

# STUDIES OF THE FAVOURED CONFORMATIONS OF CYCLOHEXANEDIOLS AND CYCLITOLS BY THE EXTENDED HÜCKEL MO (EHMO) METHOD

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## ABSTRACT

The favoured conformations of the cyclohexanediols and cyclitols have been examined by taking into account non-bonded interactions and restricted rotation of hydroxyl groups. Calculations using the extended Hückel MO (EHMO) method<sup>1</sup> have been performed to determine the conformational energy. The conformations with equatorial hydroxyl groups and with certain orientations of hydroxyl protons are shown to be the most stable.

## INTRODUCTION

The MO-LCAO method of Del Re, which takes into account only the sequence of bonds in molecules and their empirical parameters, has been employed in earlier papers<sup>2-4</sup> to calculate the  $\sigma$ -electron structure of certain carbohydrates. These calculations, however, are not able to estimate the contribution of conformational energy to the total energy of a molecule.

An attempt<sup>5,6</sup> to estimate such a contribution was based on the calculation of non-bonded interaction energy between a pair of atoms using the Kitaigorodsky type of potential functions<sup>7</sup>. Coulombic contribution to the potential energy was also taken into account<sup>4</sup> in calculating the total energy, this contribution being based on both atomic distances and partial  $\sigma$ -charges.

The positions of the hydroxyl protons in carbohydrates are uncertain because of free rotation about the C-O bond. However, this problem was solved<sup>4-6</sup> by calculation of the positions of hydroxyl protons corresponding to minimum energy. Similar calculations based on a more-exact, extended Hückel method are now reported for model cyclohexane systems.

## RESULTS AND DISCUSSION

### *Theoretical treatment*

The calculations were performed on a BESM-4 computer, with the Hoffman<sup>1</sup> EHMO programme. The orbital exponents<sup>8</sup> ( $\mu$ ) and the ionization potentials used

for  $H_{ii}$  values are listed in Table I. The off-diagonal elements  $H_{ij}$  were calculated by using the Wolfsberg-Helmholtz expression<sup>9</sup>  $H_{ij} = 0.5 K (H_{ii} + H_{jj}) S_{ij}$ , where  $K$  is taken as 1.75. The atomic co-ordinates for various atoms were calculated from the bond lengths and valency angles<sup>10</sup> given in Table II.

TABLE I

ORBITAL EXPONENTS AND IONIZATION POTENTIALS

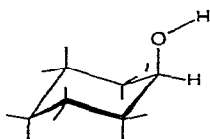
Atoms	Type of atomic orbital	Exponent	Ionization potential (eV)	References
H	1s	1.2	-13.60	11,13
C	2s	1.6083	-21.43	12,13
	2p	1.5679	-11.42	
O	2s	2.2458	-35.30	12,13
	2p	2.2266	-17.76	

TABLE II

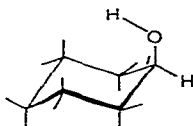
BOND LENGTHS AND VALENCY ANGLES

Bond length (Å)		Valency angles (degrees)	
C-C	1.528	C-C-C	111.6
C-O	1.43	H-C-C	109.5
C-H	1.1	O-C-C	109.5
O-H	0.96	H-O-C	109.5

If the rotational angle between the planes  $OC_1H$  and  $HOC_1$  is denoted by  $\theta$ , then the positions at  $\theta_1 = 0^\circ$  (1) and at  $\theta_1 = 180^\circ$  (2) correspond to fully eclipsed and staggered orientations between the C-H and O-H bonds, respectively, in cyclohexa-

Eclipsed conformation  $\theta = 0^\circ$ 

1

Staggered conformation,  $\theta = 180^\circ$ 

2

nol. It should be noted that the identity of energy contributions of hydroxyl groups in the same conformation and at equal  $\theta$ , follows from such choice of  $\theta$ , zero-value that was confirmed further by calculations.

We have calculated the total energy for cyclohexane to be  $-633.764$  eV for the chair form, and  $-633.380$  eV for the boat form, and find that the energy difference between these forms is  $\sim 8.8$  kcal/mole, which is in satisfactory agreement with the reported<sup>10</sup> value of  $6.9$  kcal/mole.

