Hydration of Aza-aromatic Aldehydes. I. Isolation of the Solid Hydrates and the Thermodynamic Properties in Dimethyl Sulfoxide

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The covalent hydration forming geminal diol is shown to be general in six-membered aza-aromatic aldehydes substituted by a formyl group at ortho or para-position to the nitrogen atom, and the equilibrium constants and thermodynamic quantities of the reaction are determined by NMR spectroscopic measurements. The results are compared with those of their hemiacetal formation. In several cases, solid monohydrates are isolated and identified.

In contrast to easy formation of hemiacetals,[1] hydration of carbonyl compounds is much less predominant, and only a few examples have been reported.[2,3] Trichloroacetaldehyde crystallizes as monohydrate, and its geminal diol structure is confirmed by ultraviolet spectroscopy.[2] Formaldehyde also exists to some extent as methanediol in aqueous solution. Some aliphatic aldehydes were also found to exist as equilibrium mixtures between the carbonyl and geminal diol forms in aqueous solutions.[4-6] However, the hydrate forms of most complex aldehydes are rather unstable, aldehydes behaving as normal carbonyl compounds even in aqueous or alcoholic solutions. The $n\rightarrow\pi^*$ absorption of many aldehydes including formaldehyde, acetaldehyde, and other simple aldehydes have been measure in these solutions, and their intensities were shown to be in the same order as those in aprotic solvents.[7]

Since the hydration and hemiacetal formation of carbonyl compounds both proceed *via* nucleophilic attack of water and alcohol molecules towards the carbonyl carbon atom, electron-withdrawing moieties attached to the carbonyl group should favor the formation of these addition products. The hydration of aza-aromatic aldehydes carrying so-called electron deficient rings was investigated. The position of the carbonyl function relative to the intra-ring nitrogen atoms affects the equilibrium of the hydration remarkably. The difference in equilibrium constants was interpreted in terms of the electronic effect and hydrogen bonding.

Experimental

Preparation of Materials. Most of the quinoline- and naphthyridinecarbaldehydes were prepared by the methods reported.[8] The samples of pyridinecarbaldehydes were obtained by distilling twice the commercial materials.

3-Quinolinecarbaldehyde (**5**) was perpared from 3-aminoquinoline by a modified method.[11] The starting material(3.6 g) was dissolved in diluted hydrochloric acid(3.5 M, 23 ml), aqueos sodium nitrite solution(1.75 g in 2.5 ml water) being added gradually to the solution. The pH of the diazonium salt solution thus prepared was adjusted to be *ca.* 5 by addition of sodium carbonate, and 10% aqueous formaldehyde oxime was added to the diazotized solution with efficient stirring during 30 min, the temperature of the reaction mixture being kept at 5—10 °C. The mixture was acidified with diluted hydrochloric acid (to pH=3). A ferric chloride solution(15 g in 15 ml water) was added, and the solution was digested at 100 °C for about 1 h. Neutralization by sodium carbonate, extraction by ether, and evaporation of the solvent gave the crude 3-quinolinecarbaldehyde. Colorless needles(recrystd from pentane). Mp 68—70 °C(lit, 70 °C). MS, m/e=157(M^+).

Their hydrates were prepared by crystallization from aqueous or aqueous-dimethyl sulfoxide solutions. Dimethyl sulfoxide seems to accelerate and to favor formation of the hydrates. 4-Pyridinecarbaldehyde monohydrate. Mp 65—80 °C (dec). Found: C, 57.80; H, 5.58; N, 11.32%. Calcd for $C_6H_7O_2N$: C, 57.59; H, 5.64; N, 11.20%. 1,8-Naphthyridine-4-carbaldehyde monohydrate. Mp 129—130 °C (dec). Found: C, 61.57; H, 4.39; N, 15.65%. Calcd for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.90%.

Measurement of the Spectra. The IR spectra were recorded with a Hitachi Model 225 grating infrared spectrophotometer and the UV spectra with a Hitachi EPS-3T spectrophotometer. Proton NMR spectra were measured with a JMN C-60H spectrometer equipped with a JES-VT-3 apparatus for variable temperature measurements. Chemical shifts are given in terms of part per million (ppm) downfield from TMS, and temperatures were calibrated by measuring the chemical shifts of 1,3-propanediol before and after scan of the spectrum.

