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配置와 形態에 관한 分子軌道論的 硏究 (第5報). 이노시톨의 形態

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MO Studieson on Configuration and Conformation (V). Conformation of Inositol

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요 약. EHT 및 CNDO/2 분자궤도법을 사용하여 각종 이노시톨의 형태의 안정성을 결정하였다. EHT 계산결과는 실험사실과 일치하며 산소원자간의 비결합 1,3-상호작용을 올바르게 나타내 주었다. 또 EHT 결과에 따르면 수산기의 수소와 인접 산소간의 퍼텐셜 에너지가 형태 결정의 주요 요소의 하나임을 알 수 있었다. CNDO/2 방법은 고립쌍-고립쌍간의 불안정 요인이 되는 상호작용을 올바르게 나타내주지 못했으며 이것은 1,3-상호작용이 있는 형태의 안정도를 과도하게 나타내었다. 이노시톨의 형태연구에는 CNDO/2 방법보다 EHT 방법이 우수하다.

ABSTRACT. The EHT and CNDO/2 molecular orbital calculations were performed to determine relative stabilities of various conformers of inositol. Our EHT results agree with experimental findings, and correctly predict the destabilizing effect of 1,3-nonbonded interaction of O atoms. In addition, the EHT result show that attractive potential energies between hydoxyl hydrogens and neighboring oxygens are another major factor determining conformational preferences. The inability of CNDO/2 method in predicting correct destabilizing effect of lone pair interaction caused overestimation of stabilization energies for conformers which had 1,3-interactions. The EHT method is superior to the CNDO/2 method for conformational studies of inositols.

INTRODUCTION

The term "cyclitol" is used to describe the polyhydroxy-cyclohexanes, of which the inositols form the most important group. The inositols are particularly suitable model compounds for the study of stereochemistry and conformational effects[1]: they constitute the only group of cyclohexanes substituted on each carbon atom in which every possible diastereomer is known; moreover, the hydroxyl groups, being reactive, allow a great variety of reactions. The more stable conformation for each isomers is readily predicted from the tenets of conformational analysis: it is the chair form which has fewer axial hydroxyl groups[1]. These conformations are shown, together with the distinguishing prefixes of the inositol, for each isomers in *Fig.* 1.

In this paper, we report *semi*-empirical molecular orbital (EHT and CNDO/2)[2] studies on conformations of inositols, particularly on the relative stabilities of the nine chair forms shown in ***Fig.*** 1. The two MO methods used in the calculations are then compared with a view to examine critically the suitability of the methods in conformational studies.

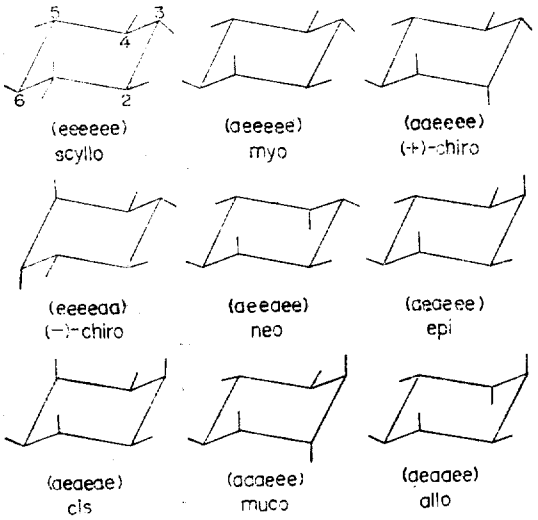

Fig. 1. The nine chair forms of inositol. C_1~C_6 are designated as a or e for axial and equatorial hydroxyl groups.

CALCULATIONS

The EHT and CNDC/2 calculations were carried out on 10 chair forms and one boat form of inositols with standard bond angle of 109.5° and bond lengths of $d_{C-C}=1.53$ Å, $d_{C-O}=1.43$ Å, $d_{C-H}=1.1$ Å and $d_{O-H}=1.0$ Å.[3,4] The hydroxyl hydrogens were fixed using additional parameter θ, the dihedral angle for H-C-O-H. For some cases, the hydroxyl hydrogens are designated as pointing certain atoms (*e. g.* $H_1 \rightarrow O_2$) instead of giving θ values. *Table* 1 contains these geometrical informations used in the calculations. The numbering of atoms is given in *Fig.* 2.

RESULTS AND DISCUSSION

The total energies calculated by EHT method for various chair conformers and a boat form are summarized in *Table* 2. For *scyllo* form the dihedral angles of rotation (θ) of OH bonds about the corresponding C-O bonds are varied uniformly for all the equatorial hydroxyl groups.

