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배치와 형태에 관한 분자궤도함수론적 연구 (제 4 보). N-아세틸피롤리돈과 그 양성자 부가물의 형태에 관한 연구

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(1977. 12. 9 접수)

MO Studies of Configuration and Conformation (IV). Conformations of N-Acetyl Pyrrolidone and Its Protonated Form

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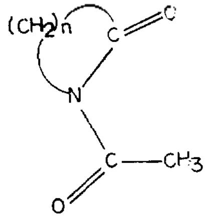
요 약. N-아세틸피롤리돈과 그 양성자 부가물의 형태에 대하여 EHT 및 CNDO/2 분자궤도함수법으로 연구하였다. 계산결과는 분자내의 무거운 원자들의 골격이 편면구조인 경우가 가장 안전하며, 평면형태에서는 트란스-트란스형이 시스-트란스형보다 더 안정함을 나타내고, 양성자화는 고리에 붙어있는 카르보닐 산소에서 더 용이하게 일어남을 나타내고 있다. 이 결과를 콘주게이션, 정전기적 및 입체효과로서 설명하였다.

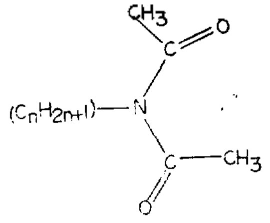
ABSTRACT. MO theoretical studies on the conformations of N-acetylpyrrolidone and its protonated form were carried out by the EHT and CNDO/2 methods. According to our calculated results, the heavy atom skeleton of this molecule is planar, and the *trans-trans* planar conformation is more stable than *cis-trans*. The protonation occurs most readily on the ring carbonyl oxygen. These results were interpreted in terms of conjugative, electrostatic and steric effect.

INTRODUCTION

N-acetyl lactams (I) are cyclic forms of N-acetyldiacetimide (II). These form a reactive group of carbonyl compounds which recently have attracted an increasing interest due to their possible role as intermediates in various types



(I)



(II)

of acyl transfer reactions, especially in the biological synthesis of peptides and proteins.[1~4]

Acid catalyzed hydrolysis of N-acetyl lactams proceed by both ring and exocyclic acyl cleavages, product ratio of the two processes being dependent on the ring size.[5] In order to gain further insights into the mechanism of the acid catalyzed hydrolysis of these compounds we have initiated molecular orbital (MO) studies on N-acetyl lactams and their protonated forms.

We report here results of our MO theoretical studies on the conformations of N-acetylpyrrolidone and its protonated form.

CALCULATION

The calculation of atomic cartesian coordinates of the molecular system for the input of the EHT and CNDO/2 program was carried out with an aid of a modified version of Quantum Chemistry Program Exchange (QCPE) at Indiana University No. 226 program by means of IBM 1130 computer.

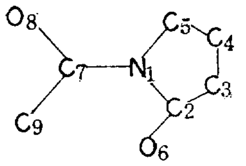


Fig. 1. Numbering scheme of heavy atoms.

Table 1. Bond length and bond angles[6,7].

Bond length (Å)		Bond angle (°)	
N_1-C_2	1.26	$\angle N_1C_2C_3$	99.1
C_2C_3	1.57	$\angle C_2C_3C_4$	113.1
C_3-C_4	1.56	$\angle C_3C_4C_5$	104.0
C_5-N_1	1.48	$\angle C_5N_1C_2$	115.4
C_2-O_6	1.23	$\angle N_1C_2O_6$	124.0
N_1-C_7	1.36	$\angle C_2N_1C_7$	122.3
C_7-O_8	1.23	$\angle N_1C_7O_8$	125.0
C_7-C_9	1.53	$\angle N_1C_7C_9$	113.0
C-H	1.09	$\angle$CCH	109.5
O-H^+	0.987		

The numbering scheme of the heavy atoms are shown in *Fig.* 1. The bond length and bond angles used in these calculations are listed in *Table* 1.

For the calculation of atomic cartesian coordinates of the molecular stsyem, the non-hydrogen heavy atoms of the ring were assumed to be planar[8~11] except C_4 ring carbon.

Koo *et al.*,[6,7] report that the dihedral angle α, between $\Delta N_1C_2C_3$ and $\Delta C_2C_3C_4$, and β, between $\Delta C_2C_3C_4$ and $\Delta C_3C_4C_5$, are 3 and 14° respectively.

