Chem. Pharm. Bull. 23(6)1256—1260(1975)

UDC 547.831.03 : 547.555.03 : 615.277.4.011.3

An MO Theoretical Study on the Tautomerism of Carcinogenic 4-Hydroxyaminoquinoline 1-Oxide and Related Compounds

Yoshiko Miyaji, Hiroshi Ichikawa, and Michihiko Ogata

Hoshi College of Pharmacy[1]

(Received October 29, 1974)

Tautomerism of hydroxypyridines is investigated by a version of the modified intermediate neglect of differential overlap method to show that the predominance of tautomerism depends on the total energy of tautomer. The calculations are carried out for 4-hydroxyaminopyridine 1-oxide (I) and 4-hydroxyaminoquinoline 1-oxide (II), leading to a conclusion that the predominant tautomer of I is formulated to be the N-oxide form and that of II is the N-hydroxy form. This structural difference is discussed in relation to difference in the biochemical behaviours of these compounds.

There are many interesting cases where the prototropic tautomerism plays an important role in chemical and/or biological behaviours of molecule, especially in the biological systems.[2] In addition to the experimental support to the stability of each prototropic tautomer, the theoretical approach may sometimes be required in order not only to predict the predominant tautomer but also to understand the behaviour of the molecule in terms of electronic structure.

Recently, much attention has been focussed on 4-hydroxyaminopyridine 1-oxide (I) and 4-hydroxyaminoquinoline 1-oxide (II) because of the striking difference between their carcinogenic activities.[3–6]

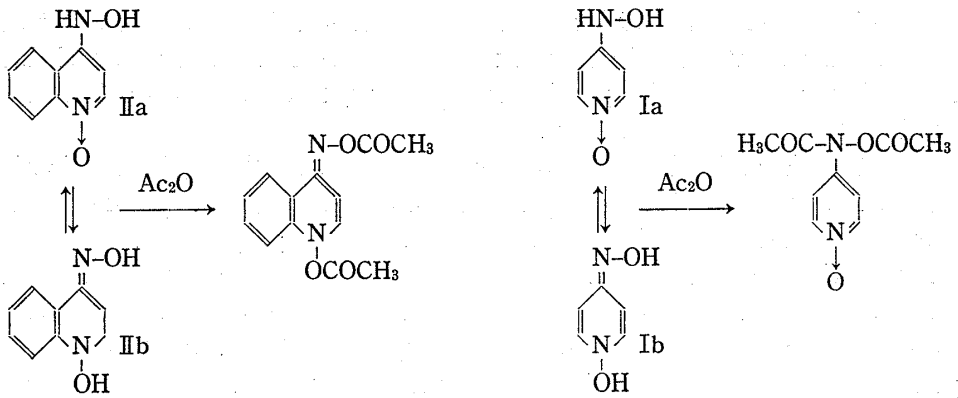


Chart 1

1) Location: *2–4 Ebara, Shinagawa-ku, Tokyo, 142, Japan.*
2) N.K. Kochetkov and E.T. Budovskii, "Organic Chemistry of Nucleic Acids," Plenum Press, London, New York, Part A 1971, pp. 121—182; P.O.P. Ts'O, "Fine Structure of Protein and Nucleic Acids," ed. by G. Fasman and S.N. Timasheff, "Fine Structure of Biological Macromolecules," 4, Marcel Dekker Inc., New York, 1970, p. 49.
3) Y. Kawazoe, M. Araki, and W. Nakahara, *Chem. Pharm. Bull.* (Tokyo), **17**, 544 (1969).
4) Y. Kawazoe and M. Araki, "Chemical Tumor Problems," ed. by W. Nakahara, Japan Society for the Promotion of Science, Tokyo, 1970, p. 45.
5) M. Araki, C. Koga, and Y. Kawazoe, *Gann*, **62**, 325 (1971).
6) Y. Kawazoe, M. Araki, and G.F. Huang, "Topics in Chemical Carcinogenisis," ed. by W. Nakahara, The University of Tokyo Press, 1972, p. 1.

As shown in Chart 1, each of these compounds has the possibility of two tautomeric structures, N-oxide form (Ia and IIa) and N-hydroxy form (Ib and IIb). Although I and II have been synthesized, spectroscopic identification of their structures has been unsuccessful. This paper deals with the semiempirical molecular orbital (MO) calculations on these compounds to determine the stable form and to offer suggestions to their chemical and biological activities.

