The Amino-Imino Tautomerization of 2,6-Diaminopyridine by Interaction with Ethanol

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The UV absorption spectrum of 2,6-diaminopyridine was measured in an ethanol-and-isooctane mixed solvent while increasing the concentration of ethanol at room temperature and changing the temperature from 20 to −100 °C at a constant concentration of ethanol. Its spectrum showed a clear shoulder band near 345 nm as the concentration of ethanol increased to over 5×10^{-1} mol dm^{-3} at room temperature and as the temperature decreased from 20 to −100 °C in 1×10^{-1} mol dm^{-3} of ethanol in the isooctane solution. The corresponding band near 345 nm was observed for 2-amino-6-methylaminopyridine and 2,6-bis(methylamino)pyridine; however, it was not found for 2-amino-6-dimethylaminopyridine, 2-methylamino-6-dimethylaminopyridine, or 2,6-bis(dimethylamino)pyridine in the same experiments. The shoulder band near 345 nm was, on the basis of the spectroscopic results and the molecular orbital method, assigned to the π–π^* absorption band of the (*E*)-6-amino-2(1*H*)-pyridinimine formed through the hydrogen-bond formation of 2,6-diaminopyridine with two ethanols. The formation of the imino form with two ethanols may be restricted to the 2,6-diaminopyridine and its methyl derivatives, in which each amino group at the 2- and 6-positions has at least one hydrogen atom. The proton transfer from ethanol to 2,6-diaminopyridine in the 2,6-diaminopyridine–ethanol complex may be energetically difficult in the ground state.

A number of studies of the keto–enol tautomerization of 2-pyridinol and its related compounds have been done,[1–6] but the number of such studies of the amino–imino tautomerization of 2-aminopyridine and its related compounds seem few in comparison. In a previous paper, judging from the UV-absorption and fluorescence-spectral data concerning the 2,6-diaminopyridine–ethanol system in isooctane (2,2,4-trimethylpentane), it has been found that the formation of 6-amino-2(1*H*)-pyridinimine (tautomer) and 2,6-diaminopyridinium (monocation) occurs in the lowest π, π^* excited singlet state by means of an interaction with ethanol.[7] No absorption band in the region expected for the tautomer by the MO calculation was observed at ethanol concentrations below 1×10^{-1} mol dm^{-3}.[7]

However, on the addition of ethanol to 2,6-diaminopyridine in isooctane, a new, weak and clear shoulder band appears near 345 nm at the tail of the main band of 2,6-diaminopyridine, and its intensity is enhanced as the concentration of ethanol increases to over 5×10^{-1} mol dm^{-3} or as the temperature decreased from 20 to −100 °C, even if the concentration is below 1×10^{-1} mol dm^{-3}. A similar absorption spectrum was observed in an EPA (ether:2-methylpentane:ethanol=5:5:2) solution as the temperature decreased.

In this paper, in order to ascertain the shoulder band near 345 nm of the 2,6-diaminopyridine–ethanol system, the UV absorption spectra of 2,6-diaminopyridine and methyl-substituted 2,6-diaminopyridine derivatives were measured at a constant concentration of ethanol and at various temperatures. On the other hand, the molecular-orbital calculation for the 2,6-diaminopyridine–methanol model was carried out in order to interpret the shoulder band near 345 nm.

Experimental

Materials. The purification of 2,6-diaminopyridine, ethanol, and isooctane were described in a previous paper.[7] 2-Amino-6-methylaminopyridine, 2-amino-6-dimethylaminopyridine, and 2-dimethylamino-6-methylaminopyridine were prepared by the method of Bernstein et al.,[8] and 2,6-bis(methylamino)pyridine and 2,6-bis(dimethylamino)pyridine, by the method of Hammond.[9] The purification of these methyl-substituted 2,6-diaminopyridines was performed by repeated silica-gel column chromatography, using ether as the eluent. The ^{1}H NMR spectra of these compounds were taken on a JEOL FX90Q spectrometer (90 MHz), using $CDCl_3$ as the solvent and TMS as the internal standard. The methyl-substituted 2,6-diaminopyridines have the following ^{1}H NMR spectroscopic properties:

2-Amino-6-methylaminopyridine: δ=2.83 (3H, d, J=5 Hz, CH_3), 4.30 (3H, m, NH_2 and NH), 5.74 (1H, d, J=8 Hz, ring), 5.83 (1H, d, J=8 Hz, ring), 7.24 (1H, t, J=8 Hz, ring).