Results and Discussion

Isolation of Crystalline Monohydrates of Aza-aromatic Aldehydes. In the course of synthetic and pharmaceutical investigations on naphthyridines and related heterocycles,[8-10] a series of aza-aromatic aldehydes were prepared and their infrared spectra were measured. Among these aldehydes, 1,8-naphthyridine-4-carbaldehyde (**8**), prepared by the oxidation of 4-methyl-1,8-naphthyridine, crystallizes to form monohydrate, and shows no carbonyl absorption in the frequency range 1750—1650 cm^{-1} when the spectrum is obtained in the solid state (as a potassium bromide pellet). Some absorption bands of the aldehyde under discussion are given in Table 1. The broad and intense absorption of 1,8-naphthyridine-4-carbaldehyde hydrate at *ca.* 3200 cm^{-1} can be assigned to the associated (or chelated) hydroxyl group. The broad bands at the lower frequencies might originate from the OH bending and CO stretching modes of vibration of geminal diol group. Mass spectrum of the hydrate shows no molecular ion peak but M−18 (m/e: 158) peak which corresponds to the parent peak of the anhydrous aldehyde. Further studies on its infrared spectrum in solution reveal the existence of the carbonyl form in aprotic solvents. The

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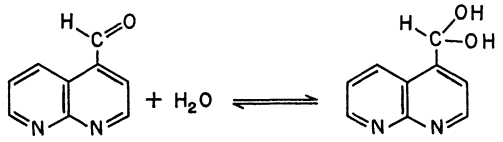
Table 1. Infrared spectra of several aza-aromatic aldehydes

Aldehyde		State	ν_{max}/cm^{-1} a)	C=O Bond order
2-Pyridinecarbaldehyde (anhydrous)	**1**	liquid	1714(s)	0.8659
3-Pyridinecarbaldehyde (anhydrous)	**2**	liquid	1707(s)	0.8618
4-Pyridinecarbaldehyde (anhydrous)	**3**	liquid	1712(s)	0.8707
(hydrate)		solid	3270(s,b)	
			1560(s)	
2-Quinolinecarbaldehyde (anhydrous)	**4**	solid	1706(s)	0.8685
3-Quinolinecarbaldehyde (anhydrous)	**5**	solid	1690(s)	0.8599
4-Quinolinecarbaldehyde (anhydrous)	**6**	liquid	1703(s)	0.8669
1,5-Naphthyridine-4-carbaldehyde (anhydrous)	**7**	solid	1697(s)	0.8630
1,8-Naphthyridine-2-carbaldehyde (anhydrous)	**8**	solid	1707(s)	0.8692
1,8-Naphthyridine-4-carbaldehyde[b] (hydrate)	**9**	solid	3200(s,b)	0.8696
			1510(b)	
			1310(s,b)	
(hydrate)		$CHCl_3$ soln	1711(s)[c]	
(hydrate)		CH_3CN soln	1706(s)[c]	

a) s: strong, b : broad. b) Anhydrous substance was not obtained by recrystallization from aqueous ethanol.
c) Carbonyl stretching absorption of the free carbonyl group (see text).

acetonitrile solution of the hydrate shows the carbonyl stretching absorption at 1706 cm^{-1} with $\varepsilon_{max}=595$. In aprotic solvents, the hydrated molecule seems to dissociate into the free aldehyde as follows.



(I) (II)

Since the carbonyl chromophore is destroyed to form the saturated dihydroxymethyl group in the course of hydration, the process of hydration is best pursued by means of ultraviolet spectrometry. The spectra of 1,8-naphthyridine-4-carbaldehyde (**9**) were measured in various solvents. The results are illustrated in Fig. 1. For the sake of comparison, the spectrum of the parent 1,8-naphthyridine is also shown. The spectrum of **9** in water resembles remarkably that of 1,8-naphthyridine. The similarity is reasonanble since the hydrated form of **9** has a 1,8-naphthyridine chromophore slightly perturbed by the dihydroxymethyl moiety. Similar

