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Conformational Analysis of Stereoselective Epoxidations in Flexible Systems.

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***Abstract** : Approaching the transition state from both ends of the reaction pathway (the initial reactive conformation and the primary final form of the product), has enabled us to understand the unusually high stereoselectivity observed.* Copyright © 1996 Elsevier Science Ltd

The stereoselectivity we have observed[1] (fig. 1), in the epoxidation of flexible cyclic olefins is outstanding enough, and so valuable for synthetic purposes, that it calls for a thorough understanding of its origin.

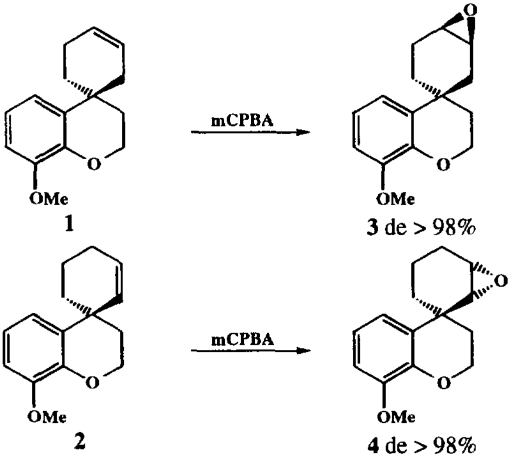
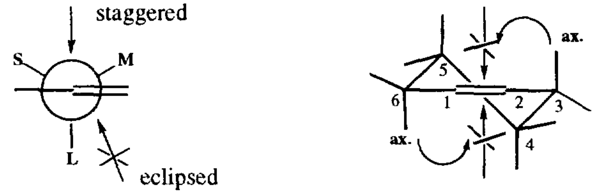


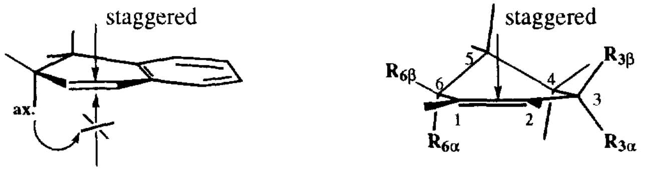
Fig. 1

Such a discussion seems particularly well timed following a recent article published by M.J. Martinelli, K.N. Houk and their co-workers[2] on the stereoselective epoxidation of conformationally locked polycyclic styrenes. These authors have shown that, in the absence of charged or highly polar groups, it is the torsional strain in the transition state which steers the face selection in additions to double bonds, in accordance with the Felkin-Anh model[3] (fig. 2, **a**). They have calculated that the magnitude of torsional strain is large enough to explain the high stereoselectivity observed with styrenes. Hyperconjugative effects cannot provide an alternative explanation; moreover, a recent theoretical study has confirmed that, for non charged molecules, their magnitude is relatively small[4]. This is a remarkable and useful clarification after years of controversy[5,6].



a : Felkin-Anh model

b : Cyclohexene in half-chair form: no face selection



c : Styrene in 1,3-diplanar form

d : Cyclohexene in 1,2-diplanar form

Fig. 2

Thus, addition to an sp^2 carbon of a cyclic double bond must proceed antiperiplanar to the vicinal axial (or pseudoaxial) substituent in order to minimize the torsional strain suffered by the forming bond. The transition state is then of the staggered type; whereas with a synperiplanar approach it would have been eclipsed. The comparison between styrenes and non styrenic cyclohexene compounds has provided the authors' main point of argument[2]: a styrene has only one axial or pseudoaxial substituent steering the attack antiperiplanar to it (fig. 2, **c**), while the non styrenic cyclohexene compounds are flanked by two axial or pseudoaxial substituents pointing in opposite directions leading to contradictory effects (fig. 2, **b**). Provided that the compounds are conformationally fixed, face selection for a concerted *cis* addition should be good for styrene compounds and only poor for non styrenic ones, as a result of internal compensation of opposite torsional effects. As our compounds show good stereoselectivity, such internal compensation cannot occur in our case.

