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Note

MM2 calculation of the chair–boat equilibrium of 1,6-anhydro-β-D-glucopyranose

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1,6-Anhydro-β-D-glucopyranose is a useful synthon in preparative carbohydrate chemistry[1], and the regioselectivity of derivatisation reactions, such as esterification[2] and etherification[3] of HO-2 and HO-4, may depend on its conformation. According to X-ray studies, the $^1C_4$ conformation **1** is present in the crystalline state[4]. ^{1}H-N.m.r. studies in D_2O[5,6] or $(CD_3)_2SO$[6,7] show that this is also the preponderant conformation in solution.

The course of the acid-catalysed butanolysis of 1,6-anhydro-β-D-glucopyranose towards butyl α- (**5α**) and β-D-glucopyranoside (**5β**), however, is best explicable by assuming the $B_{o,3}$ conformation **2** as an intermediate[8]. The presence of this boat form is conceivable by analogy with the 3-amino-3-deoxy derivative of 1,6-anhydro-β-D-glucopyranose, which exists[9] as a 1:1 mixture of chair and boat conformations in solution in $(CD_3)_2SO$.

Using Allinger's MM2 force field adapted for the anomeric effect[10] and hydrogen bonding[11], we have carried out energy minimizations for the HO rotamers of the $^1C_4$ (**1**) and $B_{o,3}$ (**2**) forms of 1,6-anhydro-β-D-glucopyranose.

Chair forms. — From the 27 starting points with staggered torsion angles around the O-2–C-2, O-3–C-3, and O-4–C-4 bonds, 20 different $^1C_4$ energy minima were obtained. The populations of the HO rotamers were calculated from the Gibbs energy differences (Table I) and only forms with either HO-2 or HO-4 *anti* appear to be abundant. This situation is caused by the favourable dipole–dipole interactions and hydrogen bonds of these HO groups with each other and with O-5. Energy minima, which lack this feature, comprise <1% of the population of $^1C_4$ forms. No energy minima were found for conformations in which *both* HO-2 and HO-4 are *anti* because of the severe van der Waals repulsion when the two hydrogen atoms are in the same region under the ring. The rotamers with HO-3 *anti* have a favourable interaction of this group with O-6. The steric hindrance from

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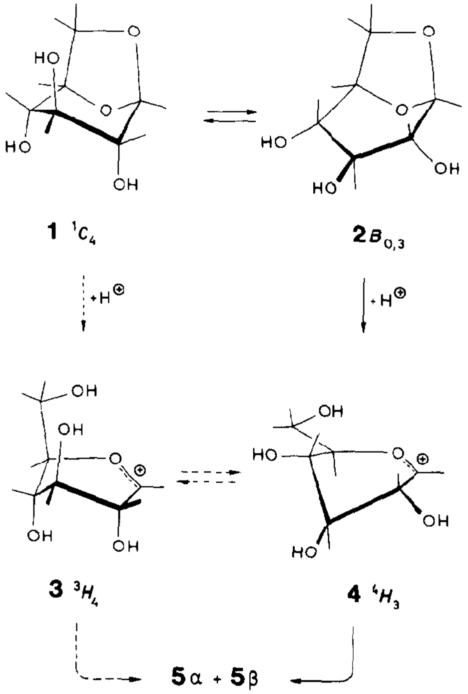


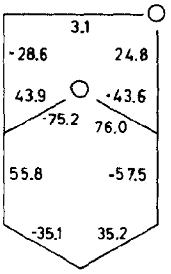
TABLE I

PERCENTAGES OF THE MOST ABUNDANT ROTAMERS OF THE $^{1}C_{4}$ (**1**) AND $B_{o,3}$ (**2**) FORMS OF 1,6-ANHYDRO-β-D-GLUCOPYRANOSE AT 25°

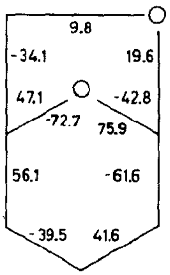
Conformation	*Torsion angles H–O–C–H (°)*			ΔE_{steric} *(kcal.mol⁻¹)*	*Percentage*[a]
	HO-2	*HO-3*	*HO-4*		
$^{1}C_{4}$	−179	148	−49	0[b]	17.2
	−179	57	−46	0.58	12.5
	50	154	178	0.26	10.9
	175	50	60	0.87	9.4
	45	−44	178	0.79	9.2
	−56	−35	−177	1.07	7.9
	−59	36	−177	1.17	7.2
	173	144	54	0.71	6.6
	49	40	177	1.27	6.1
	−54	152	−174	1.12	3.6
$B_{o,3}$	−46	58	−64	2.16	3.4
	65	−53	48	2.55	1.7
	−170	64	−62	3.24	1.6
	62	−58	170	2.57	1.2

[a] Calculated from the Gibbs energy differences at 25°. The combined percentage of the remaining 10 chair forms is 0.8% and that of the remaining 7 boat forms is 0.7%. All values are rounded off. [b] E_{steric} = 23.787 kcal.mol⁻¹.

