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REAL GEOMETRY OF MOLECULES : INFLUENTIAL SUBSTRUCTURE INFORMATION AND CONFORMATION MONITORING IN STRAINED SUGARS AND PIPERIDINES

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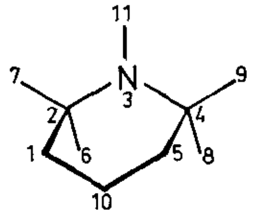
Abstract - The real structure of certain piperidines and sugars is interpreted by comparing crystallographic information with its counterpart in usual standardized information. Local distortions are due either to stabilizations by stereoelectronic effect (anomeric effect) or to the relaxation of local steric effects (gem-6 structures). These effects can act either cooperatively or competitively. Their use, for purposes of prediction of static molecular geometry and of dynamic conformational behavior, is examined in this presentation. Coordination of effects leads to excellent structural predictions for certain structure subpopulations. Structural knowledge at the level of substructure information appears to be transferable for high local constraints or special localized effects.

The existence of crystallographic data (55,000 organic structures stored in the Cambridge Crystallographic Database (CCD)) clearly establishes that complexity cannot be easily reduced to standardized average structural information. On the contrary, basic structural information is gradually more and more associated with neighboring sites[1]. Complex information expresses a more elaborate form of structural knowledge. Here we approach this latter by scrutinizing big specific substructures (SS) and their nonstandard geometry information. This characteristic crystallographic information corresponds to clear distortions as compared to local standard data. It is transferable, since we perceive it in a series of appropriate structures with a common dedicated substructure. These distortions of standard geometry, found in real complex structures, are induced and controlled either by local stereoelectronic effects or by relaxation effects of local steric hindrance. For different structural systems, we study how these effects act on complex static structures and, by heuristic approaches, we also explore the dynamic conformational potential of strained molecules.

I REPRODUCIBLE DISTORTIONS INDUCED BY STRAIN RELEASE IN GEM-6 COMPOUNDS : 2,2,6,6-TETRAMETHYLPIPERIDINE TYPE PRODUCTS.

Structures related to the 2,2,6,6-tetramethylpiperidine are considered gem-6 because they have two quaternary carbons in a geminated situation, i.e. six carbons in γ position to the nitrogen atom.



11 = H, Me, O.

Strong *synaxial interactions* (*groups* 6 *and* 8) exist in standard geometry. The relaxation of these interactions in real geometry induce strong transferable molecular distortions in various intra and intermolecular environments (42 such compounds studied here).

I.1. Ample Rotational and Bending Distortions

The chair ring is flattened by a disrotation of 1,6,7 and 5,8,9 groups around 2-3 and 3-4 bonds : the average torsion angles ϕ_1 and ϕ_2 of 1,6,7 groups (ϕ_1) and 5,8,9 groups (ϕ_2) around the corresponding CN bonds are of opposite signs. This broad disrotation is helped by the *slight pyramidization* of nitrogen.

Various important local distortions are associated : CNC bending, C_3C- symmetrical deformation by *contraction* or expansion and C_3C rocking.

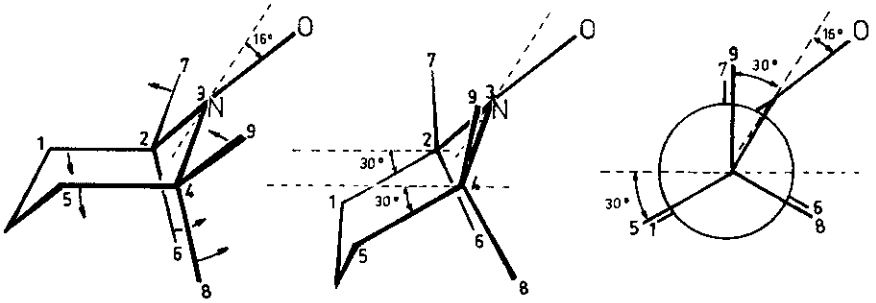
This diversity of effects voids the notion of "hard" parameters (bond lengths and angles) supposedly fixed or frozen, and "soft" parameters (torsion angles), whose *variations would suffice to* adapt the structure to the various constraints. This model is no longer valid when molecular complexity increases ; all the distortions are interdependent among themselves and are, moreover, a *function of* the pyramidization of the nitrogen.

