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Molecular Orbital Study of the Reactivity of Active Alkyl Groups of Pyridine and Pyrimidine Derivatives

Yoshinobu Goto,*,[a] Tokihiro Niiya,[a] Noriko Honjo,[a] Takao Sakamoto,[b] Hiroshi Yoshizawa,[b] Hiroshi Yamanaka,[b] and Tanekazu Kubota[c]

Faculty of Pharmaceutical Sciences, Fukuoka University,[a] Nanakuma, Nishi-ku, Fukuoka 814, Japan, Pharmaceutical Institute, Tohoku University,[b] Aobayama, Sendai 980, Japan and Gifu College of Pharmacy,[c] Mitahora-Higashi, Gifu 502, Japan

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The experimental data on the relative reactivity of active methyl groups in a given molecule for various pyridines, pyrimidines, and their *N*-oxide and oxo derivatives were compared with the charge transfer ability(CTA) values calculated by the CNDO/2 method. The reactivity of active methyl groups of these compounds was examined in nitrosation and deuterium exchange reactions, and the CTA values were calculated in the deprotonation step of these reactions. The calculated values were in good accord with the experimental results. In particular, the experimental values for the *N*-oxides could be well interpreted in terms of the CTA values only when the calculations were performed in the conformation in which a 1 : 1 complex of sodium ion with the *N*-oxides was formed.

Keywords——reactivity; nitrosation; deuterium exchange; charge transfer ability; CNDO/2; dialkylpyridines; dialkylpyrimidines; dialkylpyridinones; dialkylpyrimidinones; *N*-oxides

In the preceding paper,[1] it was shown that the reactivity of active methyl and methylene groups of pyridine and pyrimidine derivatives with alkyl nitrite could be reasonably well interpreted in terms of the charge transfer ability (CTA) values[2] in the deprotonation step of this nitrosation reaction.

As shown in Chart 1, it is well known that the α- and γ- alkyl groups of 6-membered nitrogen heterocycles are attacked by various electrophilic reagents.

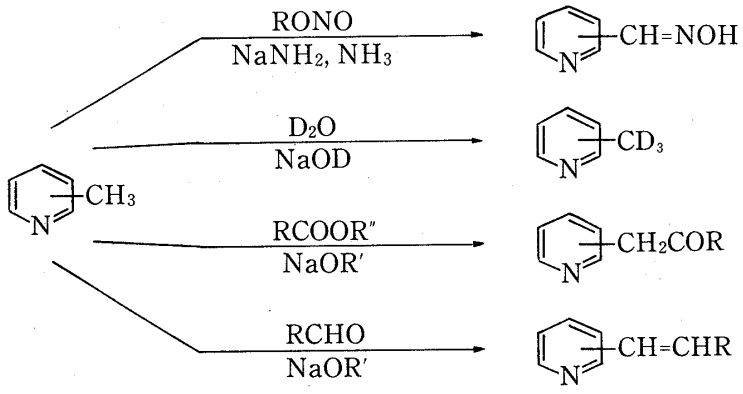


Chart 1

The relative reactivity of active methyl groups in a given molecule for various pyridines and pyrimidines was systematically investigated.[3] In the case of the reaction starting from the deprotonation step, the following conclusions were obtained. (i) The reactivity of the methyl group on the γ-position is always larger than that of the methyl group on the α-position of pyridine, quinoline, pyrimidine and quinazoline. (ii) In the case of the corresponding *N*-oxides, the circumstances are just the reverse of the situation described above, *i.e.* the

reactivity order is α-position$>\gamma$-position. (iii) In the case of the cyclic amides, the methyl groups located on the terminal position from the carbonyl group through the conjugated double bonds is more active than the others.

