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# Contribution of Molecular Modeling to Stereochemistry : an example in the morphinic series

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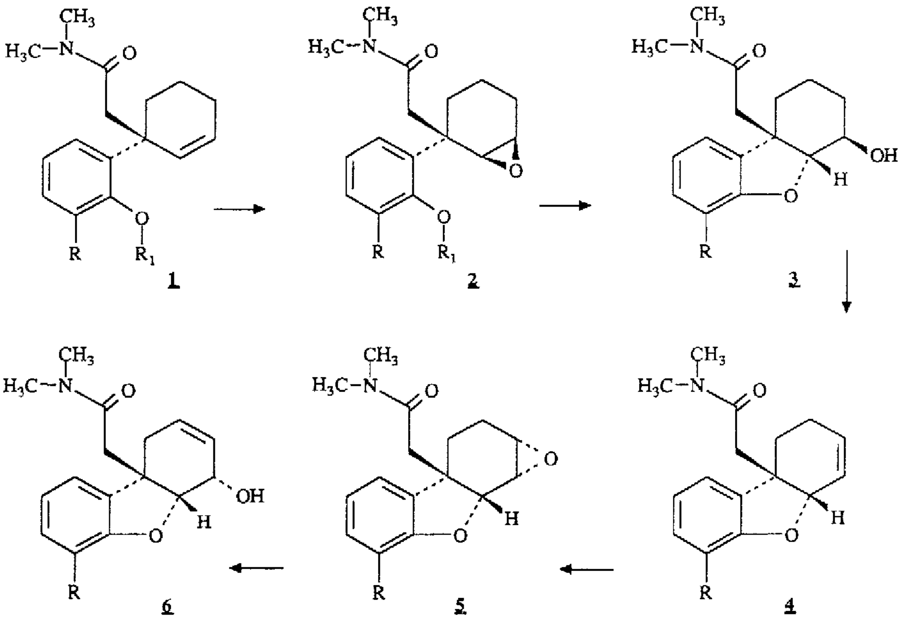
Summary : Molecular modeling is used as a help to conformational analysis in the search for conformational or stereoelectronic effects in epoxidation reactions.

A recently published[1] synthesis of morphinic analogues involved the reaction sequence depicted in scheme 1, the key steps being two selective epoxidations leading to the required stereochemistry shown in 6.



a: R = -OMOM, $R_1$ = MOM    b: R = -O-$CH_3$,$R_1$ = $CH_3$    c: R = F, $R_1$ = MOM

Scheme 1

Both epoxidations were found to be highly stereoselective, furnishing in each case the wanted isomer. The origin of such a gratifying outcome of the epoxidation steps is not obvious.

As regards the first epoxidation (**1a** ---> **2a**), the authors tentatively proposed a possible assistance of the ethanamide chain. They were led to this conclusion by the fact that they had observed a participation of the amide group in an indirect epoxidation of the double bond[1a]. This explanation has now been shown to be invalid, since a compound analogous to **1a**, with a methyl group instead of the ethanamide chain, has been found to undergo epoxidation with the same stereochemistry as **1a**[2].

A conformational preference for the half-chair form **8a** rather than **7a** in compound **1a**, could also have been put forward ; inspection of molecular models, however, gave no answer.

This problem constitutes, in fact, a typical example of a more general one in conformational analysis of flexible molecules. These molecules can adopt such a large number of conformations, involving so many interactions, that the chemist is often more confused than guided when observing molecular models. Does a chemical reaction really occur via the conformation so selected by the chemist ? Molecular modeling should help in answering this question as it associates energies and conformations.

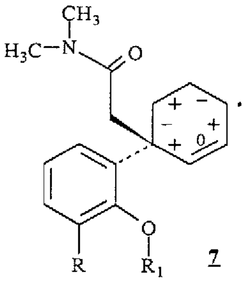
We have therefore explored the field of all possible conformations of compound **1b**[3], using the SCRIPT[4] and MACROMODEL[5] programs, assuming that the energies of these conformations reflect the transition state energies[6].