2,6-Bis(methylamino)pyridine: δ=2.84 (6H, d, J=5 Hz, $2CH_3$), 4.30 (2H, m, 2NH), 5.72 (2H, d, J=8 Hz, ring), 7.28 (1H, t, J=8 Hz, ring).

2-Amino-6-dimethylaminopyridine: δ=2.92 (6H, s, $2CH_3$), 4.12 (2H, m, NH_2), 5.69 (1H, d, J=8 Hz, ring), 5.83 (1H, d, J=8 Hz, ring), 7.15 (1H, t, J=8 Hz, ring).

2-Methylamino-6-dimethylaminopyridine: δ=2.74 (3H, d, J=5 Hz, CH_3), 2.94 (6H, s, $2CH_3$), 4.42 (1H, m, NH), 5.60 (1H, d, J=8 Hz, ring), 5.76 (1H, d, J=8 Hz, ring), 7.19 (1H, t, J=8 Hz, ring).

2,6-Bis(dimethylamino)pyridine: δ=2.96 (12H, s, $4CH_3$), 5.70 (2H, d, J=8 Hz, ring), 7.21 (1H, t, J=8 Hz, ring).

UV-Absorption Measurement. The apparatus of the UV-absorption measurement used has been described elsewhere.[7] The absorption measurement for variable temperatures was carried out on samples in 10-mm square quartz cells placed in a metallic Dewar vessel with two quartz windows.

Methods of Calculation and Molecular Models

The molecular models of 2,6-diaminopyridine, (*E*)- and (*Z*)-6-amino-2(1*H*)-pyridinimine, and 2,6-diaminopyridinium, which had been obtained by the MINDO/3 method with full geometry optimization[10] as in the previous paper,[7] were used. The methanol model was

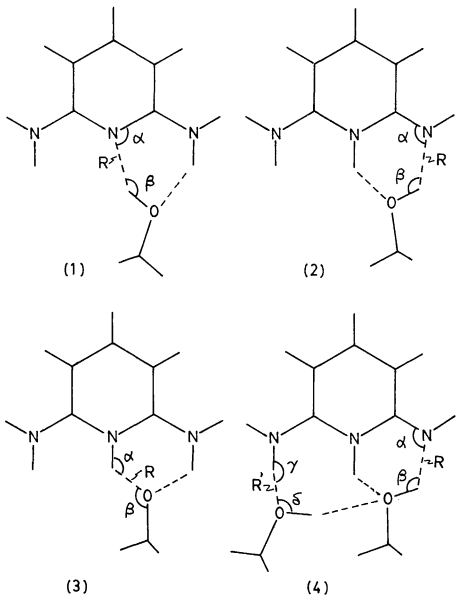


Fig. 1. The model **1** corresponds to the 2,6-diaminopyridine–ethanol complex, the model **2** to the (*E*)-6-amino-2(1*H*)-pyridinimine–ethanol 1:1 complex, the model **3** to the 2,6-diaminopyridinium–methoxide anion complex, and the model **4** to the (*E*)-6-amino-2(1*H*)-pyridinimine–ethanol 1:2 complex, respectively.

used for the ethanol model in the present calculation. The experimental values were used for the models of methanol.[11] The model of the methoxide anion was obtained by the MINDO/3 method, with full geometry optimization, as the following values:[10]

C–H: 1.167 Å; C–O: 1.260 Å; H–C–O: 119.0°.

