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니코틴의 배치와 형태에 관한 분자궤도론적 연구 (제 1 보)

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MO Studies on Nicotine (I)

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요 약. 니코틴과 그 양성자 부가물의 배치 및 형태를 분자궤도론으로 EHT와 CNDO/2 방법을 써서 연구하였다. 가장 안정한 형태는 피롤리딘 고리가 280° 회전된 꼴임을 알았으며 이것을 콘쥬게이션, 정전기적 및 입체효과로서 설명하였다.

양성자의 부가는 피리딘 고리에 일어나며 일종의 π-착물이 형성됨을 알았다.

ABSTRACT. Configuration and conformation of nicotine and its protonated form have been studied by MO theoretically using EHT and CNDO/2 methods. The form with angle of rotation $\theta = 280°$ of pyrrolidine ring was shown to be most stable and this was interpreted in terms of conjugative, electrostatic and steric effects.

It was predicted that protonation occurs on the nitrogen atom of pyridine ring and forms a π-complex.

1. INTRODUCTION

Investigations on the relationship between the conformational properties and the cholinergic neural transmission effect of nicotine have been a topic interest for many years.[1~3] Our current interest in the field of nicotine structure and its reactivity has prompted us to examine the application of molecular orbital calculation to nicotine and its protonated form.

Recently Seeman and Whidby have reported the results of nuclear overhauser enhancement (NOE) studies for the configurational analysis.[4] According to them *ca.* 90 % of nicotine exists as 1'(R)-*trans* configurtation and there is a slow nitrogen pyramidial inversion of pyrrolidine ring compared with NMR relaxation and the rate of protonation-deprotonation. Unfortunately they assumed that the protonation occurs only on the pyrrolidine ring nitrogen atom. In their further paper,[5] they have shown that the rate of alkylation of nicotine does not

depend on basicity alone, but also on kinetic factors, *e.g.*, steric hindrance and solvation. These are important since the presence of pyri dine ring destabilizes the N'-iodomethylation transition state of nicotine, and additional electronic or stereoelectronic factors can also be important controlling factors.

In this paper we are primarily concerned with protonation of nicotine, which is thought to precede the decomposition reaction of nicotine.

We have used both the EHT and CNDO/2 method of calculations in conjunction with the experimental evidence. Though the EHT method has shortcoming that the energy barriers of rotation about dihedral angle and charge densities are quantitatively exaggerated, it has neve rtheless proved to be useful in determining conformational preference. On the contrary the CNDO/2 method is more reasonable in elucidating the reactivity of nicotine, since this method is more realistic in the results of MO quantities derived from eigenvectors.[6]

2. CALCULATIONS

For the geometry of nicotine molecule the crystallographic values are used except for C–H and N–H internuclear distances. For the nitrogen atom of pyrrolidine ring and of protonated pyridine ring sp^3 hybrid angle was assumed. The calculation of atomic cartesian coordinates was carried out with COORD/1130 program. The coordinate system and numbering scheme are shown in *Fig.* 1.

The computer program for EHT was obtained from QCPE No. 64. The input data used for this program, the orbital exponent, Z, and valence state ionization potential, VSIP, are summarized in *Table* 1. The CNDO/2 program used was "CNINDO" from QCPE.[7].

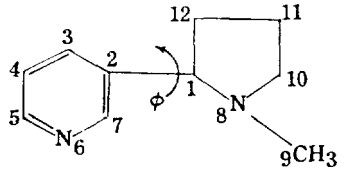


Fig. 1. Numbering scheme of nicotine molecule.

Table 1. The orbital exponents, Z, and –VSIP used.

AO	Z	–VSIP
H 1S	1.00	−13.60
C 2S	1.59	−21.01
2P		−11.27
N 2S	1.92	−26.90
2P		−14.42

3. RESULTS AND DISDUSSIONS

(1) **Conformational analysis.** The total energies calculated by EHT method are plotted against the dihedral angle of rotation of pyrrolidine ring ϕ(C3-C2-C1-N8) in *Fig.* 2 and 3. The zero angle of rotation is taken as the conformation determined by Koo[8] in which the crystal geometry is ϕ(C3-C2-C1-N8) = −60°, ϕ(C4-C3-C2-C1) = 180°, ϕ(C12-C1-N8-C10) = 17°, and ϕ(N8-C10-C11-C12) = 14°. The latter two angles are constrained because of some deviation of pyrrolidine ring from planarity.[9]

Though total energies appear to be exaggerated, two energy minima are found, differing in energy by about 0.25 kcal. The high energy barrier of rotation as shown in *Fig.* 2 and 3 may be due to three causes; the first is due to the inherent shortcoming of EHT method which neglects electron repulsion integrals, the second is due to high energy barrier of rotation about sp^2–sp^3 carbon-carbon bond[10], and finally it could be due to the use of the crystallographic input data which can result in high energy torsion of crystal bonding.

