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Hydrogen Bond of 4-Amino-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one Derivatives with Alcohols. II. Theoretical Considerations

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In a previous paper the experimental considerations on the hydrogen bonding between benzopyranopyridine derivatives including related compounds (pyridine, coumarin, and aniline) and alcohols were made, and the thermodynamic constants for the formation of the hydrogen-bonded complexes were obtained from UV spectroscopic studies. In this paper the molecular orbital calculation by the CNDO/2 method was conducted to further clarify the experimental results. Several conclusions were drawn from the present calculation: (1) Benzopyranopyridine has an intramolecular hydrogen bond between its amino and carbonyl groups. (2) The hydrogen bond energy of 2-alkyl benzopyranopyridines with alcohol is larger than that of the 1-alkyl compounds. (3) Benzopyranopyridine has four positions for hydrogen bond formation with alcohol, that is, the ring nitrogen atom, the carbonyl group, the ring oxygen atom, and the amino group. The ring nitrogen atom gave rise to the largest hydrogen bond energy among the four positions. Therefore, the corresponding hydrogen-bonded complex plays an important role in the benzopyranopyridine–alcohol system. (4) The hydrogen bond energy depended on the charge density of the atom which gave rise to the hydrogen bond with alcohol. Especially, substitution of the electron donating group such as amino and methyl groups at the position which increases the charge density of the atom giving rise to a hydrogen bond with alcohol increases the hydrogen bond energy.

Recently, the CNDO/2 method developed by Pople *et al.*[1] has been applied to elucidate the enthalpy and equilibrium distance of hydrogen bond formation. These studies[2–6] look successful and are encouraging. In a previous paper[7] the hydrogen bond between 4-amino-5*H*-[1]benzopyrano[3,4-*c*]pyridin-5-one (abbreviated to benzopyranopyridine) derivatives including related compounds (pyridine, coumarin, and aniline) and alcohols (methanol and ethanol) was discussed experimentally using the IR and UV spectral data.

In this paper the molecular orbital calculation by the CNDO/2 method was carried out to further clarify the experimental results and to compare the calculated results with the experimental ones.

Methods of Calculation and Molecular Models

The CNDO/2 method developed by Pople *et al.*[1] was used. The method has been described in detail in the literature.[1]

The molecule of benzopyranopyridine was assumed to be planar and the model substituted by a methyl group is shown in Fig. 1. The bond distance and bond angle of the molecular model used for the present calculation is as follows:

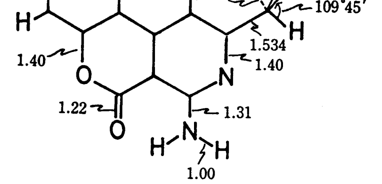


Fig. 1. A molecular model of methyl-substituted 4-amino-5*H*-[1]benzopyrano-[3,4-*c*]pyridin-5-one used for the present calculation.

Water:[8] O–H 0.9572 Å, ∠HOH 104.52°

Results and Discussion

Electronic Properties of Benzopyranopyridine Derivatives in the Ground State. The CNDO/2 method was applied to compounds **1** and **4** which correspond to the 1- and 2-methyl benzopyranopyridines and compound **7** which corresponds to the unsubstituted benzopyranopyridine in order to elucidate the total energies, dipole moments, π-bond orders of carbonyl groups, total charge densities, and π-charge densities. The calculated results are shown in Table 1 and Fig. 2. Methyl-substitution makes compound **4** more stable than compound **1** by 34 kcal/mol. The π-bond order of the carbonyl group of compound **1** is a little larger than that of compound **4**, but it is almost equal to that of compound **7**. These results suggest that the carbonyl stretching frequency of compound **1** may be a little higher than that of compound **4**, but it may be equal to that of compound **7**. The observed carbonyl stretching vibration of compound **1** appears at 1708 cm^{-1} in CCl_4 solution, but the corresponding one of compound **4** at 1706 cm^{-1}. The IR spectrum of compound **7**, however, is unavailable for comparison because the synthesis has not been successful. There is no difference in the carbonyl stretching

TABLE 1. TOTAL ENERGIES, DIPOLE MOMENTS AND π-BOND ORDERS OF CARBONYL GROUP OF 4-AMINO-1-METHYL-5*H*-[1]BENZOPYRANO[3,4-*c*]PYRIDIN-5-ONE (**1**), 4-AMINO-2-METHYL-5*H*-[1]BENZOPYRANO[3,4-*c*]PYRIDIN-5-ONE (**4**), AND 4-AMINO-5*H*-[1]BENZOPYRANO[3,4-*c*]PYRIDIN-5-ONE (**7**)