Figure 1 shows the four kinds of complex models used for the calculation. The **1** model corresponds to the 2,6-diaminopyridine–ethanol complex; the **2** model, to the (*E*)-6-amino-2(1*H*)-pyridinimine–ethanol 1:1 complex (tautomer model-A), the **3** model, to the 2,6-diaminopyridinium–methoxide anion (proton transferred model), and the **4** model, to the (*E*)-6-amino-2(1*H*)-pyridinimine–ethanol 1:2 complex (tautomer model-B). The present complex models were assumed to be planar. The geometry of each complex model was optimized with respect to the parameters of the distance and the angle, as is shown in Fig. 1. The total energies ($-E_T$), of the complex models were calculated under the assumption that the composite parts of the complex are invariant on complex formation. The total energies were obtained by changing the distance and angles until the $-E_T$ value reached a maximum, as calculated by the use of the ab initio STO-3G method.[12]

Results and Discussion

Experimentally, the addition of a small amount of ethanol to 2,6-diaminopyridine in isooctane perturbs

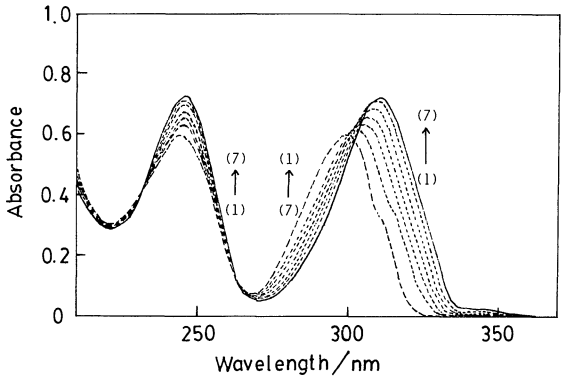


Fig. 2. The UV absorption spectra of 2,6-diaminopyridine in isooctane-ethanol mixed solvent at 20 °C. Concentration of 2,6-diaminopyridine: 8×10^{-5} mol dm^{-3}, concentration of ethanol (mol dm^{-3}): (1) 0, (2) 0.01, (3) 0.05, (4) 0.07, (5) 0.1, (6) 0.5, (7) 2.0.

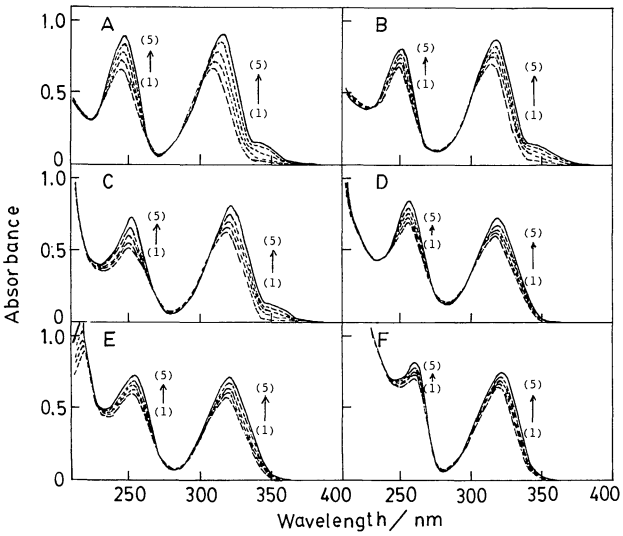
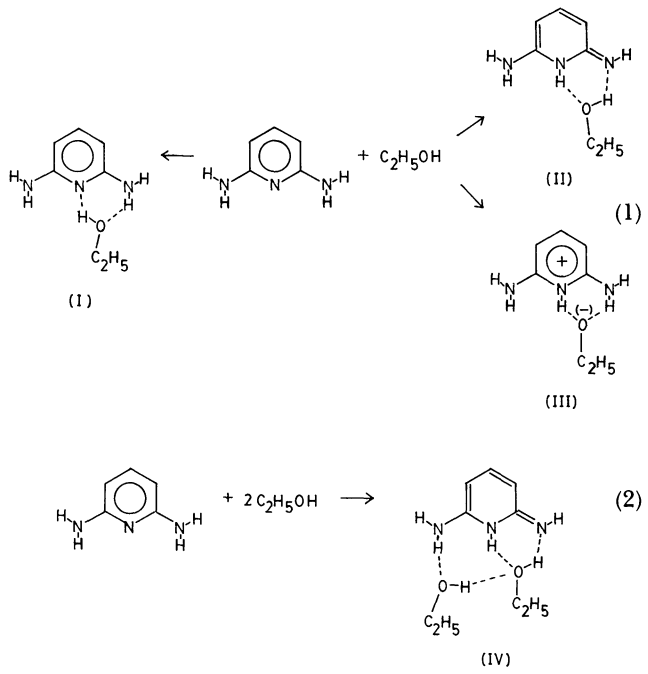