Method

Paoloni, *et al.*[7] successfully applied the Pariser-Parr-Pople (PPP) method[8] to predict the predominant tautomer of hydroxypyridines. Generally the tautomerization involves structural changes over the whole molecule, *i.e.*, the changes of π-bonds as well as σ-bonds. Since σ-bonds are generally more stable than π-bonds, the energies of σ-electrons must reflect such a skeletal change more strikingly than those of π-electrons. Therefore, the MO methods for all valence electrons should be used in this kind of study.

There are such MO methods as the extended Hückel (EH),[9] complete neglect of differential overlap (CNDO),[10] intermediate neglect of differential overlap (INDO),[11] and modified INDO (MINDO)[12] theories and their minor versions are prevalent. Each theories has its characteristics depending on the way of approximation. The EH method is obviously open to all the criticisms applying to the usual Hückel method and therefore, it may be worthless as a procedure for predicting the structures or chemical behaviour of molecules.[13] It is known that the CNDO and INDO methods reasonably reproduce the electronic structure.[14] However, as far as molecular energy is concerned, these methods are not appropriate; the calculated heats of atomization and ionization potentials being in error by huge amounts[15] and the calculated differences of energy between conformational isomers being unrealistic. The MINDO and especially the MINDO/2 (a version of the MINDO method[16]) methods give appropriate results for estimation of various kind of molecular energies.[16] Therefore, the MINDO/2 method was adopted in the present study.

In the MO theories which neglect three- and four-center integrals, the total energy of a given system can be written as the sum of one- and two-center terms:

$$E = \sum_{A} E_A + \sum_{A>B} E_{AB} \tag{1}$$

These terms can further be expanded in the form:

$$E_A = E_A^U + E_A^J + E_A^K \tag{2}$$

$$E_{AB} = E_{AB}^R + E_{AB}^V + E_{AB}^J + E_{AB}^K + E_{AB}^N \tag{3}$$

This technique of energy-partitioning has been originally proposed by Fischer, *et al.*[17] in the CNDO theory and was recently extended to the MINDO/2 theory by Dewar, *et al.*[18] showing the usefulness for the study of chemical reactions. Analysis of the energetic change on this line may disclose the nature of tautomerization from the fundamental viewpoint since those terms have the following physical implications.

E_A^U is the total one-electron atomic orbital (AO) energy of the electrons on atom A. E_{AB}^V is the potential energy of the electrons on atom A in the field of nucleus B plus that of the electrons on atom B in the field of nucleus A. E_{AB}^R is the contribution of the resonance integrals to the energy of the A–B bond and is the main feature of the covalent bond. E_A^J and E_{AB}^J are the repulsion of the electrons on atom A and that of the electrons on atom A and B, respectively. E_A^K and E_{AB}^K are the corresponding terms of the electronic exchange interactions. The sum of E_A^U and E_{AB}^R over all atoms ($E^U + E^R$) is considered to represent the molecu-

7) L. Paoloni, M.L. Tosato, and M. Cignitti, *Theoret. Chim. Acta (Berl.)*, **14**, 221 (1969).
8) R.G. Parr, "Quantum Theory of Molecular Electronic Structure," Chaps. III and IV, Benjamin Inc., New York, 1963.
9) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963).
10) *a*) J.A. Pople, D.P. Santry, and G.A. Segal, *J. Chem. Phys.*, **43**, s129 (1965); *b*) J.A. Pople and G.A. Segal, *ibid.*, **43**, s136 (1965); *c*) J.A. Pople and G.A. Segal, *ibid.*, **44**, 3289 (1966).
11) J.A. Pople, D.L. Beveridge, and P.A. Dobosh, *J. Chem. Phys.*, **47**, 2026 (1967).
12) N.C. Baird and M.J.S. Dewar, *J. Chem. Phys.*, **50**, 1262 (1969).
13) M.J.S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, 1969, p. 442.
14) J.A. Pople and D.L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, 1970.
15) R.B. Davidson, W.L. Jorgensen, and L.C. Allen, *J. Amer. Chem. Soc.*, **90**, 50 (1968).
16) M.J.S. Dewar and E. Haselbach, *J. Amer. Chem. Soc.*, **91**, 3590 (1969).
17) H. Fischer and H. Kollmar, *Theoret. Chim. Acta (Berl.)*, **13**, 213 (1969).
18) M.J.S. Dewar and D.H. Lo, *J. Amer. Chem. Soc.*, **93**, 7021 (1971).

lar energy based on covalent bond without electrostatic bicentric interaction,[19] and therefore, was used as an index of structural stability.

