Tetrahedron Vol. 36, pp 2809 to 2931
Pergamon Press Ltd., 1980 Printed in Great Britain

TETRAHEDRON REPORT NUMBER 96

DYNAMIC STEREOCHEMISTRY OF THE 5-, 6- AND 7-MEMBERED RINGS USING THE TORSION ANGLE NOTATION

E. TOROMANOFF
Centre de Recherches ROUSSEL-UCLAF,
102, route de Noisy 793230 ROMAINVILLE 5 FRANCE

(Received 11 April 1980)

CONTENTS

I. INTRODUCTION

It is the purpose of this review to introduce the average organic chemist to the dynamic stereochemistry of the common 5-, 6- and 7-membered rings using the torsion angle notation,[1] assorted with a few, generally simple, assumptions.[2]

It has often been emphasized that a better understanding of organic chemistry and its mechanisms would require a deepening of our knowledge of the stereochemistry implied in conformational changes of molecules.

Now, a better knowledge of stereochemistry depends on the development of new methods allowing the dynamic analysis of "conformational intermediates". More precisely there is a need for methods allowing us to visualize the various steps of all the conformational changes during the progress of a reaction, from the reactants up to the product, in a manner consonant with all the known experimental facts. Let us, first, give a few examples to explain what is implied hereby (Figs. 1–5).

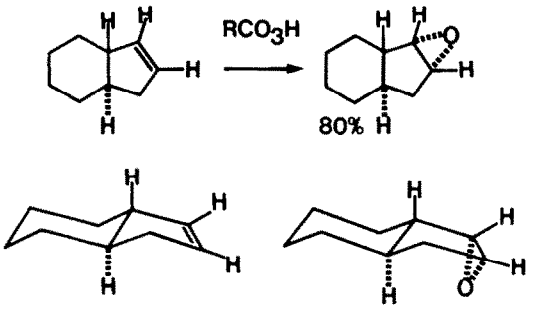


Fig. 1

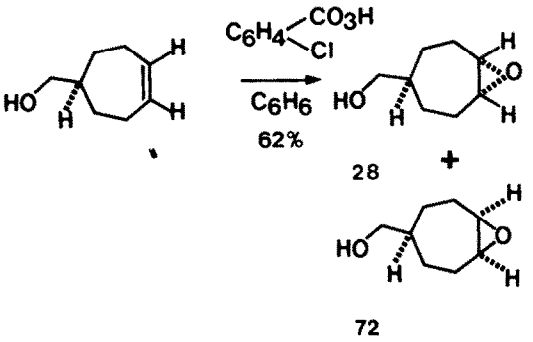


Fig. 2

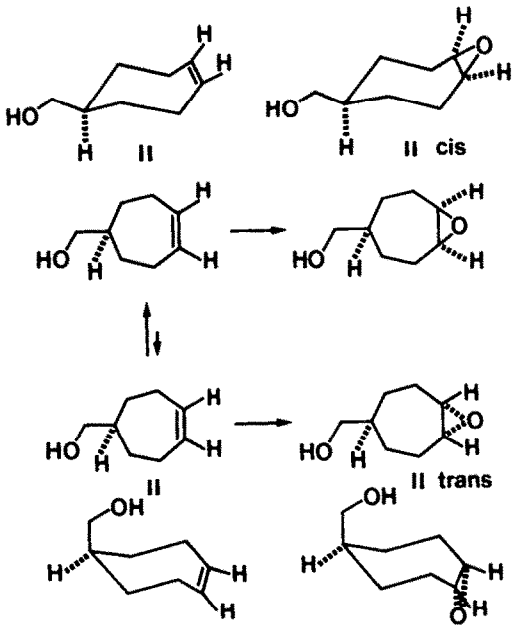


Fig. 3

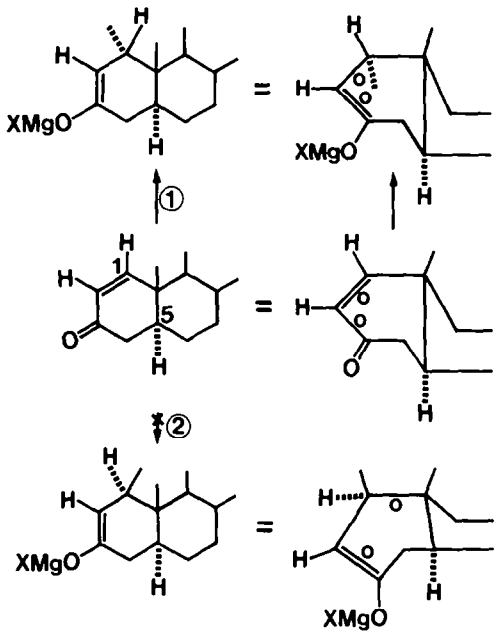


Fig. 4

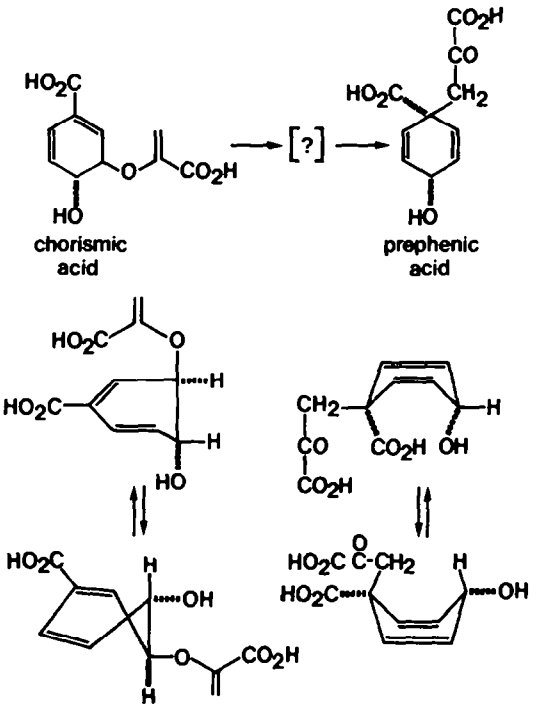


Fig. 5

Conformational intermediates

The first example (Fig 1) describes a stereospecific epoxidation: on treatment with peracids the double bond of the cyclopentene ring undergoes a *cis*-addition only on one side of the unsaturated ring.[3] Since there is no steric hindrance on either side of the molecule, as can easily be seen using molecular models, the stereospecificity of the reaction has notably to do with the reactive conformations,[4] namely the initial reactive conformation of the substrate and the conformation of the resulting product. This latter kinetic conformation of the product, which will be called throughout this text, the primary final form, is the one the most likely to result from the reaction (in this case the epoxidation)

taking into account our assumptions to be detailed later on involving the usual rules of stereoelectronic control and the principle of least conformational distortion during the reaction. The question that may be raised about these reactive conformations is whether the primary final form can be predicted knowing the initial reactive form of the substrate and by which reasoning this prediction can be made.

In the second example of Fig. 2 is shown the stereoselective peracid epoxidation of 5-hydroxymethyl-cycloheptene giving rise to the cis-epoxide as the main component of the mixture.[5]

Could this result have been predicted knowing the reactive initial conformations of the hydroxymethyl-cycloheptene? Does the OH of the substituant play a role [5] or, as we presume, would a 5-Me substituant have given similar results? We will justify our opinion later with the help of the torsion angle notation and our interpretation is given in Fig. 3. We may note (Fig. 3), that from the initial reactive conformations of the substrate up to the primary final forms of the epoxides, the distortion of the ring conformation is minimal.

Let us turn now to 6-membered rings. Figure 4 describes the conjugate addition of a methyl Grignard to the 3-keto Δ^1 unsaturated enone system of a steroid, promoted by a small amount of a copper salt. The addition appears to take place exclusively on the α side of the 1 position.[6] Again this high stereoselectivity seems to be related, as it was suggested earlier,[7] to the conformational changes during the reaction from the starting conformation of the substrate up to the primary final form of the product. Experimentally it is known that the primary final product is an eventually isolable enolate.[8]

The last example (Fig. 5) raises an interesting question in the field of biochemistry. The conversion of chorismic into prephenic acid an important biochemical step, is supposed to be a concerted reaction, a kind of vinyl-allyl-ether type rearrangement.[9]

Let us note that chorismic acid can adopt 1.3-diene type conformation with two flat sides. For this reason such forms will be called 1.3-diplanar forms, whilst prephenic acid, like 1.4-dienes, can adopt boat forms: such forms with two 1.4-flat sides are also called 1.4-diplanar forms.[10] Concerning Fig. 5, the following questions are raised:

(a) Which of the two possible conformations of the 1.3-diene is the reactive form of the substrate and what is the corresponding 1.4-diene form of the primary product?

(b) Is a concerted intramolecular rearrangement of the vinyl-allyl-ether type really possible or is it a myth?

Answers to all these questions will soon be readily apparent after having some more practice of the torsion angle notation.

In a more general way the question might arise of how to predict the conformational deformations that are induced by a *cis* or *trans* addition of an agent to a double bond of a ring which either happens to be in a determined conformation or is able to adopt several low energy conformations (the so-called preferred or privileged conformations).

II. BASIC FEATURES OF A METHOD ABLE TO ANALYZE CONFORMATIONAL CHANGES

In order to be able to predict the conformational changes that are induced by a *cis* or *trans* addition of a reagent to a double bond, we have to fulfill the following conditions:

(1) Define the direction of the *cis* or *trans* addition of the chemical agent with respect to the double bond of a ring or more generally, the direction of attack of an agent relative to a functional group.

(2.) Make a few additional assumptions about the relative levels of the various possible transition states involved in the reaction.

A summary of the rules of stereoelectronic control

Regarding the direction of addition to a double bond or the direction of attack with respect to a functional group we will implement the well known rules of stereoelectronic control, a summary of which is given hereafter:

(a.) with respect to double bonds of either cyclic or acyclic compounds, the addition will take place along the axes of the orbitals, what we call "perpendicular addition" (in short for perpendicular addition to the plane of the substituents of the double bond);[11] such an addition could equally be termed "pretetrahedral addition"[12] Conversely, the formation of a double bond will take place

preferentially when the departing groups are coplanar, in the proper periplanar orientation[13]: *anti* or *syn* periplanar conformation of the concerned groups respectively for *anti* or *syn* eliminations.

(b.) as for allylic systems, we will admit the principle of the maintenance of orbital overlap during the reaction,[14] which implies that the allylic bond which is broken or formed always has an axial orientation with respect to the reactive conformation of the ring containing the allylic double bond.

These stereochemical rules are merely the recognition that the corresponding transition states are those of least energy.

For saturated systems, we also adhere to the usual stereoelectronic rules; for instance, in the nucleophilic displacement of a leaving group which takes place with configurational inversion at the centre undergoing the displacement, we admit that the reaction requires a backside approach of the incoming nucleophile along the axis of the breaking bond. We also consider this same rule to be valid for the nucleophilic opening of epoxides: again the incoming nucleophile comes along the axis of the bond to be broken and on the backside of this bond.[15]

A further assumption

The principle of least conformational distortion. In order to evaluate the relative energy levels of the various transition states, for a given reaction involving conformational changes from the reactants to the products of the types shown in Figs. 1–5, it is assumed that, from the initial reactive form of the substrate up to the corresponding primary final form of the product, the reaction will, preferentially, take place with the least amount of conformational distortion. Thus the preferred pathway will correspond to the least expenditure of energy. This amounts to saying that, most of the constraints of the transition state are already present in the initial conformation of the substrate and in the primary final form of the product. Strictly speaking such a statement is valid only if we are dealing with reagents of small or moderate size and in the absence of strong steric hindrance or strong polar effects to the approach of reagents.

From a mechanical standpoint the principle of least conformational distortion for the selection of the preferred pathway appears quite reasonable since distortions require energy in order to take place. This is quite clear if we resume the example of Fig. 4 using several Dreiding or Framework molecular models: one for the initial reactive conformation of the substrate and two other models for the kinetic enolates corresponding to the primary final products expected from the conjugate addition depending on the side of attack.

The initial reactive conformation of ring A, is supposed to be the 1.2-diplanar form of lowest energy: for cyclohexenones 1.2-diplanar forms and half chairs are equienergetic.[16] Starting from the 1.2-diplanar form (shown in Fig. 4), in which all carbons of ring A are on a plane except carbon 5 which is below the plane of the ring, and assuming a perpendicular addition of the anion to either side of the double bond at position 1, two enolates may result depending on which side the addition occurs (Fig. 4). In the first pathway the initial 1.2-diplanar form gives rise to a 1.2-diplanar enolate without appreciable conformational distortion, whereas in the second pathway the initial 1.2-diplanar form gives rise to a 1.3-diplanar form. Since there is more conformational distortion in this latter pathway, taking into account our hypotheses, we presume that the first pathway will be preferred, a conclusion in agreement with the experimental result.[6] In this example, since usually the 1.3-diplanar form is of higher energy than the corresponding 1.2-diplanar form,[10a] it could have been surmised that the energy levels of the two primary final enolates would reflect those of the corresponding transition states, which in fact appears to be the case.

A planar graphic representation of conformations as a privileged tool for conformational analysis

As stressed in the preceding case, organic chemists are often trying to guess what kind of conformational changes occur in a given reaction and to do so they often have recourse to molecular models of the Dreiding or Framework types. There is no objection at all to the use of molecular models and, indeed, their use is nearly always commendable.[17] However, in common practice such models are mainly used for saturated or unsaturated 6-membered rings, but less so for 5- or 7-membered rings. In any case, conformational analysis through manipulation of molecular models is only readily performed in simple cases. In more complex cases the plasticity of models often prevents one reaching a definite conclusion as to the steric outcome of a reaction. For example trying to determine with models the steric outcome of the conjugated addition of methyl magnesium bromide,

promoted by cuprous chloride, to the unsaturated $\Delta^{10(9)}$-11-keto-enone system of the 5βH norsteroid of Fig. 6[18] requires outstanding skills. Experimentally it was found that formation of the bond at position 10 on the β side (on the same side as the 5β hydrogen) was predominant. The interpretation of this result will be dealt with later on.

Now the use of tridimensional models has another drawback with respect to their representation on two-dimensional paper since it is often neither easy nor convenient to represent the conformation in the space of ring compounds, when they are not in their usual chair or boat forms.

It appears clear, therefore, that a planar graphic representation of conformations, simple enough to be easily grasped by any chemist would be of great advantage in conformational analysis, whether static (description of low energy forms) or dynamic (description of the passage from one form to another under the influence of reagents as in the examples of Figs. 1–4).

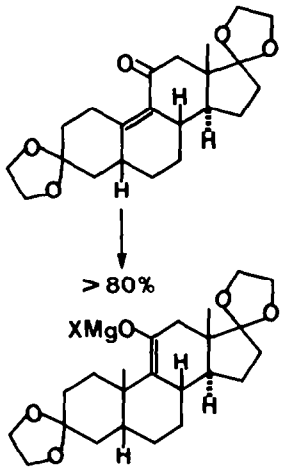


Fig. 6

III. THE TORSION ANGLE NOTATION

In this respect the graphic method of torsion angles of Klyne and Prelog,[19] as it was developed by Bucourt[1,20] allows a convenient planar description of the conformations of saturated and unsaturated cyclic compounds.

Another presentation of the torsion angle notation

Leaving aside, for the time being, the physical meaning of the torsion angle concept, we may simply consider the torsion angle notation as a planar description of ring conformations using only in a determined sequence the algebraic signs +, − and 0 (the last one corresponding to a double bond or to a fragment of eclipsed butane). The three algebraic signs allow the description of any particular type of conformation and, among others, the most commonly encountered, the so-called preferred or privileged forms of lowest energy and this description appears precise enough for most purposes of dynamic conformational analysis.[21]

Understanding the code

Before using the torsion angle notation to solve various stereochemical problems we have to learn and to master the code, which is fairly simple. This means that we must be able to readily perform the following two operations:

(a.) recognize a particular conformation of the ring from a look at the overall sequence of the algebraic signs.

(b.) recognize the axial, equatorial or isoclinal [bisectional[1,22]] orientations of a substituant of the ring from the algebraic signs around the carbon bearing this substituant.

In other words, we have to learn the code and know how to decipher it.

Conformation

The first element for recognition of conformations such as those of Fig. 7 is the complete sign sequence of torsion angles, the sequence being taken while going clockwise along each successive atom of the ring. For instance a regular alternation of + and − signs is characteristic of the two inverted chair forms (Fig. 7b). It should be pointed out here that the sign sequence, thus defined, unambiguously describes one type of conformation.[23] More details on the representation of conformations will be given shortly, after having first exposed the code for the determination of the axial orientation of any substituant of the ring.

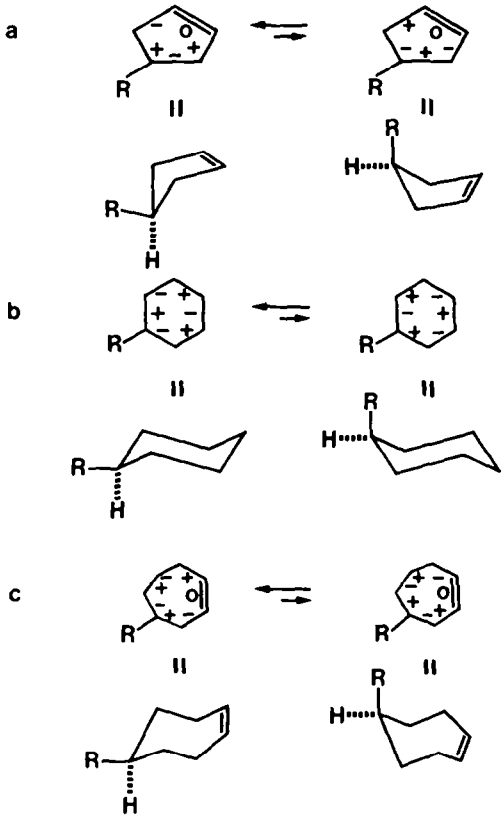


Fig. 7

How to recognize an axial substituant: the characteristic environment

The axial orientation of a substituant of an atom (mostly a carbon in this text) of the ring corresponds to a definite sequence of the algebraic signs of torsion angles before and after the concerned atom when moving along the successive atoms of the ring *always in a clockwise fashion* (see Code: Fig. 8).

When a positive angle is followed by a negative one the substituant is axial above the mean plane of the ring (axial above: + then −). The reverse sequence is characteristic of any axial substituant below the mean plane, that is to say when a negative sign is followed by a positive one (axial below: − then +) as shown in Figs. 7, 9–16. In both these sequences one (and only one) of the signs may be replaced by a zero.

Let us stress that the characteristic sequence of torsion angle signs for an axial substituant above or below the mean plane of the ring can be applied to all remarkable forms whatever the size (5, 6 or 7) of the ring and its saturated or unsaturated nature. It also applies to carbocyclic and heterocyclic compounds.