Table 2. Ultraviolet spectra of several aza-aromatic aldehydes

Aldehyde	λ_{max}/nm ($\varepsilon_{max}/1\ mol^{-1}\ cm^{-1}$)		
	in H_2O	in CH_3CN	in CH_3OH
4-Pyridinecarbaldehyde (**3**)	225 (11200)	223 (6760)	251 (1820)
	259 (2000)	284 (1780)	258 (2340)
	264sh (1700)		265sh (1860)
	286 (1260)		
4-Quinolinecarbaldehyde (**6**)	248 (11300)	224 (35900)	250 (2140)
	316 (7050)	250 (14700)	285b (3880)
	330b (4910)	325b (7660)	303 (3660)
			316 (3530)
1,5-Naphthyridine-4-carbaldehyde (**7**)	263 (9490)	320 (8080)	263 (7480)
	273 (8420)	275 (7260)	272 (5920)
	306 (10500)		290 (4550)
	312 (10600)		299 (6980)
	330sh (3070)		309 (8240)
1,8-Naphthyridine-2-carbaldehyde (**8**)	242sh (7960)	274b (8230)	258 (6340)
	302 (7660)	320b (5630)	299 (9390)
	311 (8640)		303 (10300)
	330sh (1910)		311 (10600)
1,8-Naphthyridine-4-carbaldehyde (**9**)	268b (7880)	278 (4910)	265 (10700)
	303 (9410)	322 (4910)	296 (9440)
	311 (9700)		303 (11500)
	330sh (2350)		311 (11200)

sh: shoulder, b : broad.

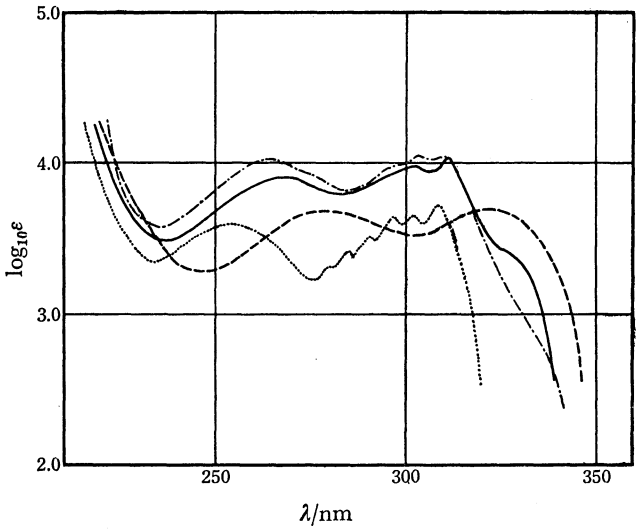


Fig. 1. Ultraviolet spectra of 1,8-naphthyridine-4-carbaldehyde. [—— in water, – – – in acetonitrile, -·-·- in methanol (hemiacetal), and ····· 1,8-naphthyridine (as reference) in acetonitrile].

changes in spectra have been observed during the course of acetal formation of some heteroaromatic aldehydes.[3] The hypsochromic shifts of the bands caused by acetal formation are also explained to be due to the saturation of the carbonyl chromophore to form the geminal dialkoxy-compound.

Crystalline hydrates can also be obtained in several cases (*e.g.* 1,8-naphthyridine-2-carbaldehyde (**8**), 4-pyridinecarbaldehyde (**3**)) as solids which deposit spontaneously on the wall of the sample tube when their NMR spectra were measured in aqueous organic solvents (especially in D_2O–DMSO solvent system). Their geminal diol structures were proved by observing the presence of the two OD stretching bands (2438 and 2322 cm^{-1} in the case of **3**) and the absence of the C=O stretching band in their infrared spectra. In the case of **3**, the solid hydrate ($C_6H_5NO \cdot H_2O$) obtained from aqueous solution is identified by the NMR spectrum in DMSO-d_6 [δ=6.58 (d, 2, J=7.5 Hz, OH's of *gem*-diol) and 5.77 ppm (α-CH) and also by elementary analysis (see Experimental). The ultraviolet spectra of the aldehydes in water are also compared with those in aprotic solvents, hypsochromic shifts attributable to the covalent hydration being again observed (Table 2).

Determination of the Equilibrium Constants and Thermodynamic Quantities of the Hydration and Hemiacetalization of the Aza-aromatic Aldehydes. Further investigation on their NMR spectra shows that hydration of the heteroaromatic aldehydes of this class occurs generally, and proceeds reversibly in various solvents.[12] Thus, the measurement provides a suitable means to study the reaction quantitatively. An example of the NMR spectra of 4-pyridinecarbaldehyde–D_2O-dimethyl sulfoxide-d_6 ternary system is given in Fig. 2. The rate of the hydration is sufficiently small to make it possible to observe the proton signals of the free and the hydrate species of the aldehyde separately, the CHO and the $CH(OD)_2$ protons resonating at about 10.1 and 6.0 ppm, respectively. The relative intensities of these