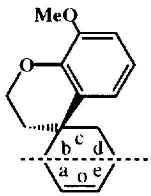
It must be pointed out that the internal compensation in non styrenic cyclohexene compounds is a consequence of the binary axis of symmetry of the half chair form. Should this form be distorted and the symmetrical anti-disposition of both vicinal axial substituents disappear, face selection in *cis* addition could be restored. Distorted forms of cyclohexene are infinite in number; a way to apprehend their description is to put emphasis on some particular forms along the spectrum of distorsion[7], that is the ones having a second zero torsion angle in the ring and called, for this reason, diplanar forms[8]. The less costly in energy of these forms is the 1,2-diplanar form, only 0.7 kcal/mol higher in energy than the half-chair form. It derives directly from the latter by pushing one of the homoallylic carbons of the ring into the plane of the double bond, *e.g.* moving C_4 of figure 2 upwards: b -> d. By such a move, substituents on C_3 are tilted, becoming equally inclined with respect to the double bond plane and consequently neutral towards face selection. This leaves the pseudoaxial substituent on C_6 free to exert its full discriminating action, and thus allowing stereoselective epoxidation. It is this 1,2-diplanar form (fig. 2, **d**) which must be considered in dealing with *cis* addition to cyclohexenes.

E. Toromanoff has already emphasised the crucial role played by the 1,2-diplanar form in *cis* additions to cyclohexenes[9] and has, more generally, developed a method of dynamic conformational analysis in stereochemical studies using the torsion angle notation. According to him, transition state geometries and their relative energy levels are approached from both ends of the reaction pathway : the initial reactive conformation and the primary final form of the product. We have proceeded in this way.

This led us to consider two criteria for the choice of the most probable transition state:

- The first is the absence of any axial synperiplanar torsional strain during the attack (antiperiplanar epoxidation).
- The second is steric hindrance which we generally estimate by examination of molecular models. It has been better quantitatively estimated by relative energy calculations of the corresponding epoxide in its conformation directly arising from the initial reactive conformation by antiperiplanar attack.

Conformations in which torsional strain and steric hindrance apply to the same face, leaving the other face free of any impediment for an approaching reagent, are the only ones to be considered for high stereoselectivity. Conversely, conformations in which both effects (torsional and steric) apply to opposite faces cannot be considered as probable, because for each face there is an energy barrier to cross.



1

Forms of Compound 1	**Dihedral angles** $\frac{b\ c\ d}{a\ o\ e}$	**Type of conformation**	**Relative energies (kCal/mol)**
A	$\frac{-\ +\ -}{+\ 0\ +}$	half chair	0.00
B	$\frac{-\ +\ -}{+\ 0\ 0}$	1,2 diplanar	0.60
C	$\frac{-\ +\ -}{0\ 0\ +}$	1,2 diplanar	0.91
D	$\frac{+\ -\ +}{-\ 0\ -}$	half chair	2.03
E	$\frac{+\ -\ +}{-\ 0\ 0}$	1,2 diplanar	2.28
F	$\frac{+\ -\ +}{0\ 0\ -}$	1,2 diplanar	3.26
G	$\frac{-\ +\ 0}{+\ 0\ -}$	1,3 diplanar	4.40
H	$\frac{0\ +\ -}{-\ 0\ +}$	1,3 diplanar	5.19
I	$\frac{0\ -\ +}{+\ 0\ -}$	1,3 diplanar	5.33
J	$\frac{-\ 0\ +}{+\ 0\ -}$	1,4 diplanar	6.32
K	$\frac{+\ -\ 0}{-\ 0\ +}$	1,3 diplanar	6.53
L	$\frac{+\ 0\ -}{-\ 0\ +}$	1,4 diplanar	7.23

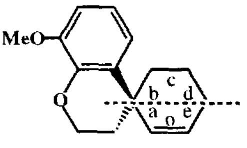
Table I

Thus we have calculated all typical conformations of compounds **1** and **2** (half-chair and diplanar forms for the cyclohexene part) as possible initial reactive conformations using Macromodel's MM2 force fields[10].