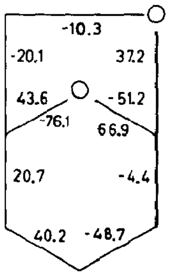
H-6*endo* decreases the HO-3 torsion angle to ~150°. Derivatives of 1,6-anhydro-β-D-glucopyranose show $^3J_{H,OH}$ values[2] in accordance with these results. Surprisingly, an energy minimum corresponding to the HO rotamer present in the crystal (HO-2 −165°, HO-3 −20°, and HO-4 −38°)[4] could not be located, although forms with HO-2 *anti* and HO-4 − *gauche* are the most abundant. Changing the torsion angle[12] HO-3 in the conformer with ΔE 0.58 kcal.mol^{-1} from 57° through 0° to −98° in steps of −5° did not reveal an energy minimum. In the crystal, the torsion angles involving the HO bonds are determined strongly by intermolecular hydrogen bonds[4]. This situation may explain also the rather large differences between the experimental and the calculated values of the endocyclic torsion angles of the five- and six-membered rings. A comparison between the values[4] for the solid state and those calculated for the global $^1C_4$ minimum is given in **6**–**7**. The larger puckering along most bonds in the calculated geometry, **7**, can be explained by the intramolecular hydrogen bonds.



6 X - ray



7 $^1C_4$ calculated



8 $B_{0,3}$ calculated

Boat forms. — From the 27 initial geometries of the boat conformation with staggered HOCH torsion angles, 11 different $B_{o,3}$ energy minima were obtained (Table I). The torsion angles calculated for the global $B_{o,3}$ minimum are given in **8**. Strong interactions of the hydroxyl groups and O-5 or O-6 are not possible in **2**. In the four most abundant $B_{o,3}$ forms, the alignment of the HO bonds of the three equatorial hydroxyl groups is such that two hydrogen bonds are present and HO-3 is both donor and acceptor. Each of the less abundant $B_{o,3}$ forms has only one hydrogen bond between the hydroxyl groups. No minima are present in which the hydrogen atoms of two vicinal hydroxyl groups clash in the same region (HO-2/HO-3 +*gauche*/+*gauche* or HO-3/HO-4 −*gauche*/−*gauche*).

Chair–boat equilibrium. — Table I indicates that the $^1C_4$ forms are much more abundant than the $B_{o,3}$ forms. At 25°, the overall ratio between chair and boat forms is 91.4:8.6 when based upon Gibbs energy differences. Entropy differences favour the boat forms and the ratio increases to ~98:2 when they are ignored. The former ratio corresponds to a Gibbs energy difference of 1.4 kcal.mol^{-1}. The calculated Gibbs energy difference between the chair and boat forms of the 2,3,4-trideoxy-2,3,4-tri-*C*-methyl derivative of 1,6-anhydro-β-D-glucopyranose amounts to 0.3 kcal.mol^{-1}. Thus, it is concluded that the net result of the intramolecular hydrogen bonding in 1,6-anhydro-β-D-glucopyranose favours the population of $^1C_4$ forms.

Implications for butanolysis. — The rate-determining step in the acid-catalysed butanolysis of 1,6-anhydro-β-D-glucopyranose to butyl α- (**5α**) and β-D-glucopyranoside (**5β**) is supposed to be the cleavage of the C-1–O-6 bond in O-6-protonated 1,6-anhydro-β-D-glucopyranose, with the formation of the oxycarbonium ions **3** and **4** as intermediates energetically close to the transition state[8]. Molecular mechanics calculations on these oxycarbonium ions are not possible because no force-field parameters are available. However, it can be predicted that the $^3H_4$ form **3** will be destabilised relative to the $^4H_3$ form **4** because the substituents occupy axial positions and the positive charge on O-5 will diminish the strengths of the hydrogen bonding with HO-2 and HO-4. This hydrogen bonding plays a major role in the stabilisation of **1** over **2**. The energy of activation to convert the $^1C_4$ form **1** into the $B_{0,3}$ form **2** will be lower than that of the C–O bond cleavage, so probably the reaction path of the butanolysis of 1,6-anhydro-β-D-glucopyranose contains the $B_{0,3}$ form **2** and the $^4H_3$ form **4**.

EXPERIMENTAL

The calculations were carried out using DELPHI, the Delft Computer Program for Molecular Mechanics[12]. This program now contains an option to generate initial geometries in internal co-ordinates for all possible combinations of rotational forms around up to ten torsion angles. All energy minima are characterised by six zero eigenvalues of the final force constants matrix. The entropies are calculated using statistical thermodynamics[13] and the harmonic approximation of the vibrational levels.

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