C O D E

(axial orientation)

Orientation of the axial substituant	Sign sequence, taken clockwise before and after the carbon center
ABOVE the mean plane of the ring (β in the steroid series)	+ − or + 0 or 0 −
BELOW the mean plane of the ring (α in the steroid series)	− + or − 0 or 0 +

Fig. 8

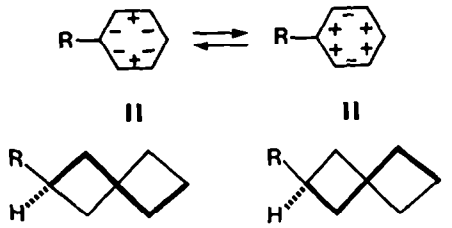


Fig. 9

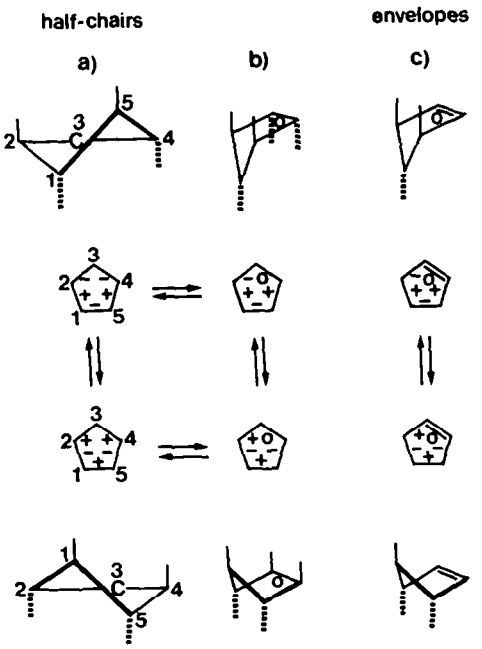


Fig. 10

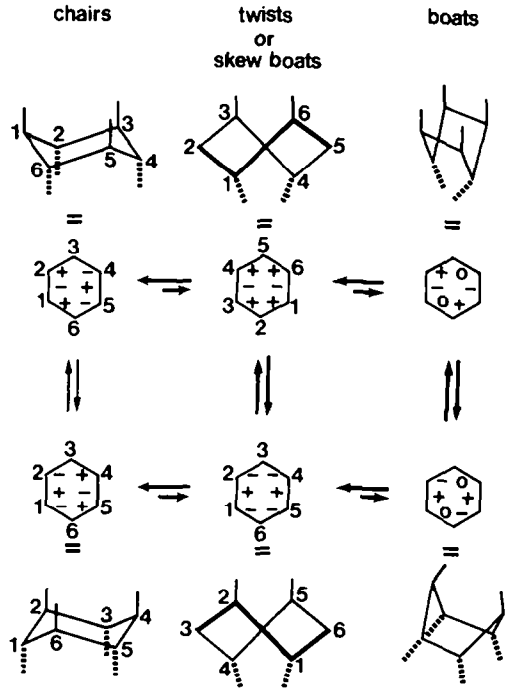

chairs
twists
or
skew boats
boats

Fig. 11

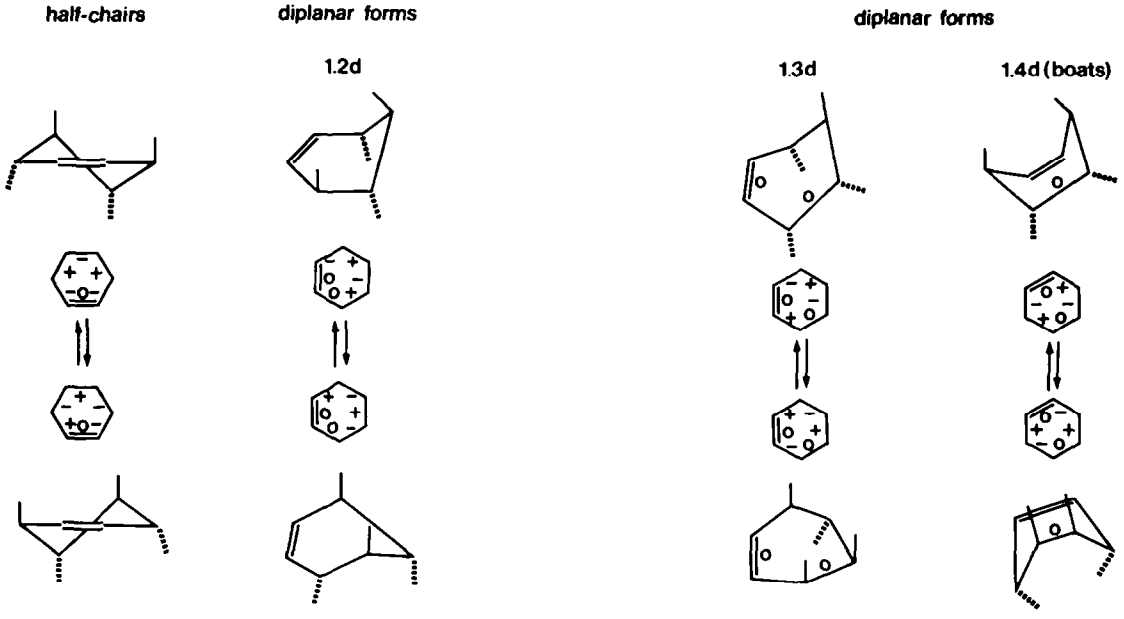

half-chairs
diplanar forms
1.2d
diplanar forms
1.3d
1.4d (boats)

Fig. 12

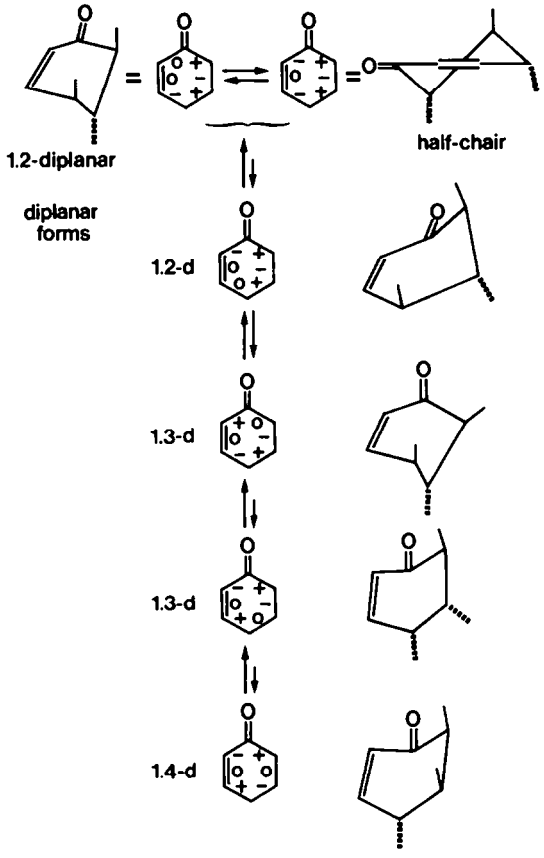

1.2-diplanar
half-chair
diplanar forms
1.2-d
1.3-d
1.3-d
1.4-d

Fig. 13

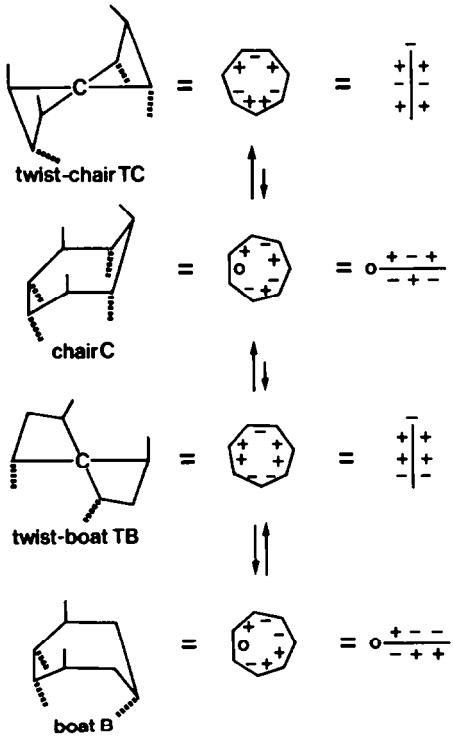

twist-chair TC
chair C
twist-boat TB
boat B

Fig. 14

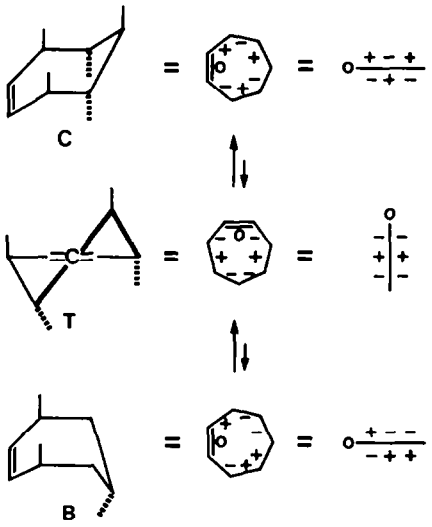


Fig. 15

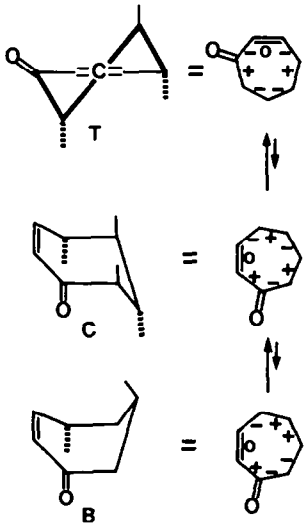


Fig. 16

The following mnemonic device may help to retain the code: one only has to remember the value of these algebraic signs:

+ is above − and 0 (+ > −, + > 0) and therefore these sequences taken clockwise imply that the substituant is *above* the mean plane of the ring (β in the steroid series).

− is below + and 0 (− < +, − > 0) and therefore these sequences taken clockwise imply that the substituant is *below* the mean plane of the ring (α in the steroid series).

To be complete it should be said that for some remarkable forms, namely the twist forms (also called skew-boats) a sequence of two identical signs + + or − −, as in Fig. 9 may be encountered. Such a sign sequence means that the substituant is neither axial nor equatorial but in between and such substituants are therefore called isoclinical or bisectional.[1,22]

Keeping in mind the code, let us now first have a look at static conformational analysis, involving the description of the various low energy conformers of the common rings before dealing with the dynamic aspects of conformational analysis.

Static description of conformations using the torsion angle notation[1,20]

The reader is advised to practice the torsion angle notation using Fig. 9–16: it can easily be verified that axial orientations of substituants of the rings conform to the indications of the code. Moreover

recognizing the axially oriented substituants of a ring allows one to represent the ring in the usual perspective representation and conversely it is possible from the usual perspective representation of rings to draw the same form in the torsion angle notation.

5-Membered rings. Cyclopentane (Fig. 10). The half chair and envelope forms are of comparable energy[1,24,25] and are readily interconvertible by pseudorotation. There are generally two inverted half-chairs and two inverted envelopes available for cyclopentane derivatives (Fig. 10a, b).

In the envelope conformation, four carbons are on a plane and the last is out of the plane and it should be noted here, that in the envelope there are two consecutive axial directions on the same side of the ring, corresponding to the sequence ($-\ 0\ +$) or its reverse ($+\ 0\ -$) (see Code).

Cyclopentene (Fig. 10c) – Only the envelope is available for cyclopentene and its derivatives: four carbons are on a plane and the last carbon is outside. Generally there are two inverted envelopes, as shown in Fig. 10c, which interconvert through the planar form of low energy.[1,25,26]

Cyclopentenone. The cyclopentenone ring is assumed to adopt the envelope conformations of cyclopentene. Due to the trigonal carbon of the carbonyl group there is a flattening of the ring so that the envelope form is close to the planar form and both forms are readily interconvertible.[1,25,27]

6-membered rings. Cyclohexane (Fig. 11). Chairs are of lower energy than flexible forms (twists and boats). Twist forms (also called skew-boats) are of lower energy than boats. Let us note that each flat side of the boat, corresponding to zero torsion angle, has two consecutive axial substituants on the same side of the ring (sequences $-\ 0\ +$ or $+\ 0\ -$).

In the twist forms two small torsion angles ($\sim 30°$, small by comparison with those of the chair $\sim 56°$) are followed by a large one (around 70°) of the opposite sign: the sequence is $-\ -\ +$ or $+\ +\ -$. The unsubstituted molecule has a symmetry axis and substituants located at the carbon atom between angles of the same sign are called bisectional or isoclinal.

Cyclohexanone. The replacement of a methylene in a cyclohexane ring by a ketone does not greatly change the preferred conformations of the 6-membered rings which are the same as those of cyclohexane but since there is less steric interaction the energy difference between chair and twist forms is lower for cyclohexanone than for cyclohexane. This has to be taken into account in the interpretation of the alkylation of cyclohexanones.

Cyclohexene (Fig. 12). The various low energy forms of cyclohexene are shown in Fig. 12. The energy of these forms increases from half-chair to 1.2-diplanar forms (of slightly higher energy than chairs) and up to 1.3- and 1.4-diplanar forms. The boats (1.4-diplanar forms) in the cyclohexene series as in the cyclohexane one are the least stable of the privileged forms.[1,28] To help visualize these forms let us remember here that 1.2-diplanar forms have five carbons on a plane and the last one outside, for this reason this 1.2-diplanar form is also called envelope or sofa.[29]

1.3-Diplanar forms appear fairly often, in various reactions of cyclohexenones, especially as primary enolates intermediates in the conjugate additions to cyclohexenones and they deserve special interest in so far as they represent the alternative to the usual pre-1.2-diplanar (or pre-half-chair) transition state (see Fig. 4).

Cyclohexenone (Fig. 13—only one set of conformers is represented, the other set corresponds to the inverted series).

The presence of a CO group imparts some lowering of the rotational barrier in its vicinity and there are less non-bonded interactions so that half-chairs and the 1.2-diplanar forms that have the zero torsion angle between the double bond and the ketone, are of comparable energy and can be used indifferently. The other 1.2-diplanar forms are of higher energy than the half-chairs. The same relationship holds for the corresponding 1.3-diplanar forms as shown in Fig. 13. For these forms and for the other remarkable forms the stabilities correspond to those of cyclohexene: the energy of the forms increases from the 1.2-diplanar to 1.3-and 1.4-diplanar forms.[16]

Cyclohexadienes. As already mentioned (Fig. 5) for chorismic acid (1.3-diene) and prephenic acid (1.4-diene) there are usually two inverted 1.3-and 1.4-diplanar forms.

It should be noted here, that in the 1.3- and 1.4-diplanar forms as in the envelope form of cyclopentane there are two consecutive axial orientations on the flat side corresponding to the clockwise sequence $+\ 0\ -$ or its reverse $-\ 0\ +$. This has a bearing on the relative reactivity of the corresponding unsaturated forms (as compared to half-chairs of cyclohexene) towards *cis*- addition

(epoxidation and the like) and cyclo-additions of the 1.3-dipolar or Diels–Alder type as will be shown in the following chapter.

Mnemonic rules. For unsaturated 5- or 6-membered rings two mnemonic rules can be used to remember the sequences of the preferred conformations:

(a) except for half-chairs, there is always a regular alternation of + and − signs if zero torsion angles are left aside. For half-chairs the alternation is regular but the signs are the same on either side of the double bond.

(b) for all unsaturated forms there never are two identical + or − contiguous signs.

It is easily inferred from the conformational tables (Figs. 9–16) that two corresponding inverted forms have opposite signs of torsion angles (compare the signs for each set in Figs. 10 and 12).

7-membered rings. Cycloheptane (Fig. 14, for convenience only one set of conformers has been represented the other inverted set can easily be drawn by the reader). There are four basic conformations for cycloheptanes, these are in order of decreasing stability twist-chair, chair, twist-boat and boat. The twist-chair seems to be generally considered as the most stable form and twist-boat and boat as forms of comparable energy.[1,30] The pairs twist-chair, chair and twist-boat, boat are readily interconvertible by pseudorotation.

Cycloheptanone. Twist-chairs seem to be the most stable forms and we may assume that the other forms will be similar in stability to those of cycloheptane, but literature lacks data to support this affirmation.[30c,31]

Cycloheptene (Fig. 15). The most stable forms appear to be chairs of slightly less energy than the twists (by approximately 0.5 kcal/mole). Both these forms are of much lower energy than the boats.[26,28,32]

Cycloheptenone (Fig. 16). There is reversal of stability with respect to cycloheptene since twist forms are slightly (by *ca.* 0.5 kcal/mole) more stable than chairs. Both forms are of lower energy than boats.[33] Whereas the overlapping of orbitals in the conjugated enones is generally good for cyclopentenone, cyclohexenone and their derivatives, it is different in the cycloheptenone series due to a distinct non planarity of the double bond and the carbonyl group of the conjugated enone. The most stable conformation thus appears as a compromise between the minimization of steric interactions and the requirement of maximum orbital overlap of the conjugated enone. The orbital overlap is poor for chair and boat forms since the axis of the carbonyl is nearly orthogonal to the plane of the double bond thereby reducing more or less strongly the conjugation.

From perspective representations to torsion angle notation and vice versa

It was said earlier that if the orientation of the axial substituants of a ring is known it is fairly easy to represent the corresponding conformations in the torsion angle notation: there is an unequivocal correspondence between the torsion angle notation and the usual perspective representation and vice versa.

For instance let us show how to write the torsion angle sign sequence in the case of the substrate of Fig. 1. First (Fig. 17) one has to note that the substituants of the two carbons at the *trans* ring junction are necessarily axially orientated: one hydrogen is β axial, the other is α axial. For each ring we move along the successive carbons of the ring in a clockwise fashion (Fig. 17, drawings 1–3). For the unsaturated cyclopentene ring there is a zero torsion angle corresponding to the double bond and the sign sequence is known for both angular substituants: for the α orientated hydrogen the code indicates (Fig. 8) − + and + − for the β orientated hydrogen. Therefore we have the known − + − 0 sequence, which is completed to 0 + − + − since it is also known (Fig. 10c) that the preferred form of cyclopentene is an envelope with a regular alternation of all positive and negative signs. With the other hexagonal ring one proceeds in the same manner (Fig. 17, drawings 4–6). Starting from the axial substituants of the *trans* ring junction one can write the sequence + − + and if it is admitted that the ring happens to be in its most stable chair form the sequence can be completed since there is a regular alternation of signs + and − in the chair form. Whereas the cyclopentene ring can only adopt a single low energy envelope form, the cyclohexane ring can adopt any one of the chair, twist or boat forms (Fig. 17 at the bottom) provided enough energy is given to the molecule.

A perspective representation from the one with the torsion angle notation can also be drawn in the following way (Fig. 18). One has to note that in the 5-membered unsaturated ring there are two axial

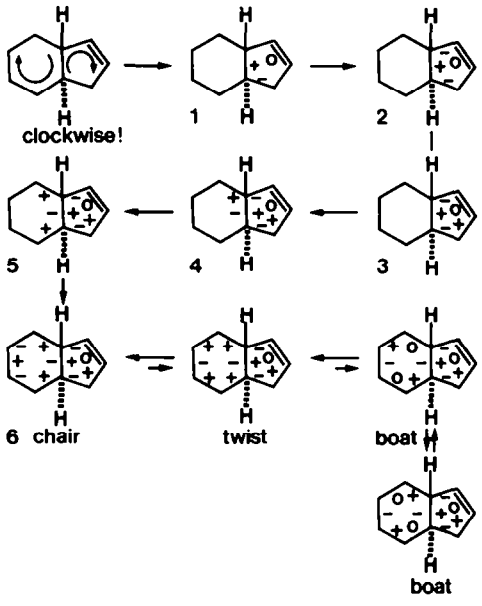


Fig. 17

hydrogens which determine the envelope and for the hexagonal ring it can readily be seen (always in a clockwise fashion along the carbons of the ring) that there are three β axial hydrogens which unequivocally determine the chair conformation of that ring (Fig. 18).

In this example, owing to the rigid *trans* junction of the perhydrindene rings, the unsaturated ring can only adopt one low energy envelope form (there is no other). Generally speaking conformational equilibrium may exist and there are two envelope conformers in equilibrium as shown for the 4-substituted cyclopentene of Fig. 19. In one of the conformers the 4-alkyl (R = alkyl) is in the equatorial orientation (Fig. 19, the 4-hydrogen is axial, the sign sequence taken clockwise is $- +$), in the other conformer the 4-alkyl is axial (clockwise the sign sequence is $+ -$).

Distortions. So far we have left aside the physical meaning of a torsion angle which can now be described as shown in Fig. 20: when a chain of four atoms a b c d is looked at down bc, the torsion angle corresponds to the angle between the two planes defined by abc and bcd. It is positive when the superposition of the two planes abc and bcd needs a clockwise motion, it is negative in the opposite case. Now, throughout this text, a b c d correspond mainly to four successive carbons of three consecutive sides of a ring and the torsion angle is best visualized through Newman's projection as in the example of Fig. 21 where the [3. 4. 5. 6] torsion angle of the chair clearly appears to be positive.