Two facts have emerged from this study :

a) The group of the more probable conformations does not show any notable preference for one of the two half-chair forms **7b** and **8b**. This means that both faces of the cyclohexane moiety are statistically equally accessible to the epoxidation reagent.

b) In both half-chair forms **7b** and **8b**, there is a conformation (among the more probable ones) in which the oxygen atom of the ortho methoxyl lies under the double bond and close to the proximal $sp^2$ carbon atom. One of the lone pairs of the oxygen atom can thus exert an electron donating effect toward the double bond during the epoxidation reaction as in an $Ad_E3$ process[7]. The calculated minimal energy conformations of **7b** and **8b** showing this particular feature are shown in figure 1, where are indicated the distances between the oxygen atom and the proximal carbon of the double bond. Calculations have shown that the longer methoxymethyl ether chain in compound **1a** extends outwards, thus not disturbing the role of assistance attributed to the ortho alkoxy oxygen atom.

As regards the second epoxidation (4 ---> 5), calculations have shown that in compound 4c conformation 9 is preferred (9 $\rightleftarrows$ 10 : $\Delta H \sim 1.6$ kcal/mole, using the SCRIPT program). Thus the epoxidation agent attacks the less crowded α-face (fig. 1).



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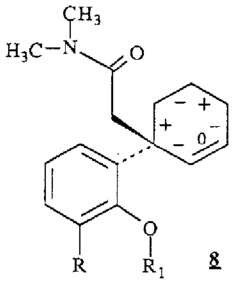

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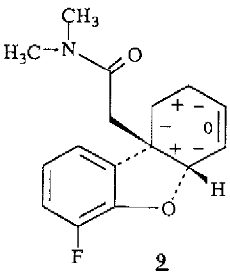

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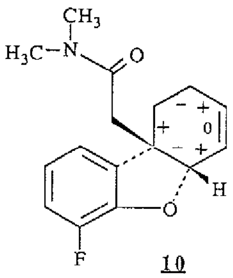

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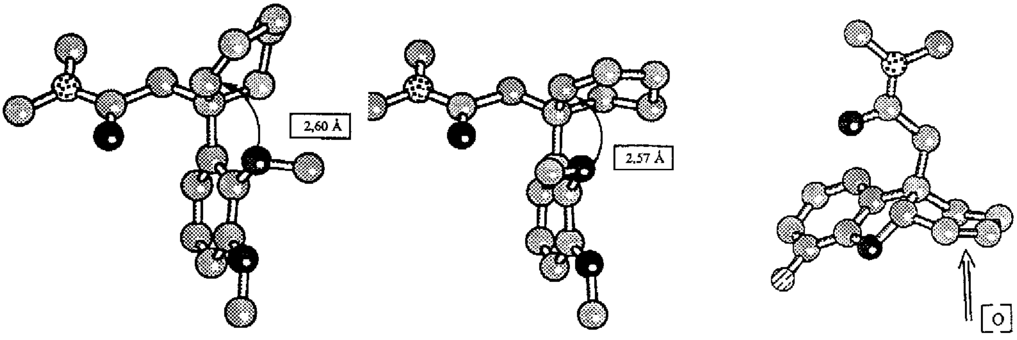
a: $R = OMOM, R_1 = MOM$ b: $R = OCH_3, R_1 = CH_3$



7b 8b 9

Figure 1

A more refined treatment (to be published later) will show that this combination of molecular modeling and conformational analysis by means of the torsion angle notation[8] can be a very valuable tool in stereochemistry.

Acknowledgements :

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## References :

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2. A. Reynet, Thèse de Doctorat, July 1, 1988, Université Paris-Sud.

3. To simplify the calculations, we have "substituted" the methoxymethyl ethers of compound **1a**, on which the epoxidation was performed, by methyl ethers **1b**.

4. SCRIPT : Interactive molecular geometrical treatment on the basis of computer-drawn chemical formula.: N.C. Cohen, P. Colin and G. Lemoine, **Tetrahedron**, 1981, 37, 1711. We thank the Roussel-Uclaf Company for access to the original SCRIPT program.

5. W.C. Still, N.G.J. Richards, W.C. Guida, M. Lipton, R. Liskamp, G. Chang and T. Hendrickson, MacroModel V1.5, Department of Chemistry, Columbia University, New York, NY 10027.

6. The transition states to be considered might be better simulated by 1,2-diplanar forms : E. Toromanoff, **Tetrahedron**, 1979, 37, 893. ibid., 1980, 36, 2829. These forms are energetically equivalent, moderately deformed, half-chair conformations. In this brief account we have limited the discussions to the half-chair conformations given by the minimal energy calculations.

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9. Fig. 1 was drawn using MOLDRAW program ; J.-M. Cense, Ecole Nationale Supérieure de Chimie de Paris.

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