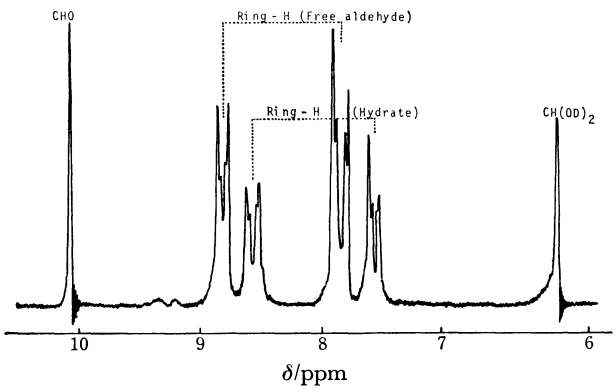


Fig. 2. The proton NMR specrum of 4-pyridinecarbaldehyde in deuterium oxide–dimethyl sulfoxide-d_6.

signals vary with the displacement of the equilibrium between the free and hydrate species. The relative intensities of the signals were determined as the average of integrated intensities recorded by the scan of the integrator. The scan was repeated at least three times to obtain a reliable equilibrium constant, the data with larger deviations being omitted. When the proton NMR signals of the ring are relatively simple (as in the spectrum of 4-pyridinecarbaldehyde in Fig. 2), the intensity measurement on these signals gives a more reliable equilibrium constant. The equilibrium constants thus obtained are given in Table 3. The temperature dependence measurements gave the enthalpies and

Table 3. Equilibrium constants at various temperatures for the hydration of aza-aromatic aldehydes in D_2O–DMSO-d_6

2-Pyridinecarbaldehyde (**1**)					
T/K	281	287	298	307.5	316
$K\times10^2$/1 mol^{-1}	1.64	1.32	1.10	0.861	0.673
4-Pyridinecarbaldehyde (**3**)					
T/K	291.5	303	307.5	315	325.5
$K\times10^2$/1 mol^{-1}	5.24	3.65	3.16	2.57	2.08
2-Quinolinecarbaldehyde (**4**)					
T/K	297	303	307.5	316	325.5
$K\times10^2$/1 mol^{-1}	3.33	2.65	2.27	1.71	1.07
4-Quinolinecarbaldehyde (**6**)					
T/K	307.5	316.5	328	338	
$K\times10^2$/1 mol^{-1}	5.10	3.93	3.33	2.14	
1,5-Naphthyridine-4-carbaldehyde (**7**)					
T/K	307.5	316	331	338	
$K\times10^2$/1 mol^{-1}	9.83	6.70	3.96	2.69	
1,8-Naphthyridine-2-carbaldehyde (**8**)					
T/K	307.5	314.5	325.5	335.5	
$K\times10^2$/1 mol^{-1}	8.43	5.00	3.76	2.66	
1,8-Naphthyridine-4-carbaldehyde (**9**)					
T/K	307.5	315.5	325	334.5	347.5
$K\times10^2$/1 mol^{-1}	12.9	9.86	6.25	3.67	3.12

Table 4. Thermodynamic quantities for the hydration of aza-aromatic aldehydes in D_2O–DMSO-d_6

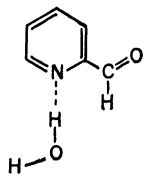
Aldehyde	K(34.5°C)/1 mol^{-1}	ΔH/kJ mol^{-1}	ΔS/mol^{-1} K^{-1}
2-Pyridinecarbaldehyde (**1**)	8.61×10^{-3}	−16.3	−92
3-Pyridinecarbaldehyde (**2**)	3.6×10^{-3} a)	—	—
4-Pyridinecarbaldehyde (**3**)	3.16×10^{-2}	−21.7	−99
2-Quinolinecarbaldehyde (**4**)	2.27×10^{-2}	−26.7	−110
3-Quinolinecarbaldehyde (**5**)	b)	—	—
4-Quinolinecarbaldehyde (**6**)	5.10×10^{-2}	−21.8	−95
1,5-Naphthyridine-4-carbaldehyde (**7**)	8.43×10^{-2}	−32.1	−126
1,8-Naphthyridine-2-carbaldehyde (**8**)	1.29×10^{-1}	−34.8	−130
1,8-Naphthyridine-4-carbaldehyde (**9**)	9.83×10^{-2}	−35.2	−134
4-Nitrobenzaldehyde (**10**)	1.51×10^{-2}	—	—

a) The reaction proceeds slowly taking several days to attain equilibrium.
b) No signals of the hydrate from were observed even after standing for two weeks.