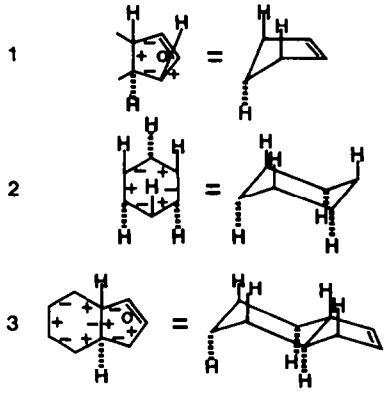


Fig. 18

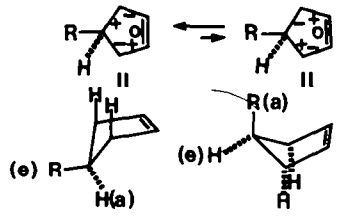


Fig. 19

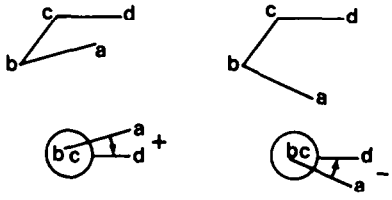


Fig. 20

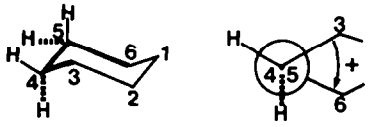


Fig 21

When two rings are fused, as in the case of trans perhydrindene of Fig. 18, the torsion angles at the junction of the rings have to be mutually compatible. This means that the distortion induced by one ring into the other, as a consequence of the ring fusion, does not result in a prohibitive strain on the bicyclic system.

In a similar manner, each time the end of a double bond of a ring happens to be at the junction of fused rings (as in the case of the octalin and perhydrindenes of Fig. 22) it is to be expected that addition of chemical reagents to the double bond (hydrogenation, epoxidation, peroxidation, halogenation, etc.) will cause a distortion not only of the ring's conformation (and therefore of the torsion angles) containing the double bond but also of the other fused ring's conformation. Such conformational transmission appears important in interpreting or predicting the outcome of a few addition reactions to the double bond of bicyclic compounds, when the end of the double bond is at the ring junction. Therefore, we first recall hereafter the main rules concerning the transmission of distortions[34] in the decalin and octalin series and we shall extend these rules to include fused rings of other sizes.

cis *and* trans *Decalins: their characteristics.* Whereas the *cis*-decalin, shown in Fig. 23a, can have two conformers in equilibrium with both rings in the chair form, only one conformer with both rings in the chair form can be drawn for the *trans*-decalin (Fig. 23b).

quasi-cis *and* quasi-trans *Fused bicyclic rings.* Special attention has to be given to the case of cyclohexenes, cyclohexenones, cyclohexadienes or cyclohexadienones fused to any other 6-membered ring in which the trigonal carbon at the end of the unsaturated system is common to both rings as in the case of the octalin in Fig. 24 and steroidal octalone, dienolate and dienone in Fig. 25

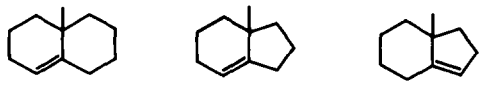


Fig. 22

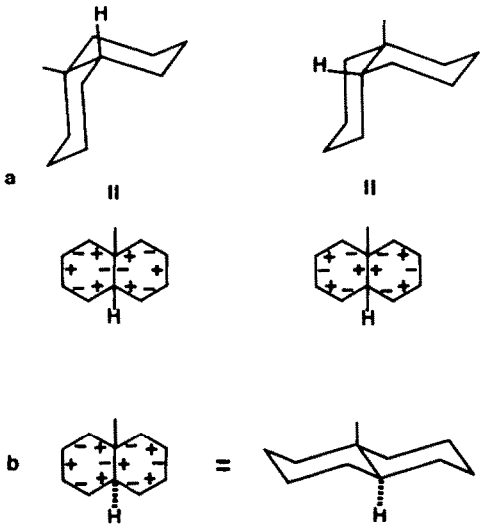


Fig. 23

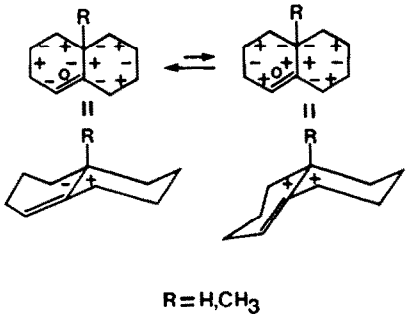


Fig. 24

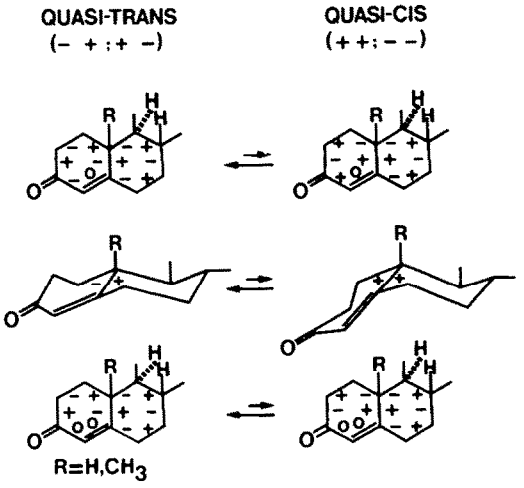


Fig. 25

and 26. In such cases two types of conformers, usually in equilibrium, are available. They have been designated as "*quasi-trans*" and "*quasi-cis*" to recall their similarity with "*trans*" and "*cis*" octalins and octalones.[35] In the *quasi-trans* fused rings the signs at the junction are opposite whilst in the *quasi-cis* fused rings they are identical.

Usually and independently of other steric or polar factors the *quasi-trans* type of junction is of lower energy than the corresponding *quasi-cis* conformer[36] but, of course, substitution of the rings may reverse this order of stability.

Transmission of deformations. cis-Decalin. As already mentioned for the *cis*-decalin the signs of torsion angles on either side of the fused rings are the same. This can be used to remind us of the transmission of distortions at the ring junction: any increase (opening) or decrease (closing or flattening) of the torsion angle at the junction of one ring is transmitted to the adjacent torsion angle at the other ring's junction: an increase corresponds to an increase and a decrease to a decrease,[34] this is readily apparent from Newman's projections (Fig. 27).

trans-Decalin. At the ring junction of *trans*-decalins the torsion angles' signs are opposite which recalls that the closing of a torsion angle of junction corresponds to the opening of the adjacent angle on the other ring and vice versa[34] (Fig. 28).

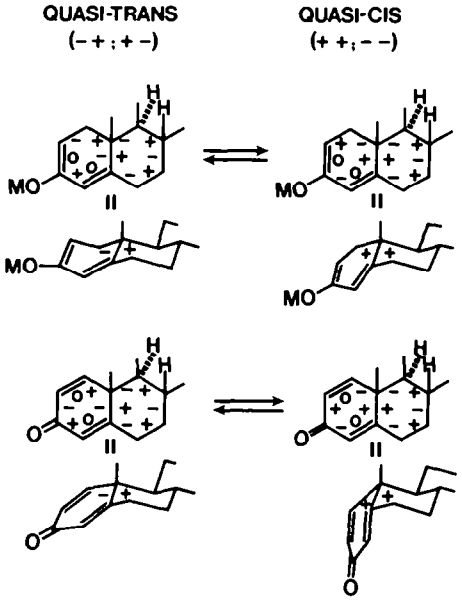


Fig. 26

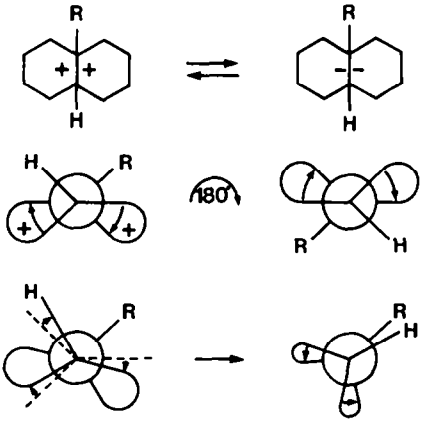


Fig. 27

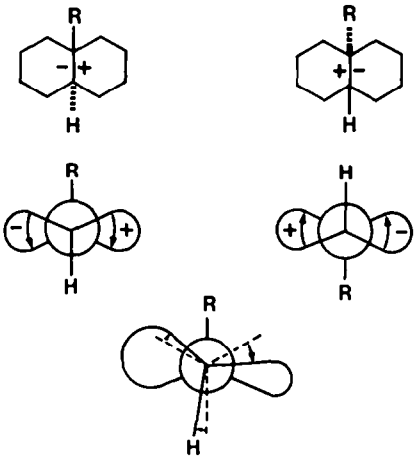


Fig. 28

The notion of a balance between *quasi-trans* and *quasi-cis* in unsaturated fused rings is a general one and it can be extended to rings of different sizes, provided the end of a double bond of one ring is at the junction of the fused rings. It applies to 6-membered rings fused to cyclopentene or cyclopentane fused to cyclohexene and also to 7-membered rings fused to cyclopentene or to cycloheptene fused to cyclopentane.

Torsion angle changes at the site of an addition to a double bond. At the site of addition to a double bond the trigonal carbon and its environment undergo a conformational distortion. From the zero value, the positive or negative variation of the torsion angles surrounding the trigonal carbon can be predicted since the assumed principle of perpendicular addition implies the axial introduction of the chemical agent, which in turn determines one of the following sign sequences, which are precisely those of the code (Fig. 8).

Perpendicular addition to a double bond { above the mean plane: + −, + 0 or 0 − ; below the mean plane: − +, − 0 or 0 +

IV. APPLICATIONS

(1) *Putting the torsion angle notation into practice: how to write the primary final product*

To analyze the steric course of any reaction, we usually carry out several successive steps, which we will now detail. First of all, taking into account the specific stereoelectronic requirements of the reaction, we start from a privileged form of lowest possible energy and then, the next problem is to find the primary products, the most likely to be formed in the reaction. A further step in this direction is to translate the conformational distortion at the site of the reaction into the torsion angle notation, with the help of the code (Fig. 8), as explained earlier. Proceeding in such a manner gives a set of primary final forms and at this point in order to find the steric outcome a choice has to be made, based on energy level considerations, as to which one of all these primary forms corresponds to the transition state of lowest energy. As a rule, in the absence of steric hindrance or strong polar effects, we admit that the transition state of lowest energy will correspond to the primary final form of lowest energy. Therefore, usually, the choice is a simple one; from among the various possible remarkable forms that are available for the primary final product, the form of lowest energy is nearly always chosen: for instance 1.2-diplanar forms are preferred to 1.3-diplanar or boat forms for unsaturated 6-membered rings, a twist is preferred to a boat for saturated 6-membered rings. With respect to the initial reactive conformation of the substrate the rule, in the absence of steric hindrance or strong polar effects, is to keep as many as possible of the torsion angles' signs from the starting form up to the form of the primary final product. This rule is the explicit translation of the principle of least conformational distortion during the reaction.

To show how to operate, let us start with the conjugate addition of Fig. 4, which is reformulated on Fig. 29 using the torsion angle notation. First ring A is written in its 1.2-diplanar form of low energy, with the second zero torsion angle between the double bond and the ketone. The perpendicular addition of an anion to the 1 position of the A ring causes a distortion of this part of the molecule and

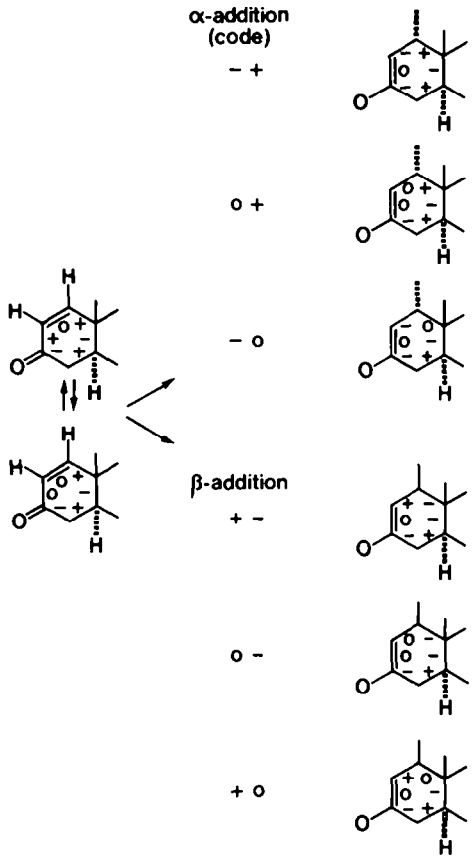


Fig. 29

looking at the code (Fig. 8) it can be seen that the axial bond, which is formed, if α orientated, corresponds to one of the following three sequences (always clockwise!) − + or 0 + or − 0. Trying the first one gives a half-chair for the primary final form, using the second one (0 +) we have a 1.2-diplanar form equienergetic with the half-chair and finally the third sequence (− 0) yields a primary final form of high energy. The choice, therefore, is between the half-chair and the 1.2-diplanar form and since they are equienergetic, we may select either one. With respect to the 1.2-diplanar form there is no torsion angle change during the whole reaction for the conjugate addition to the α-side.

For the conjugate addition of the anion to the β-side one proceeds in the same way: for the distortion the code gives the following sequences: + − or 0 − or + 0. The first two sequences lead to remarkable forms of much higher energy than the 1.3-diplanar form resulting from the third sequence (+ 0). Therefore from among these three forms the last 1.3-diplanar form is selected. Now, to decide about the outcome of the conjugate addition we compare the energy of the primary final products resulting from the conjugate addition to the α and β side of the ring. Since the 1.2-diplanar form is of lower energy than the 1.3-diplanar one, we admit that the relative energy of the corresponding transition states is in the same order: in this case the transition state of least energy corresponds to the least change of angle signs during the reaction.

In this particular example ring A, owing to its trans fusion to ring B of the steroid, can only adopt one of the two equivalent, low energy forms, half-chair or 1.2-diplanar. In the general case, a mobile equilibrium of low energy half-chair or 1.2-diplanar forms may exist as in the example of Fig. 30, where the writing of the torsion angles of the primary final forms is done in the same manner as in the case of Fig. 29. As it has already been stated elsewhere,[2] there are generally four transition states, the relative energy of which has to be evaluated in order to interpret or predict the outcome of the conjugated addition. More time will be devoted to conjugated additions to 6-membered rings in due course, but we will halt the discussion about this reaction here, so that we can give further examples showing how to implement the torsion angle notation.

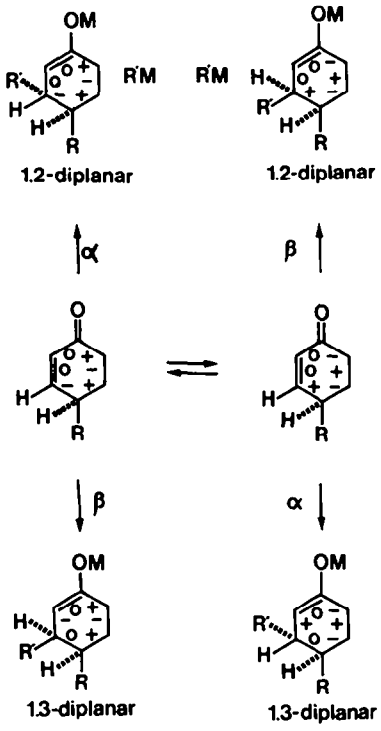


Fig 30

The next example deals with the ionic bromination of the Δ^2 enol of a 3-keto 5α-steroid (Fig. 31). First the signs that characterize the low energy half-chair of ring A are written; since the 10β orientated R group, like the 5α-hydrogen are both axial, the sequence of signs is readily determined and completed to half-chair (see Table of unsaturated forms Fig. 12). Now the addition of the bromine cation is assumed to take place through perpendicular addition to position 2 and on either side of the ring. In each case the new carbon–halogen bond, thus formed, is axial and the sequence of torsion angles resulting from the distortion of the Δ^2 enol double bond is given by the code (Fig. 8) and, moreover, we know that the preferred low energy forms of the ensuing brominated cyclohexanones are, like those of cyclohexanes, the chair, the twist and the boat. Thus for addition to the α side, the sequence − + yields a form of high energy, which can be converted to a twist form by changing one more torsion angle. Therefore in this case, with respect to the initial form, there is a sign change for two torsion angles, besides the zero torsion angle, which has become negative.

For the two other sequences it can readily be seen that −0 again leads to a cyclohexanone form of high energy, the closest preferred form being a boat and 0 +, yields a high energy form, which can

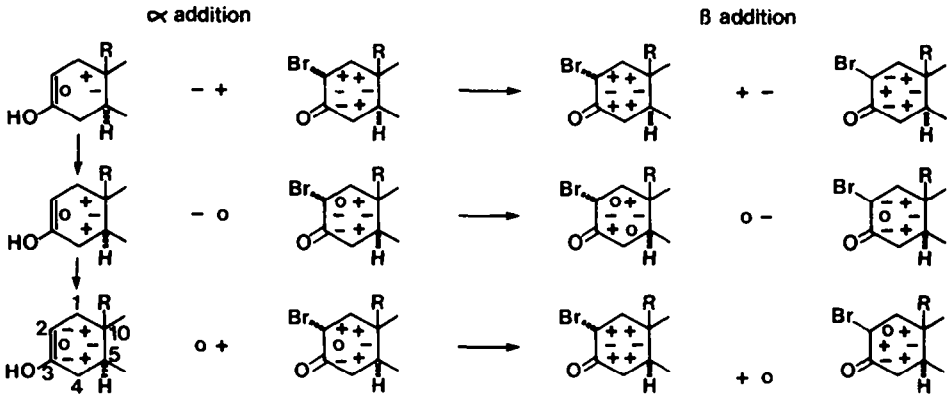


Fig. 31

stabilize itself by conversion to the already mentioned twist form. Since twist forms are of lower energy than boats we select this twist form as the primary final form of the addition to the α side.

The addition of ionic bromine to the β side gives rise either directly to a low energy chair (sequence $+\ -$) without much conformational distortion (the torsion angle of zero value has become positive and there is only one torsion angle change). The other two sequences lead to forms of higher energy and can be ignored. Summing up we have two primary final products that may result from the addition to either side of the enol double bond. Now, when R = H, there is no steric hindrance to the approach of the halogen and therefore in the nor-series the addition of the reagent to the β side should be largely predominant, which is indeed the case,[37] but when R = Me we can no longer, mechanically, apply the rule and we have to evaluate the importance of steric interactions and their consequences on the transition state level. Steric hindrance does manifest itself not only in the approach of the bromine to the double bond, but also in the corresponding transition state, since the steric interactions, of the 1.3-type[38] between the axial bromine and the axial angular Me are strong enough to destabilize the transition state leading to the chair ("pre-chair transition state") with respect to the one leading to the twist form ("pre-twist transition state").[39] Furthermore, since it was already mentioned that the energy differences between twist and chair forms in the cyclohexanone series are lower than in the cyclohexane one, we are led to believe that the steric hindrance to the approach and the energy increase in the ensuing transition state causes the pre-twist transition state to become of lower energy than that of the pre-chair. Therefore, owing to strongly increased steric interactions in the transition state leading to the primary final chair form kinetic bromination will occur mainly on the α side yielding the primary final twist form.

Here we see the limits of the torsion angle method, which is only a planar representation of conformations: it gives valuable results, even in complex cases, only if the right hypotheses have been injected into the reasoning and if a correct evaluation of the relative energies of the various transition states has been performed, after having taken into account all factors, whether steric, electronic or polar.