In this study we employed optimization method with which we could determine the most preffered conformation by calculating the total energy ranging from the angle β, 14 to 10, 5° gradually with the dihedral angle α fixed at 3°.

Finally, we calculated the energy by placing all the heavy atoms of the ring on the same plane.

The dihedral angles, α and β, and rotation angle θ, exocyclic acetyl group rotamer, were varied and thier ensuing conformers were designated respectively as shown in *Table* 2, and the protonated forms in *Table* 4.

RESULTS

The results of the calculated total energies for various conformation of N-acetylpyrrolidone and its protonated conformers are summarized in *Table* 2 and 5.

DISCUSSION

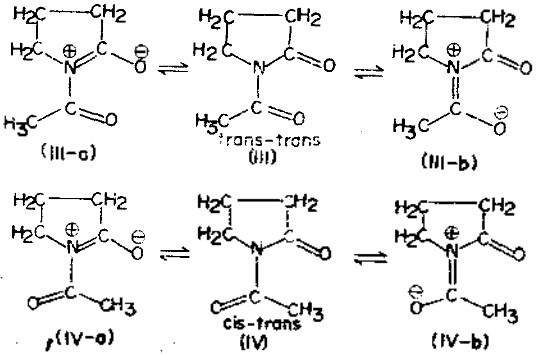
1. N-Acetylpyrrolidone

Results of our EHT and CNDO/2 calculations (*Table* 2) both predict that the heavy atom (non-hydrogn) skeleton of this molecule is planar. This is rather surprising since there are three sp^3 carbons and one sp^3 nitrogen. The planar configuration of amino group was however reported for the nitrogen which is electron

Table 2. Determination of conformation of N-acetyl pyrrolidone by EHT and CNDO/2. (Values in parenthesis are the result by CNDO/2).

	α(°)	β(°)	θ(°)	Total energy (kcal/mole)	Order of stability
1	3	14	0	−22374.03	18
2			30	−22380.74	15
3			60	−22414.97 (−61274.82)	8
4			90	−22414.59	9
5			120	−22413.12	10
6			150	−22411.32	11
7			180	−22409.15	12
8	3	10	0	−22333.99	23
9			30	−22341.37	22
10			60	−22375.72 (−61221.90)	16
11			90	−22375.11	17
12			120	−22372.95	19
13			150	−22370.85	20
14			180	−22368.84	21
15	3	5	0	−22390.93	13
16			30	−22386.06	14
17			60	−22305.29	24
18			90	−22430.53 (−61289.29)	5
19			120	−22427.91	6
20			150	−22264.54	25
21			180	−22426.38	7
22	Planar, one C-H bond in CH_3 group coplaner		0	−22475.33 (−61360.05)	4
23			180	−22512.72 (−61363.58)	1
24	Planar, C-H bond in CH_3 group out of plane		0	−22494.55	3
25			180	−22509.82	2

deficient due to strong π-electron acceptor substituents.[8~11] For N-acetylpyrrolidone, two electron withdrawing carbonyl groups are directly attached to the nitrogen atom which may be thus forced to take up a planar form. The π-bond population obtained by CNDO/2 method shows that there are strong π-conjugative effect operating between the N and two carbonyl oxygen atoms and π bond orders (double bond character) of 0.4~0.5 were found for the two C-N bonds involved for both the *cis-trans* and *trans-trans* forms. Of the two possible planar

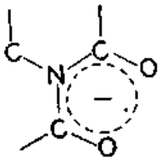


conformation, III and IV, Lee and Kumler[12] reported the *cis-trans*, IV, to be preferred based on their dipole moment studies in dioxane at 30°C. In direct contradiction to these dipole moment studies, the CNDO/2 and EHT results predict that the *trans-trans* is more stable by 4 and 37 kcal respectively. The latter value for the energy difference between the two forms may well be unrealistic and exaggerated as generally expected from the EHT results.[13] The significance of our MO results however is not in the absolute value of energy difference but in the fact that both calculations agreed in predicting the preference of the *trans-trans* form.[14] This is especially striking in view of completely different method of calculation used in the EHT[13] and CNDO/2;[13] in the EHT, electron repulsion integrals are neglected and overlap integrals are calculated whereas in the CNDO/2 diferential overlaps are neglected and repulsion integrals are calculated.[13,14]

If we accept the small energy difference between the two forms in vapor phase, it is not unreasonable to expect still smaller energy difference, or even the slight reversal of preference, in liquid and solution.