The energy of cyclohexanol has been calculated for the chair conformations having equatorial and axial hydroxyl groups. Minimum and maximum energy corresponds in both cases to  $\theta = 180^\circ$  and  $0^\circ$ , respectively, the difference being 1.22 kcal/mole for the axial hydroxyl group and 0.97 kcal/mole for the equatorial hydroxyl group. These results are in reasonable agreement with those of Allinger *et al.*<sup>8</sup> who used an entirely different method of calculation. The minimum energy for the axial hydroxyl group is 0.49 kcal/mole higher than the minimum energy for the equatorial hydroxyl group, which is in good agreement with previously reported data<sup>10</sup>. The calculated energies are listed in Table III, with the rotational angle  $\theta$  being taken at intervals of  $30^\circ$ . Taking into account the identity of the values for  $E(\theta)$  and  $E(360^\circ - \theta)$ , Table III contains all the necessary data. Differences between energies corresponding to different rotational angles  $\theta$ , and minimum energy (at  $\theta = 180^\circ$ ) are also given. The respective potential energy diagrams are shown in Fig. 1.

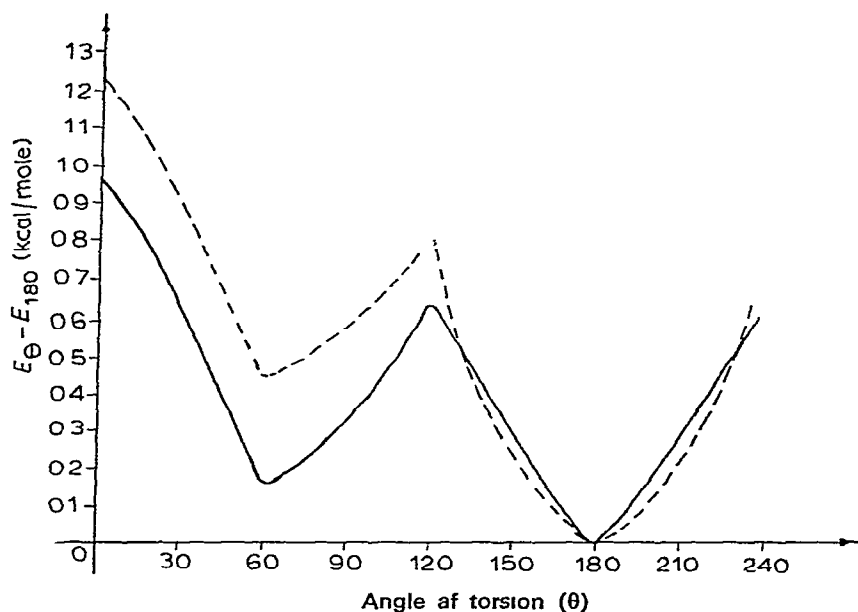


Fig. 1 Potential energy diagrams for the chair forms of cyclohexanol —, equatorial hydroxyl group, ----, axial hydroxyl group

In order to discuss cyclohexanediols, further assumptions are necessary. If the energies of cyclohexane and cyclohexanol are denoted by  $E_0$  and  $E_i$ , respectively, then the difference  $\Delta E_i = E_i - E_0$  is the energy contribution of the hydroxyl group. Hence, the total energy of cyclohexanol is expressed as

$$E_i = E_0 + \Delta E_i \quad (1)$$

Considering the hydroxyl groups of cyclohexane-*i,j*-diol as bonded to the *i*-th and *j*-th carbon atoms, respectively, let the energy of the cyclohexanediol be

denoted by  $E_{ij}$ . Let us suppose further that these hydroxyl groups do not interact. Hence, the total energy of cyclohexane- $i,j$ -diol is expressed by the additive formula

$$E_{ij} = E_0 + \Delta E_i + \Delta E_j \quad (2)$$

It is of interest to compare energies of cyclohexanediols calculated by expression (2) with those calculated by the Hoffman<sup>1</sup> method. Thus, for cyclohexane-*cis*-1,4-diol