The last two examples, to be analyzed, deal with borohydride reduction of cyclic imines and immonium salts. These reactions may be viewed as additions of hydride ion from relatively small donors to the trigonal carbon of the imine or immonium salt.[40] Starting with the quinolizidinium salts of Fig. 32 we proceed in the usual manner. First the low energy conformations of the rings are drawn, chair for the saturated ring, half-chair for the ring containing the immonium double bond. Since the immonium end of this heterocyclic double bond is at the ring's junction there are two

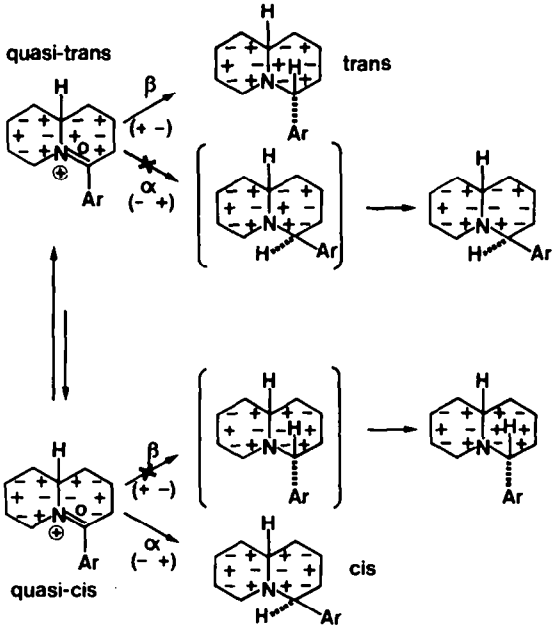


Fig. 32

equilibrating quasi-*trans* and quasi-*cis* conformers, the former being assumed to be the more stable one by analogy with the carbocyclic series.[36] From each of these initial forms of the substrate two primary final products are conceivable depending on the side of hydride addition to the trigonal carbon of the immonium. As shown on Fig. 32, in each case for the arylated ring the chair form of the primary final product is preferred so that the choice is between two low energy primary final forms of *cis* and *trans* perhydroquinolizidines. If it is admitted that the stabilities of perhydroquinolizidines are comparable to those of *cis* and *trans*-decalins with the latter being of lower energy, we can expect the *trans*-perhydroquinolizidine to be the dominant product of reduction since, starting from the immonium form of lower energy, we arrive at the amine form of lower energy presumably through a transition state of lower energy. Such an interpretation is in agreement with the experimental results.[41]

Similarly, the kinetic addition of hydride and other anions to cyclic imines or immonium salts may be interpreted or predicted (Fig. 33[42]). The interpretation is not limited to 6-membered rings, thus the reduction of the 5-membered immonium salt of Fig. 34 by sodium borohydride is readily explained using simple arguments: there are two envelope forms for the 5-membered ring and owing to strong steric interactions with the adjacent rings, the aldehydic substituant should prefer the axial orientation which implies that the other *trans*-ethyl substituant has also to be in the axial orientation. Now if the form with both *trans*-diaxial substituants is predominant at equilibrium, as we believe, the addition of a hydride ion will occur from the β-side (sequence: + 0) giving the reduced alcohol in 70% yield. As it will be detailed in one of the next sections the sequence of the preferred envelope at the immonium double bond (+ 0 −) implies that a *cis*-addition (catalytic hydrogenation for instance) should also take place on the β side and this inference appears to be in agreement with the experimental results.[43]

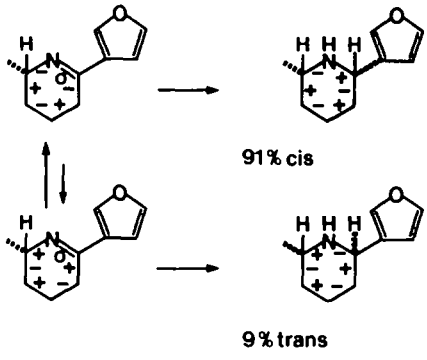


Fig. 33

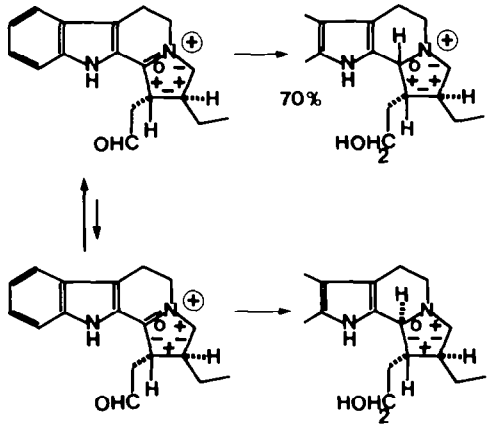


Fig. 34

(2) *A few rules about reactions involving syn-additions, syn-eliminations and cycloadditions*

The torsion angle notation may be able to predict or interpret the steric course of *syn*-additions to double bonds (such as peracid epoxidation, hydroboration, hydroxylation, catalytic hydrogenation, etc.) and cycloadditions (such as diene synthesis or 1.3-dipolar additions, etc.) if, as claimed in the literature,[44] it is assumed that most of the customary *syn*-additions or cycloadditions are more or less concerted reactions with the two following features: the formation of the two bonds is not simultaneous but stepwise and the formation of the first bond determines the spatial orientation of the primary final product.

With our usual stereoelectronic hypotheses and the principle of least conformational distortion the description of the common rings in the torsion angle notation implies a specificity or, at the very least a strong stereoselectivity for *syn*-additions (and their reverse *syn*-eliminations) and for cycloadditions to low energy forms of unsaturated 5- and 7-membered rings and also to a few forms of unsaturated 6-membered rings.

The origin of this selectivity is to be found in the sequence of torsion angle signs around the double bond of an unsaturated ring, and in this respect, we have to distinguish between low energy forms of odd (cyclopentene, cycloheptene) and even (cyclohexene) membered rings.

In odd membered rings, the torsion angle signs are opposite on each side of the double bond for the low energy forms, envelope of cyclopentene (Figs. 7a, 10c) and chair of cycloheptene (Figs. 7c, 15). In this latter case the boat but not the twist form of cycloheptene also has opposite signs on each side of the double bond (Fig. 15).

In cyclohexene, the only even membered ring we deal with, the torsion angle signs are identical on both sides of the double bond in the low energy half-chair (Fig. 12) but they are opposite in the 1.3- and 1.4-diplanar forms of higher energy (Fig. 12). Now a sequence of dissimilar signs before and after the double bond of an unsaturated ring may explain the specific cis-additions of a reagent to the double bond for the following reason. The stepwise *cis*-addition to the double bond of a given low energy conformer starts with the perpendicular addition of an ionic or radical fragment to one of the trigonal carbons of the double bond (any one of them if the double bond is unsubstituted, the least substituted carbon, according to Markownikow's rule, if the fragment is electrophilic). The important point is that there is only one direction of approach to the double bond, which allows the formation of the first axial bond and which precisely, corresponds to the clockwise sign sequence of torsion angles. Since the first bond determines the overall stereochemistry of the primary final adduct, the *syn*-addition generally, corresponds to the torsion angle sequence namely:

syn-addition to double bond	Clockwise sequence
– above the mean plane of the ring	+ 0 –
– below the mean plane of the ring	– 0 +

These sign sequences correspond to those of the code (Fig. 8) by inserting zero between + – or – +.

For instance in the epoxidation of Fig. 1, where the cyclopentene ring has only one envelope form, as shown on Figs. 17 and 18, owing to its trans fusion with the adjacent ring, the clockwise torsion angles sign sequence before and after the double bond (– 0 +) implies a specific epoxidation from the side of the axial hydrogen of carbon 4, which is indeed the experimental result.[3]

The origin of the specificity of *syn*-addition in the case of Fig. 1 and in the analogous cases may be traced back to the fact that trying to add stepwise the ionic fragment OH^+ for the epoxidation with peracids[45] on the side opposite to the axial hydrogen of carbon 4, would give rise to an epoxide only through very high energy intermediates.

The same type of reasoning applies to each of the envelope conformers of 4-substituted cyclopentene in mobile equilibrium (Figs. 35 and 36) and it can be used to interpret the experimental result, concerning the peracid expoxidation of 5-hydroxymethylcycloheptene, indicated in Fig. 2 and detailed in Fig. 3. With the help of the torsion angle notation (Fig. 37) it becomes clear that the main product of epoxidation corresponds to the chair conformer of cycloheptene with the 5-hydroxy-Me group equatorial (the hydrogen of carbon 5 is axial, sequence – +). The minor product is related to the chair conformer of cycloheptene with the 5-hydroxymethyl group axial (sequence +, –). These results follow closely those found in the cyclopentene series for the epoxidation of 4-methylcyclopentene[46a] (Fig. 35): the selectivity is comparable and in the cyclopentene as in the cycloheptene series the main product of epoxidation corresponds to the more stable conformer with the alkyl group equatorial on the lower energy conformer.[46]

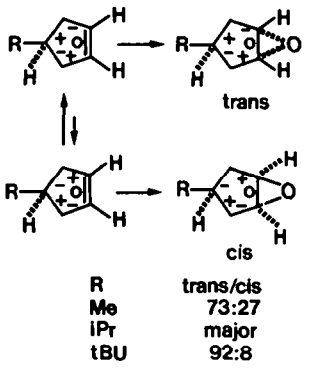


Fig. 35

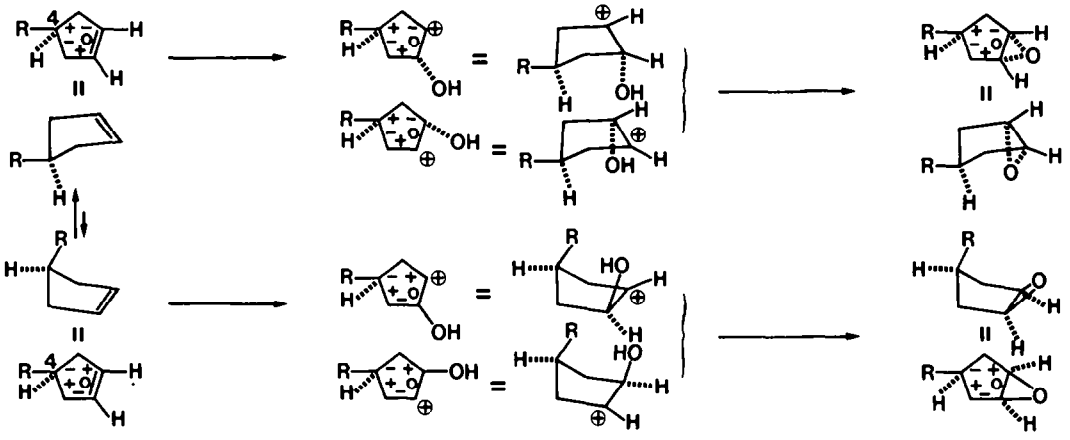


Fig. 36

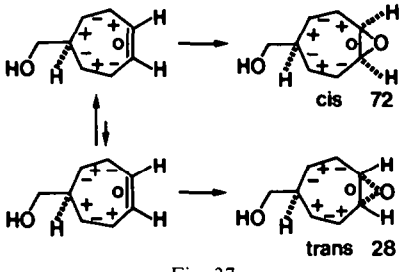


Fig. 37

The sequence rule given above appears valid for all *syn*-additions and cycloadditions to double bonds of cyclopentene, of the chair and boat conformers of cycloheptene and of the diplanar forms of cyclohexene and their derivatives. More examples will be provided in the following sections.

The same sequence rule can help to predict or interpret the steric course of kinetic anti-additions to double bonds in all the cases where the reactions occur through a transitory *syn*-adduct of the halonium, sulfonium or mercurinium ion type and similar 3-membered polarized rings. In this respect it is possible to readily interpret a few reactions the rationality of which has escaped the chemist.[47]

Finally, according to the principle of microscopic reversibility[48] since eliminations are the reverse of additions, the steric course of *syn*-eliminations should obey the sequence rule given for the *syn*-addition, which is the case. We are going to discuss this point in the next section.

Comparison of the reactivity of the various common rings. Whereas in the case of peracid epoxidation of a cyclopentene or cycloheptene there is practically no conformational change from the low energy starting reactive conformer up to the low energy conformer of the primary final product, it could be argued that it might be different for reactions such as hydroboration or catalytic hydrogenation or cycloadditions, since again, we start from a low energy conformer of an unsaturated ring but, now we end up with a conformer of the corresponding saturated ring, not necessarily a low energy conformer.

From this point of view the mere knowledge of the low energy conformations of unsaturated and saturated 5-, 6- and 7-membered rings already permits a qualitative evaluation of the relative reactivity of the various unsaturated rings towards *syn*-additions and their reverse *syn*-eliminations and towards cycloadditions.

For instance thermal *syn*-eliminations of a sulfoxide or selenoxide group of a cyclopentane ring ought to be readily performed if it is assumed that such *syn*-eliminations imply a coplanar arrangement ("*syn*-periplanar") of the leaving hydrogen and sulfoxide or selenoxide.[49] As shown on Fig. 38, an envelope conformation of the ring, with the leaving group axial, is suitable and the reaction gives rise to a low energy envelope form of cyclopentene with the minimal amount of distortion and presumably a low energy transition state.

By comparison the cyclohexane homolog (Fig. 39) has to adopt a relatively high energy boat form, (a twist form is unsuitable) in order to ensure both the axiality and the coplanarity of the leaving group and the departing *cis* hydrogen: this requires a substantial amount of energy before the reaction sets on and moreover the boat gives rise to a 1.3-diplanar form (or less likely a boat) through a transition state of much higher energy than the one involved in the thermal conversion of the cyclopentane derivative to cyclopentene.

We can already conclude, even without knowing the experimental result[50] that under comparable conditions the thermolysis of the cyclopentane selenoxide ought to be much faster than the thermolysis of the corresponding cyclohexane selenoxide.

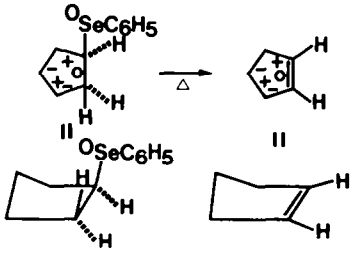


Fig 38

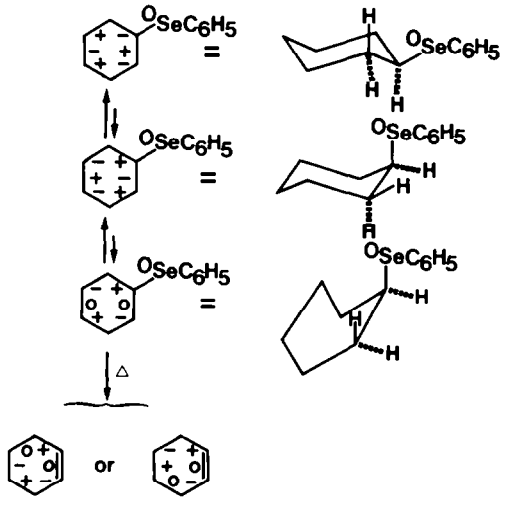


Fig. 39

Since the cycloheptane ring can adopt a low energy chair (Fig. 14), which would give rise by syn selenoxide or sulfoxide elimination to a low energy chair of cycloheptene (Fig. 15), we can expect the reactivity of cycloheptane with respect to syn eliminations to be similar to that of cylopentane and again, much greater than that of cyclohexane.

In the same way the relative tendency of unsaturated 5-, 6- and 7-membered rings to undergo cycloaddition, whether of the 1.3-dipolar or Diels–Alder type, may be evaluated. We would expect the unsaturated 5- and 7-membered rings to undergo cycloaddition much faster than cyclohexene since in the two former cases the reaction proceeds from a low energy envelope conformation of cyclopentene or chair of cycloheptene with minimal distortion up to a low energy conformation of the resulting envelope of cyclopentane or chair of cycloheptane. The outlook is quite different in the 6-membered series since stepwise formation of the bonds requires a 1.3-diplanar form or a boat of comparatively high energy and leads to a boat form, presumably through a high energy transition state. From the literature data it appears that, indeed, unsaturated 5- and 7-membered rings are more reactive towards syn-additions and cycloadditions than mono unsaturated 6-membered analogues.[51,52] Whereas cyclohexene derivatives generally have a low propensity to *syn*-addition or cycloaddition, the literature reveals that the corresponding 1.3-and 1.4-cyclohexadienes are much more prone to such reactions.[51,53] For instance, whereas cyclohexene does not react with phenylazide at room temperature, 1.3-cyclohexadiene does react albeit slowly (18 days at room temperature 77% yield of adduct). This result is not surprising and it can be interpreted in the customary manner (Fig. 40): the 1.3-diplanar conformers of the 1.3-cyclohexadiene can give rise to a 1.3-diplanar form of the primary final adduct with axial orientation of the two newly formed bonds (sequences $-0+$ or $+0-$) without much conformational distortion and through a transition state of comparatively low energy, at any rate lower than the one corresponding to the cycloaddition to cyclohexene (1.3-diplanar form or boat).

Axiality requirements of epoxide and similar 3-membered rings with respect to the larger ring's reactive conformation. Attention has to be focused here upon the fact that, with regard to the ring's reactive conformation, the axiality of the bonds involved in *syn*- or *anti*-eliminations or additions, has general implications, especially so for the reactions of epoxides or of analogous transitory 3-membered rings of the halonium, sulfonium, selenonium and mercurinium ions types. Throughout this text the orientation of a 3-membered ring (epoxide or 3-membered ion of the halonium type) with respect to the reactive conformation of the larger ring, is necessarily the axial one with the torsion angles' signs corresponding to one of the following sequences (always clockwise around the ring):

(β) axial epoxide above the mean plane of the ring, sequences: $+0-$, $+00$ or $00-$

(α) axial epoxide below the mean plane of the ring, sequences: $-0+$, -00 or $00+$

Bisectional epoxides or 3-membered rings (of the halonium, sulfonium types) which do not correspond to the preceding sequences have to undergo a conformational change to become "axial" before any reaction, involving them, can proceed. Examples of such reactions as anion opening of

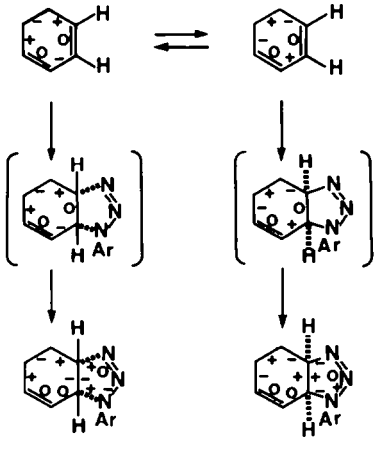


Fig. 40

three membered rings or epoxide isomerizations to allylic alcohols in the presence of strong bases will be given hereafter. This axiality requirement of 3-membered rings will be detailed now with the help of a few examples pertaining to reactions of selenolactonization, halolactonization and also of epoxide opening and isomerization.

The phenylselenolactonization shown on Fig. 41[54] is quite analogous to halolactonization reactions the stereochemstry of which can be depicted along a similar line: formation of the selenonium ion takes place on the side opposite to the substituant in the corresponding low energy conformer (sequence $-0+$) and the internal nucleophilic attack of the carboxylate anion on this axial selenonium intermediate occurs with configuration inversion at the carbon undergoing the displacement, yielding a bicyclic lactone without much conformational distortion of the initial reactive cyclopentene ring and, presumably, through a low energy transition state. It should be noted that the remaining C–Se bond and the newly formed O C bond of the cyclohexane ring are trans diaxial with respect to each other on the primary final form.

Phenylselenolactonization of the homolog (Fig. 42[54]) can be interpreted in the same manner but in the cyclohexene series there are at least two possible pathways involving 1.2-or 1.3-diplanar forms as starting reactive conformers.