Our minima corresponding to ϕ(C3-C2-C1-N8) = 100°, 280° for *trans*-nicotine and ϕ =

120°, 300° for *cis*-nicotine are the two preferred conformations. Depending on the mode of attachment of N-methyl group to the pyrrolidine ring, there are two geometrical isomers which correspond to the *trans* and *cis* arrangements of N-methyl with respect to the pyridine ring, and these have been identified by NMR studies.[4,11] According to the report of Seeman the abundance ratio of *trans* and *cis* is 90.9 %:1%, and hence we will examine the *trans* form only.

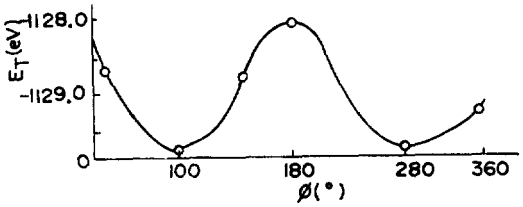


Fig. 2. Total energy, E_T, *vs.* angle of rotation, ϕ, of pyrrolidine ring for *trans*-nicotine.

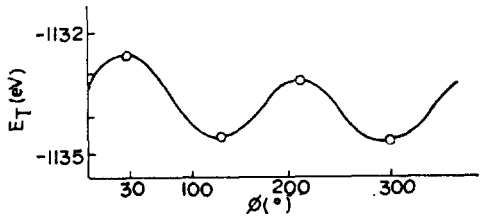


Fig. 3. Total energy, E_T, *vs.* angle of rotation, ϕ, of pyrrolidine for *cis*-nicotine.

Table 2 summarizes the preferred conformations reported together with the method and parameters used in the calculation. Though there is no absolute standard to judge these results of MO studies, agreement in the preferred forms between ours and those of Kier and Pullman is striking in view of the difference in method and parameters used.

For the interpretation of conformational preference of *trans* form we have considered MO factors controlling the stability for 280° (I), 100° (II), and 180° (III) conformers. The (III)-

Table 2. Summary of preferred forms calculated by MO calculations.

Investigator	Calculation method used	Preferred form ϕ(C3-C2-C1-N8)	Bond length and angles (input data)
Kier[1]	EHT	120°, 300°	Standard Value
Radna and Beveridge[9]	INDO	160°, 360°	Crystal data
Radna and Beveridge[9]	INDO	140°, 320°	assuming the pyrrolidine ring to be planar
Pullman *et al.*[3]	PCILO	100°, 280° (*trans*) / 120°, 320° (*cis*)	Standard Value
Testa and Jenner[12]	CD Studies	120°-170°, 300°-350°	
Present work	EHT	100°, 280° (*trans*) / 120°, 320° (*cis*)	Crystal data

Table 3. Energy component analysis for the 280°-, 100°-, and 180°-conformation of free base nicotine. (scaled energy in Hartree, by CNDO/2).

	280° (I)	100° (II)	180° (III)
Total energy, E_T	−100.2986	−100.3052	−100.2899
Electronic energy, E_{el}	−468.6236	−469.2364	−469.5322
Orbital energy, $2\sum^{occ}\varepsilon_i$	− 67.8362	− 58.0254	− 57.8610
Attractive potential, V_{ne}	−568.5152	−579.5318	−580.3337
Repulsion potential, V_{ee}	400.7874	411.2110	411.6712
Repulsion potential, V_{nn}	368.3250	368.9312	369.2423

form is the most unstable one, and the other two are the stable forms (*Table* 3). *Fig.* 4 shows the atomic charges and bond indices from CNDO/2 for free base forms of each conformer. Three main factors are known to control the conformational preference; (1) electrostatic, (2) conjugative, and (3) steric interactions.[13,14] Drakenberg *et al.* reported that the electrostatic effects are of a major importance in determining the most stable conformation of methylformate.[15] We have carried out the electrostatic energy calculation,