As regards compound **1**, table I shows all its possible conformations listed in order of increasing energy.

Perspective views of the four possible 1,2-diplanar forms of compound **1** are depicted in figure 3. We note that conformations 1B and 1F can be rejected as both faces show a constraint to epoxidation. Conformations 1C and 1E show a face totally free of any constraint to an approaching epoxidation reagent. From the steric point of view they are equivalent: epoxides 3Cβ and 3Eα have the same energy. However, from the torsional point of view, they show an energy difference of 1.4 kCal/mol; this corresponds to a stereoselectivity of 92:8 in favor of 1C giving 3Cβ which is in accordance with the experimental result[1] (de > 98%).

We have proceeded in the same way for compound **2**. Table II shows the relative energies of all its remarkable conformers, and figure 4 the perspective views of the 1,2-diplanar forms . Analysis of the two criteria for facial selectivity shows that probable conformers are 2D and 2F. In this case, both conformations lead to the same face selection for an attacking reagent: the α face. That is in complete agreement with the experimental result[1].

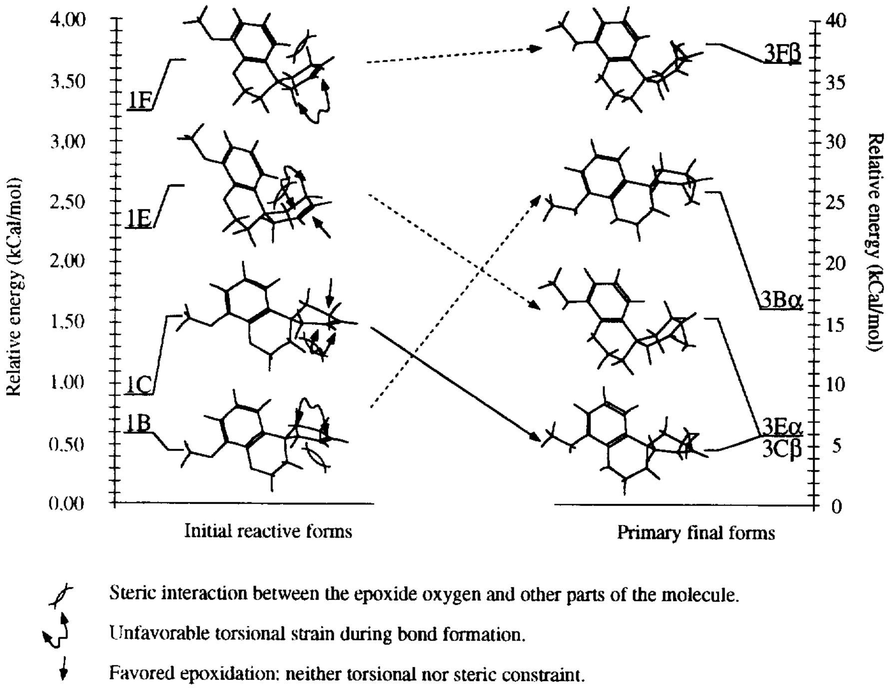


2

Forms of Compound **2**	Dihedral angles $\frac{b\ c\ d}{a\ o\ e}$	Type of conformation	Relative energies (kCal/mol)
A	$\frac{+\ -\ +}{-\ 0\ -}$	half chair	0.00
B	$\frac{-\ +\ -}{+\ 0\ +}$	half chair	0.55
C	$\frac{+\ -\ +}{-\ 0\ 0}$	1,2 diplanar	0.62
D	$\frac{+\ -\ +}{0\ 0\ -}$	1,2 diplanar	0.68
E	$\frac{-\ +\ -}{0\ 0\ +}$	1,2 diplanar	0.83
F	$\frac{-\ +\ -}{+\ 0\ 0}$	1,2 diplanar	1.32
G	$\frac{+\ -\ 0}{-\ 0\ +}$	1,3 diplanar	3.07
H	$\frac{0\ +\ -}{-\ 0\ +}$	1,3 diplanar	3.71
I	$\frac{0\ -\ +}{+\ 0\ -}$	1,3 diplanar	4.84