Fig. 3. The temperature effect on the UV absorption spectra of methyl-substituted 2,6-diaminopyridines (8×10^{-5} mol dm^{-3}) in isooctane–ethanol (1×10^{-1} mol dm^{-3}) mixed solvent: (1) 20 °C, (2) −10 °C, (3) −40 °C, (4) −70 °C, (5) −100 °C. A; 2,6-diaminopyridine/EtOH, B; 2-amino-6-methylaminopyridine/EtOH, C; 2,6-bis(methylamino)pyridine/EtOH, D; 2-amino-6-dimethylaminopyridine/EtOH, E; 2-methylamino-6-dimethylaminopyridine/EtOH, F; 2,6-bis(dimethylamino)pyridine/EtOH.

the absorption spectrum, as is shown in Fig. 2. The large band-shift to the longer wavelength and the enhancement of the band intensity were attributed to the formation of a hydrogen-bonded 1:1 complex, as is shown by the **1** model of Fig. 1.[7] At concentrations of ethanol larger than 5×10^{-1} mol dm^{-3} a new shoulder band appears near 345 nm, as is shown in Fig. 2. The UV absorption spectra of 2,6-diaminopyridine and its methyl-substituted derivatives at a constant concentration of ethanol but under various temperatures are shown in Fig. 3. The UV spectrum of 2,6-diamino-

pyridine showed a clear shoulder band near 345 nm with a decrease in the temperature. In Fig. 3, the corresponding band near 345 nm was observed for 2-amino-6-methylaminopyridine and 2,6-bis(methylamino)pyridine; however, it was not found for 2-amino-6-dimethylaminopyridine, 2-methylamino-6-dimethylaminopyridine, and 2,6-bis(dimethylamino)pyridine. The reason why the shoulder band near 345 nm was not observed for the latter three methyl-substituted compounds may be attributed to the steric hindrance of the methyl group. These experimental results suggest that the appearance of a shoulder band may be connected with the NH_2 groups at the 2- and 6-positions and that the amino groups have at least one hydrogen atom each. In Table 1 the total energies and the dipole moments of the 2,6-diaminopyridine and its related molecules, as calculated by the ab initio STO-3G method,[12] are given. The present calculation shows that 2,6-diaminopyridine is more stable than (*E*)- and (*Z*)-6-amino-2(1*H*)-pyridinimine by 86.6 and 107.9 kJ mol^{-1} respectively in the ground state. It is interesting that (*E*)-6-amino-2(1*H*)-pyridinimine is more stable than (*Z*)-6-amino-2(1*H*)-pyridinimine, while in the MINDO/3 calculation the latter was more stable than the former.[7] The energy differences between the amino and imino forms are larger in the ab initio STO-3G method than in the MINDO/3 method.[7] The results calculated by the two methods show that 2,6-diaminopyridine prefers the amino form to the imino form in the ground state.

2,6-Diaminopyridine in the ethanol–isooctane mixed solvent may be expected to form the following four complexes:



In the present calculation, Complexes **I**, **II**, **III**, and **IV** correspond to the **1**, **2**, **3**, and **4** models respectively. The total energies, $-E_T$, and the equilibrium distances and bond angles of four complex models were obtained, after the optimization of the distance and angles, by means of the ab initio STO-3G method. The calculated results are shown in Table 2. The total energy of each of the complex models was compared with the energy of the initial state—that is, the sum of the total energies of 2,6-diaminopyridine and ethanol. In Table 2 the **1** model is shown to be the most stable among the four models. The ΔE_T of the **1** model

Table 1. Total Energies ($-E_T$), Energy Differences (ΔE_T), and Dipole Moments (μ) of the Optimized MINDO/3 Models of 2,6-Diaminopyridine and Its Related Molecules as Calculated by the Ab Initio STO-3G Method