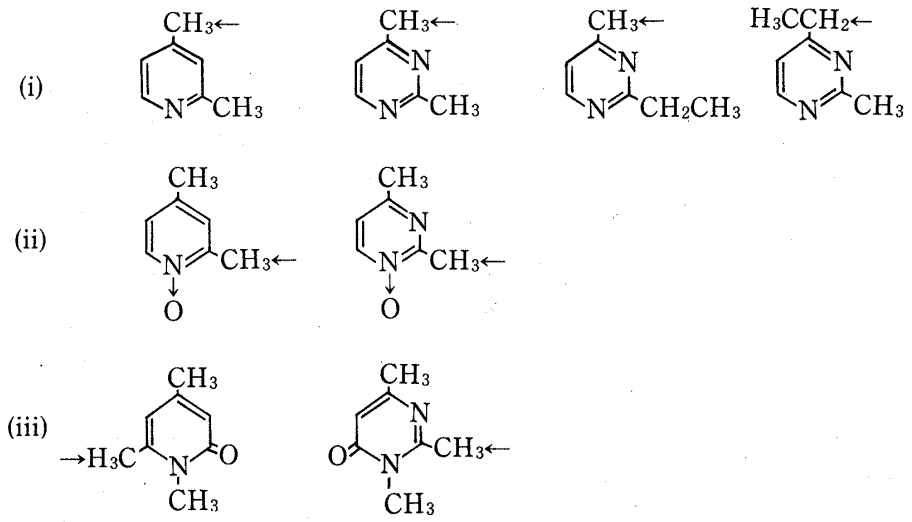


Chart 2. Methyl or Methylene Groups indicated by Arrows are exclusively attacked by Electrophilic Reagents

These conclusions (i), (ii) and (iii) were derived from the results of nitrosation, acylation, styrylation, and deuterium exchange reactions of 2,4-dimethyl-*N*-heteroaromatics, without exception.[3]

In order to rationalize the above conclusions, we analyzed the nitrosation and deuterium exchange reactions by the application of the molecular orbital (MO) theory. The present MO study was carried out to interpret the deprotonation step of these reactions in the same manner as was reported in the previous paper.[1]

Method of Calculation

In view of the object of our work and the character of the studied compounds, we chose all-valence semiempirical MO calculation at the CNDO/2 level, and the calculations were carried out with FACOM M-200 and ACOS 600 computers. The values of the parameters included in the CNDO/2 calculation are the same as those used in the foregoing papers.[4] The molecular geometries of picolines, pyrimidines, pyrimidinones and their *N*-oxides were taken from appropriate references.[5] All the CTA calculations were performed using the methyl group conformation shown in Fig. 1. The adoption of this conformation for the methyl group is discussed in detail in the previous paper.[1]

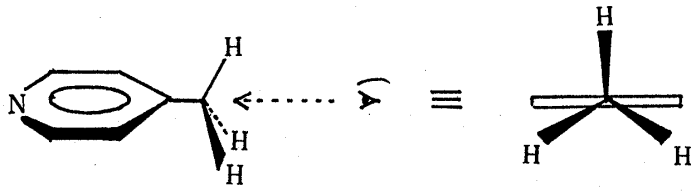


Fig. 1. The Conformation of 4-Picoline for CTA Calculation using the CNDO/2 Method

The geometrical orientation of the *N*-oxide with respect to the sodium ion was considered to be as shown in Fig. 2, *i.e.*, the sodium ion approaches the oxygen atom of the *N*-oxide group along the *z*-axis. This conformation is energetically most stable on the basis of CNDO/2 calculation when the sodium ion rotates around the oxygen atom of the *N*-oxide group.

In the previous paper[1] the intermolecular perturbation energy was calculated for the deprotonation step, and the coulombic, exchange repulsion, induction, dispersion and charge transfer energies were ex-

