The Use of a Molecular Orbital Approach to the Conformational Analysis of Glucopyranose

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Using molecular orbital theory, calculations of the preferred conformation of α-D-glucopyranose were made. These were predicted from total energy minimization as a function of geometry. The calculations indicated a stable conformation of glucose that was identical with the prediction made on the basis of cuprammonium complexes. The use of quantum chemistry in analyzing the properties of biologically important molecules continues to be very promising.

One of the long-range goals in this laboratory is to design greater and greater specificity and selectivity into our biological agents. First, more must be learned about the respective roles that the conformation and reactivity[1] of drugs play in controlling or modifying biological reactions.

It is conceivable, for example, that contact between an enzyme and a substrate might occur when the latter was in an unusual high-energy conformation. Such a conformation might provide the energy necessary to drive the reaction to completion. An example of this type of argument based on keto–enol tautomerism was used to explain some results of various inhibitors of the dihydrofolic acid reductase system.[1b,2] Shape also has an important function as far as reactivity is concerned. This was originally demonstrated by Barton[3] who pointed out the chemical consequences of the difference between equatorial and axial substituents in cyclohexane (see also ref 4).

The problem of studying conformational analysis from a quantitative point of view lies with the difficulty in measuring the energies of the various conformers. The present investigation is an attempt to use molecular orbital calculations as a tool for determining these energies. The compounds that will be treated by this technique are various conformations of α-D-glucopyranose. These were chosen for two reasons: (1) Reeves[5] has examined the complexes of sugars in cuprammonium solution and was able to measure which conformations were the most stable; consequently, it is possible to compare the present theoretical analysis with his experimental data; (2) the pyranose structure is a reasonably complicated structure of great biological importance and the analysis will provide both a rationale for examining structures where experimental data are lacking as well as interpreting the reactivity of glucopyranose.

The molecular orbital approach used in this study is the extension of the Hückel technique by Hoffmann[6] generally referred to as EHT. The method has met with considerable success in calculating the preferred conformations of hydrocarbons, both aliphatic and aromatic.[7–13] A theoretical analysis of EHT by Allen and Russell[14] has given credence to the use of this quantum mechanical treatment for predicting conformational energies.

Experimental Section

Calculations.—The valence-state ionization potentials in electron volts were taken from Pritchard and Skinner.[15] For C they were −21.4 for the 2s electrons and −11.4 for the 2p electrons. Oxygen had values of −35.30 and −17.76 for the 2s and 2p electrons, respectively. The computer program is essentially the same as used by Hoffmann.[6]

Coordinate system.—The bond distances (in Ångstroms) used in these calculations were as follows: C–C = 1.54, C–H = 1.09, C–O = 1.46, and O–H = 0.96. The tetrahedral angle of 109° was assumed for all bond angles. The coordinate system was found by an application of simple trigonometrical ratios. The complete coordinate system is available upon request. The glucose conformations that were studied are shown in Figure 1. All of the interatomic distances are output from the program and the values may be compared with measured values from wire models. This serves as a useful check on the coordinate system adopted.

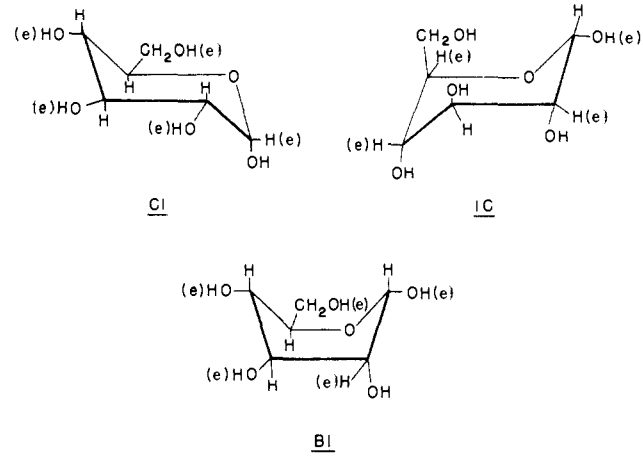

Figure 1.—The three conformations of α-D-glucopyranose that were studied. The β-D-glucose is conformation C1 with the anomeric OH in the equatorial position. The galactose studied is C1 above with the OH at carbon 4 in an axial position.

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Results

The total energy of the various sugars as calculated by EHT is shown in Table I. This energy is twice the sum of the energies of all occupied orbitals, to account for the double electron occupancy. The conformer having the lowest calculated total energy is assumed to be the most stable. The calculated net charge densities for the various atoms in the stable glucose conformer were also calculated; the values for the carbon atoms are shown in Table II.

Table I

Total Energy of Various Conformations of Glucose and Related Sugars

		EHT	
Sugar	Conformation	Energy, kcal	Difference[a]
Glucopyranose	α-D-C1[b]	−34,969	0
	β-D-C1	−34,978	−9
	α-D-1C	−34,920	+48
	α-D-B1	−34,963	+6
Galactopyranose	α-D-C1	−34,958	+11

[a] This represents the difference in kilocalories between glucose in the α-D-C1 conformation and the other types. A negative difference indicates a structure that is energetically more stable. [b] This is the designation used by Reeves[5c] for the various chair and boat conformations.

Table II

Total Net Charge Density for the Carbon Atoms in Glucopyranose (C1 Conformation)

Atom[a]	Charge[b]	Net charge
C-1	2.924	1.076
C-2	3.524	0.476
C-3	3.504	0.496
C-4	3.469	0.531
C-5	3.476	0.524
C-6	3.656	0.344

[a] C-1 is the anomeric carbon while C-6 represents the terminal carbon. [b] The charges on the various oxygens and hydrogens did not show any interesting differences.

It must be remembered that the absolute value of these calculations is not important. What is important is the relative differences and the concepts that these relative differences translate into a quantitative language.

Discussion

Using the values for the interaction energies, the anomeric effect, and the Δ2 conditions as discussed by Angyal,[16] the nonbonded energies of the sugar conformations were determined (Table III). It is interesting to note that these calculations agree in a relative way with the calculations made by EHT (Tables I and III) in this study and agree with the observations made by Reeves.[5] In other words, the C1 conformation of α-D-glucopyranose is the most stable, and conversion of the α isomer of glucose to the β form results in a still more stable molecule. This, again, reflects the observation that in mutarotation experiments there is a higher concentration of the β-D-glucose at equilibrium. Finally, the axial hydroxyl on C-4 in galactose causes this sugar to have a smaller total energy and, hence, is more unstable than the corresponding glucose where the hydroxyl group is equatorial.

Table III

Total Calculated Interaction Energies (in kcal/mole) of the Sugars in Table I

		Calcd energies		
		EHT	I	II
Sugar	Conformation	(this work)	(ref 12)	(ref 17)
Glucopyranose	α-D-C1	0	2.3	1.00
	β-D-C1	−9	1.95	
	α-D-1C	48	7.1	11.88
	α-D-B1	6	2.4	4.79
Galactopyranose	α-D-C1	11	3.2	

Rao[17] has recently made use of the Buckingham potential-energy function to calculate the nonbonded interaction energy in the various conformations of α-D-glucopyranose. His results where applicable are shown in Table III. It is seen from this table that the absolute values for the energies vary with the method used. However, each method places the conformations in the same relative order of stability.

Finally, the electron-distribution data in Table II is in line with experimental observations that the anomeric carbon is the most reactive center for nucleophilic attack. It will be interesting to investigate the electron distribution of the glucosides to see which of the remaining carbons is the most reactive.

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(16) Reference 4, p 378.

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