Molecules	$-E_T$/a.u.	ΔE_T/kJ mol^{-1}	μ/D
2,6-Diaminopyridine	352.26267	0	0.381
(*E*)-6-Amino-2(1*H*)-pyridinimine	352.22954	86.6	3.575
(*Z*)-6-Amino-2(1*H*)-pyridinimine	352.22156	107.9	5.481
2,6-Diaminopyridinium	352.74097	−1255	
Methanol	113.54577		1.493
Methoxide anion	112.69712		

Table 2. Total Energies ($-E_T$), Equilibrium Distances and Angles of 2,6-Diaminopyridine–Ethanol Complexes, Energy Differences (ΔE_T) between the Complex and Initial State, and Dipole Moments (μ) as Calculated by the Ab Initio STO-3G Method

Complex	$-E_T$/a.u.	ΔE_T/kJ mol^{-1}	R/Å	R'/Å	α/deg	β/deg	γ/deg	δ/deg	μ/D
Model **1**	465.82038	−31.3	1.845		106.6	157.6			1.558
Model **2**	465.79430	37.1	1.850		115.0	138.0			2.336
Model **3**	465.68509	323	1.385		142.5	142.5			7.417
Model **4**	579.35807	−10.1	1.834	1.642	115.0	150.0	170.0	113.0	3.031

corresponds to the hydrogen bond energy of the 2,6-diaminopyridine–ethanol system. The calculated value of 31.3 kJ mol^{-1} is in good agreement with the experimental value of 32.3 kJ mol^{-1} for the 2,6-diaminopyridine–ethanol system.[7] However, it is noteworthy that the **2** model is more unstable than the initial state, while the **4** model is more stable than the initial state, although the stabilization energy of the **4** model is smaller than that of the **1** model. The **4** model may be reasonable as a tautomer model, judging from the spectroscopic results. The **4** model suggests that: (i) the indirect formation of a tautomer may be possible energetically in the ground state through the complex formation with two ethanols, and (ii) the formation of a tautomer with ethanol may be restricted to the 2,6-diaminopyridine and its methyl derivatives, in which each amino group at the 2- and 6-positions has at least one hydrogen atom. Such a weak shoulder band was not observed on the addition of large amounts of ethanol to a dilute solution of 2-aminopyridine in isooctane.[13] The observed UV absorption spectra for the methyl-substituted 2,6-diaminopyridines support the **4** model. In the **4** model the hydrogen bond between the O atom of the first ethanol and the H atom of the hydroxyl group of the second ethanol plays an important role in the stabilization of the tautomer-B. However, judging from the value of ΔE_T (323 kJ mol^{-1}) of the **3** model the proton transfer from ethanol to 2,6-diaminopyridine may be difficult in the ground state.

The charge densities of the **1** and **4** models are shown in Fig. 4. 2,6-Diaminopyridine and methanol have dual characters, such as a proton donor and a proton acceptor, in the present models. In the **1** model, the electron-charge transfer occurs from 2,6-diaminopyridine to methanol by 0.033 electron units, while there is no electron-transfer in the π-electron system. However, in the **4** model the electron-transfer occurs from the second methanol hydrogen-bonded with the NH_2 group to 2,6-diaminopyridine and from the first methanol by 0.025 and 0.019 electron units respectively, while there is no electron-transfer in the π-electron system. In both models, charge-transfer occurs in the σ-electron system through the hydrogen bonds. As the amount of charge-transfer is connected with the magnitude of stabilization in the hydrogen-bond energy, the stabilization of the **4** model may be larger in energy than that of the **1** model.

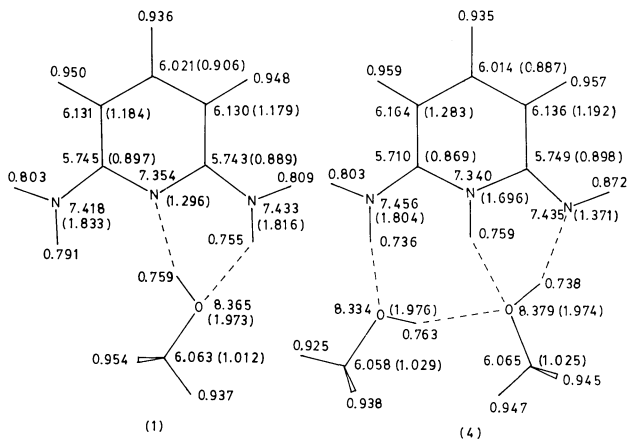


Fig. 4. The charge densities of the models **1** and **4** in the 2,6-diaminopyridine–ethanol system calculated by the ab initio STO-3G method. The values of π-charge density are shown in parentheses.