J	$\frac{-\ +\ 0}{+\ 0\ -}$	1,3 diplanar	4.86
K	$\frac{+\ 0\ -}{-\ 0\ +}$	1,4 diplanar	5.51
L	$\frac{-\ 0\ +}{+\ 0\ -}$	1,4 diplanar	8.30

Table II

If any necessary conformational adjustment (1,2-diplanar form involvement) prior to a *cis* addition is ignored, relative energy calculations of the epoxides directly formed from the lowest energy half-chair forms of compounds **1** and **2** give energy differences between α and β attack that are too small (0.8 and



Steric interaction between the epoxide oxygen and other parts of the molecule.

Unfavorable torsional strain during bond formation.

Favored epoxidation: neither torsional nor steric constraint.

Figure 3

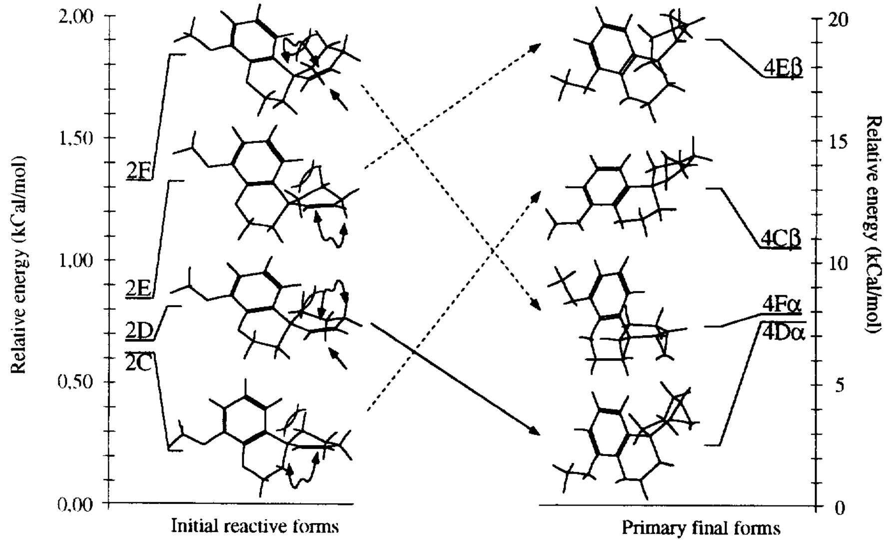
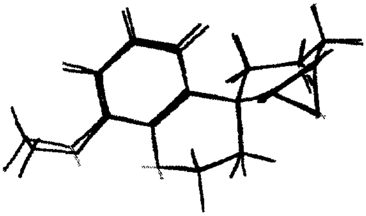


Figure 4

0.9 kCal/mol, respectively) to explain the high stereoselectivity observed. Thus, an additional factor must play a role. This is the one played by the 1,2-diplanar form.



We have calculated the ground state conformation of compound **4**. The geometry we have thus obtained is in accord with its X-ray structure[11] as shown in the adjoining drawing.

This is a rewarding result with respect to our MM2 force field calculations.

CONCLUSION

On the basis of theoretical considerations on stereoselective epoxidations[2] and with the help of molecular geometry calculations associated with the torsion angle notation used as a tool in dynamic stereochemistry[7], we have been able to comprehend the most probable origin of two cases of relatively rare stereoselective epoxidations of flexible systems. This is a powerfull illustration of how fruitfully the method developed by E. Toromanoff[9] some years ago can be applied to solve complex problems in stereochemistry.

Acknowledgements

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