Let us now consider MO theoretical factors controlling the stability of preferred form. Three main factors are normally considered to be responsible in determining stability of molecular conformation.[15]

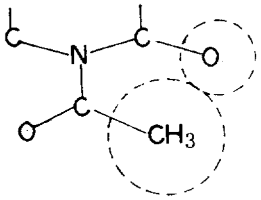
Conjugative Effect. *Fig.* 2 shows the atomic charges and π-bond orders of interest for the two forms. The exocyclic carbonyl group is seen to interact conjugatively with the ring carbonyl group through the intermediary nitrogen atom. This effect is more efficient in the *trans-trans* form judging by larger π-bond order of C_7-N bond. According to π-bond orders resonance form (IIIb) is prevalent in the *trans-trans*, while form (IVa) is prevalent in the *cis-trans*. The pseudo pentadiene system forms a ring in the *trans-trans* system, which contains calculated surplus π-electrons of 1.04. This means that the cyclopentadiene system is nearly anionic, rendering extra stabilization according to $4n+2$ rule of Hückel.[16] In this respect the structure of pentadienyl part of the *trans-trans* is better represented as (V), and this contributes to extra stabilization of this form over the *cis-trans*.



(V)

Electrostatic Effect. Approximate point charge calculation of electrostatic effect[17] indicates that the *trans-trans* is unfavorable by ~4 kcal compared to the *cis-trans* form due to the repulsion of neighboring oxygen atoms.

Steric Effect. *Table* 3 shows the energy components for the two forms. According to the energy component analysis, the *cis-trans* form has larger-electron and nuclear-nuclear repulsions, which are in excess of the attractive energy gained over that for the *trans-trans*. This shows that there is some steric crowding, VI, in the *cis-trans* form as compared to the *trans-trans* form.



(VI)

Table 3 also shows that the *trans-trans* form has more stabilization energy of conjugation, which is evident from the lower orbital energy; the stronger conjugation or resonance lowers the occupied levels in greater amount. We therefore

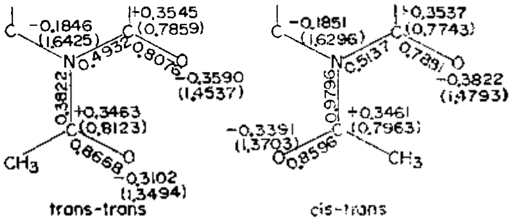


Fig. 2 Formal atomic charges and π-bond orders of the *trant-trans* and *cis-trans* forms. Numbers in parenthesis are π-electron densities of atoms.

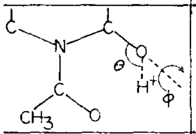
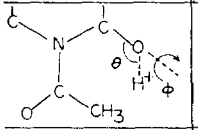
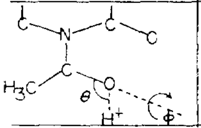
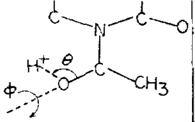
Table 3. Energy components Analysis for *trans-trans* and *cis-trans* N-acetylpyrrolidone (by CNDO/2, energy in Hartrees).

	trans-trans	*cis-trans*
Total energy, E_T	−97.79	−97.78
Electronic energy, E_{elec}	−352.46	−353.99
Orbital energy, $2\sum^{occ}\varepsilon_i$	−46.75	−46.68
Attractive energy V_{ne}	−755.95	−757.07
Electronic repulsion, V_{ee}	305.70	307.30
Nuclear repulsion, V_{nn}	254.67	256.20

can see that slight preference of the *trans-trans* form to the *cis-trans* form is the net result of the three, *i.e.*, conjugative, electrostatic and steric effects.