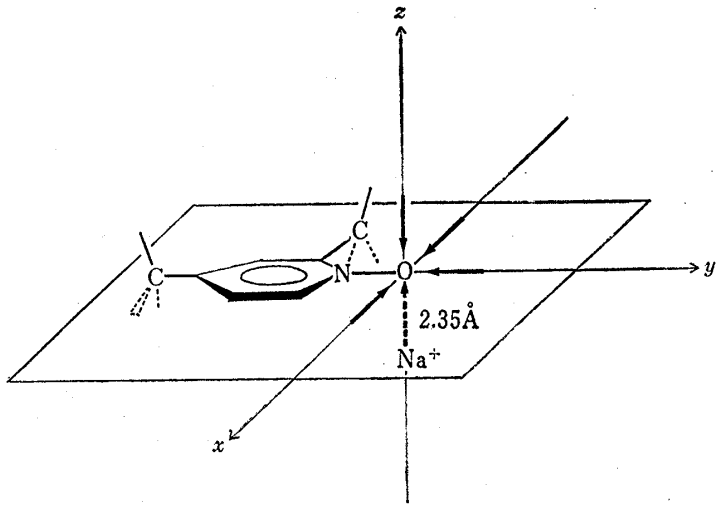


Fig. 2. Orientation of Na^+ towards the Oxygen of 2,4-Lutidine 1-Oxide

The distance between the O atom of the *N*-oxide and the Na^+ ion is 2.35Å. The separation $d=2.35$Å is approximately equal to the sum of the van der Waals radii of the oxygen and the sodium cation.

amined.[6] Among these energies, only the charge transfer energy was consistent with the experimental reactivity. Therefore, in this report, the reactivity of the methyl groups was investigated in terms of the charge transfer ability values calculated by the same equation (1) as that used in the previous paper.[1]

$$(\mathrm{CTA})_{\mathrm{H}} = \sum_{j}^{VAC} \frac{(C_{\mathrm{M}.j}^{\mathrm{H}})^2}{(\varepsilon_{\mathrm{R.HO}} - \varepsilon_{\mathrm{M}.j})} \quad (1)$$

Here the symbols $C_{\mathrm{M}.j}^{\mathrm{H}}$, $\varepsilon_{\mathrm{M}.j}$ and $\varepsilon_{\mathrm{R.HO}}$ are the coefficient of the atomic orbital (AO) of the active hydrogen in the j-th MO, the j-th MO energy of the methylheterocyclic compound, and the energy of the highest occupied MO (HOMO) of the reagent, respectively.

Results and Discussion

The CTA Values in the Nitrosation Reaction

The CTA Values in the depronation step of the nitrosation are shown in Table I.

Table I. CTA Values in the Deprotonation Step of the Nitrosation

Compound		CTA $\times 10^2$ (eV^{-1})	Yield of oxime (%)	Ref. No.
2,4-Di-Me-pyridine	4-Me	−7.08	37	3b
	2-Me	−6.89	0	
2,4-Di-Me-pyrimidine	4-Me	−7.43	79	3b
	2-Me	−6.90	0	
2-Et-4-Me-pyrimidine	4-Me	−7.42	53	3d
	2-Et	−7.06	0	
4-Et-2-Me-pyrimidine	4-Et	−7.51	70	3d
	2-Me	−6.95	0	
2,4-Di-Me-quinoline	4-Me	−7.80	59	3b
	2-Me	−7.16	0	
2,4-Di-Me-quinazoline	4-Me	−8.74	71	3b
	2-Me	−7.08	0	
2,3,6-Tri-Me-4(3*H*)-pyrimidinone	6-Me	−7.55	0	3d
	2-Me	−8.52	74	
2-Et-3,6-Di-Me-(34*H*)-pyrimidinone	6-Me	−7.47	0	3d
	2-Et	−8.53	50	
6-Et-2,3-Di-Me-4(3*H*)-pyrimidinone	6-Et	−7.51	0	3d
	2-Me	−8.45	78	

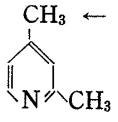
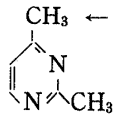
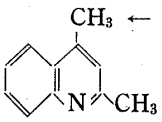
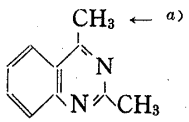
Me=CH_3, Et=C_2H_5.