Compound	Total energy (a. u.) E_T	Dipole moment (D) μ	π-Bond order $P_{C=O}$
1	−160.1193	3.643	0.822
4	−160.1734	3.995	0.819
7	−151.4720	3.735	0.821

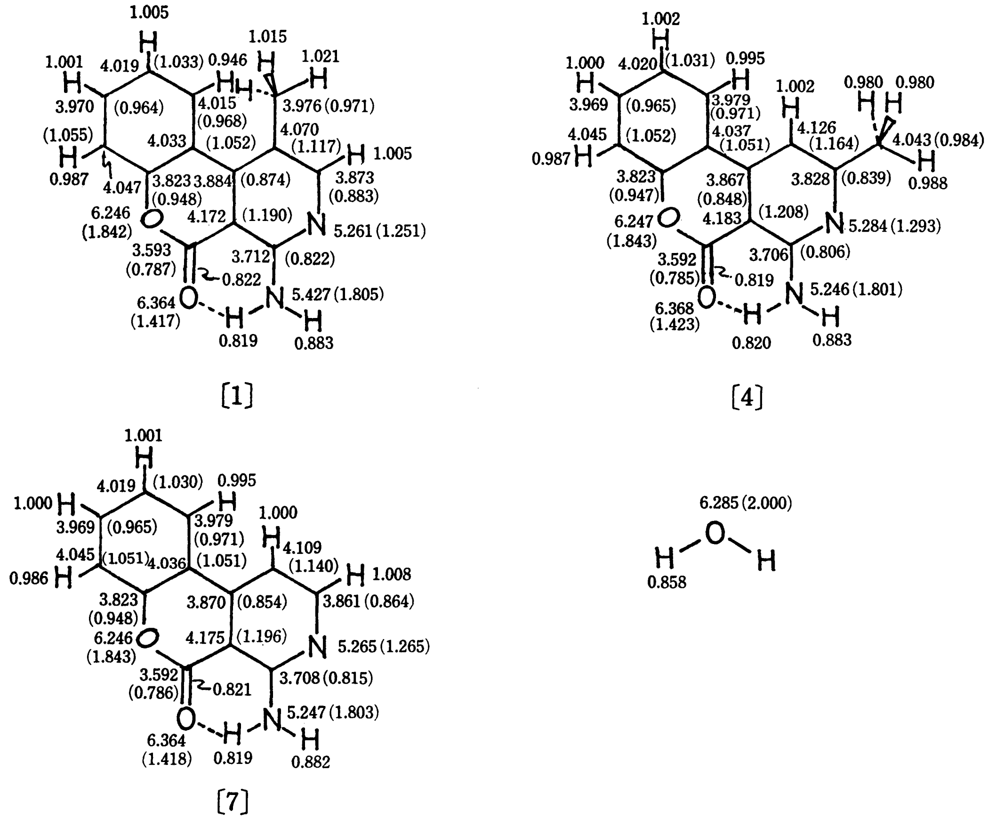


Fig. 2. Total charge densities and π-charge densities of **1**, **4**, **7**, and water.

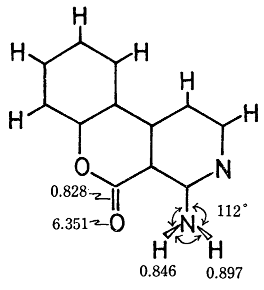
frequency of compounds **2**, **3**, **5**, and **6**[7] which have an alkyl group longer than the methyl group.

The calculated dipole moment of **1** is smaller than that of **4** but it is approximately equal to that of compound **7**. In Fig. 2 the effect of methyl substitution on the charge density of **7** is mainly limited to that of the pyridine ring. It is significant that the 2-methyl-substitution increases the charge density of the ring nitrogen atom while the 1-methyl-substitution decreases the charge density compared with that of **7**.

Intramolecular Hydrogen Bond. (i) The charge density on the two hydrogen atoms of the amino group of compounds **1**, **4**, and **7** are 0.882—0.883 and 0.819—0.820, respectively. The former values correspond to the charge density of the hydrogen atom adjacent to the ring nitrogen atom and the latter values to the hydrogen atom of the opposite side (Fig. 2). The charge densities of the hydrogen atoms of the amino group of 2-aminopyridine are 0.883 and 0.882, the former value corresponding to the values 0.882—0.883 of compounds **1**, **4**, and **7**, and the latter values to the values 0.819—0.820. The charge densities of the hydrogen atom near the ring nitrogen atom is almost equal in the four compounds, even if they are different in molecular structure. However, the charge density of the hydrogen atom of the opposite side is different in 2-aminopyridine and benzopyranopyridine derivatives. The large decrease in charge density from 0.882—0.883 to 0.819—0.820 may be attributed to the intramolecular hydrogen bonding between the carbonyl and amino groups, because the charge density of the hydrogen atom concerned with hydrogen bond formation decreases to a large extent due to the charge migration.