Protonated N-Acetylpyrrolidone.
First of all it is necessary to determine the position of protonation. There are two oxygen and one nitrogen atoms which are negatively charged and therfore are likely to be protonated. *Table* 5 shows that protonation of nitrogen is unfavorable energetically. For both *trans-trans* and *cis-trans* forms, the ring carbonyl oxygen has the larger negative charge compared with exocyclic carbonyl oxygen (*Fig.* 2). Since the proton is a hard acid, the protonation should occur on an atom which has larger total electronic charge (charge controlled process[19]), and hence the protonation of

Table 4. Various form of protonation.

	Rotation angle	Symbol
 θ H^+ ϕ CH_3	trans-trans, ring C=O	
	θ=120, ϕ= 0	TTR1
	θ=120, ϕ= 90	TTR2
	θ=120, ϕ=180	TTR3
	θ=180, ϕ= 0	TTR4
 θ H^+ ϕ CH_3	cis-trans, ring C=O	
	θ=120, ϕ= 0	CTR1
	θ=120, ϕ= 90	CTR2
	θ=120, ϕ=180	CTR3
	θ=180, ϕ= 0	CTR4
 H_3C θ H^+ ϕ	trans-trans, acetyl C=O	
	θ=120, ϕ= 0	TTA1
	θ=120, ϕ= 90	TTA2
	θ=120, ϕ=180	TTA3
	θ=180, ϕ= 0	TTA4
 H^+ θ ϕ CH_3	cis-trans, acetyl C=O	
	θ=120, ϕ= 0	CTA1
	θ=120, ϕ= 90	CTA2
	θ=120, ϕ=180	CTA3
	θ=180, ϕ= 0	CTA4

θ:$\angle COH^+$, coplanar; ϕ:angle of rotation around C-O bond. clockwise above the plane.

Table 5. Energy component analysis for various protonated forms (in Hartrees).

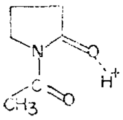
	E_T	$E_{\mathrm{elec.}}$	$2\sum\varepsilon_i$	V_{ne}	V_{ee}	V_{nn}	Order of stability	$\Delta V_{(iii)}$
TTR1	−98.34	−364.34	−59.08	−767.94	305.26	266.00	1	
TTR2	−98.31	−363.31	−58.87	−766.06	304.44	265.00	6	a
TTR3	−98.33	−362.77	−58.83	−765.03	303.93	264.44	2	a
TTR4	−98.29	−362.72	−58.42	−765.30	304.30	264.43	12	a
TTA1	−98.31	−362.84	−58.71	−765.27	304.13	264.53	8	a
TTA2	−98.29	−363.19	−58.64	−766.03	304.55	264.90	10	a
TTA3	−98.33	−364.25	−58.88	−767.95	305.37	265.92	3	r
TTA4	−98.27	−362.62	−58.24	−765.27	304.38	264.34	14	a
CTR1	−98.16	−366.64	−59.21	−772.23	307.43	228.47	19	r
CTR2	−98.29	−365.16	−59.04	−769.57	306.12	266.87	11	r
CTR3	−98.31	−364.33	−58.98	−767.99	305.35	266.02	5	r
CTR4	−98.26	−364.65	−56.57	−770.99	308.08	266.39	16	r
CTA1	−98.30	−364.90	−58.78	−769.32	306.11	266.59	7	r
CTA2	−98.28	−364.43	−58.59	−768.55	305.84	266.15	13	r
CTA3	−98.30	−364.27	−58.67	−768.16	305.59	265.96	9	r
CTA4	−98.27	−363.83	−58.19	−767.73	305.63	265.56	15	a
TTB1$_{(i)}$	−98.33	−365.64	−59.10	−770.50	306.54	267.31	4	r
TTB2$_{(i)}$	−94.52	−358.97	−57.58	−754.88	301.39	264.45	20	a
TTN$_{(ii)}$	−98.21	−366.05	−59.60	−770.70	306.45	267.84	17	r
CTN$_{(ii)}$	−98.19	−367.67	−59.60	−773.92	308.06	269.47	18	r

(*i*) TTB1 is pentagonal bridge and TTB2 is hexagonal bridge forms.

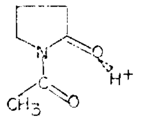
(*ii*) TTN=*trans-trans*-nitrogen protonated, CTN=*cis-trans*-nitrogen protonated

(*iii*) ΔV; comparison of attractive and repulsive potential energies with the most stable form, TTR1; "a" indicates that the destabilization from the TTR1 is due to decrease in attractive term $\Delta V_{ne}<0$, whereas "r" indicates the destabilization due to increase in repulsive terms, $(\Delta V_{ee}+\Delta V_{nn})>0$. see Ref. (18).