For the parent heterocycles having two alkyl groups at different positions, *i.e.* α- and γ-positions, in the same nucleus, even if there are different kinds of substituents, the γ-alkyl group is always more reactive than the others. On the other hand, in the case of pyrimidinones, the alkyl groups located on the terminal position from the carbonyl group through the conjugated double bonds are exclusively attacked by alkyl nitrite. The CTA values in the deprotonation with amide ion are in good agreement with these experimental results.

The CTA Values in the Deuterium Exchange Reaction

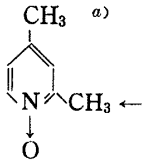
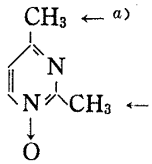
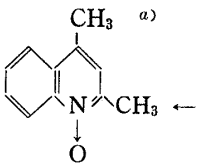
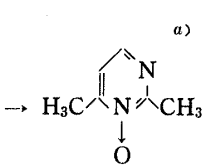
(i) **The CTA Values of the Heterocycles calculated in the Free States**——The experimental results and the CTA values of the deuterium exchange reaction of the parent heterocycles and their *N*-oxide and oxo derivatives are shown in Tables II, III and IV. The rate constants of deuterium exchange of the active hydrogens were determined by measuring the time-dependent decrease of the areal intensity of the PMR signals due to the methyl groups in D_2O–CD_3OD solution at an appropriate concentration of NaOD.[3d] As is evident from Table II, bicyclic compounds are generally more reactive than monocyclics, and moreover the reactivity is affected more strongly by the ring-nitrogen than by the benzene ring. Quinazoline is thus the most reactive among these compounds in Table II. Under these conditions the 4-methyl group is exclusively deuterated. These experimental results can be well interpreted in terms of the CTA values.

Table II. CTA Values of the Parent Heterocycles in the Deprotonation Step of Deuterium Exchange

				
$k(s^{-1})$	6.4×10^{-5}	9.1×10^{-5}	1.2×10^{-5}	7.7×10^{-4}
NaOD in D_2O–CD_3OD (%)	5	1	5	0.1
Reaction temp. (°C)	100	20	50	20
CTA $\times10^2$ (eV^{-1}) 4-CH_3	−7.18	−7.54	−7.96	−9.01
2-CH_3	−6.98	−7.05	−7.28	−7.18

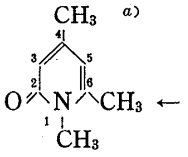
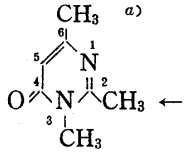
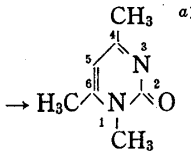
a) Methyl groups indicated by arrows are exclusively deuterated.

Table III. CTA Values of the *N*-oxides in the Free States in the Deprotonation Step of Duterium Exchange

				
$k(s^{-1})$	1.8×10^{-4}	4.2×10^{-4} (4-CH_3) 8.1×10^{-4} (2-CH_3)	8.4×10^{-4}	6.1×10^{-4}
NaOD in D_2O–CD_3OD (%)	1	0.1	1	0.01
Reaction temp. (°C)	50	20	20	20
CTA $\times10^2$ (eV^{-1}) 4-CH_3	−7.75	−8.38	−9.01	−8.38 (6-CH_3)
2-CH_3	−7.50	−7.65	−7.96	−7.62

a) Methyl groups indicated by arrows are exclusively deuterated.

Table IV. CTA Values of the Oxo Derivatives in the Deprotonation Step of Deuterium Exchange

	 [a]	 [a]	 [a]
$k(s^{-1})$	7.0×10^{-5}	2.5×10^{-3}	2.9×10^{-3}
NaOD in D_2O–CD_3OD (%)	1	0.1	0.01
Reaction temp. (°C)	50	20	20
CTA$\times10^2$ (eV^{-1}) 4-CH_3[b]	−7.65	−7.67 (6-CH_3)	−9.66
2-CH_3[b]	−8.60 (6-CH_3)	−8.68	−9.94 (6-CH_3)

a) Methyl groups indicated by arrows are exclusively deuterated.
b) The numbering of the atoms of the parent heterocycles.