I.2. Conformational Dynamics

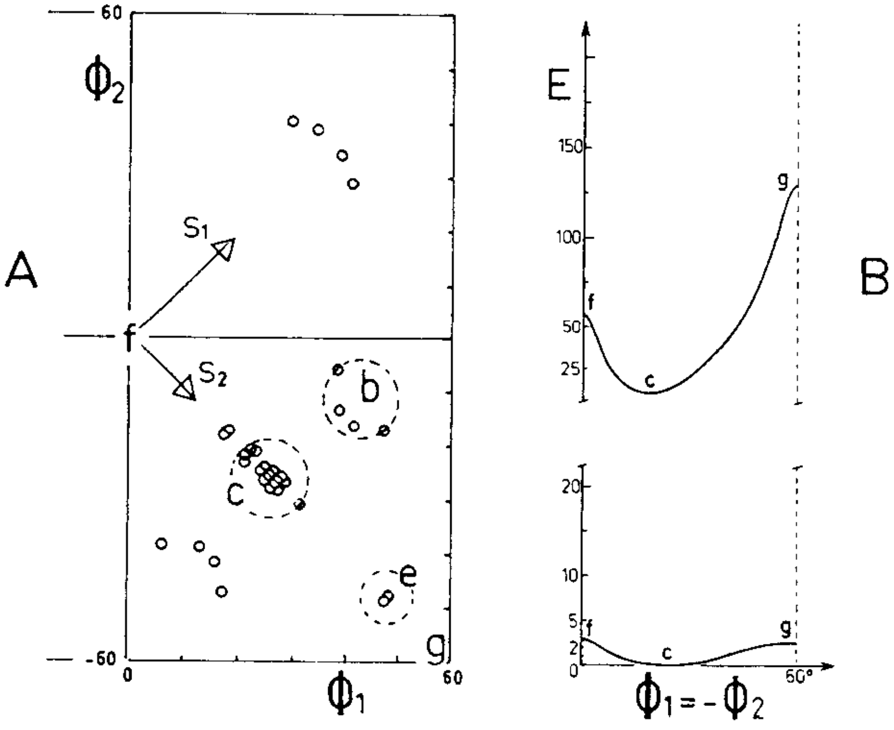
One would expect such hindered structures to be frozen when considered as isolated molecules. In fact, they are surprisingly flexible.

The disrotatory process, for a standard geometry molecule, would require more than 100 kcal.mol^{-1} (M.O. calculation).With real (distorted) geometry, the barrier is only 2.4 kcal.mol^{-1}. Therefore, the bending distortion allows the interconversion mechanisms, otherwise impossible (with the standard model).

DERIVATIVES OF THE 2,2,6,6-TETRAMETHYLPIPERIDINE-1-OXYL



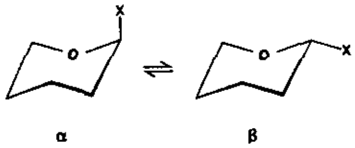
Local flattening of the ring by a broad disrotation (≈ 30°), helped by the slight pyramidization of nitrogen (≈ 16°).



Disrotation from the chair form f. A: Crystallographic data. Symmetrical path f → c → e → g following the S_2 disrotatory component ($\Phi_1 = -\Phi_2$) or unsymmetrical (f → b). B : INDO modelization. Standard (above) and optimized (below) geometries. Energies in kcal.mol^{-1}.

II SHAPES INDUCED BY STEREOELECTRONIC CONTROL : CARBOHYDRATES

In carbohydrates, well characterized distortions are rarer. Indeed, in these compounds there is competition between small effects : the stereoelectronic anomeric effects due to oxygen lone pairs[2] and the steric repulsion effects. The dominant lone pairs effect results in the axial orientation of polar substituents X at the anomeric center, privileged by comparison with related hydrocarbons.



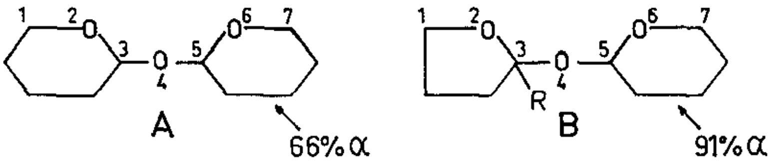
In pyranoses (X = OR; 314 structures examined), this axial orientation is clear[3] but statistically limited (51% α). *For a single compound, we often note the coexistence of the α and β forms.* However, the energy balance between the anomeric electronic effect and the steric effect can even enhance the anomeric effect.

II.1. Enhancement of the Anomeric Electronic Effect in Furanoses : a ring torsion angle assistance

In pyranoses, the endocyclic oxygen p pair is not well located in space for a good overlap with the antibonding orbital σ^* C-X; the torsion angles of the rigid ring, naturally close to 60° or 180°, distance themselves from the expected torsion angles suited to a good overlap (90°). On the contrary, in the flexible five-membered ring of furanoses, there is agreement between expected and natural torsion angles. The geometric conditions required by the anomeric effect are fulfilled optimally. Thus, nearly all 53 crystallized furanoses that we studied (tertiary anomeric carbon) are *pseudoaxial (conformer α')*.