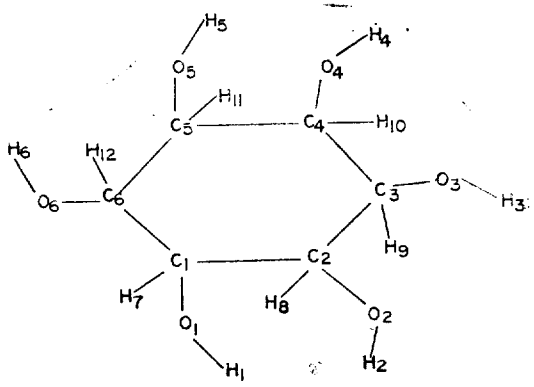

Fig. 2. Numbering of atoms.

Table 1. Geometrical information used in calculation.

Conformer		Geometrical information[a,b]
scyllo,	I	*gauche* $\theta=60°$, for all H-C-O-H
	II	*trans*, $\theta=180°$ for all H-C-O-H
	III	*cis*, $\theta=0°$ for H-C-O-H
myo	I	$\theta=120°$ for axial H-C-O-H; $H_6\rightarrow O_1$, $H_1\rightarrow O_2$
	II	$\theta=180°$ for axial H-C-O-H; $H_6\rightarrow O_1$, $H_1\rightarrow O_2$
	III	$\theta=60°$ for axial H-C-O-H; $H_6\rightarrow H_7$, $H_1\rightarrow O_2$
epi	I	$H_1\rightarrow O_2$, $H_5\rightarrow O_1$, $H_6\rightarrow O_1$
	II	$H_5\rightarrow O_4$, $H_1\rightarrow O_2$, $H_1\rightarrow H_{11}$, $H_6\rightarrow$up
	III	$H_5\rightarrow O_4$, $H_6\rightarrow$up, $H_1\rightarrow O_6$
neo		
(−)-*chiro*		$H_1\rightarrow O_2$, $H_2\rightarrow$out, $H_3\rightarrow O_4$, $H_4\rightarrow O_5$
(+)-*chiro*	I	$H_6\rightarrow$out, $H_5\rightarrow H_6$, $H_2\rightarrow O_1$
	II	$H_6\rightarrow$out, $H_5\rightarrow O_6$, $H_2\rightarrow O_3$
allo		$H_3\rightarrow O_2$, $H_4\rightarrow$out, $H_5\rightarrow O_1$, $H_6\rightarrow O_1$, $H_1\rightarrow O_2$, $H_2\rightarrow O_3$
muco		$H_4\rightarrow O_5$, $H_5\rightarrow O_1$, $H_6\rightarrow$out, $H_1\rightarrow O_2$, $H_2\rightarrow O_3$
cis	I	$H_5\rightarrow O_6$, $H_6\rightarrow O_1$, $H_1\rightarrow O_2$, $H_2\rightarrow O_3$, $H_3\rightarrow O_4$
	II	$H_3\rightarrow O_5$, $H_5\rightarrow O_1$, $H_1\rightarrow O_3$, $H_6\rightarrow O_1$, $H_2\rightarrow O_3$, $H_4\rightarrow O_5$
axial		
boat form (eeeeee)		This means *scyllo*-inositol was changed into boat-form

[a] $\theta=60°$ *i.e.*, *gauche* forms are adopted for all other hydroxyl groups not mentioned in this table except for *scyllo* forms.

[b] $H_i\rightarrow O_j$ indicates that H_i points O_j.

Three forms considered are: I, *gauche* form for which $\theta=60°$; II, *trans* form for which $\theta=180°$; III, *cis* form which $\theta=0°$. In the *gauche* form, all hydroxyl hydrogens are directed to neighboring O atoms so that coulomb attraction becomes maximum and the conformer becomes the most stable one. We therefore kept the *gauche* form for equatorial hydroxyl group wherever it was possible in the determinations of stable conformers in other chair forms. The order of decreasing stability found is; *scyllo*>*myo*>*epi*>*neo*> (−)-*chiro*>*allo*> (+)-*chiro*>*muco*>*cis*. Angyal[5] reported the relative stability of chair conformers based on the equilibrium constants of the complex formation with boric acid as,

scyllo>*myo*>*epi*>*cis*.

Our EHT results in *Table* 2 agree well with this order of stability. On the other hand Rao *et al.*,[4] performed free energy calculations and reported the following order of decreasing stability.

myo>*scyllo*>*neo*>*muco*>*allo*>*epi*>*cis*

This order is somewhat at variance with our EHT results. However, results of these various studies generally agree that *myo* and *scyllo*

Table 2. Summary of the total energies for nineteen conformers of Inositol by EHT method.