Results and Discussion

In order to confirm the reliability of the employed MO method, was examined the relationship between the calculated energy and the tautomeric stability in the derivatives of pyridine which have been determined experimentally. 2-Hydroxypyridine (III) and 4-hydroxypyridine (IV) are known to exist predominantly in the pyridone form (IIIa and IVa),[20,21] while 2-aminopyridine (V) as the amino form (Vb).[21,22]

Table I shows the total energies and the values of (E^U+E^R) for III, IV, and V in units of a.u., while Table II shows the differences of energy between geometries in units of kcal/mole. The molecular energy is generally dependent on the molecular geometry; the structures adopted for calculation were shown in Fig. 1, where IIIa was based on X-ray analysis,[23] from which IVa was estimated. IIIb and IVb were set to have the same ring geometry as bare pyridine and the OH groups with the distance of 1.35Å at 2 and 4 positions, respectively. Va was estimated from the crystal structure of 2-pyridone and Vb has the same ring geometry as bare pyridine and the NH_2 group with the distance of 1.46Å at 2 position.[24] The geometries as estimated above are not, of course, optimized. In order to investigate the degrees of error due to the assumed geometries, we also obtained the molecular energies for IIIc, IVc, and Vc, which are, as extreme erroneous cases, set to have the ring geometries of IIIa, IVa, and Va and the substituents with geometries of IIIb, IVb, and Vb respectively.

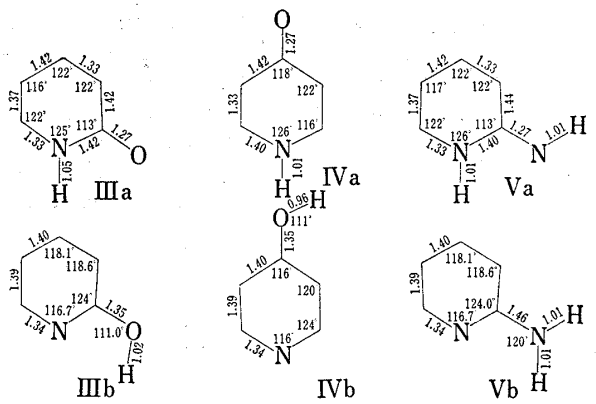


Fig. 1. Molecular Geometries for Derivatives of Pyridine

Bond distances are given in Å and bond angles.

Table I shows that the total energy as well as any partitioned energy were not significantly influenced by the small change of ring geometry. In accordance with experimental results, the total energies of IIIa, IVa, and Vb are all lower than those of IIIb, IVb, and Va, respectively. None of the energetic terms partitioned in Eq. 2 and 3 gives any suggestion about the predominance of tautomers. Although a combination among partitioned energetic terms may give a certain physical implication on the difference of total energy between tautomers, such trials were all unsuccessful.

In Table II the difference, *e.g.*, a—b, appears to be the minus value which indicates that the state a is more stable than the state b.

From the results in Table I and II it may be concluded that the predominance of tautomer consists in the balance of partitioned energies and that only the total energy is regarded as the measure of the predominance of tautomers.

Table III shows the calculated values for I and II. As described above, the influence of small change of ring geometry to the molecular energy being negligible, the ring geometries

19) The detail will be soon reported.
20) S. Albert and J.N. Phillips, *J. Chem. Soc.*, **1956**, 1294.
21) J.N. Gardner and A.R. Katritzky, *J. Chem. Soc.*, **1957**, 4375.
22) S.J. Angyal and C.L. Angyal, *J. Chem. Soc.*, **1952**, 1461.
23) "Tables of Interatomic Distances," ed. by L.E. Sutton, The Chemical Society London, London, 1958, Supplement 1965.
24) G. Favini, A. Gamba, and I.R. Bellobono, *Spectrochim. Acta*, **23A**, 89 (1967).

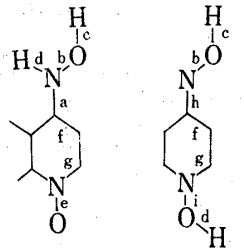
Table I. Total Energies and E^U+E^R Values (in a.u.[a])

Geometry	E_{total}	E^U+E^R	Geometry	E_{total}	E^U+E^R
III a	−45.4761	−72.2393	IV c	−45.4250	−72.3222
b	−45.4732	−72.3734	V a	−42.0516	−66.0524
c	−45.4677	−72.2966	b	−42.0723	−65.9433
IV a	−45.4530	−72.2215	c	−42.0664	−65.9144
b	−45.4368	−72.3289			

a) 1 a.u.=628. 3kcal/mole

Table II. Differences of Energies (in kcal/mole)

Geometry	ΔE (E_{total})	ΔE(E^U+E^R)
III a—b	− 1.9	84.3
b—c	− 3.5	−48.3
IV a—b	−10.2	67.5
b—c	− 7.4	− 4.2
V a—b	13.0	−68.5
b—c	− 3.7	−18.2



a = 1.45 Å
b = 1.37
c = d = 1.00
e = 1.25
f = 1.40
h = 1.32
i = 1.39

∠bc = 119°
∠di = 111°
∠ab, ∠af, ∠eg, ∠bd, ∠bh, ∠fh, ∠gi, = 120°

All atoms are coplanar.
The ring is regular hexagon with C-H (1.09 Å).