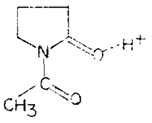
ring carbonyl oxygen is expected to be favorable as was found from the CNDO/2 calculations (*Table* 5). Among the various protonated forms considered in *Table* 5, the proton lying in the molecular plane with trigonal angles at carbonyl oxygen is always more stable than other forms[20]; thus TTR1 and TTR3 are more stable than TTR2 and TTR4 etc., But there is one exception, which is CTR1. In this case the proton interfers with the methyl group sterically and destabilized by high repulsive energies. In general it is also true that for the same proton position of the ring carbonyl oxygen, the *trans-trans* form is more stabilized by protonation; thus TTR1 is more stable than CTR1 and TTR 3 is more stable than CTR3. This is because of reduction in electron density of the oxygen protonated, which reduces inter-oxygen repulsion in the *trans-trans* case (*Table* 5).



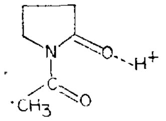
TTR1



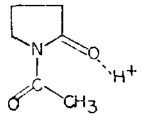
TTR2



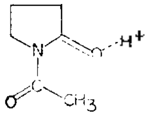
TTR3



TTR4



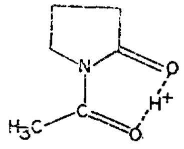
CTR1



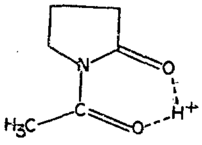
CTR3

The last column of *Table* 5 shows the prevalent contribution of potential energy terms in destabilizing the structure as compared with the most stable one, *i.e.*, TTR1. The destabilizing is due to less attractive, (*a*), energy if $|\Delta V_{ne}|>|\Delta V_{nn}+\Delta V_{ee}|$, and it is due to more repulsion, (*r*), if $|\Delta V_{ne}|<|\Delta V_{nn}+\Delta V_{ee}|$, where $\Delta V_{ne}=V_{ne}-V_{ne}$ (TTR1), $\Delta V_{nn}=V_{nn}-V_{nn}$ (TTR1) etc.[18] It is interesting to note that in general other *trans-trans* protonations than the TTR1 are less favored due to less attractive potential while the *cis-trans* protonations are less favored due to larger repulsion as compared with the TTR1.

We have also considered two types of proton bridge across the two oxygens. One is TTB1 where the proton lies at midpoint of the line connecting two oxygens, (pentagonal bridge), and the other is TTB2 where the proton is at equi-distance from the oxygens keeping the trigonal angles (hexagonal bridge).

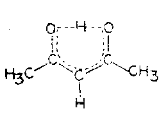


TTB1

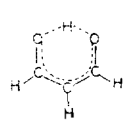


TTB2

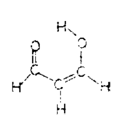
The pentagonal bridging of proton, TTB1, is much more stable than the hexagonal bridging, TTB2, mainly because of large increase in the attractive potential term, $|V_{ne}|$, (*Table* 5,) which is more stabilizing. This result is in agreement with the experimental findings of Lowrey *et al.*, on acetylacetone.[21] More sophisticated MO calculations on the *enol* tautomer of malondialdehyde[22~24] indicated that C_s symmetry (non-bridging structure, like TTR1), was more favorable than C_{2V} symmetry (the bridging structures like TTB1 or TTB2) but for the bridging structures C_{2V} symmetry (TTB2 type) was found to be more stable than C_s symmetry (TTB1 type).



Acetylacetone



Molondialdehyde(C_{2V})



Molondialdehyde(C_s)

Characteristics of protonation of N-acetylpyrrolidone can be summerrized as follows.

(1) The protonation occurs most readily on the ring carbonyl oxygen which has larger negative charge.

(2) In general, the protonation of the *trans-trans* form is preferred to that of the *cis-trans*

form where some steric crowding causes destabilization.

(3) The pentagonal bridging type of protonation is more favored than the hexagonal bridging type of protonation for the *trans-trans* form.

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