$$\sum_{i<j} Q_iQ_j/R_{ij},$$

where Q_i is the formal charge of atom i and R_{ij} is the interatomic distances between atoms i and j. Results of these calculations indicate that the (I)-conformer is most favorable approximately by 1.5 kcal compared with others due to less interaction between N_6 and N_8. This is due to the larger interatomic distance, 5.16 Å than others; 4.68 Å for (II)-conformer and 4.80 Å for (III)-conformer. The decrease in C_4-C_5 bond index for (III)-conformer compared with those for other forms will contribute to destabilizing this form, because of the less conjugative effect leading to less stabilization of pyridine ring. *Table* 3 shows the energy component analysis for the three forms. According to *Table* 3, the (III)-conformer has larger electron-electron (V_{ee}) and nuclear-nuclear (V_{nn}) repulsion potentials than (I) and (II)-conformers. The total repulsion potential increment for (III) is in excess of the attractive energy (V_{ne}) increment giving net destabilization for (III). We believe that there is some steric crowding between the two rings. Lower orbital enery of (I)-conformer compared with others may be a good indication of strong conjugation in (I)-conformer, and hence increased stability. It may therefore be concluded that

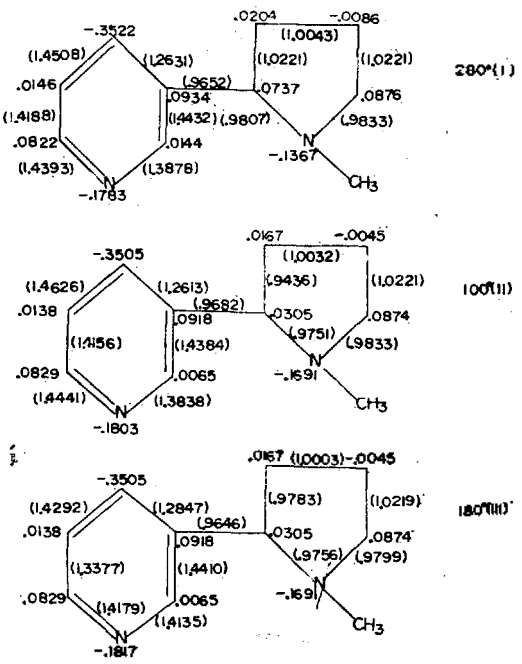


Fig. 4. Formal atomic charges and bond indices of 280°-, 100°-, and 180°-conformation forms for free base nicotine (by CNDO/2).

the most preferred conformation is probably the (I)-form considering conjugative, electrostatic, and steric effects alone. Fink and Allen,[25] Pederson and Morukuma,[27] and Eilers and Liberles[28] analyzed the potential energy components in terms of V_{ee}, V_{nn}, and V_{ne} when "bulky" or "sizable" groups or atoms are brought into closer proximity (especially, in the case of ethanelike internal rotation). Such a partition of the conformational energy is useful in understanding the conformational stability or preference quantitatively. The stability is due to greater attractive energy, (*a*), if

$$|\Delta V_{ne}| > |\Delta V_{nn} + \Delta V_{ee}|,$$

and it is due to less repulsion, (*r*), if

$$|\Delta V_{ne}| < |\Delta V_{nn} + \Delta V_{ee}|,$$

where $\Delta V_{ne} = V_{ne} - V_{ne}(\mathrm{II})$, $\Delta V_{nn} = V_{nn} - V_{nn}(\mathrm{II})$ etc.

(2) Protonated *trans*-Nicotine. We carried out a calculation on the protonation of *trans*-nicotine(I, II, and III-forms, respectively) using CNDO/2 method with each conformer structure retained. A proton was placed directly near above the nitrogen atom (N_6) of pyridine ring except pyrrolidine ring, since this was the most stable position. This corresponds to a π-complex, which may play an important role in electrophilic aromatic substitution as suggested by Dewar.[16] This type of structure for protonated aromatics with a tetrahedral site of protonation is favored according to various experimental evidences (*i.e.*, IR[17], UV[18,19], and NMR[20,21]). However, it is difficult to differentiate energetically the two modes of protonation on one conformer, since the protonation on N_8 is a σ-complex, and the basicity is larger by three orders of magnitude than that of N_6. However, *Fig.* 4 shows that the protonation on N_6 is likely due to its greater negative charge calculated (*via* charge controlled process).