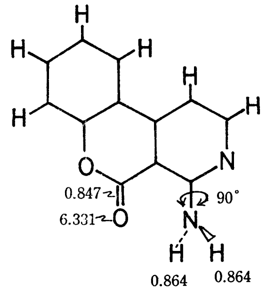
(ii) The carbonyl stretching vibration of the six benzopyranopyridine derivatives in a previous paper[7] appeared in the range of 1706 to 1711 cm^{-1}. The corresponding one of coumarin, which is split into two peaks shows a large difference appearing at 1757 and 1742 cm^{-1}. The large decreases in the carbonyl stretching frequencies of benzopyranopyridine derivatives may be largely attributed to intramolecular hydrogen bonding.

(iii) The two models **8** and **9** were used to investigate the effect of intramolecular hydrogen bonding in the charge densities of the oxygen atom of the carbonyl group and the hydrogen atoms of the amino group and on the π-bond order of the carbonyl group. Model **8** has a non-planar amino group with three valence angles of 112° with respect to the nitrogen atom. Model **9** has a planar amino group twisted by 90° about the C–N bond. If an intramolecular hydrogen bond exists between the oxygen atom of the carbonyl group and the hydrogen atom of the amino group, it may be weaker in **8** than in **7** but it may be broken in **9**. The values of the charge densities and π-bond order of the carbonyl group and the charge densities of the hydrogen atoms of the amino group are shown in the models **8** and **9** with the total energies. The model **8** is higher in energy than **7** with a planar amino group by 1.52 kcal/mol. The 2-aminopyridine with a non-planar amino group and three valence angles of 112° is more stable than that with a planar amino group by 4.22



−151.4718a.u..

[8]



−151.4369a.u.

[9]

kcal/mol. The charge density of the oxygen atom of the carbonyl group of **8** decreases more than that of **7**. At the same time the charge density of the hydrogen atom of the amino group of the **8** increases more than that of the **7**. These trends are more conspicuous in **9** than in **8**. Added to this the π-bond order of carbonyl groups increases in the order from **7** to **9**. These results suggest that an intramolecular hydrogen bond exists between the carbonyl and amino groups.

Intermolecular Hydrogen Bond. Benzopyranopyridine has four positions which give rise to the hydrogen bond with alcohol, that is, the ring nitrogen atom, the carbonyl group, the ring oxygen atom, and the amino group. Each of these charge densities of the atom in the four positions shown in Fig. 2 are almost equal to each other except for the ring nitrogen atom among the three compounds. The charge density on the ring nitrogen atom of compound **4** is larger than that of compounds **1** and **7**, but the charge densities of the ring nitrogen of the latter two compounds are approximately equal. From this result it may be expected that the hydrogen bond energy of compound **4** may be larger than that of compounds **1** and **7**, but approximately equal in **1** and **7**, if there is hydrogen bond formation between the ring nitrogen atom and alcohol. However, if hydrogen bonding between the remaining three positions and alcohol occurs, it is expected that there will be no interpretable differences in energy of the corresponding hydrogen bonds among the three compounds.

In order to calculate the four kinds of hydrogen bond energies for the benzopyranopyridine–alcohol system the following models were used as shown in Fig. 3. In order to simplify the present calculation a water molecule was used in place of alcohol, and the unsubstituted benzopyranopyridine used.

Model A: The equilibrium distance between the ring nitrogen atom and the hydrogen atom of water, 1.6 Å of model A corresponds to the value determined for the pyridine–water system. The two molecules lie in the same plane and the O–H bond of water lies along the n-orbital of the ring nitrogen atom.

Model B: The equilibrium distance between the oxygen atom of the carbonyl group and the hydrogen atom of water, 1.6 Å and bond angle between the carbonyl axis and hydroxyl bond, 60° were used for model B refering to the values determined for the *s-trans*-acrylaldehyde–water system. The equilibrium distance 1.6 Å and bond angle 60° correspond to the conformation with the maximum hydrogen bond energy.