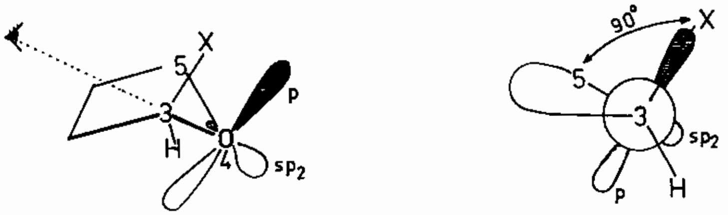
II.2. Axial Orientation Reinforced by Local Crowding : global syn orientation

In certain dissacharides, some special local crowding cooperates with the anomeric effect in axial stabilization.

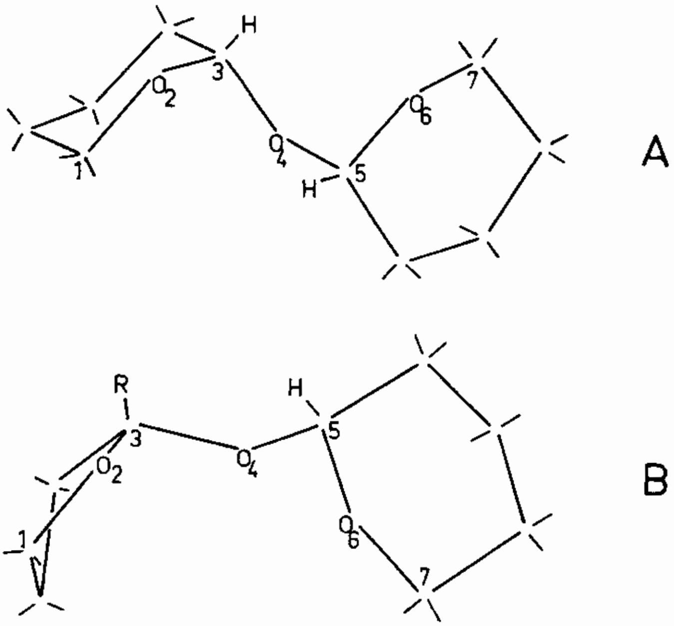


In B structures, the axial orientation of the six-membered ring is the nearly absolute rule (91%), whereas it is limited in A structures (66%). The presence of the R substituent also modifies the

CARBOHYDRATES



In furanoses (unlike pyranoses) the torsion angles, naturally close to 90°, favor a good lone pair/σ^* C-X overlapping of the sp_2 hybrid endo oxygen.



Relative trans positions of the two pyranose rings in structure A: relative syn positions of the two rings in structure B with $R \neq H$.

relative position of the two rings, from anti (structure A) to syn position (structure B). This major conformational modification is associated with local conformational readaptations around anomeric centers C-3 and C-5 as well as with modifications of the so-called "hard" parameters (bond lengths and angles). The local crowding effect is propagated from one end of the molecule to the other. In other words, the cooperative action of local effects results in a relaxation of interactions between the axial six-membered ring and the rest of the molecule.
Using the CCD, we have shown that the predictive power of sugar conformations is relatively weak for pyranoses ($\alpha \simeq \beta$). On the contrary, for certain heterocycle subpopulations, it becomes either excellent (91% for furanosic compounds - all α' or α-; 100% for dissacharides B).

The real molecular structure is the result of a balance (cooperation or opposition) between diverse effects that can be classified, in a first analysis, as stabilizing conjugation or hyperconjugation effects and steric effects. When one effect clearly predominates, the distorted shape of the molecular fragment concerned retains its identity in various intra and intermolecular environments. Some global relational changes and local distortions and adaptations can be carefully evaluated. When the balance is uncertain, prediction is more difficult: prediction of some realistic geometry by modelization calls for more research.

CONCLUSION

The concept of a standard shape opened the way to tremendous progress in the chemistry of simple compounds, but for the past few decades, the real shape and size of molecules including their local conformations has become necessary for "structure-property" or "structure-activity" relationships, particularly for drug design, molecular biology and immunology based on topological and real molecular recognition methodology. Chemistry is entering an era of diversity and precision, and chemical representations have become tools that grasp the real molecular objects more and more. This evolution from the chemical formula, a generic description of topology, to the real molecular shape and its conformations was largely initiated by Sir Derek Barton in his work on ring conformation. Chemistry is indeed indebted to such precursors as Derek Barton, both for their vision and for the tools they shaped.

REFERENCES

1. J.E. Dubois, Israël J. of Chem., 1975, **14**, 17 ; F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen, and R. Taylor, J.Chem.Soc.Perkin Trans. 2, 1987, **12**, S1.
2. O. Eisenstein, T.A. Nguyen, Y. Jean, A. Devaquet, J. Cantacuzène, and L. Salem, Tetrahedron, 1974, **30**, 1717; S. David, O. Eisenstein, W. Hehre, and L. Salem, J.Am.Chem.Soc., 1973, **95**, 3806.
3. A. Cossé-Barbi and J.E. Dubois, J.Am.Chem.Soc., 1987, **28**, 1169 ; J.E. Dubois and A. Cossé-Barbi, J.Am.Chem.Soc., 1988, **110**, 1220.

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