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WHEN LOCAL CROWDING REINFORCES AN ANOMERIC EFFECT

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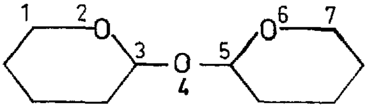
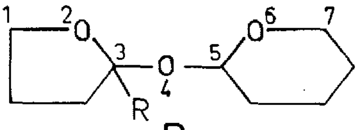
ABSTRACT.- In furanose-pyranose structures, a bulky substituent at the anomeric center of the furanose ring induces an axial conformation of the pyranosic part. The relative positions of the two rings are also modified: syn instead of anti with regard to the C-3/O-4/C-5 plane. These conformational adaptations are monitored by a subtle balance between anomeric effects and non bonded atom interactions.

We report some results concerning the structure of complex disaccharides **A** and **B**.



A



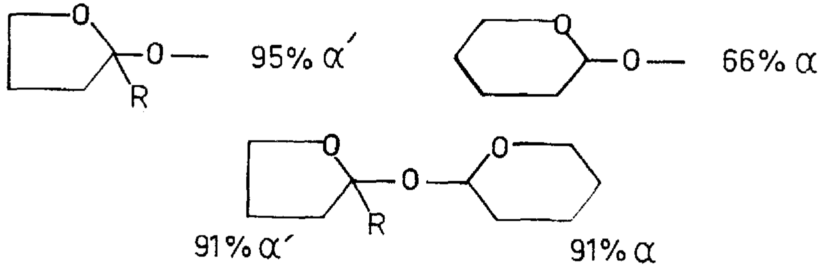
B

The axial orientations of exocyclic CO bonds are controlled by two (endo) anomeric effects and some special stress due to the R group on the furanose ring.

One would expect the O-2 and O-6 oxygens to orient axially, and independently, C-3/O-4 and O-4/C-5 bonds. On the contrary, our statistical study of 677 COCOC fragments taken from the Cambridge Crystallographic Database (CCD) (1) shows an important enhancement of the axial orientation for the pyranose ring in **B** structures.

Occurrence of axial and pseudoaxial conformers

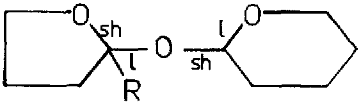
In **A** structures, the occurrence of axial α conformers (66%) is comparable to that observed in CCD for methoxypyranoses (70%) or acetoxypyranoses (63%). For **B** structures, the diagram below summarizes our analysis: i) similar axial (α) or pseudoaxial (α') orientations for the five-membered ring, either isolated (95%) (2) or included in the **B** structure; ii) on the contrary, an enhanced axial orientation (from 66% to 91%) for the pyranose ring included in the **B** structure.



Nearly all the **B** structures studied have a bulky (R ≠ H) substituent (5 to 26 atoms). Under these conditions, we can posit the following rule: in **B** compounds, the R bulky substituent provokes the axial orientation of the pyranose ring.

Short and long CO bond lengths

Bond lengths are good indicators of the n/σ^* "conjugation" between a lone pair of oxygens and the σ^* antibonding orbitals of neighboring polar bonds, conjugation related to the conformational anomeric effect (3). In the hindered αα' **B** structures (R ≠ H), we observed a specific alternation between short (sh) and long) (ℓ) CO bond lengths, illustrating a **dominant endoanomeric effect for the furanose ring** and a **dominant exoanomeric effect for the pyranose ring.** It should be noticed that these dominant effects are precisely those for which the torsion angles Φ endo 1 (1-2-3-4) and Φ exo 2 (3-4-5-6) are close to 90°. This important fact may be related to the non equivalence of oxygen lone pairs (4,5).



Conformational changes induced by the R substituent

The three dimensional representation of **A** structures (PLUTO program (1), fig. 1) shows the two pyranose rings located on different sides of the C-3/O-4/C-5 plane. The single **B** structure with a tertiary **C-3** carbon (R = H) at our disposal behaves in the same way. On the other hand, the **B** structures with a quaternary C-3 carbon (R ≠ H) show two **syn** rings, located on the same side of the C-3/O-4/C-5 plane.