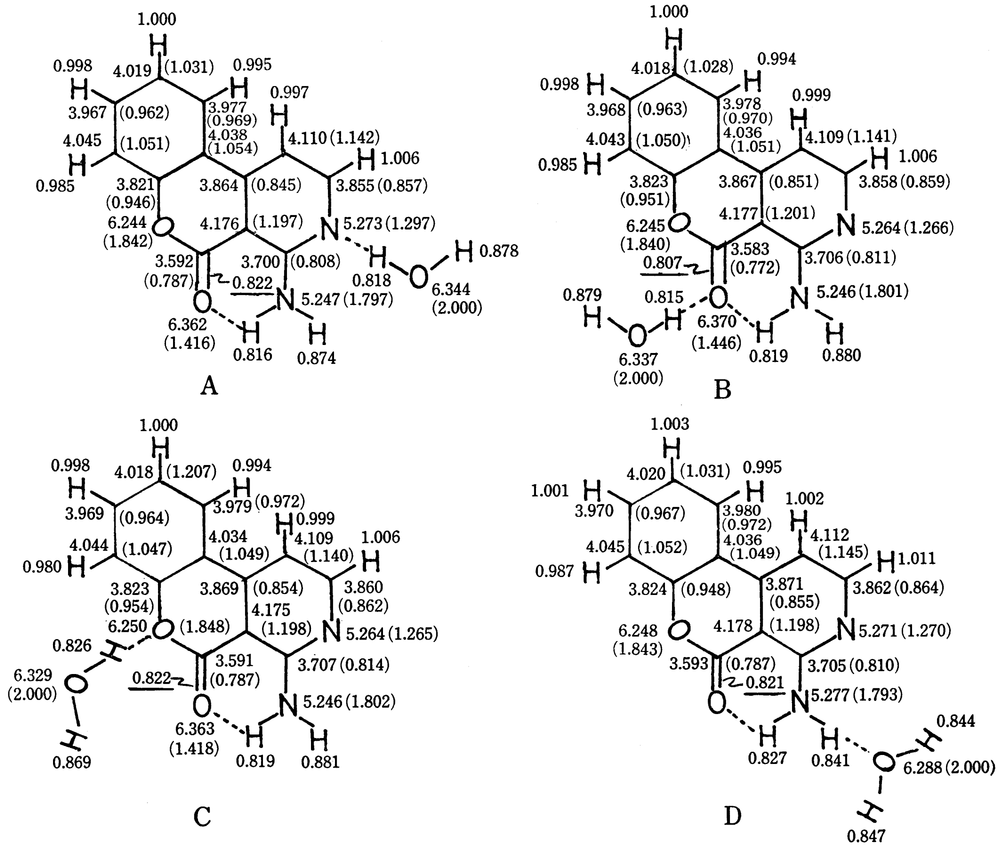


Fig. 3. Hydrogen-bonded complex models between **7** and water.

Model C: The two molecules were assumed to lie in the same plane refering to the calculated results of conformation of the hydrogen-bonded complex for the tetrahydrofuran (THF)–water and THF–methanol systems.[9] The equilibrium distance between the ring oxygen atom and the hydrogen atom of water, 1.6 Å which was determined for the coumarin–water system was used.

Model D: The equilibrium distance between the hydrogen atom of the amino group and the oxygen atom of water, 1.6 Å which was determined for the 2-aminopyridine–water system was used.

TABLE 2. HYDROGEN BOND ENERGIES, DIPOLE MOMENTS AND π-BOND ORDERS OF CARBONYL GROUP OF THE HYDROGEN-BONDED 1 : 1 COMPLEXES FORMED BETWEEN 4-AMINO-5*H*-[1]BENZOPYRANO[3,4-*c*]PYRIDIN-5-ONE AND WATER

Hydrogen-bonded complex	Hydrogen bond energy $-\Delta H$ (kcal/mol)	Hydrogen bond energy $-\Delta H_c$ (kcal/mol)	Dipole moment μ (D)	π-Bond order $P_{C=O}$
A	9.41	4.99	6.291	0.822
B	7.96	4.22	6.432	0.807
C	6.61	3.51	3.828	0.822
D	5.04	2.69	2.883	0.821

The calculated hydrogen bond energy, dipole moment, and π-bond order of the carbonyl group for the four models are listed in Table 2. The calculated hydrogen bond energies are larger than the observed energies in a previous paper.[7] The same methods was applied to the pyridine–methanol system to compare the calculated hydrogen bond energy with the observed value. The calculated value was 8.29 kcal/mol while the observed value was 4.4 kcal/mol.[10] The values $-\Delta H_c$ in Table 2 were corrected by multiplying by the factor 4.4/8.29 to the values $-\Delta H$ on the assumption that the same ratio applies to the present calculated and observed values. The corrected value $-\Delta H_c$ is better than the uncorrected value for a comparison with the observed value.