The absorption band maximum of the 2,6-diaminopyridine in a highly acidic aqueous solution appears at 330 nm, while that of the 2,6-diaminopyridine–trichloroacetate salt appears at 332 nm. They were attributed to the first π–π* absorption band of 2,6-diaminopyridinium.[7] The first π–π* absorption band of 2,6-diaminopyridinium appears at a shorter wavelength than the present shoulder band. In Figs. 2 and 3, if it is assumed that the shoulder band is to be assigned to (*E*)-6-amino-2(1*H*)-pyridinimine, and if its band maximum is at 345 nm, the energy difference between the band maxima of 2,6-diaminopyridine and (*E*)-6-amino-2(1*H*)-pyridinimine at 300 and 345 nm is about 4300 cm^{-1}. On the other hand, the corresponding value calculated by the CNDO/CI method is 4600 cm^{-1}.[7] The calculated value is in good agreement with the observed value. The absorption bands of 1-methyl-2-pyridone imine as the tautomer model of 2-aminopyridine were observed at 362 and 255 nm in cyclohexane by Mason.[14] The value of 362 nm is close to the present observed value of 345 nm, although the two models are different from each other. Therefore, the present assignment seems reasonable judging from the calculated and spectroscopic results. It is interesting that the fluorescence spectrum resulting from excitation at 340 nm for the shoulder band near 345 nm was observed at 389 nm. No fluorescence spectrum which corresponds to 6-amino-2(1*H*)-pyridinimine was observed near 410 nm.[7] These experimental results suggest that the (*E*)-6-amino-2(1*H*)-pyridinimine–ethanol complex is converted rapidly into the cation complex, as is shown in the **3** model in the lowest excited π, π* singlet state.

Finally, in this paper the shoulder band near 345 nm was interpreted by a 1:2 tautomer model such as the **4** model, but a 1:1 tautomer model like the **2** model can not be neglected if the present calculated results are not correct because of the inaccuracy of the ab initio STO-3G method.

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References

1) P. Beak, F. S. Fry, Jr., J. Lee, and F. Steele, *J. Am. Chem. Soc.*, **98**, 171 (1976).
2) P. Beak, *Acc. Chem. Res.*, **10**, 186 (1977).
3) P. Beak, J. B. Convington, and J. M. White, *J. Org. Chem.*, **45**, 1347 (1980).
4) M. J. Scanlan, L. H. Hillier, and R. H. Davies, *J. Chem. Soc., Chem. Commun.*, **1982**, 685.
5) H. B. Schlegel, P. Gund, and E. M. Fluder, *J. Am. Chem. Soc.*, **104**, 5347 (1982).
6) M. Kuzuya, A. Noguchi, and T. Okuda, *Bull. Chem. Soc. Jpn.*, **57**, 3454 (1984).
7) A. Fujimoto and K. Inuzuka, *Spectrochim. Acta, Part A*, **44**, 1035 (1988).
8) J. Bernstein, B. Stearns, E. Shaw, and W. A. Lott, *J. Am. Chem. Soc.*, **69**, 1151 (1947).
9) P. R. Hammond, U. S. Patent 589489 (1975); *Chem. Abstr.*, **84**, 137228j (1976).
10) R. C. Bingham, M. J. S. Dewar, and H. Lo, *J. Am. Chem. Soc.*, **97**, 1285 (1975).
11) K. Kimura and M. Kubo, *J. Chem. Phys.*, **30**, 151 (1959).
12) W. J. Hehre, W. A. Lathan, R. Ditchfield, M. D. Newton, and J. A. Pople, GAUSSIAN70, QCPE#236, University of Indiana, Bloomington, Indiana 47401, U.S.A.
13) K. Inuzuka and A. Fujimoto, *Spectrochim. Acta, Part A*, **42**, 929 (1986).
14) S. F. Mason, *J. Chem. Soc.*, **1960**, 219.