TABLE III

ENERGY OF CYCLOHEXANOL AT DIFFERENT ROTATIONAL ANGLES

<i>Axial hydroxyl group</i>			<i>Equatorial hydroxyl group</i>	
	<i>Energy</i> $E(\theta_i)$ (eV)	$E(\theta_i) - E(180^\circ)$ (kcal/mole)	<i>Energy</i> $E(\theta_i)$ (eV)	$E(\theta_i) - E(180^\circ)$ (kcal/mole)
0°	-781.426	1.22	-781.458	0.97
30°	-781.440	0.88	-781.473	0.61
60°	-781.460	0.43	-781.493	0.15
90°	-781.453	0.58	-781.485	0.33
120°	-781.4444	0.80	-781.472	0.65
150°	-781.469	0.22	-781.488	0.28
180°	-781.479	0	-781.500	0
210°	-781.469	0.22	-781.488	0.28

with  $\theta_1 = \theta_4 = 0^\circ$ , the Hoffman energy is  $-929.0879$  eV, whereas the energy calculated by formula (2) is  $-929.0875$  eV, the difference ( $0.0004$  eV) being  $\sim 9$  cal/mole. This value shows that hydroxyl interaction in cyclohexane-*cis*-1,4-diol is negligible. Indeed, the distances between the oxygen and hydrogen atoms of the respective hydroxyl groups are great, being  $4.56$  and  $6.36$  Å respectively. It follows from these assumptions that the divergence of the energy values calculated by the Hoffman method and by the additive formula (2) may be considered as the energy of interaction of the hydroxyl groups.

Table III shows that minimum energy contribution is associated with a hydroxyl group having  $\theta = 180^\circ$ . Additive calculations result in the same minimum energy for all cyclohexane- $i,j$ -diol isomers at  $\theta_i = \theta_j = 180^\circ$ . However, the Hoffman method gives different values of energy for different isomers in the same conformations, the minimum energy being observed not only for  $\theta_i = \theta_j = 180^\circ$ , such as in the cases of the diaxial conformation of cyclohexane-1,3-diol and the diequatorial conformation of cyclohexane-1,2-diol. In Table IV, the minimum Hoffman energies are listed together with the divergences of these values from those of the additive scheme, the distances between the oxygen and hydrogen atoms of the hydroxyl groups, and values of the rotational angles  $\theta_i$  and  $\theta_j$ .

It follows from these calculations that the greatest energy difference between the Hoffman and additive-scheme energies (ranging from  $0.4$  to  $1.9$  kcal/mole) is observed in cyclohexane-1,2-diol, which is indicative of the strong interaction of

vicinal hydroxyl groups For the other cyclohexanediols, the difference is negligible and does not exceed 0.067 kcal/mole

For each cyclohexanediol isomer, the calculated order of stability of the conformations is equatorial-equatorial, equatorial-axial, axial-axial (see Table IV)

TABLE IV  
CALCULATED ENERGIES OF THE CYCLOHEXANEDIOLS

Isomer	Conformation	Energy (eV)	Divergence from additive scheme $E_{ij} - E_{ad}$ (kcal/mole)	$\theta_1, \theta_2$	HO separation distances (Å)	
					O-O	H-H
<i>trans</i> -1,4	(ax,ax)	-929.191	+0.066		4.56	4.31
<i>cis</i> -1,4	(ax,eq)	-929.214	+0.011	180°, 180°	4.56	3.53
<i>trans</i> -1,4	(eq,eq)	-929.233	+0.067		5.61	6.04
<i>cis</i> -1,3	(ax,ax)	-929.163	+0.050	60°, 150°	2.72	2.69
<i>trans</i> -1,3	(ax,eq)	-929.217	-0.047	180°, 180°	4.29	4.56
<i>cis</i> -1,3	(eq,eq)	-929.238	-0.046		4.83	4.76
<i>trans</i> -1,2	(ax,ax)	-929.111	+1.908	180°, 180°	3.66	4.14
<i>cis</i> -1,2	(ax,eq)	-929.183	+0.731		2.77	2.59
<i>trans</i> -1,2	(eq,eq)	-929.207	+0.366	60°, 60°	2.35	3.34

For the isomers in diaxial conformation, cyclohexane-1,4-diol has the minimum energy and cyclohexane-1,2-diol has the maximum energy. This difference may be explained by taking into consideration the fact that the dipole-dipole interaction which destabilises a molecule decreases with increasing distance between hydroxyl groups, as shown in formulae 3-5 (see also Table IV).

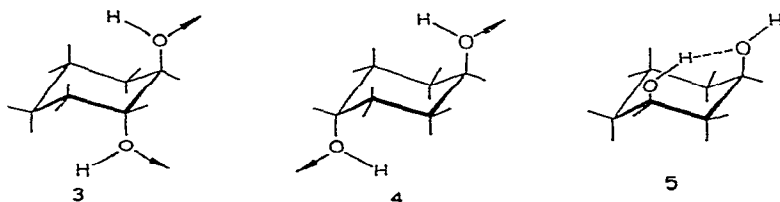
Cyclohexane-1,3-diol in the diaxial conformation has minimum energy at  $\theta_1 = 60^\circ$ ,  $\theta_2 = 150^\circ$ , which might be due to the formation of a hydrogen bond, as shown in 5, thereby stabilizing the molecule.