The calculated hydrogen bond energy of model A is the largest among the four models. The order of hydrogen bond energy from model A to D seems reasonable. The ratio of the models from A to D in equilibrium concentration at 300 K was evaluated by use of the values $-\Delta H_c$ assuming the Boltzmann distribution. The calculated ratio, A : B : C : D became 0.72 : 0.20 : 0.06 : 0.02. These values suggest that the hydrogen bond such as model A is the most important one. The numerical values of the Boltzmann distribution ratio indicate the possibility of model B, however it is not significant. The hydrogen-bonded complexes such as models C and D may be negligible.

The observed average hydrogen bond energy for 1-alkyl benzopyranopyridines was about 4.6 kcal/mol, while that of 2-alkyl ones was about 5.1 kcal/mol. This indicates that the 2-alkyl substituted benzopyranopyridines are larger in hydrogen bond energy than the 1-alkyl compounds. The calculated value 4.99 kcal/mol may correspond to the observed value 4.6 kcal/mol for 1-alkyl benzopyranopyridines as discussed in the previous section. The hydrogen bond energy 3.8 kcal/mol, observed for the coumarin–ethanol system[7] was assigned to the energy of the hydrogen bond formation between the carbonyl group and alcohol from the IR spectrum, since coumarin showed a sharp carbonyl band split into two peaks located at 1757 and 1742 cm^{-1} in CCl_4 solution while a new band appeared at 1728 cm^{-1} by an addition of methanol to coumarin.[7] The observed value 3.8 kcal/mol corresponds well to the calculated value 4.22 kcal/mol for model B.

Experimentally, the presence of the hydrogen bond such as model A was confirmed by IR spectrum but the remaining species, like the models B, C, and D were not clearly determined.[7]

The calculation of π-bond order indicates that the hydrogen bond formation between carbonyl and hydroxyl groups gives rise to large decreases in the π-bond order of the carbonyl group in model B as shown in Table 2. This suggests that a large carbonyl frequency shift due to hydrogen bond formation may be expected. However, experimentally a small frequency shift (1—2 cm^{-1}) was observed in addition of methanol in large amounts. The small shift suggests that the intramolecular hydrogen bond disturbs the hydrogen bond formation. The formation of the hydrogen-bonded complex such as model B may be difficult because model B may correspond to the 1 : 2 complex with respect to the carbonyl group. The entropy change $|-\Delta S|$ for the formation of the 1 : 2 complex may become larger than that for the 1 : 1 complex.

The calculated energy $-\Delta H_c$ for the coumarin–water hydrogen-bonded complex between the ring oxygen atom and hydroxyl group such as model C became 3.44 kcal/mol. If the observed value 3.8 kcal/mol for the coumarin–ethanol system is assigned to the energy value for the formation between the ring oxygen atom and alcohol, it is difficult to explain the large frequency shift in the carbonyl vibration, because the above coumarin-water model makes no change in the π-bond order of the carbonyl group.

The calculated hydrogen bond energy 2.69 kcal/mol for model D shows a good correspondence to the observed value 2.1 kcal/mol for the aniline–alcohol system where it is expected a hydrogen bond is formed between the amino group of aniline and ethanol.[7]

Charge Density Distribution in Hydrogen-Bonded Complex. In model A there are variations of the charge densities in the pyridine ring and water, in which the charge densities of the α- and γ-carbon atoms of the pyridine ring decrease but the charge density of the nitrogen atom increases. The charge density of water increases by 0.039. This increase denotes that the charge migration occurs from the proton acceptor to the donor. Locally, the charge variation occurs such as $\overset{-}{N}\cdots\overset{+}{H}\text{–}\overset{-}{O}$ on the atoms of the hydrogen bridge. In model B the large charge density variation occurs mainly in the carbonyl group and in water. In model B also the charge density increases in water by 0.031 the same as in model A. In model C the charge density increases in water by 0.023 and in model D it decreases by 0.021 and the charge migration occurs from water to benzopyranopyridine. In models A to C the amount of the charge migration is proportional to the hydrogen bond energy, while in model D the direction of the charge migration is reverse to that of the other three models.

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