In the alkylation of nicotine in acid medium, the protonation should precede the nitrogen quarternization of N_6 in the pyridine ring. However Seeman *et al.* found that the alkylation of nicotine in acid medium involves unusual competitive nitrogen alkylation between N_6 and N_8.[5] The π-complex formed by protonation of pyridine ring contributes mostly to stabilize energetically the protonated nicotine. It is interesting to note that the protonation on N_6 (with a hard acid,[23] proton) is preferred despite of the weaker basicity compared with N_8. We may conclude that the N_6 acts to control the reactivity of N_8 and leads to the more stable π-complex intermediate for the protonated nicotine. In a related study on protonated benzene, Heidrich and Grimmer[24] also found the π-complex to be more stable than the σ-complex using CNDO/2. This means that π-complexes do play an important role, initially, on the electrophilic reaction path, *i.e.*, reaction between nicotine-organic oxides, nicotine-iodomethane, and nicotine-peroxides, etc.[22] In this respect our results may provide a theoretical foundation that these reactions proceed by two step mechanisms; in the first step π-complex is formed and then forms σ-complex which may be attacked by an electrophilic reagents.[25] This is in agreement with the experimental findings of an unusual competitive nitrogen alkylation by Seeman. They reported that in the alkylation of nicotine in either methanol or acetonitrile it was found that the products A and B (below) were obtained in the ratio of 2.5 to 1, but by treating nicotine with acetic acid solution the yield of the alklation changes to 58 % of the product B.[5]

Among various protonated forms as shown in *Tables* 4 and 5 the proton lying on the nitrogen atom (N_6) of pyridine ring is more stable than

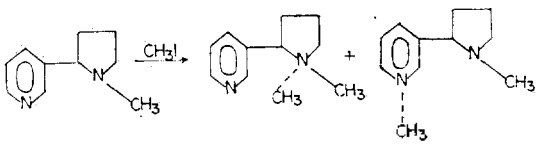
Table 4. Energy componemt analysis for various protonated forms (scaled energies in Hartrees).

order of stability			E_T	E_{ele}	$2\Sigma\varepsilon_i$	V_{nn}	V_{ee}	V_{ne}	ΔV
I	4	280°-Pyrro	−100.8425	−481.4984	−70.7980	380.6559	410.7004	−580.6713	*a**
II	1	280°-Pyrid	−100.8591	−482.0571	−72.1350	381.1980	409.9221	−589.4019	
III	6	180°-Pyrro	−100.8285	−482.4496	−84.3200	381.6211	398.1296	−578.0937	*r*
IV	3	180°-Pyrid	−100.8454	−482.8254	−71.9202	381.9800	410.9052	−591.1944	*a*
V	5	100°-Pyrro	−100.8359	−482.3074	−70.9758	381.4715	411.3316	−591.1313	*a*
VI	2	100°-Pyrid	−100.8585	−482.5000	−72.1038	381.6414	410.3962	−590.3204	*a*

*a: attractive interaction term $|\Delta V_{ne}| > |\Delta V_{ee} + \Delta V_{nn}|$, where $\Delta V_{ne} = V_{ne} - V_{ne}(II)$, $\Delta V_{nn} = V_{nn} - V_{nn}(II)$, $\Delta V_{ee} = V_{ee} - V_{ee}(II)$, and vice versa.

Table 5. Comparision of atomic charges for various protonated conformations (by CNDO/2).

	280°		100°		180°	
	I-Pyrrol	II-Pyrid	V-Pyrrol	VI-Pyrid	III-Pyrrol	IV-Pyrid
C_1	0.0372	0.1086	−0.0090	0.0794	0.0000	0.0784
C_2	0.0774	0.0962	0.0797	0.0915	0.0541	0.0794
C_3	−0.3506	−0.0672	−0.3301	−0.0681	−0.3218	−0.0587
C_4	0.0346	−0.0542	0.0318	−0.0533	0.0283	0.0596
C_5	0.0973	0.2017	0.0993	0.2041	0.1057	0.2025
N_6	−0.1435	−0.0900	−0.1479	0.0965	−0.1460	−0.1039
C_7	0.0405	0.2396	0.0201	0.2443	0.0458	0.0596
N_8	0.0692	−0.1338	0.0738	−0.1516	−0.9289	−0.1411
C_{10}	0.0779	0.0888	0.0775	0.0890	0.0813	0.0908
C_{11}	−0.0137	0.0016	−0.0175	0.0001	−0.0304	−0.0101
C_{12}	0.0255	−0.0033	0.0226	−0.0045	0.0393	0.0070
C_9	0.0597	0.0786	0.0588	0.0797	0.0596	0.0792



(A) : (B)

the proton on N_8. The results of energy decomposition analysis show that some protonated forms such as II, IV, and VI are more stable than the others.

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