		E(eV)	E(kcal/mole)	Order of stability
scyllo	I	−1542.362	standard	1
	II	−1542.222	3.2	6
	III	−1542.019	7.9	14
myo	I	−1542.284	1.8	2
	II	−1542.281	1.9	3
	III	−1542.260	2.4	5
epi	I	−1542.270	2.1	4
	II	−1542.210	3.5	8
	III	−1542.122	5.6	10
neo		−1542.212	3.5	7
(−)-*chiro*		−1542.140	5.1	9
(+)-*chiro*	I	−1642.074	6.7	12
	II	−1542.039	7.5	13
allo		−1542.084	6.4	11
muco		−1542.018	7.9	15
cis	I	−1541.393	22.4	19
	II	−1540.971	32.1	19
axial		−1541.415	21.9	17
boat form (equatorial)		−1541.591	17.8	16

forms are more stable than *muco*, *allo* and *epi* forms. In the latter, there is so-called 1, 3-nonbonded interaction[1,6] of the axial oxygens while no such interaction is present in the former. Thus the EHT calculation correctly predicts the destabilizing effect of the 1, 3-interaction. In the case of *neo* and *chiro* forms, there is no possibility of 1, 3-interaction, but the two axial hydroxyl groups nevertheless have destabilizing effect comparable to the 1, 3-interaction. Comparison of energy value for *scyllo* III (*cis-scyllo*) with that of *scyllo* I (*gauche-scyllo*) provides us some insights into the nature of this destabilizing effect: although *scyllo* III has no axial hydroxyl group, it is actually less stable than *epi*-I which has 1, 3-axial oxygen destabilizing interaction. The *scyllo* III (and II) has all the hydroxyl hydrogen pointed away from O atoms causing less attractive potential energy and hence less stability. In the *neo* and *chiro* forms, the presence of axial OH groups force some of the hydroxyl hydrogens to point away from neighboring O atoms, causing destabilization due to the decrease in attractive potential energies. This indicates that the attractive potential between hydroxyl hydrogen and neighboring O atom is one of the major factor determining conformational stability.

The *cis* (aeaeae) and axial (aaaaaa) forms have similar energies which are much greater than *epi* (aeaeee) form. This also shows that 1, 3-nonbonded interaction alone is not responsible for the conformational stability; the *cis* and axial forms have three-fold and six-fold 1, 3-interactions respectively while the *epi* has single 1, 3-interaction. Thus energies are not linearly correlated with the degree of 1, 3-interaction.

We have also calculated the FHT energy for boat form which contained equatorial hydroxyl groups only. (This means *scyllo*-inositol was changed into boat-form.) The energy obtained is less than those for *cis* and axial forms as expected, since the boat form dontained no axial hydroxyl group.

The CNDO/2 energies for some inositols are summarized in *Table* 3. And the order of stibility is

$$muco > allo > epi > scyllo > (-)chiro > myo > neo > \text{boat} > cis$$

First of all, we note that the order of stability is quite different from that obtained with the EHT calculations. The principal difference is the reversal of order of stability for *muco*, *allo* and *epi* as compared with *scyllo* and *epi*; the former three are now more stable than the *scyllo* inspite of their 1, 3-nonbonded interac-

Table 3. CNDO/2 energy component analysis far Inositols (kcal/mole).

	ΔE_T[a]	$-\Delta V_{ne}$[b]	ΔV_{ee}[c]	ΔV_{nn}[d]	$\mu(D)$[e]
muco	−2.9	22137.2	11094.7	11036.6	2.68
allo	−1.4	24060.0	12031.9	12025.1	3.39
epi I	−1.1	21297.0	10624.0	10670.8	2.79
scyllo I	0.0	0.0	0.0	0.0	0.00
scyllo II	18.1	2462.3	1154.4	1344.1	0.01
scyllo III	7.0	−2305.9	−1982.6	−1199.4	0.00
(−)-*chiro*	0.3	12223.0	6132.1	6091.4	2.97
myo I	0.8	7580.6	3799.1	3782.9	0.00
neo	1.3	14000.0	7013.2	6989.4	0.00
boat	5.8	8900.2	4451.6	4460.2	2.00
cis I	88.2	31676.0	16114.9	15737.6	3.05

[a] The difference in total energy. [b] The negative value of the difference in attractive potential; the increase of this value indicates more attration and stabilizing, whereas the decrease indicates less attraction and destabilizing. [c] The difference in electron-electron repulsion potential. [d] The difference in nuclear-nuclear repulsive potential. [e]Dipole moment in Deoye unit.

tions.

This is due to a well-known recognized weakness of the CNDO method:[7] CNDO (and INDO) closed-shell restricted Hartree-Fock MO method is unable to account properly for nonbonded interactions and give too much stability to systems containing N and/or O atoms separated from one another or from π bonds by less than 4 Å. When diatomic overlap is neglected (as in CNDO, INDO, MINDO methods) the "closed-shell" or "exchange" repulsion, which takes into account the greater destabilizing interaction of two lone-pair electrons, is also neglected and overestimates stabilization energies.

Energy comeponent analysis in *Table* 3 show that for *muco*, *allo* and *epi* forms the increase in attractive potential energy is greater than the increase in repulsive potential energies, *i.e.*,

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

Thus, the lone pair repulsive interactions of 1, 3-axial oxygens are underestimated due to the complete neglect of diatomic overlaps. Our results therefore provide unequivocal evidence that the CNDO/2 method is not reliable for the conformational studies of compounds which have direct σ-type interaction between two lone pairs; in this respect, the EHT method is superior and correctly predicts relative stabilities of conformers having atoms with lone pair electrons.

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