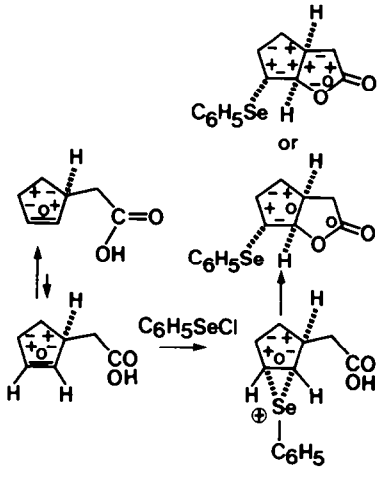


Fig. 41

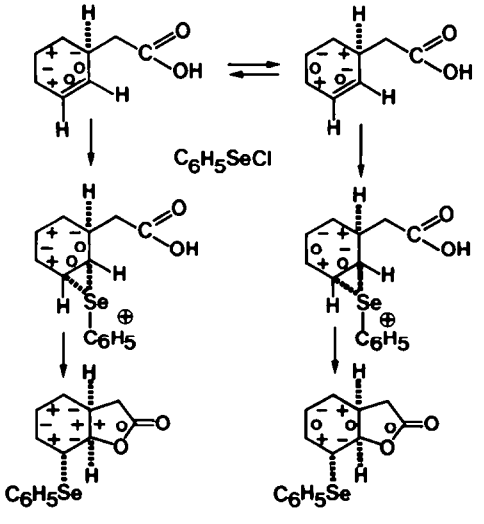


Fig. 42

From the initial reactive conformer in the 1.3-diplanar form bearing the axial side-chain, formation of the selenonium intermediate takes place on the opposite side of the chain and subsequent nucleophilic displacement by the carboxylate group of the chain yields a primary boat.

The 0 0 + sequence of the other reactive 1.2-diplanar conformer means that the *syn*-addition of selenonium ion will take place on the side opposite to the substituant of the ring and the configurational inversion at the displaced carbon gives rise to a primary final chair form for the 6-membered ring of the resulting bicyclic lactone. In both pathways the remaining C–Se bond and the newly formed O–C bond of the cyclohexane ring are *trans*-diaxially orientated on the primary final conformer.

Similarly the iodolactonization of the cycloheptene derivative of Fig. 43[55] may be viewed as involving precisely that low energy conformation of cycloheptene that is bearing the side chain in the axial orientation. Iodonium formation takes place with minimal conformational distortion and the ensuing lactonization leads to a primary final product that can adopt either a low energy chair or twist-chair form.

Chlorohydrin formation starting from cyclic allylic alcohols[56] can also be analyzed as shown in Fig. 44. The Bu group being kept in the equatorial orientation, the OH group is axial on the only low energy reactive 1.2-diplanar conformer that allows the formation of the β-axial chloronium ion. The ensuing epoxide formation takes place with configuration inversion of the breaking chloronium bond and the result is a 1.3-diplanar primary final form (a boat seems less likely).

Turning now to the isomerization of epoxides under strongly basic conditions, we can easily interpret the steric course of the reaction as illustrated in Fig. 45,[57] but it should be pointed out here that the outcome of the reaction depends on the size of the ring and on the experimental conditions, especially, on the nature of the solvent.[58]

Under the usual conditions (lithium diethylamide in ether or tetrahydrofuran[57]) for cyclohexene derivatives, such as the one of Fig 45, the hydrogen *cis* with respect to the breaking bond of the epoxide is selectively removed from the reactive 1.2-diplanar form with the epoxide in the "axial"

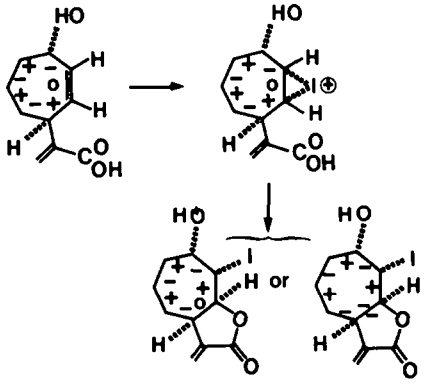


Fig. 43

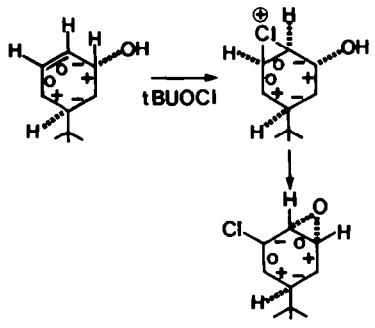


Fig. 44

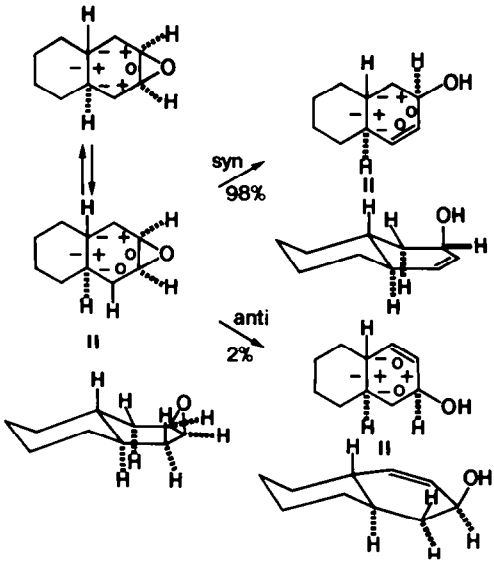


Fig. 45

orientation (sequence + 0 0). The minor allylic alcohol formed in this reaction may be the result of an *anti*-elimination giving rise to a 1.3-diplanar primary final form.

In the cyclohexadiene series or in the conformationally equivalent norcarene series of Fig. 46[59] epoxide isomerization necessarily involves the hydrogen *anti* to the axial epoxide. Even though the conformer with the "axial" epoxide is not the preferred one, it is the only reactive conformer that can lead to the allylic alcohol of isomerization.

For similar reasons epoxide isomerization in the cyclopentene series also involves the *anti*-departure of a hydrogen with respect to the breaking bond of the epoxide[60] as shown in Fig. 47.

Incidentally the synthetic interest of this epoxide isomerization method is worth mentioning since such axial allylic hydroxyls are not readily prepared from the corresponding unsaturated ketone.

To close this section we propose the analysis of the nucleophilic opening of an epoxide Fig. 48[61] occurring with configurational inversion of the breaking bond. The incoming nucleophile approaching at the rear of the bond to be displaced, the reactive 1.2-diplanar form with the axial epoxide can give rise to two primary forms depending on the displaced bond. In the absence of steric hindrance or

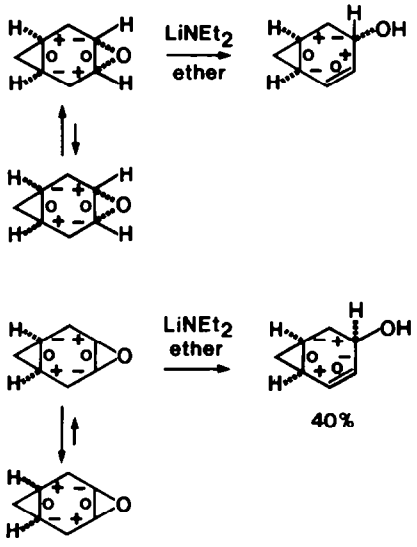


Fig. 46

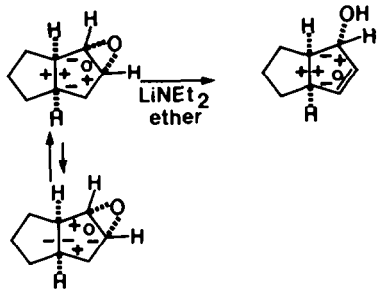


Fig. 47

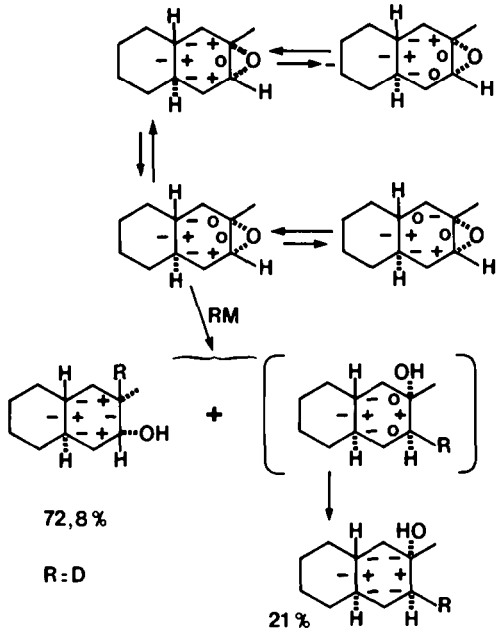


Fig. 48

strong polar effects, a primary final chair is preferred to a primary twist form, a result which reflects the energy level of the corresponding transition states. However, we could have expected the reverse result, had the angular β hydrogen been replaced by a Me since, in this case, strong steric interactions in the corresponding transition states would have destabilized the pre-chair transition state with respect to the pre-twist one becoming that of lowest energy.

V. STERIC COURSE OF ADDITIONS TO UNSATURATED RINGS

Steric course of additions to mono-unsaturated odd membered rings

It has already been mentioned, with examples to support it, that *syn*-addition of reagents to cyclopentenes (Figs. 35 and 41) and cycloheptenes (Figs. 37 and 43) took place stereoselectively with respect to the reactive low energy conformers of the substrate to yield the "axial" *syn*-adduct. This appears quite general and, from this point of view, a few reactions, the steric course of which has been considered as "unpredictable" or "not attributable to any reasonable explanation" can now be interpreted in the usual manner.

The knowledge of the steric course of *syn*-additions to ring olefins is important for two reasons. On the one hand, it allows one to interpret or predict the outcome of many useful reactions such as peracid epoxidations, osmium tetroxide or permanganate glycolation, hydroboration, catalytic hydrogenation among others. On the other hand, the knowledge of the steric course of *syn*-additions

means also the knowledge of *anti*-additions to ring olefins since many *anti* (or *trans*) additions take place stepwise, through transitory 3-membered *syn*-adducts,[62] the formation of which occurs according to the usual rules of *syn*-addition. In this respect, the steric course of reactions such as halogenation, halohydrination, halo or selenolactonization, oxymercuration[63] can be interpreted or predicted taking into account two successive steps. First to take place, through a non synchronous process, is the transitory formation of polarized 3-membered rings of the halonium, episulfonium, episelenonium or mercurinium ion types (cf: examples of Figs. 41–44). This first step is followed by an anion backside displacement of any one of the polarized carbon-heteroatom bonds of the 3-membered ring yielding the primary final product of *anti*-additions. This rationalization is not a new one and, for instance, it is well known for ring olefins, that epoxidation with a peracid and through an intermediate bromohydrin gives sterically reverse results. In both cases the direction of *syn*-additions is the same for the reactive fragment of the peracid[45] and for the positive bromine (Fig. 49) but, in the latter case, subsequent nucleophilic attack by the OH anion on the intermediate bromonium ion, taking place with configurational inversion, determines the orientation of the final epoxide.[3]

Before leaving this discussion it should be mentioned that doubts have been expressed as to the obligatory character of such transient 3-membered ring intermediates.[64] Although the existence of the postulated polarized 3-membered rings is certainly questionable, it so happens that in most cases, the overall result of the reaction may be interpreted or predicted as if such transient 3-membered rings were indeed formed.

We now recall a few rules that have been given in our previous communication devoted to this topic[65] and which appear fairly general.

One reactive low energy conformer available: stereospecificity. When only one reactive low energy conformer of the odd-membered ring is available as in the examples of Figs. 49 and 50, drawn mostly from the steroid series (the *trans* or *cis* fusion of rings C D locks the envelope form of the unsaturated D ring), the *syn*-addition of reagents to the double bond takes place in a stereospecific manner, be it catalytic hydrogenation (Fig. 50*c*[66]), peracid epoxidation (Fig. 50*a*[3], *b*,[67] *d*[68]) osmium tetroxide glycolation (Fig. 50*b*[67]), in the direction corresponding to the clockwise torsion angles' sign sequence.

Further specific additions to conformationally locked cyclopentenes may be found in the addition of various reagents to bicyclo [3.2.1.] octene (Fig. 51[69]) and to bicyclo [2.1.1.] hexene and norbornene derivatives.[70] Norbornene (Fig. 52) may be viewed as a cyclo-hexene in a boat form with a methylene bridge or as a cyclopentene with an ethano bridge. To each representation corresponds

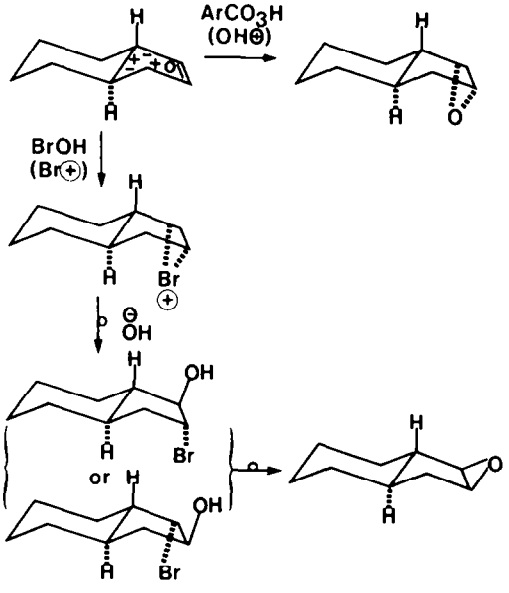


Fig. 49

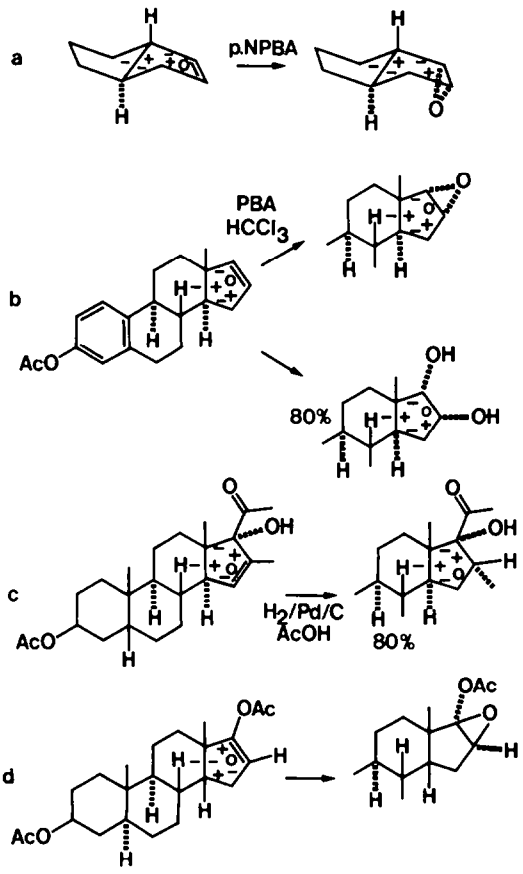


Fig. 50

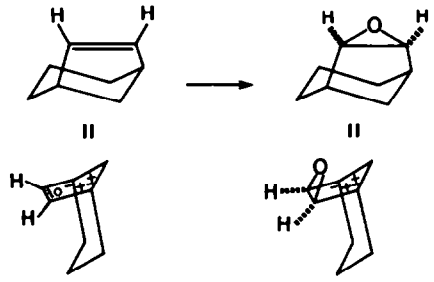


Fig. 51

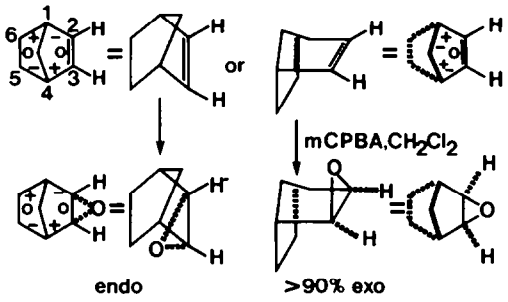


Fig. 52

one specific direction of addition to the double bond. From the numerous experimental results (Figs. 52[71] 53[72]) it can be concluded that the disubstituted cyclopentene representation fits the picture better as far as the reactivity and stereoselectivity of norbornene reactions are concerned. The clean *syn*-addition of mercuric salts to norbornene and bicyclo [2.1.1] hexene[72b] is worthy of note since such salts generally add in a *trans* fashion to cyclobutene or cyclohexene derivatives.[70] Locked conformers of cycloheptenes are not so common as locked envelopes of cyclopentenes, still there are a few examples of them, scattered in the literature, such as the one shown in Fig. 54, where both steric and conformational factors orientate the addition of the reagent in the same direction, thus contributing jointly to the stereospecificity of the reaction.[73]

Several reactive low energy conformers available: stereo selectivity. Whenever there is a mobile equilibrium of low energy conformers of the odd-membered ring the *syn*-addition to the double bond is stereo-specific with respect to each conformer but the overall result corresponds to a stereoselective reaction and the higher the selectivity, the larger the energy difference between the conformers as it will be shown in the following examples (see Figs. 35 and 37).

For monosubstituted cyclopentenes it appears that the envelope conformer with the equatorial substituent is the more stable whether the substituent is at position 3 or 4 (Figs. 19, 35, 55, 56), the larger the substituent, the larger the conformer population,[74] which explains the results of epoxidation (Fig. 55[46b, 75]) hydroboration Fig. 56[72a] oxymercuration (Figs. 57a and b[47]).

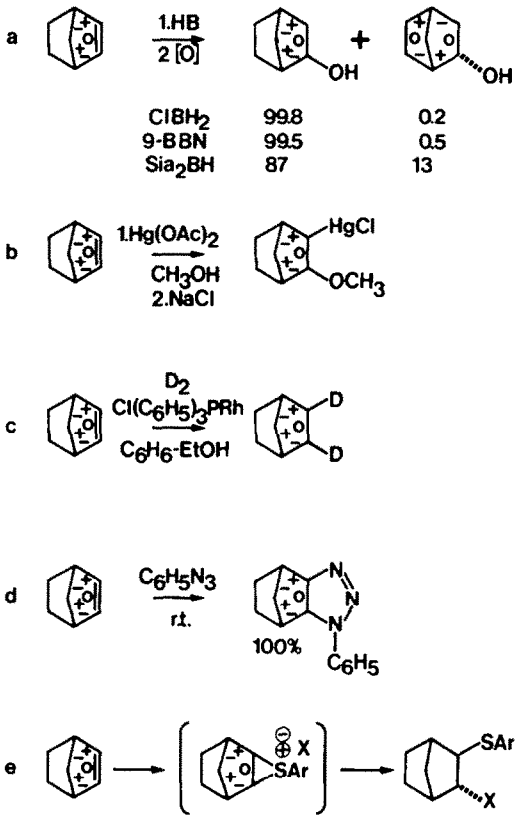


Fig. 53

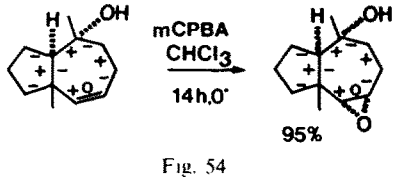


Fig. 54

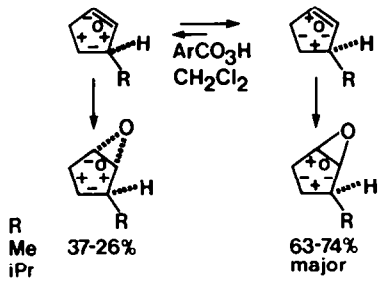


Fig. 55

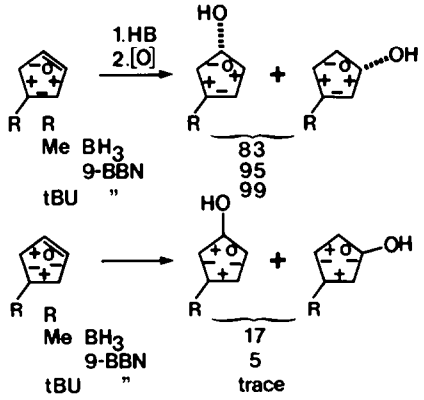


Fig. 56

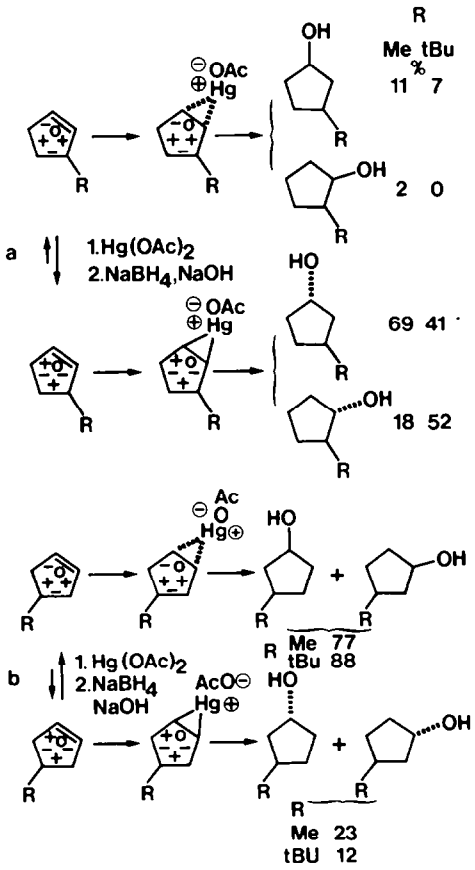


Fig. 57

For monosubstituted cycloheptenes, also, the chair conformation with the equatorial 5-substituant appears more stable than the one with the axial substituent (Fig. 37). For the other positions of monosubstituted cycloheptenes it is not known whether the chair conformer with the equatorial substituant is the more stable of the two as it would seem, by analogy to the 5-membered unsaturated ring.