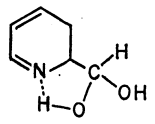
entropies of hydration as shown in Table 4. Since 3-pyridine- and 3-quinoline-carbaldehydes show by far less inclination to form hydrates than the rest of the aza-aromatic aldehydes (Table 3), the hydration would be strikingly favored by the mesomeric effect of the ring nitrogen atoms. The electonegative nitrogen atom in the six-membered heteroaromatic ring attracts the π-electrons on the ring, producing positive charges on ortho- and para-carbon atoms. The charges, in turn induce the positive charges on the carbonyl carbon atoms by displacement of the σ-bonding electrons, facilitating the nucleophilic attack of water and the alcohol molecules.

Bond orders have often been used as reactivity indices for the addition reactions,[13–16] a higher C=O bond order being expected to favor the addition reaction of the water molecule. The PPP[17] bond orders for aldehydes **1**—**9** were calculated and tabulated together with their C=O frequencies (Table 1). Since the stretching force constant of the bond increases with increase in the bond order, the C=O stretching frequency can be a measure for its bond order. Trichloroacetaldehyde, which forms a very stable hydrate, has its C=O absorption band at a remarkably higher frequency (1764 cm^{-1}) than those of simple aliphatic aldehydes. When compared with isomers of the above aza-aromatic aldehydes, the C=O stretching absorption of the "meta"-aldehydes (**2** and **5**) are considerably lower than those of the other aldehydes capable of forming the hydrate to a larger extent. This is in line with the above discussion. The bond order as well as the amount of the positive charge on carbon atom predicts the tendency of covalent hydration.

When the equilibrium constants and other thermodynamic properties are compared, the hydration of the para-isomer is more favorable than that of the ortho-isomer in the three series of the aldehydes, *i.e.* pyridinecarbaldehydes (**1** and **3**), quinolinecarbaldehydes (**4** and **6**), and 1,8-naphthyridinecarbaldehydes (**8** and **9**). The mechanism of this ortho-effect has not been clarified as yet. However, the effect can be interpreted in the following way. The dihydroxymethyl group generated in the course of hydration is bulkier than the formyl group and might cause the desolvation of the water molecule originally hydrogen-bonded to the ring



(III)



(IV)

nitrogen atom ortho to the carbonyl group (at least partially) by the steric hindrance. As a result, an energetically more favorable OH···N intermolecular hydrogen bond in III is replaced by a weaker intramolecular hydrogen bond in IV during the course of hydration. Thus, a somewhat unfavorable effect is expected with the hydration of "ortho"-aldehydes **1**, **4**, and **8**. The hydration of the naphthyridinecarbaldehydes seems a little more favorable than in the cases of other monoaza-aromatic aldehydes.

Table 5. Thermodynamic quantities for the hemiacetal formation of 4-pyridinecarbaldehyde

Alcohol	Solvent	K(34.5 °C) / 1 mol^{-1}	ΔH / kJ mol^{-1}	ΔS / J mol^{-1} K^{-1}
Methanol	DMSO-d_6	5.77×10^{-1}	−27.7	95
	Acetone-d_6	4.72×10^{-1}	—	—
Ethanol	DMSO-d_6	2.85×10^{-1}	−33.3	118
Isopropyl alcohol	DMSO-d_6	8.79×10^{-2}	−25.8	105
t-Butyl alcohol	DMSO-d_6	4.3×10^{-3}	—	—
Methanol with aldehyde **10**	DMSO-d_6	2.35×10^{-1}	−33.1	−119

In order to compare the hydration reactions with hemiacetal formation of these aldehydes, similar measurements were carried out on the ternary system of the aldehyde–alcohol–solvent (mostly dimethyl sulfoxide-d_6). The results are given in Table 5. In general, hemiacetal formation is more predominant than hydration, due probably to the stronger nucleophilicity of alcohols. However, the equilibria tend to be less favorable as the alkyl groups of the alcohols become bulkier,[4,5] and the acetal formation is remarkably hindered in *t*-butyl alcohol. The equilibrium constant for the hydration

is comparable with that of ethyl or isopropyl alcohol.

The experiments on *p*-nitrobenzaldehyde (**10**) reveal the fact that hemiacetalization is again more favorable than hydration in benzaldehydes carrying electron-withdrawing substituents, and the hydration of benzaldehydes without electron-attracting groups is practically negligible even in aqueous solutions. The hydration of **10** is considerably less favorable than those of 4-pyridinecarbaldehyde (**3**) and its analogs but more favorable than those of 3-pyridine- and 3-quinoline-carbaldehydes. This indicates that the electron-withdrawing power of intra-ring nitrogen atom is more predominant than that of nitro group attached to the aromatic ring. The hydration reactions are sensitive to the nature of the solvents, and the hydrogen accepting power of the solvent in hydrogen bond formation seems to favor the reaction remarkably.[12)]

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