For isomers in axial-equatorial and equatorial-equatorial conformations, cyclohexane-*trans*-1,3-diol has minimum energy, whereas cyclohexane-*trans*-1,2-diol has maximum energy (see Table IV).

As in the case of the diaxial conformation of cyclohexane-*cis*-1,3-diol, the diequatorial conformation of the *trans*-1,2-diol has no energy minimum at  $\theta_1 = \theta_2 = 180^\circ$ , as anticipated by calculations using the additive scheme. The minimum is reached when  $\theta_1 = \theta_2 = 60^\circ$ , and this phenomenon can be also explained in terms of the formation of a weak hydrogen bond. The possibility of intramolecular hydrogen-bond formation in *cis* (eq,ax) and *trans* (eq,eq) cyclohexane-1,2-diol was recognised by Orloff<sup>14</sup>. The fact that the energies of the axial-axial conformation of cyclohexane-*cis*-1,3-diol and the equatorial-equatorial conformation of cyclohexane-*trans*-1,2-diol are fairly great, in spite of the possibility of intramolecular hydrogen-bond formation, follows from over-emphasis of steric factors inherent in the Hoffman method. During

the calculation of the divergence of the energies derived by the Hoffman and additive schemes for cyclohexane-*cis*-1,3-diol and cyclohexane-*trans*-1,2-diol, the deviation of the rotational angles from 180° was taken into consideration.

Calculations also show that isomers of cyclohexane-1,3-diol and cyclohexane-1,4-diol cannot be separated because of the small differences in their energies. This situation was also mentioned by Orloff<sup>14</sup>.



For the inositols, the number of possible combinations of axial and equatorial orientations of six hydroxyl groups is 64. Ignoring the enantiomeric forms having equal energies, only 13 isomers must be taken into account. Calculated energies of the isomers at  $\theta_i = 0^\circ$  ( $i = 1, 2 \dots 6$ ) are listed in Table V. The results are in agreement with a general principle of conformational analysis, namely that substituent groups on a cyclohexane ring are more stable in the equatorial than in the axial positions. As expected, *scyllo*-inositol (with all equatorial hydroxyl groups) and *myo*-inositol (with one axial hydroxyl group) are the most stable. The conformation of *scyllo*-inositol with all axial hydroxyl groups is the most unstable, having an energy  $\sim 9.5$  kcal/mole more than that of the preferred conformation. In Table V, the differences in energies between each isomer and *scyllo*-inositol, as calculated by the Hoffman method and as

TABLE V

CALCULATED ENERGIES OF THE INOSITOLS

Inositol	Hydroxyl configuration	No of axial hydroxyl groups	Energy (eV)	$E_i - E_{\text{scyllo}}$ (kcal/mole)	
				Calc.	From ref. 15
<i>scyllo</i>	1e2e3e4e5e6e	0	-1519 768	0	0
<i>myo</i>	1a2e3e4e5e6e	1	-1519 724	1 01	0 9
<i>neo</i>	1a2e3e4a5e6e	2	-1519 682	1 99	
<i>epi</i>	1a2e3e4e5a6e		-1519 675	2 15	2 8
<i>dextro</i>	1a2a3e4e5e6e		-1519 659	2 51	
<i>cis</i>	1a2e3a4e5a6e	3	-1519 621	3 40	5.7
<i>allo</i>	1a2c3a4a5c6c		-1519 610	3 64	
<i>muco</i>	1a2a3a4e5e6e		-1519 592	4 06	
	1a2a3e4a5a6e	4	-1519 538	5 31	
	1a2e3a4e5a6a		-1519 537	5 32	
	1a2a3e4e5a6a		-1519 524	5 63	
	1a2a3a4a5a6e	5	-1519.449	7 36	
	1a2a3a4a5a6a	6	-1519 357	9 48	

obtained by Angyal and McHugh<sup>15</sup>, are also listed. Of the inositols having equal numbers of axial hydroxyl groups, the most stable are those where axial hydroxyl groups are maximally separated. These results are similar to those obtained for the cyclohexanediols.

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