Similar relative stability relationships also hold for disubstituted cyclopentenes: for *trans* disubstituted derivatives, usually, the envelope with two diequatorial substituents seems the more stable (Fig. 58[76]) for *cis* disubstituted cyclopentenes, the more stable of the two envelope conformers is the one with the larger substituent in the equatorial orientation (Fig. 59[76]).

Influence of various effects on the equilibrium of low energy conformers. (a) Steric affects. Steric interactions appear very important in the cyclopentene series. For instance, when the double bond is substituted, as in the case of 2-alkyl-3-methylcyclopentenes, the conformational equilibrium with respect to the parent 3-methylcyclopentene is shifted towards the 3 axially orientated conformers and the more so the larger the substituents at 2 on the double bond and at the allylic 3 position. A steric effect of this type has already been mentioned in the borohydride reduction (or catalytic hydrogenation) of the *trans* disubstituted cyclopentene heteroanalogue of Fig. 34.[43] It may also explain the experimental results reported in Fig. 60–64. The interpretation of the cycloaddition of Fig. 60[77] and of the allylvinyl ether rearrangement of Fig. 61[78] has to take into account the envelope conformer of the cyclopentene derivative with the substituent (respectively Me and aryl) in the axial orientation. Catalytic hydrogenation of the substituted cyclopentene aldehyde of Fig. 62[79] seems to involve preferentially the conformer with the isopropyl group axially orientated. Similarly in the hydrogenation of Fig. 63[80] both Me groups (of the 5- and 7-membered rings) are likely to adopt the axial orientation: the corresponding conformations of both 5- and 7-membered rings direct the hydrogenation mainly on the side opposite to these Me groups; steric and conformational factors

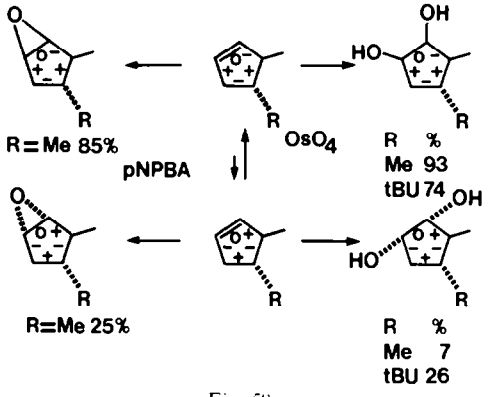


Fig. 58

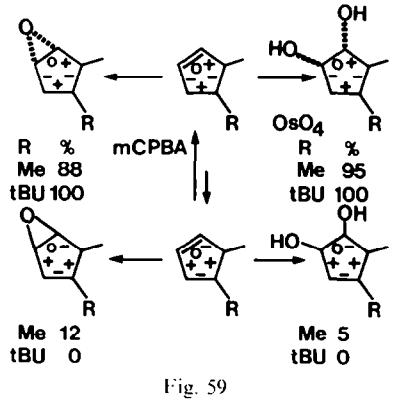


Fig. 59

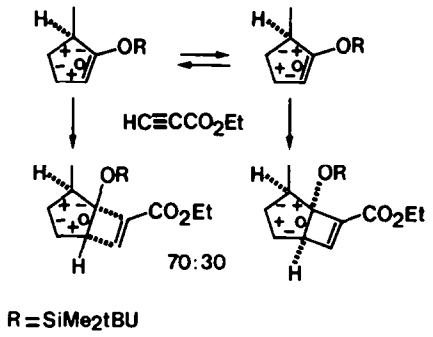


Fig. 60

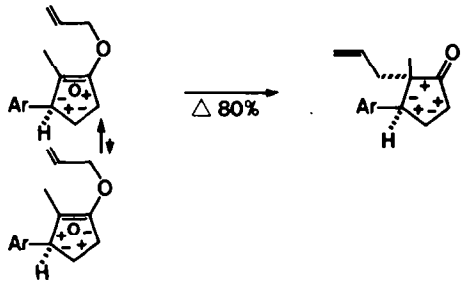


Fig. 61

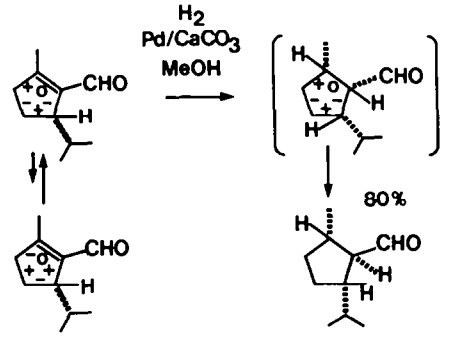


Fig. 62

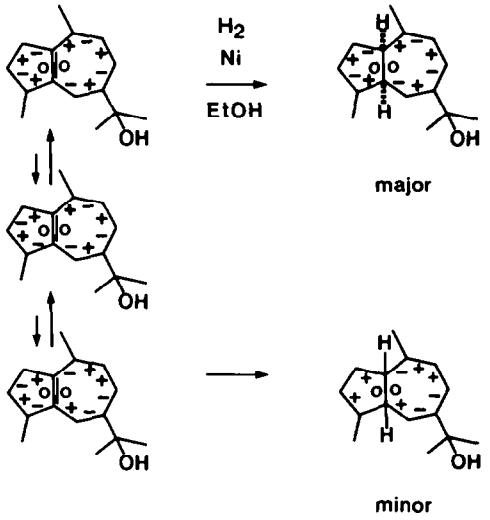


Fig. 63

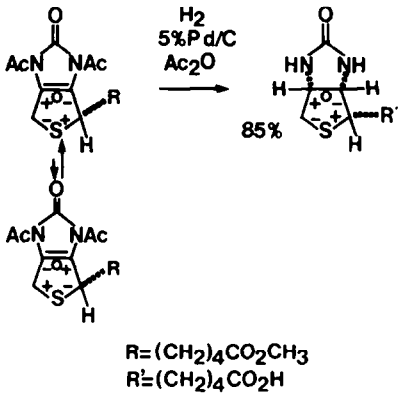


Fig. 64

drive the reaction in the same direction. An interpretation of the same type may be given for the highly stereoselective outcome of the catalytic hydrogenation of the dehydrobiotin derivative of Fig. 64.[81]

(b) *Polar effects.* Depending on the more or less polar nature of the reaction medium the equilibrium of conformers may be shifted towards the one or the other of the low energy conformers if polar substituents are present in the molecule. At any rate the stereoselectivity of a reaction is strongly affected by polar effects and, in some cases, polar effects may induce highly stereo and often regioselective reactions.

Halogens, methoxyl and varius hydroxyl derivatives such as acetate, trialkylsilyloxy groups in an allylic position or in the vicinity of a cyclopentene double bond tend to adopt, in weakly polar solvents, an axial orientation on the reactive form and, therefore, this determines the reactive envelope form of the cyclopentene.

In the case of the halogeno-, methoxy- or acetoxy-cyclopentenes of Fig. 65[82] [X = Cl, Br, OMe, OAc, etc.] it has been found that nitrile oxide 1.3-dipolar addition to the double bond took place nearly exclusively from the side opposite to the halogens (or polar groups), even though, in the case of chlorine (X = Cl, Fig. 65) the form corresponding to the equatorial chlorine seems slightly favoured over the inverse axial envelope. Furthermore, it appears significant that the *syn*-adduct with respect to the chlorine amounted to less than 1% of the total mixture of regioisomeric adducts.[82]

Since inductive effects are especially strong in non-polar solvents it does not appear surprising that the regio and stereoselectivity of such dipolar additions are solvent dependent.

In polar solvents the inductive effects are smaller than in non-polar solvents and the ordering of molecules does not favour the conformer with the polar substituant in the axial orientation as much as in non polar solvent. This reasoning is in agreement with the experimental results of 1.3-dipolar additions (Fig. 65) or epoxidation (Fig. 66[83]): in both examples the steric outcome of the reaction is solvent dependent and results may be opposite in solvents of opposite polarities (polar vs non-polar). This is precisely what has been observed in the example of Fig. 66.[83]

In the latter case two reactive envelope forms of cyclopentene may be involved, one with the acetic side chain of the lactone in the axial orientation and the other with the O -CO bond of the lactone in

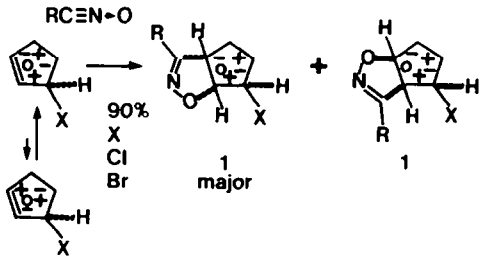


Fig. 65

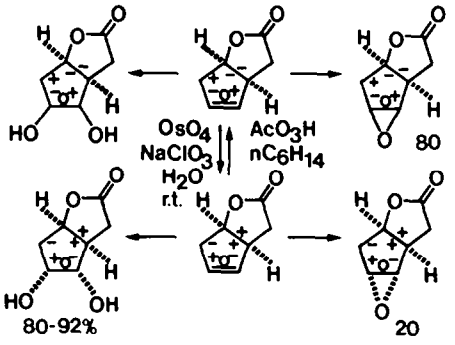


Fig. 66

the axial orientation. Generally only the former envelope is considered for such bicyclic systems and steric arguments are often advanced to exclude *a priori* an approach of the reagent inside the fold of the two rings. The experimental results show clearly that the steric outcome of the epoxidation with peracetic acid is solvent dependent: in n-hexane the conformer with the axial O–CO bond is the reactive species since epoxidation occurs mainly (> 80%[83a]) on the side opposite to angular hydrogens and, therefore, within the cavity of the folded rings, whereas in other solvents (ether, carbon tetrachloride) the steric outcome is just the opposite and epoxidation occurs mainly on the same side as the angular hydrogens.[83]

With bulky reagents like those used for the glycolation of olefins, steric factors are generally dominant and moreover, using an aqueous medium (example of Fig. 66[83b]) presumably decreases the importance of the "polar" conformer, therefore, it is not surprising that the chief product of osmylation corresponds to the envelope form of the cyclopentene with the axial acetic side-chain.

Often steric and polar effects are mingled and the outcome of a reaction can be interpreted or predicted by taking into account both these effects as in the examples of Fig. 67[84] and 68[85] involving cyclopentene hetero-analogues.

(c) *Proximity effects.* The directing influence of various groups such as hydroxyl, amine, amides, ethers, generally in an allylic or homo-allylic position with respect to a double bond, on the steric course of addition of various reagents, such as peracids[86] mercuric acetate,[87] diimide,[88] iodomethyl zinc iodide,[89] is well known for 5-, 6- and 7-membered unsaturated rings.[90,91] A simple conformational analysis (Fig. 69) shows that, in order to influence the steric course of epoxidation, an allylic OH group has to be equatorial on the low energy forms of the cyclopentene (Fig. 69a) or the

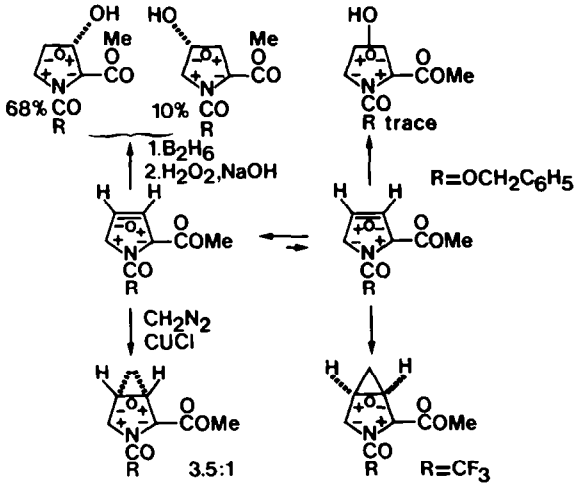


Fig. 67

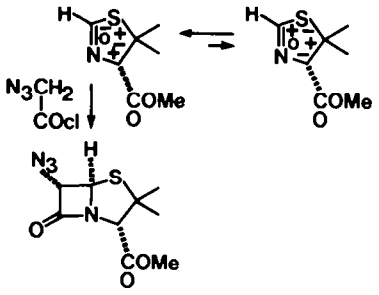


Fig. 68

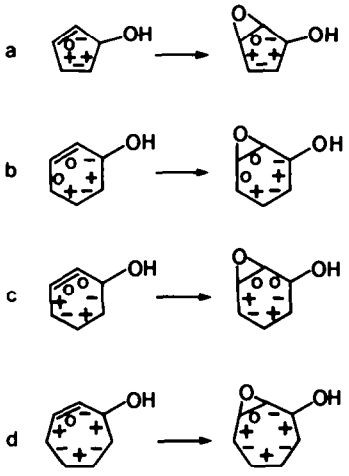


Fig. 69

cycloheptene rings (Fig. 69d) but may be equatorial or axial on the reactive 1.2-diplanar forms of cyclohexene (respectively Figs. 69b and c).

A few examples of the directing effect of OH groups are given in Fig. 70.[92,94a]

Addition to the double bond of cyclopentenes involved in quasi-trans, quasi-cis *conformational equilibrium.* As it was formerly mentioned (see Fig. 22), when one end of a double bond of a cyclopentene, fused to another ring, happens to be at the ring's junction, an equilibrium of *quasi-trans* and *quasi-cis* forms ordinarily exists (Fig 71), similar to the one depicted for fused 6-membered rings (Figs. 24 and 25). The interpretation or prediction of any *syn* or *anti*-addition to such olefinic bonds has therefore to take into account the existence of this conformational equilibrium and the possibility of its more or less complete shift towards the *quasi-trans* or the *quasi-cis* conformer. Such a conformational shift depends on the substituants of the rings taking part in the bicyclic system and also on the degree of bulkiness of the reagent involved in the addition to the double bond. As it was pointed out previously for the equilibrium shift of mono- and disubstituted cyclopentene conformers, steric, polar and proximity effects do play a role in stabilizing or destabilizing one conformer with respect to the other.[95]

Usually in unsubstituted hydrindenic and hydroazulenic systems such as those shown in Fig. 71, the *quasi-trans* conformers appear more stable than the *quasi-cis* ones. Therefore, with small reagents, like common peracids, the main product of double bond epoxidation will correspond to the *quasi-trans* conformer (Fig. 72a[94b]). Since the relative levels of the transition states are in the same energy order as the starting reactive conformers. On the other hand, with bulky reagents the stereoelectronic requirements of the transition state generally favour the *quasi-cis* conformer. This appears to be the case for the glycolation of double bonds by osmium tetroxide or potassium permanganate and also often, for catalytic hydrogenation (72b[96]). Thus, it does not appear surprising that epoxidation with peracids and glycolation with osmium tetroxide gives sterically opposite results for *syn*-addition to

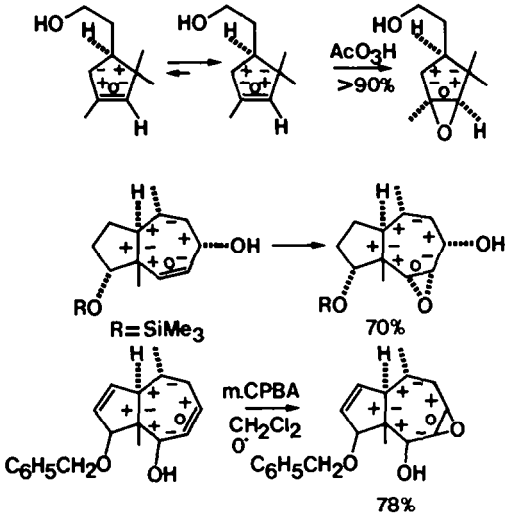


Fig. 70

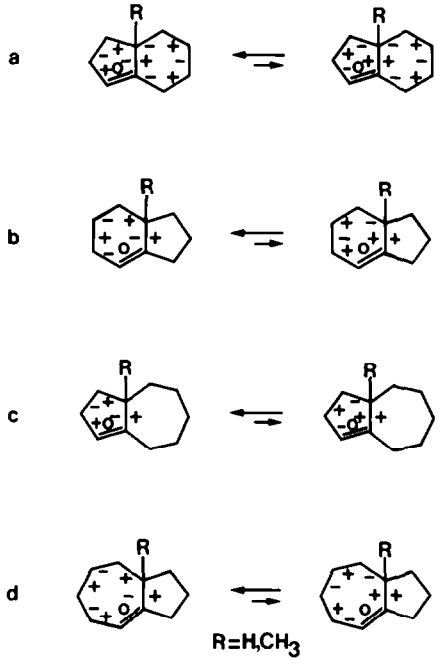


Fig. 71

the double bond of a cyclopentene of bicyclic systems involved in *quasi-trans quasi-cis* conformational equilibrium Fig. 73.[92]

Steric course of the catalytic hydrogenation of double bonds of bicyclic systems involving quasi-trans, quasi-cis *conformers in equilibrium.* It appears possible to understand the steric course of catalytic hydrogenation of cyclopentenes or cycloheptenes particular double bonds, one end of which is at the junction of another ring as in the case of Δ^{14} steroids of Fig. 74[98] or the hydroazulene derivatives of Fig. 72b.[96]

In the case of Δ^{14} steroids (Fig. 74) the equilibrium of *quasi- trans* and *quasi-cis* conformers may be shifted towards the *quasi-trans* or the *quasi-cis* envelope by the nature and the orientation of ring D