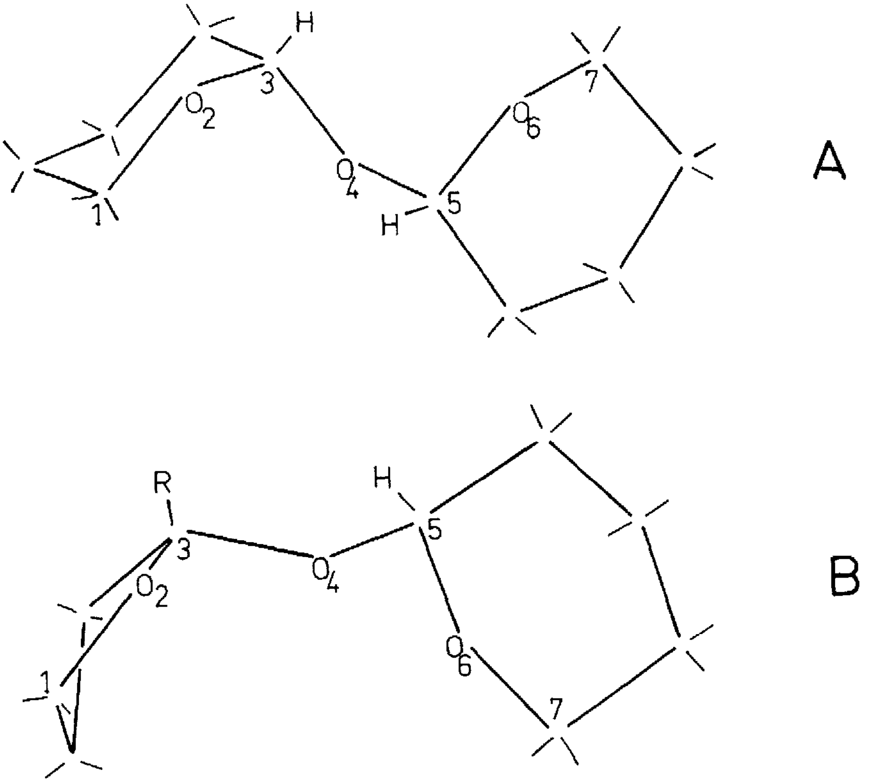


Figure 1. **Relative anti positions** of the two rings in **A** structures (above) ; **relative syn positions** of the two rings in **B** structures with R ≠ H (below).

This major conformational change is related to finer conformational modifications around the two anomeric centers C-3 and C-5 (fig.2, a and c). From three local C_2 symmetries, in the **A** *structures, we go to three very distorted* C_2, C_s, C_2 *symmetries in the* **B** *structures for* R ≠ H.

Cooperative mechanism: anomeric and crowding effects

A global modelization taking account of local crowding is complex. Here, we shall discuss a simplified approach centered on the 1-2-3-4-5-6-7 fragment. We shall consider:

- anomeric stabilizations that favor perfect or distorted C_2 or C_s arrangements;
- the proximity of atoms situated in respective δ positions (C-1 and C-5, O-2 and O-6, C-3 and C-7). This proximity leads to strong repulsive interactions. These are more critical for the approach of two carbons (C-1 and C-5 or C-3 and C-7) than for the approach of the two oxygens (O-2 and O-6); the hydrogens bonded to the carbons (as well as eventual substituents exert indeed strong mutual repulsion. On the contrary, the repulsion between lone pairs of oxygen atoms is rather weak.

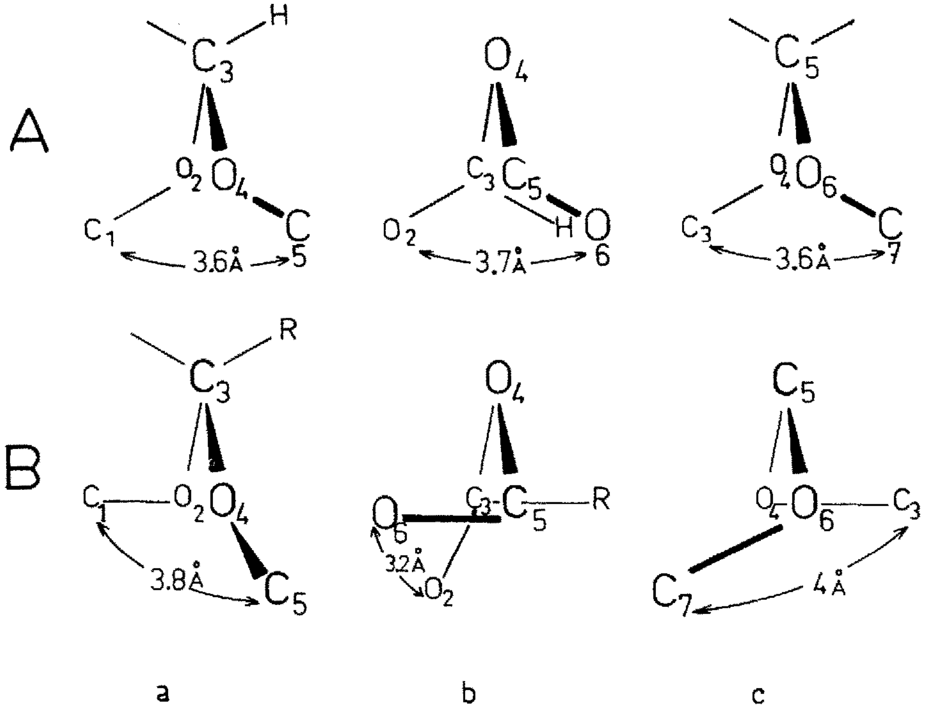


Figure 2. Perpendicular projections to O-2/O-4, C-3/C-5, O-4/O-6 axes showing the three C_2 local symmetries above (**A** structures) and the distorted C_2, C_s, C_2 symmetries below (**B** structures, R ≠ H). Mean values for distances are given.

In **B** structures, the conformational adjustments provoked by the R substituent result in removing from each other C-1 and C-5 (from 3.6 to 3.8 Å), C-3 and C-7 (from 3.6 to 4 Å) without bringing too close together O-2 and O-6; thence the greater stabilization of the axial six-membered ring.

It would be interesting to have certain structures that are either absent or poorly represented in the CCD (non substituted **B** structures in 3 position or substituted **A** structures in 3 position) in order to confirm these observations and modelizations.

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