While in the case of the *N*-oxides the 2-methyl group is experimentally more reactive than the 4-methyl group (Table III), the CTA values calculated for the *N*-oxides in the free states show opposite results to the experimental findings (Table III), *i.e.* the absolute CTA values of 4-methyl groups are larger than those of 2-methyl groups. Only in the case of 2,6-dimethylpyrimidine 1-oxide are the CTA values consistent with the experimental results. The 6-methyl group is located not only at the α-position with respect to the *N*-oxide group but also at the γ-position with respect to the nitrogen atom of the 3-position, while the 2-methyl group is located at the α-position with respect to both the *N*-oxide group and the nitrogen atom of the 3-position. The effect of the ring-nitrogen on the reactivity of the γ-methyl group is larger than that of the *N*-oxide group on the reactivity of the α-methyl group. This is the reason why both the experimental reactivity and the absolute CTA value of the 6-methyl group are larger than those of the 2-methyl group.

In contrast to the experimental results concerning the *N*-oxides described above, in the case of the oxo-compounds, the methyl groups located on the terminal position from the carbonyl group through the conjugated double bonds are always more active than the others. The CTA values of these oxocompounds agree well with the experimental results.

(ii) The CTA values of the *N*-Oxides as 1: 1 Na^+-complexes——The following resonance structures (I—III) can be considered for pyridine 1-oxide (Chart 3).

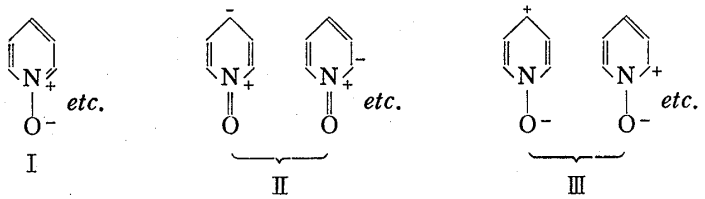
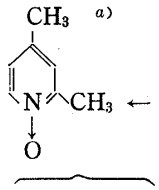
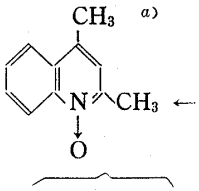
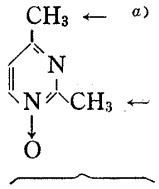
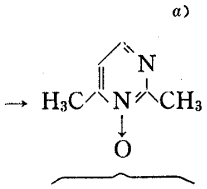


Chart 3

In the chemistry of aromatic amine oxides, it is well known that the π-π^* intramolecular charge transfer bands of *N*-oxide compounds undergo a marked blue shift in protic solvents mainly due to the hydrogen bonding effect.[7] These ultraviolet(UV) spectra can be interpreted as follows. The blue shift of π-π^* bands indicates that the π^* level is considerably less stabilized by polar solvents and the hydrogen bonding ability is much more reduced in the excited π-π^* states than in the ground state. Thus, in the π-π^* states, the structure (II) should be more important, and in these states, the oxygen atom loses much or most of its charge.

On the other hand, under our experimental conditions, it is considered that the intramolecular charge transfer effect written as formula (II) is much more reduced by the addition of Na^+ to the oxygen atom of the *N*-oxide group in a protic solvent such as liquid ammonia, methanol, water and so on. Therefore, the CTA values calculated for the *N*-oxide in the free state do not reflect the actual reaction conditions. This may be the reason why the CTA values of the *N*-oxides in the free state were inconsistent with the experimental results. Consequently, the CTA values of the *N*-oxides were recalculated for the addition of Na^+ to the oxygen atom of the *N*-oxide group according to the conformation shown in Fig. 2. As shown in Table V, the experimental results, which are in just the reverse order of reactivity between 2-methyl and 4-methyl groups compared with that of the parent heterocycles, can be well interpreted in terms of the CTA values of the *N*-oxides by considering complex formation of Na^+ with the *N*-oxide.