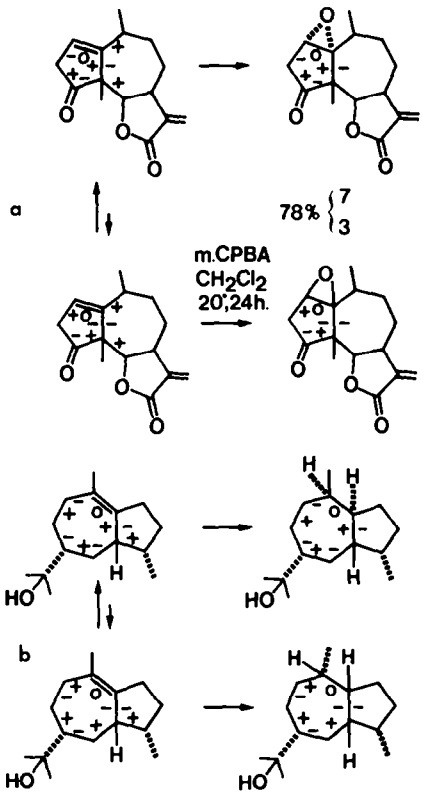

a
78% 7
3
m.CPBA
CH_2Cl_2
20°;24h.
b
HO
HO
HO
HO

Fig. 72

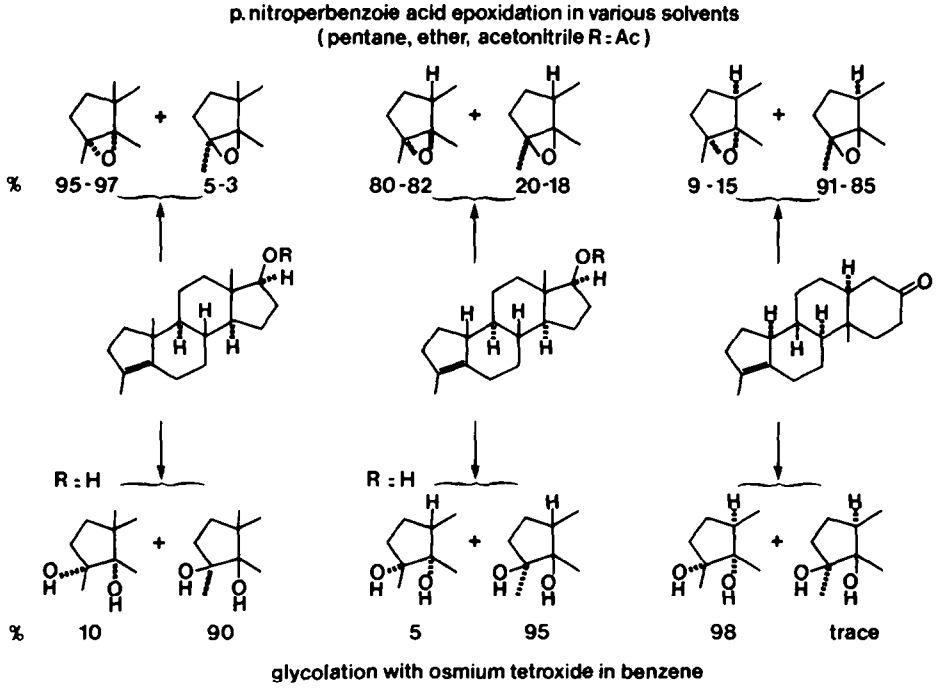

p. nitroperbenzoïe acid epoxidation in various solvents
(pentane, ether, acetonitrile R : Ac)
%
95-97
5-3
80-82
20-18
9-15
91-85
OR
H
R : H
R : H
%
10
90
5
95
98
trace
glycolation with osmium tetroxide in benzene

Fig. 73

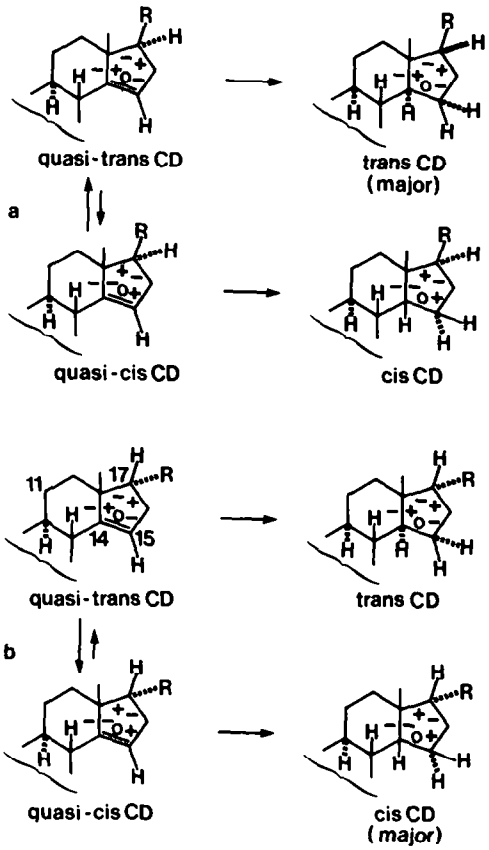


Fig 74

substituants. A bulky 19-β substituent, (R = iPr, Fig. 74a) has a stabilizing effect on the *quasi-trans* envelope of ring D, favouring the addition of hydrogen chiefly or exclusively to the α side,[98] conversely a bulky 17-α substituent (R = iPr, Fig. 74b) destabilizes the *quasi-trans* envelope with respect to the *quasi-cis* conformer which now appears as the main reactive conformation and directs the hydrogen addition predominantly or exclusively to the β-side.[98]

These results may be compared to those obtained in the catalytic hydrogenation of the unsubstituted analogue of Fig. 75 (R = H[99] Fig. 75, similar results with R = Me[100]), where the *quasi-cis* envelope appears to be the major but not unique reactive conformer, leading at least to a 2 : 1 mixture of A-nor B *cis* and A-nor B *trans* hydrogenated derivatives.

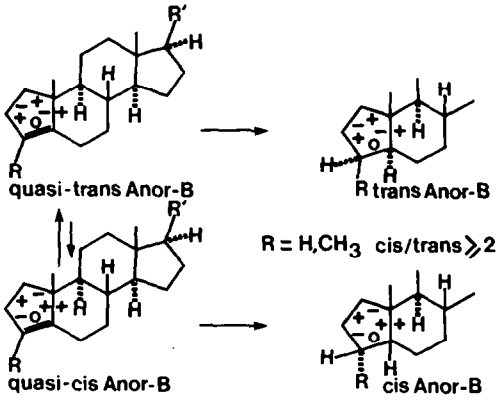


Fig 75

We believe that the results of catalytic hydrogen addition to cycloheptene double bonds of Fig. 72b may again be interpreted as shown, using the postulated existence of a conformational equilibrium of *quasi-trans* and *quasi-cis* conformers. Again in this series, as in the Δ^{14} unsaturated steroid series, steric effects (bulk of the substituents), polar effects (substituents with strong inductive effect) and proximity effects can influence, more or less significantly, the direction of catalytic hydrogen addition to the double bond. Furthermore, we feel that in the coming years, chemists will take advantage of all these effects to improve the stereoselectivity of *syn* or *anti* additions to double bonds of this type and even to specifically direct the addition of reagents.

Steric course of addition to double bonds of unsaturated 6-membered rings

Additions to cyclohexadienes. The application of the formerly given rules allows a ready interpretation or prediction of *syn*-additions to double bonds of 1.3- and 1.4-cyclohexadienes, since the torsion angles sign sequences unambiguously define for each possible conformer the direction of the *syn*-addition.[101] Let us recall that to the $+0-$ sequence corresponds an addition above the mean plane of the ring (β addition in the steroid series), whilst to the $-0+$ sequence, corresponds an addition below the mean plane of the ring (α-addition in the steroid series). If only one low energy conformer is available for the diene, stereospecificity of addition is the rule, whereas stereoselectivity is generally the case when an equilibrium of low energy conformers exists. In the cyclohexadiene series, as in the cyclopentene series, steric, polar and proximity effects, as well as the experimental conditions and the bulk and nature of the reagent, all come into play to determine the degree of stereoselectivity of the addition.

Additions to 1.3-cyclohexadienes. The only available 1.3-diplanar form of rings B in the aromatic steroids of Fig. 76a[102] and b[102] and of ring C in Fig. 76c[103] is responsible for the stereospecific *syn*-addition of reagents, be it epoxidation with peracids (Fig. 76a) or glycolation with osmium tetroxide (Fig. 76b). In the case c of Fig. 76, epoxidation and glycolation take place on the side of the angular Me, axial with respect to ring B.

Similarly catalytic hydrogenation of the olefinic bond of ring B in the steroid examples of Fig. 77a[104] and b[105] and in the case of thebaine (Fig. 77c[106]), occur in a stereospecific manner as expected from the torsion angles' sign sequence.

Taking into account the planarity of the amide group the stereospecific course of ynamine cycloaddition to the double bond of the unsaturated lactam of Fig. 78[107] can be interpreted.

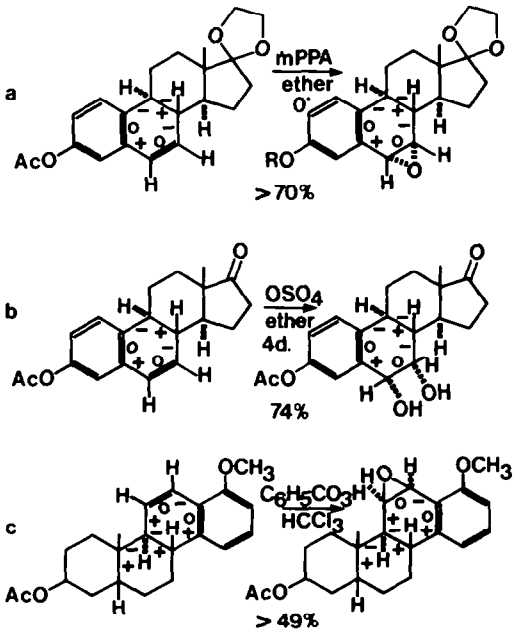


Fig. 76

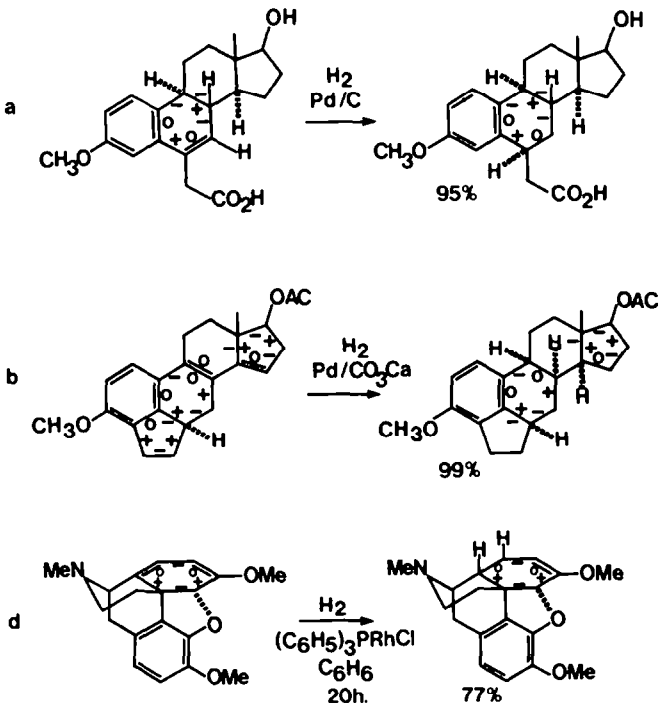


Fig. 77

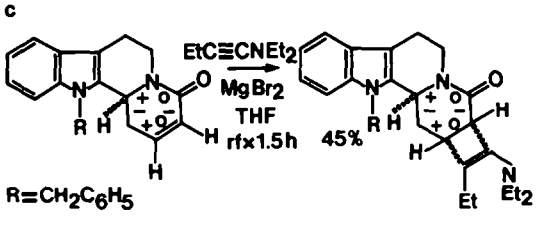


Fig. 78

Cases of stereoselective reactions, resulting from the existence of two low energy 1.3-diplanar conformers are given in the examples of Fig. 79[108] and 80[109,110] The stereoselectivity of addition depends mainly here on steric and polar factors. Thus, in the epoxidation of Fig. 79, the sterically preferred conformer gives rise to the main product of addition with the approach of the reagent taking place inside the fold of the rings, but a polar contribution of the axial C–O bond of the ketal is not excluded. The stereoselectivity of cycloaddition to the mixture in equilibrium of *quasi-trans* and *quasi-cis* forms in the examples of Fig. 80, depends on the reagent: it is clear that the stereoelectronic requirements of the respective transition states are different for dichloroketene addition Fig. 80a[109] and for cyclopropanation (Fig. 80b[110])

Steric factors appear dominant and impose the steric course of acrolein cycloaddition in the Diels–Alder reaction of Fig. 81[111] on the side opposite to the substituted cyclopropane bridge.

Let us note than when one of the double bonds of a cyclic diene is replaced by a cyclopropane or an epoxide as in the examples of Figs. 82[112] and 83[113]), the direction of additions can still be predicted: in such cases the predominant conformer corresponds to the axial 3-membered rings; apparently steric, electronic and conformational factors jointly determine the direction of addition.

Addition to 1.4-cyclohexadienes. Much of what has been previously said about the steric course of additions to 1.3-cyclohexadienes could be repeated for the additions to 1.4-cyclohexadienes since the same rules are still valid.

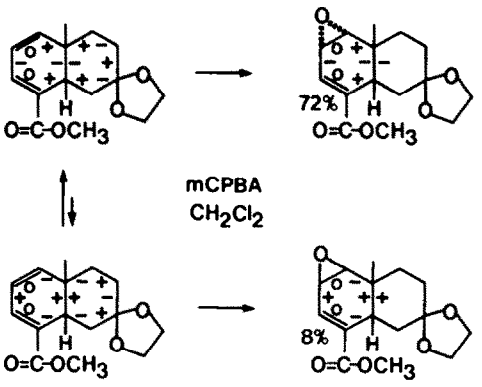


Fig. 79

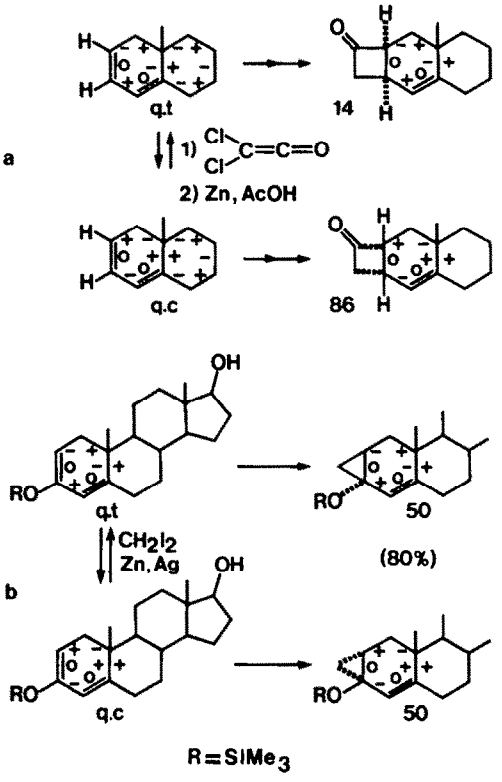


Fig. 80

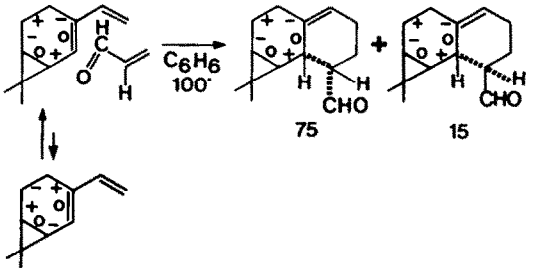


Fig. 81

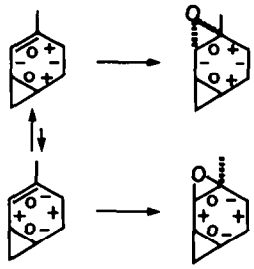


Fig. 82

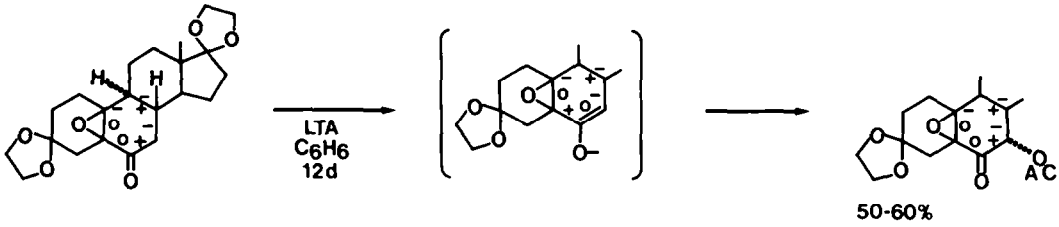


Fig. 83

Thus, whenever only one low energy reactive 1.4-diplanar conformer is available for the ring, the addition is stereospecific, as in the examples of Figs. 84 and 85. Example a of Fig. 84[114] is the more striking in that, despite its axial orientation on the reactive form, the 3β OH wields no influence on the direction of epoxidation which depends only on the 1.4-diplanar conformation imposed on the ring by the 4.5α, axial, epoxide and the Δ^1 double bond. The rigid 1.4-diplanar form of example 84b[115] gives rise to the expected epoxide, the addition occurring below the mean plane of the ring (sequence $-0+$). Catalytic hydrogenation of the Δ^5 double bond of ring B in the example c of Fig. 84 takes place, as expected from the torsion angles' sign sequence, exclusively on the α side; in the conditions of hydrogenation the primary Δ^3 enol ether isomerizes to the more stable Δ^2 enol ether.[116]

The stereospecific cyclization of the immonium salt of Fig. 85[117] can be interpreted in the following way. To avoid steric interactions with the adjacent side chain at the nitrogen, the Me

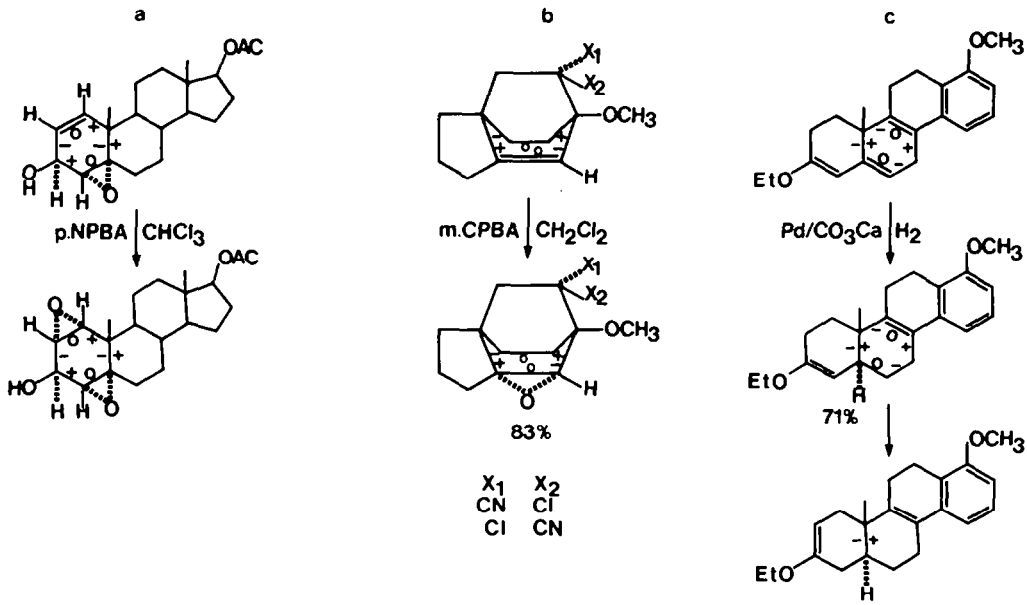


Fig. 84

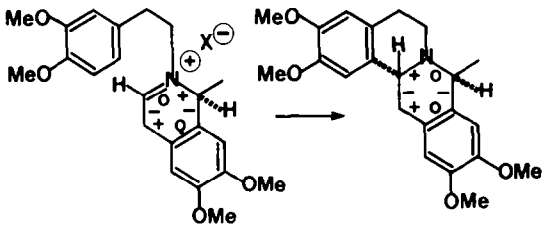


Fig. 85

substituent of the boat ring takes the axial orientation and this determines the reactive 1.4-diplanar form and, in turn, the creation of the new bond below the mean plane of this boat form.

