energies of hydrogen bond formation in the product system, 4-(hydroxymethyl)pyridine was used as a model compound and the enthalpy of association with dimethyl sulfoxide was determined by the infrared spectroscopic method. Ternary 4-(hydroxymethyl)pyridine–dimethyl sulfoxide–carbon tetrachloride system shows two O–H absorptions at 3637 and 3380 cm^{-1}, which are assigned to the free and the hydrogen-bonded species, respectively. Then the temperature dependence measurement of their intensities gives the enthalpy of hydrogen bond formation to be 5.03 kcal/mol. As 4-(hydroxymethyl)-pyridine has a similar structure to the geminal diol and the additional α-hydroxyl group is expected to favor the hydrogen bond by its electronic effect, the hydrogen bond in the geminal diol is assumed to be stronger than that in the reactant. The geminal diol can exist as the two types of associated species given by (A) and (B).

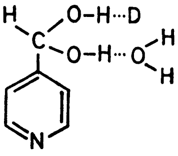
TABLE 2. THERMODYNAMIC QUANTITIES FOR THE HYDRATION OF 4-PYRIDINECARBALDEHYDE IN SEVERAL ORGANIC SOLVENTS

Solvent	K(34.5 °C)	δ:ppm (formyl proton) aldehyde	*gem*-diol	$\frac{\Delta H}{\text{K J mol}^{-1}}$	$\frac{\Delta S}{\text{J mol}^{-1}\text{ K}^{-1}}$	ε	$\frac{\Delta\nu_D}{\text{cm}^{-1}}$	D_n
HMPA	4.26×10^{-2}	10.25	5.98	−23.1	−102	30.0	177	38.8
Pyridine-d_5	3.76×10^{-2}	10.21	6.41	−24.3	−107	12.1	168	33.1
DMSO-d_6	3.16×10^{-2}	10.18	6.03	−21.7	−99	45.0	141	29.8
DMF	2.27×10^{-2}	10.21	6.03	−22.6	−104	36.1	107	26.6
Dioxane	2.04×10^{-2}	10.22	5.95			2.2	77	
Acetone-d_6	1.75×10^{-2}	10.08	6.05	−14.7	−82	20.7	64	17.0
D_2O	1.62×10^{-2}			−25.8	−118	81.0		18.0
Acetonitrile-d_3	1.32×10^{-2}	10.20	5.96	−10.2	−69	38.0	49	14.1

HMPA: Hexamethylphosphoric triamide, DMSO: Dimethyl sulfoxide, DMF: *N,N*-Dimethylformamide.



(A)



(B)

The second hydrogen bonds in these species might be a little weaker. Thus, the stabilization caused by the hydrogen bond in the 1 : 2 associated species, (A) or (B), is expected to overcome that in the reactant system.

The solvent polarity can be another factor which controls the hydration reaction. If a polar molecule (dipole moment μ, radius r) is transferred from the vaccum ($\varepsilon=1$) to a medium of which dielectric constant is ε, the energy change ($\Delta\Delta G$) is given by the Kirkwood Eq. 2.

$$\Delta\Delta G = -\frac{\mu^2}{r^3}\,\frac{\varepsilon-1}{2\varepsilon+1} \tag{2}$$

Therefore, the contribution of the solvent polarity to $\Delta G°$(hydration) should be proportional to $(\varepsilon-1)/(2\varepsilon+1)$. In practice, no definite correlation is observed between log K and $(\varepsilon-1)/(2\varepsilon+1)$, implying that the polar effect of solvent is not a predominant factor to affect the equilibrium of hydration. However, by comparison of the results in deuterium oxide with those in acetonitrile-d_3 and acetone-d_6 it is probable that the polarity of solvent favors the hydration secondarily. Since acetone and acetonitrile are less donable than water, effect of the polarity which is masked by the effect of hydrogen bonding in cases of more strongly donable solvents becomes apparent in cases of acetone and acetonitrile solutions.

Influence of the Composition of Reaction Medium on the Equilibrium Constant. In the experiments discussed above, the mole fractions (x) of the solvents were kept approximately 0.30, which is the most convenient concentration to observe NMR signals of the hydrated and the unhydrated species accurately. However, the eqilibrium constant (K) is dependent upon the composition of the reaction medium, *i.e.* the mole fractions of the components. Thus the equilibrium constants were determined as a function of the mole fraction of solvent in the ternary aldehyde–water–solvent mixture. Results are given in Table 3 and Fig. 2. The solvents can be classified into two groups from the shape of their concentration *vs.* log K plots. The first group consists of strongly donable solvents such as hexamethylphosphoric triamide, pyridine, and dimethyl sulfoxide. The other consists of less donable solvents such as acetone and acetonitrile. In a solvent more donable than water, K increases almost linearly with the mole fraction of solvent in the region of $x \lesssim ca.$ 0.5. This phenomenon is explained by the formation of stronger hydrogen

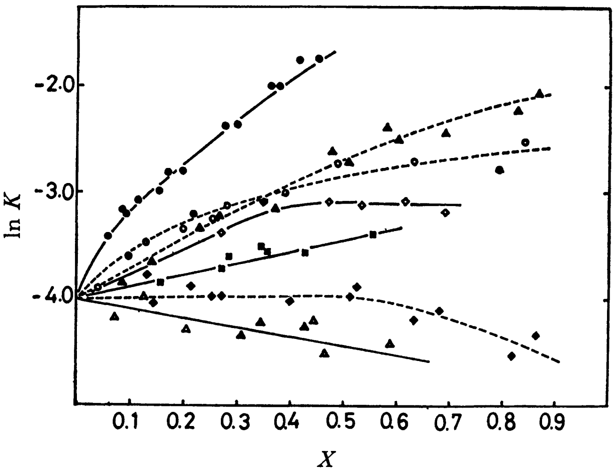


Fig. 2. The dependence of equilibrium constant K values on the mole fraction (X) of solvent molecule.
—●—: Hexamethylphosphoric triamide, —▲—: pyridine-d_5, —○—: dimethyl-d_6 sulfoxide, —◇—: N,N-dimethylformamide, —■—: dioxane, —◆—: acetone-d_6, —△—: acetonitrile-d_3.