Table III. Total Energies for Tautomers of I and II

	E_{total} (in a.u.[a])		ΔE (in kcal/mole)
	a	b	b—a
I	−64.9823	−64.9818	0.3
II	−84.9636	−84.9775	−8.7

a) 1 a.u.=628.3 kcal/mole

of I and II were assumed to be the same as those of benzene and naphthalene, respectively. The bond length and bond angles of substituents were shown under Table I.

As for the derivatives of quinoline (II) the total energy of the N-hydroxy form (IIb) is lower by 8.5 kcal/mole than that of N-oxide form (IIa), while there is no remarkable difference in the total energies between Ia and Ib.

From many aromatic hydroxylamines such phenylhydroxylamine, 4-hydroxyaminoquinoline 1-oxide (II) is distinguished by many points of chemical and biological properties.[4] The results in Table III indicate that II involves bifunctional hydroxyamino groups as stable form, while I is rather close to the normal aromatic hydroxyamino form. It may be speculated that such a difference in the tautomeric structures between quinoline and pyridine may be related to the difference in the reactivity of these compounds toward acylating agent such as acetic anhydride and benzoyl chloride.[4] It has been, hitherto, reported that acylation of I gives N,O-diacyl derivatives while II does O,O′-diacyl derivatives as shown in Chart 1.[4] 4-Hydroxyaminoquinoline 1-oxide binds covalently with deoxyribonucleic acid not only *in vivo* but also *in vitro*, while 4-hydroxyaminopyridine 1-oxide does not at all.[25] In addition, there was found a marked difference in the biological activity between I and II; I is a very weak carcinogen, while II being a potent one.[3]

25) Y. Kawazoe, G.F. Huang, M. Araki, and C. Koga, *Gann*, **63**, 161 (1972).

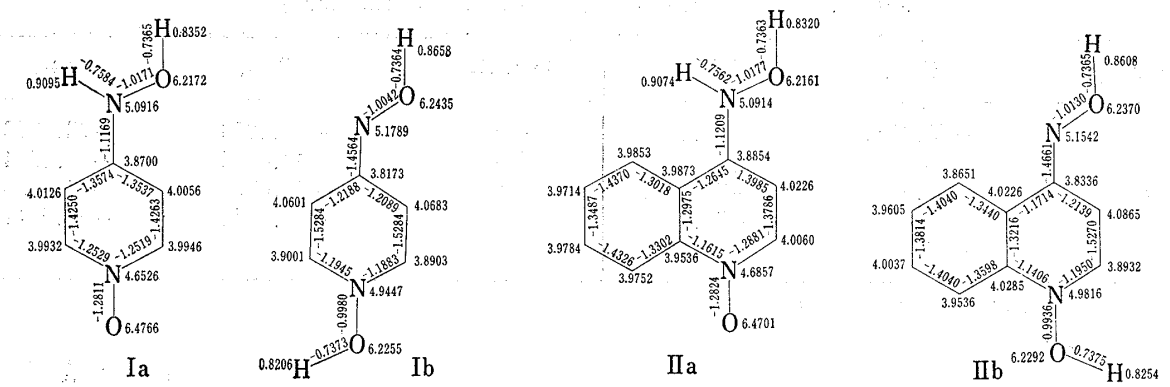


Fig. 2. Electron Densities and Bond Indices of Tautomers of I and II

The molecular diagrams of I and II in Fig. 2 were based on the INDO theory, since this theory has been considered to give an appropriate electronic structure. Figure 2 shows that the electronic structures of Ia and Ib are close to those of IIa and IIb, respectively; the benzene ring of II hardly contributes to the electronic structures of functional groups, indicating that the difference of biological activities is caused not by that of electronic structures of the functional groups but by the difference of tautomerization.

As a conclusion, it is very probable that the mode of chemical and biological actions of these derivatives might be related to the structural difference by tautomerization.

Acknowledgment The authors are greatly indebted to Dr. Yutaka Kawazoe (National Cancer Center Research Institute) for his valuable suggestions and discussion.

The calculations were carried on HITAC 5020E computers at Computation Center of University of Tokyo.