Table V. CTA Values of the *N*-oxides in the Deprotonation Step of Deuterium Exchange ($CTA \times 10^2(eV^{-1})$)

								
	2-CH_3	4-CH_3	2-CH_3	4-CH_3	2-CH_3	4-CH_3	2-CH_3	6-CH_3
— [b]	−7.50	−7.75	−7.96	−9.01	−7.65	−8.38	−7.62	−8.38
Na^+ [c]	−13.05	−11.74	−76.47	−64.29	−13.15	−12.44	−12.98	−14.41

a) Methyl groups indicated by arrows are exclusively deuterated.
b) The CTA values of the *N*-oxides in the free states.
c) The CTA values of the *N*-oxidse in the 1: 1 complexes of Na^+ with the *N*-oxides.

In contrast, if the CTA calculation for the parent heterocycles was performed with addition of Na^+ to the nuclear nitrogen, the absolute CTA values were changed, but the relative reactivity order remained unaltered. This result is fully consistent with the fact that extent of shift of the π-π^* bands of the parent heterocycles is small as the dielectric constant of the solvent increases, which is different from the case of the corresponding *N*-oxides.

Consideration of the CTA Values of the Oxo Compounds

The CTA values and Ehrenson's bond indices[8] of pyridine, pyrimidine and their hydroxy and oxo derivatives obtained by means of the CNDO/2 calculations are shown in Chart 4. The geometries of the hydroxy and oxo compounds are the same as those of the corresponding parent heterocycles. As shown in Chart 4, the six bond indices of the parent heterocyclic nucleus (IV and V) take almost the same values. Even if a hydroxylic group is introduced into the parent nucleus (VI and VII), the circumstances are similar, *i.e.* the aromaticity is still maintained. The absolute CTA value of the 4-methyl group is larger than that of the 2-methyl group. However, in the case of the oxo compounds (VIII—XI), in which the oxo group is introduced into the parent heterocycles, the bond indices change distinctly, and the bond alternation in the nucleus is evident. The absolute values of bond indices of the bonds 2—3 and 4—5 are much larger than the others, *i.e.* these calculation results indicate that the introduction of an oxo group results in an increase in the double-bond character of the bonds 2—3 and 4—5, and the aromaticity of these oxo compounds decreases. The CTA values of these oxo compounds show clarly that the methyl group located on the terminal position from the carbonyl group through the conjugated double bonds is more active than the others.

In the open-chain conjugated carbonyl compounds, the absolute CTA values decrease a little with increasing distance from the carbonyl group (XII, XIII and XIV). However, in