TABLE 3. EQUILIBRIUM CONSTANTS (K) IN SEVERAL SOLVENTS WITH VARIOUS MOLE FRACTIONS (X) OF SOLVENTS

HMPA		Pyridine		DMSO		DMF		Dioxane		Acetone		Acetonitrile	
X	ln$K$	X	ln$K$	X	ln$K$	X	ln$K$	X	ln$K$	X	ln$K$	X	ln$K$
0.060	−3.420	0.084	−3.860	0.038	−3.869	0.131	−3.785	0.213	−3.893	0.141	−4.045	0.074	−4.195
0.085	−3.170	0.137	−3.637	0.097	−3.592	0.274	−3.378	0.272	−3.719	0.255	−3.976	0.127	−3.983
0.090	−3.212	0.229	−3.431	0.126	−3.439	0.354	−3.069	0.284	−3.598	0.270	−3.913	0.202	−4.310
0.115	−3.080	0.262	−3.232	0.204	−3.329	0.474	−3.080	0.347	−3.516	0.402	−4.049	0.294	−4.442
0.155	−2.946	0.374	−3.150	0.217	−3.201	0.534	−3.120	0.357	−3.562	0.512	−3.904	0.309	−4.343
0.172	−2.821	0.477	−2.623	0.257	−3.272	0.618	−3.074	0.427	−3.560	0.521	−3.987	0.343	−4.236
0.199	−2.811	0.508	−2.727	0.279	−3.104	0.625	−3.434	0.553	−3.383	0.525	−3.806	0.427	−4.294
0.278	−2.373	0.581	−2.376	0.388	−3.023	0.634	−3.322			0.632	−4.195	0.443	−4.204
0.299	−2.360	0.600	−2.498	0.413	−3.170	0.694	−3.187			0.681	−4.094	0.463	−4.566
0.358	−2.276	0.641	−2.567	0.489	−2.690					0.819	−4.553	0.591	−4.422
0.365	−1.993	0.691	−2.431	0.632	−2.701					0.865	−4.334		
0.378	−1.999	0.829	−2.238	0.794	−2.778								
0.416	−1.725	0.869	−2.056	0.848	−2.492								
0.452	−1.721												

Cf. in D_2O, ln $K = -3.984$.

bond between geminal diol and solvent in the product system than those in the reactant system. As the hydrogen bonded species of the geminal diol is supposed to increase in proportion to x, K becomes larger than that in water. The increase in log K becomes gradually less when the mole fraction of donable solvent is larger than 0.5. In some instances, the log K *vs.* x plots become flat or turn to decrease in a higher mole fraction range of the solvent. In this range of mole fraction, polarity of the medium seems to be decreased in comparison with that of water, since all solvents employed in the experiments have dielectric constants lower than water (Table 2). Therefore the equilibrium of the hydration reaction is not so favorable as expected from the solvent donicity alone.

Another factor suspected to affect the equilibrium constants is the decrease of the number of the O–H···N hydrogen bonds between water and 4-pyridinecarbaldehyde molecules during the process of hydration, since one molecule of water is consumed in this process. The produced geminal diol molecule can form two hydrogen bonds alternatively. If the solvent is a stronger donor than pyridine, the effect is less predominant because O–H···D (where D refers to a donable solvent molecule) hydrogen bond might be more favorable than O–H···N hydrogen bond both in the reactant and the product systems. In case when the solvent is less donable than pyridine, the O–H(in water)···N hydrogen bond in the reactant is replaced by the O–H(in the geminal diol) ···D hydrogen bond during the hydration, disfavoring the equilibrium to a certain extent. Another O–H···N hydrogen bond can be formed by the self-association of the aza-aromatic geminal diol. However, the concentration of the aldehyde is kept to be relatively low, preventing the produced geminal diol from self-associating to a measurable extent. The former case is the reaction in hexamethylphosphoric triamide, the typical examples of the latter case being those in dimethyl sulfoxide and in *N,N*-dimethylformamide.

In contrast to the results in strongly donable solvents, the dependence of the equilibrium constants on x was not remarkable in several less donable solvents which does not perturb the hydrogen-bonded structure of water considerably. As shown in Fig. 2, the equilibrium constants in acetone and acetonitrile tend to decrease monotonously in the wide range of X. The lowering of K values in these solvents are due to the decrease in polarity of the solvent, because the molecules of such solvents are unable to interact strongly with water and geminal diol molecules. It is deduced from the results in these less donable solvents that the effect of polarity which is masked by the effect of hydrogen bonding in cases of strongly donable solvents will also contribute to the hydration reaction apparently.

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7) S refers to a solvent molecule in Eq. 1. Hereafter, the members of the left side in Eq. 1 are called reactant system and those of the right side product system.

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