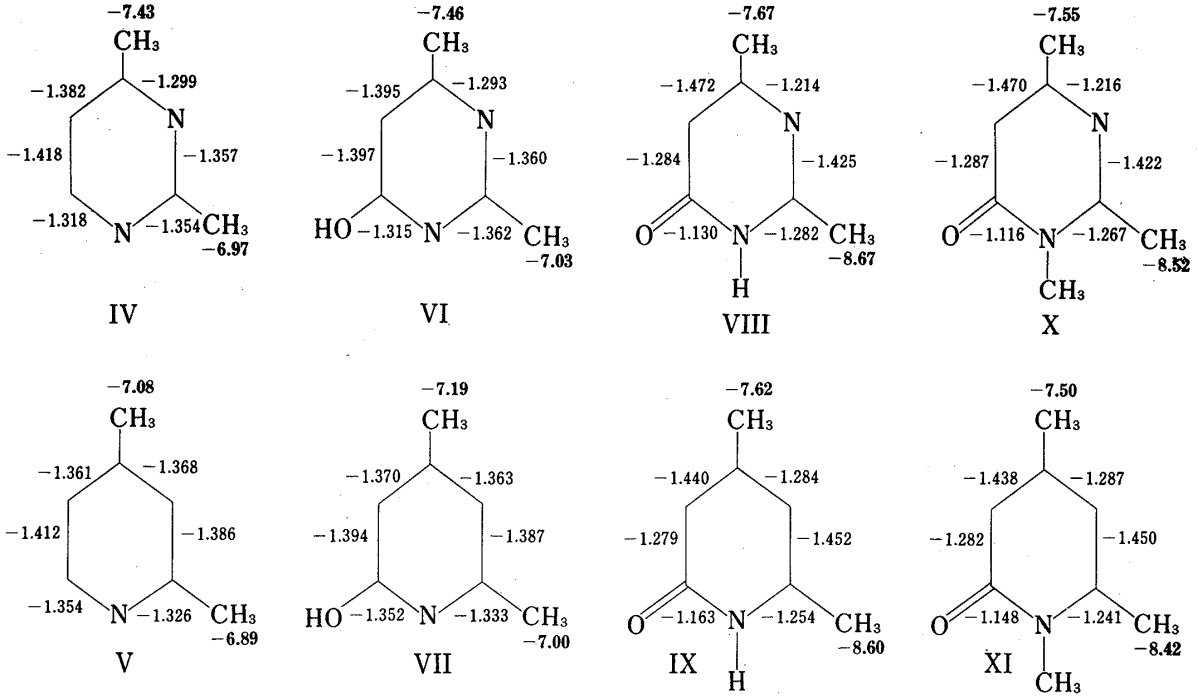


Chart 4. Bond Indices (a.u.) and CTA Values (Boldfaced Numbers, CTA $\times 10^2$ (eV^{-1})) of the Parent Heterocycles and Their Hydroxy and Oxo-Derivatives

In the case of the oxo compounds, the numbering of the atoms is considered, in Charts 4 and 5 only, to be the same as that of the parent heterocycles.

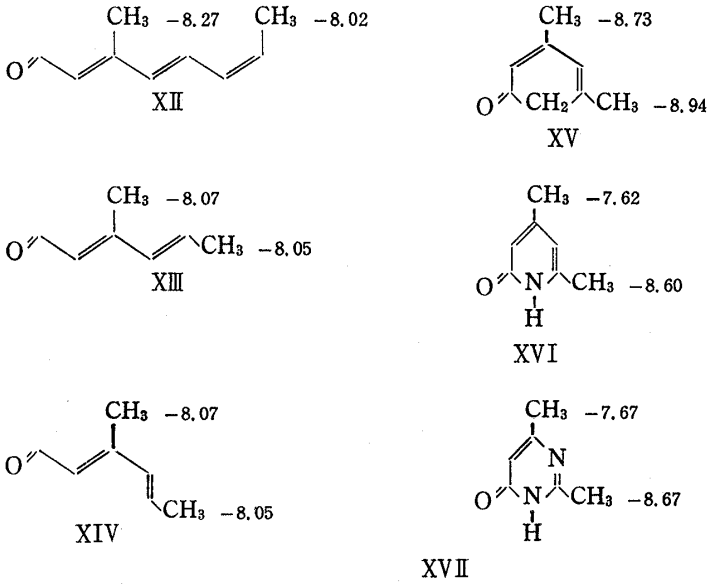


Chart 5. CTA Values (CTA $\times 10^2$(eV^{-1})) of the Methyl Groups of the Open-chain and Cyclic Unsaturated Carbonyl Compounds and the Cyclic Amides

the case of a ring compound such as XV, the absolute CTA value of the methyl group located on the terminal position from the carbonyl group through the conjugated double bonds is slightly larger than that of the other.

On the other hand, when the methylene group in XV is replaced by an imino group (XVI and XVII), the absolute CTA value of the methyl group on the 2-position becomes significantly larger than that of the other.

In view of the above results, it can be concluded, *e.g.* in dimethylpyridinone, that the γ-methyl group is activated by the oxo group only through one double bond, while the α-methyl group is activated not only through the conjugated double bonds but also through the imino group. This is the reason why the α-methyl group is more active than the γ-one.

Acknowledgement The calculations were performed on an ACOS 600 computer at the Computation Center of Fukuoka University and on a FACOM M-200 computer at the Computer Center of Kyushu University.

References and Notes

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