Even if two 1.4-diplanar forms are in equilibrium a highly stereoselective addition can still take place when steric or polar or proximity factors are strong enough to orientate the reaction, as shown in the examples of Figs. 86 and 87.

In Fig. 86a[118] the 1.4-diplanar form with the substituent axial is destabilized with respect to the other form with the equatorial substituent. To the latter form corresponds the main product of epoxidation. In the example b of Fig 86[119] borane addition and subsequent alkaline oxidation to the diene ring occurs regio and stereoselectively on the more stable *quasi-trans* form: again steric and conformational factors orientate the reaction in the same direction.

When a double bond of a 1.4-diene is replaced by a cyclopropane the usual reasoning still appears valid and in this manner the reactions of carene and norcarene derivatives of Fig. 87 can readily be interpreted. For Δ^3 carene itself it is well known that most of the *syn*-additions take place stereospecifically from the side opposite to the bulky substituted cyclopropane (catalytic hydrogenation: 98% yield,[120] epoxidation,[121] hydroboronation,[122] etc.). The addition of sulfonyl isocyanate is no exception to the rule and the exclusive product of additon is that shown of Fig. 87a,[123] corresponding to the more stable 1.4-diplanar conformer with a bisectional orientation of the 3-membered ring with respect to the 6-membered one.

Looking at examples b[59, 124] and c[59] of Fig. 87 we can estimate the importance of the substitution at the methylene of cyclopropane on the conformational equilibrium: still the 1.4-diplanar conformer

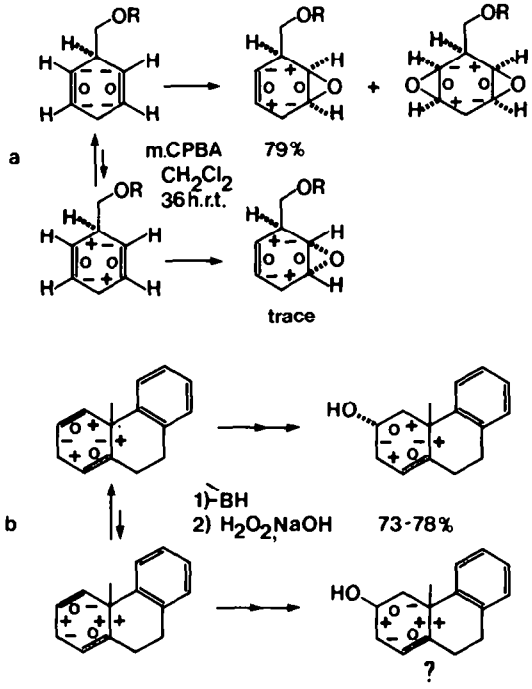


Fig. 86

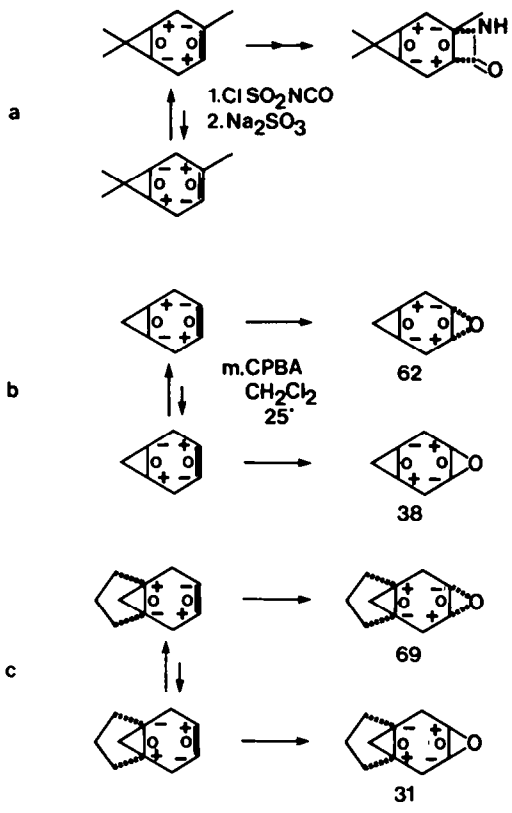


Fig. 87

with the axial 3-membered ring (sequence + 0 −) seems the less stable. Furthermore, even though it would be expected that the approach of the reagent in the case of 87c to be more hindered on the side opposite to the 3-membered ring than on the other one, again the dominant product of epoxidation corresponds to the 1.4-diplanar form with the 3-membered ring in the bisectional orientation (sequence: − 0 +). Apparently, additional electronic factors contribute to stabilizing this type of conformation.

As it was underlined earlier the steric outcome of additions is also dependent on the nature and not only on the bulk of the reagent. To take a simple example, it has been found many times and, it is true in particular for the examples of Figs. 87b and c, that the addition of hypobromous acid, followed by basic treatment is much more stereoselective than the direct epoxidation with peracids taking into account the expected reversal in the ratio of isomers. Thus in the case of 87c whilst *meta* chloroperbenzoic acid epoxidation in methylene chloride at room temperature supplies a 69: 31 ratio of the (α) *trans* and (β) *cis* epoxides, this ratio is 7 : 93 for hypobromous addition followed by basic treatment.[59,124] Therefore, one has to admit that the complexed Br cation, arising from N-bromosuccinimide, water and glyme,[125] is more stereoselective with respect to the addition to the double bonds of Figs. 87b and 87c than a peracid not on account of its steric bulk (which should product the opposite stereo selectivity) but for some other reason, which is not readily obvious since experimental conditions are not the same in both cases.

Additions to cyclohexenes. Several reviews have been devoted to particular aspects of additions to cyclohexenes such as catalytic hydrogenation[126] and epoxidation[91] but—, so far, no really general explanation has been given for the peculiar stereoselectivity of these reactions, which most often, is attributed to the operation of dominant steric effects.[127]

A complete survey of additions, and especially *syn*-additions, to cyclohexenes is beyond the scope of this report and deserves a monograph of its own. Therefore, rather than attempt to analyze the whole field we have purposely chosen to present a few examples of *syn*-additions in order to show the

mode of approach with the torsion angle notation and the reasoning that can (or cannot) be used to interpret or predict the steric outcome of these additions.

As it was emphasized earlier, the lowest energy form of cyclohexenes, namely the half-chair cannot be the initial reactive form for *syn*-additions to the double bond since, under our previous assumptions, the elements of the reagent have to be introduced stepwise, in an axial orientation. With respect to *syn*-additions or even cyclo-additions, the reactive cyclohexene conformations may respectively be, in their decreasing order of stability, the 1.2-, 1.3- and 1.4-diplanar forms.

Two main cases have to be distinguished, depending on whether or not the reagent used in the *syn*-addition keeps the geometry and the unsaturated character of the cyclohexenic ring during the course of the addition to the double bond, that is, starting from the initial reactive form of the unsaturated ring and arriving at the primary final product of the reaction.

Thus, epoxidation and methylenation of cyclohexenes keep to a large extent, the unsaturated character of the ring, only a small distortion of the initial reactive form taking place during the reaction. Even ketene cyclo-addition keeps to some extent the unsaturated character of the ring and results in a slight distortion of the initial reactive form. On the other hand, catalytic hydrogenation, hydroboration (followed by alkaline oxydation or acidic hydrolysis), glycolation all turn the unsaturated cyclohexene ring into a saturated cyclohexane derivative: the reaction starts from a reactive form of cyclohexene to end up as a primary final form of cyclohexane. This latter type of *cis*-addition will be discussed first with reference to the catalytic hydrogenation of 2.3- and 2.4-dimethyl cyclohexenes and also of the Δ^5 double bond of steroids. We believe that our reasoning is general, and may be widely used for the other *cis*-additions of this type, such as glycolation, hydroboration and the like.

Catalytic hydrogenation. There is a wide range of experimental conditions and many catalysts may be used,[128] with the possibility that several mechanisms of hydrogen addition may be implicated in the reaction. Moreover, except in a very few cases, the stereoelectronic requirements of the catalytic hydrogenation and the geometry of the intermediate steps are not accurately known. To make up for the lack of precise knowledge concerning hydrogenation intermediates we admit, even if it may not be valid for all catalysts, that both hydrogens add stepwise and are delivered in a *syn* periplanar fashion to the double bond of the preferred form of lowest energy compatible with this requirement.[129] This means that the initial reactive forms have to be 1.2-, 1.3- or 1.4-diplanar forms (boats). Only 1.3- and 1.4-diplanar forms of cyclohexenes are readily convertible into the 1.4-diplanar forms of cyclohexanes with the least amount of conformational distortion and the least expenditure of energy (Fig. 88 and 89). However, this does not exclude the 1.2-diplanar forms of cyclohexenes since, as in the case of the

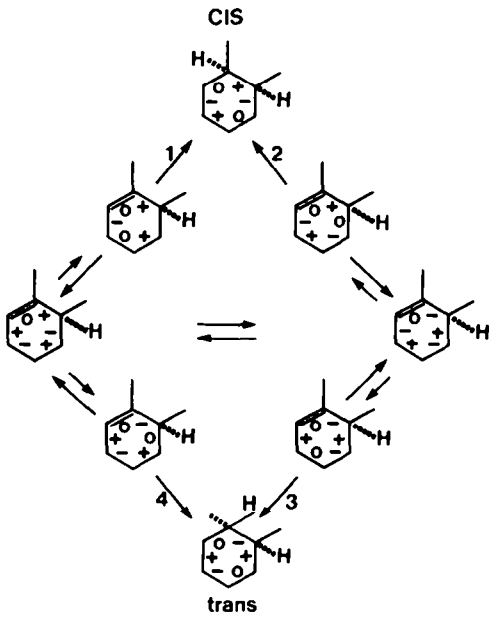


Fig. 88

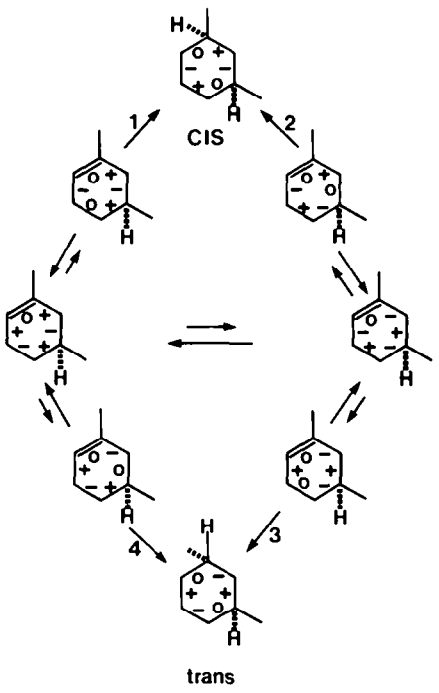


Fig. 89

Δ^5 double bond of steroids (Fig. 90) no primary final boat is available for the hydrogenated product and, therefore, the primary final forms of the hydrogenated B ring are likely to be the high energy 1.2-diplanar forms of cyclohexanes.[130]

At the present time a competitive involvement of 1.2- and 1.3-diplanar forms as the initial reactive forms of cyclohexenes cannot be excluded. We believe at the moment that, whenever a primary final boat is available for the hydrogenated ring, the 1.3-diplanar form is more likely to be the initial reactive form of the reaction, whereas if no primary final boat is available for the hydrogenated ring then 1.2-diplanar forms are likely to be the reactive forms of the substrate; in the latter case hydrogenation should take place less readily than when a primary final boat is available from an initial 1.3-diplanar form. This conclusion stems from the fact that 1.2-diplanar forms have to change first to 1.3-diplanar ones and from there to the 1.4-diplanar forms of the saturated compound in order to follow the pathways of least energy. For instance, the two half-chair conformers of 2.3-dimethylcyclohexene in equilibrium, have to adopt either one of the four 1.3-diplanar forms shown in Fig. 88, in order to undergo *cis*-addition of hydrogen leading ultimately to either one of the two primary final boats of the resulting *cis* or *trans* 2.3-dimethylcyclohexanes.

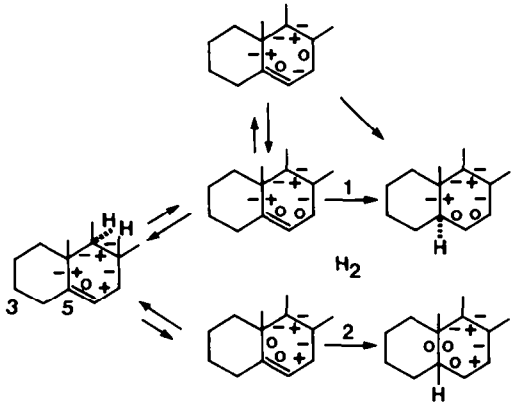


Fig. 90

To evaluate the relative energy of the four transition states, corresponding to the pathways numbered 1–4 in Fig. 88, we assume that the complexation of the fairly bulky catalyst with the double bond takes place preferentially on the reactive conformation that corresponds to the least amount of steric compression during the reaction, from the initial reactive forms up to the primary final ones. From that point of view, pathway 1 appears very favourable since no steric hindrance to complexation on the side of the double bond opposite to the axial 3-Me prevents the addition of hydrogen that takes place without any apparent increase of steric compression. Analyzing all the other pathways in the same manner, one notices that torsional interactions between the two adjacent Me substituents occur during the conformational changes that accompany hydrogen addition, in pathways 3 and 4. These steric interactions certainly raise the level of the corresponding transition states with respect to pathway 1 involving the least amount of conformational distortion and steric interactions of the substituted ring, from its unsaturated reactive form up to its primary final form. A minor contribution may come from pathway 2, even if the passage of the low energy half-chair to the reactive 1.3-diplanar form involves a change of orientation of the 3-Me from equatorial to *quasi*-axial. Although this is a rather crude qualitative analysis of the catalytic hydrogenation, the more so that neither the solvent nor the experimental conditions (temperature, pressure, pH) are incorporated in our reasoning, the conclusion can be drawn that, with Pt or Pd catalysts, *cis*-2.3-dimethylcyclohexane ought to be the main product of hydrogenation, in agreement with the experimental results. In fact the *cis-trans*-isomers ratio is dependent only to a slight extent on the experimental conditions and the *cis* isomer is dominant (70–81% of *cis* 2.3-dimethylcyclohexane[131]).

With groups bulkier than a Me, hydrogen additions to the double bond of a 2.3-disubstituted cyclohexene may be more stereoselective than in the case of 2.3-dimethylcyclohexene. Thus the catalytic hydrogenation of 2.3-dicarbomethoxycyclohexenes occurs nearly exclusively on the side opposite to the ester group at 3, to give the *cis* hexahydrophtalic ester derivative.[132] In this case the polar effect of the carboxylic ester presumably contributes also to the outcome of the reaction, as well as to its steric effect.

In contrast to the preceding examples the interpretation of the catalytic hydrogenation of 2.4-dimethylcyclohexene is somewhat less straight forward.[131] Looking at the various 1.3-diplanar conformers of Fig. 89, it may be concluded that the main contributions come from pathways 1 and 4 with a minor contribution from pathway 2. Pathway 3 can be excluded since hydrogen addition to the side of the 4-Me is prevented because of the axial orientation of the substituent.

Let us now turn to the catalytic hydrogenation of the Δ^5 double bond of steroids: as shown in Fig. 90 there are only low energy conformers available for the unsaturated B ring. Besides the half-chair there are only two 1.2-diplanar and one 1.3-diplanar forms. In pathway 1, α-addition of hydrogen to the reactive 1.2- and 1.3-diplanar forms leads to a primary final product of hydrogenation in a 1.2-diplanar conformation. In pathway 2, β addition of hydrogen to the reactive 1.2-diplanar form (the only reactive form) also leads to a primary final product of hydrogeneration in a 1.2-diplanar form. In the absence of polar effects the preferred pathway, corresponding to the transition state of lower energy should be pathway 1 since it involves the least amount of conformational distortion during the reaction, whereas in pathway 2 a conformational change has to occur at the A, B rings' junction. In agreement with this conclusion, catalytic hydrogenation of cholesterol with platinum oxide in ethyl acetate in the presence of perchloric acid yields 81% of 5α-cholestanol[133] the catalytic hydrogenation of the 3-acetate of cholesterol with platinum oxide in ethyl acetate yields 88% of α addition and around 11% of β addition[134] and, for comparison, hydroboration of cholesterol followed by alkaline oxidation affords 70% of 3β, 6α-dihydroxy cholestanol and 15–20% of 3β, 6β-dihydroxy coprostanol.[135]

Whilst β-orientated, polar groups at position 3 (hydroxyl, acyloxy, benzoyloxy etc.) tend to favour α addition of hydrogen to the Δ^5 double bond of cholestene derivatives,[133,134] α-orientated polar groups at position 3 of cholestene (acetate[134,136]) or at position 17 (N, N-dimethyl carboxamide[137]) of substituted Δ^5 steroids impose the preferential addition of hydrogen on the β side. The nature of the catalyst (Pt, Pd or Rh), the acidity of the medium and the solvent (acetic acid, ethanol) and proximity effects all play a part in the steric outcome of the catalytic hydrogenation of Δ^5-unsaturated steroids.[134]

We stop here the treatment of the catalytic addition of hydrogen to cyclohexenes and we analyze now a few examples of peracid epoxidation concerning the 2.3- and 2.4-dimethylcyclohexenes and the Δ^5 double bond of cholestene derivatives.

Peracid epoxidation. The epoxidation of 2.3-dimethylcyclohexene[138] may be analyzed, using the four reactive 1.2-diplanar conformers corresponding to the transition states numbered 1–4 in Fig. 91. From an examination of molecular models there are steric interactions between the hydrogens of adjacent Me's in the 1.2-diplanar forms (with the equatorial Me) corresponding to the initial reactive conformers of pathways 1 and 4.

In pathway 1, epoxidation increases the steric interactions whereas in pathway 4 epoxidation decreases these interactions and this last reaction occurs with steric decompression. Since the reactive conformers of pathway 2 and 3 do not seem to undergo any steric compression during the epoxidation it can be concluded that the main contributors to the epoxidation are pathways 2, 3 and 4. On this basis, the experimental result[138] reported: *cis*-dimethyl versus *trans*-dimethyl epoxides 36:64, may receive a satisfactory interpretation.

As could have been expected, replacement of one of the substituents of 2.3-dimethylcyclohexene by a larger group results in an increase of the stereoselectivity of peracid epoxidation,[138] that is again readily interpreted by the involvement of pathways 3, 2 and 4.

Turning now to the epoxidation of 2.4-dimethylcyclohexene[139] one could argue that in the absence of torsional interactions and notable steric hindrance to peracid approach pathways 1, 2 and 4 of Fig. 92 should contribute to the final result; pathway 3 is excluded, owing to the axial orientation of the 4-Me that prevents a ready epoxidation on the side of this axial substituent. Therefore, one could have expected a slight excess of the epoxide with both Me's *cis*, whereas the experimental result shows that there is no preference for either isomer (*cis*-dimethyl to *trans*-dimethyl epoxides ratio 1:1 according to Ref. 139).

Finally we examine briefly the epoxidation of cholesterol derivatives namely cholesterol 3-acetate and Δ^5-cholestene, with perlauric acid in benzene yielding as expected, a mixture of α and β epoxides in a 70 80:30–20 ratio.[140] Here again (Fig. 93), as in the corresponding catalytic hydrogenation (Fig. 90), we attribute these results to the lower energy of the transition state corresponding to pathway 1 relative to that of pathway 2. There is a striking similarity between the results of epoxidation and catalytic hydrogenation of Δ^5 steroids the origin of which is conformational and derives from the similar relative energies of pathways 1 and 2 in both cases.

Again, in the Δ^5-steroid series polar effects and especially inductive effects of axial 3α-alkoxyls are able to invert the isomeric ratio of epoxides with respect to Δ^5 cholestene:[141,142] this inductive effect

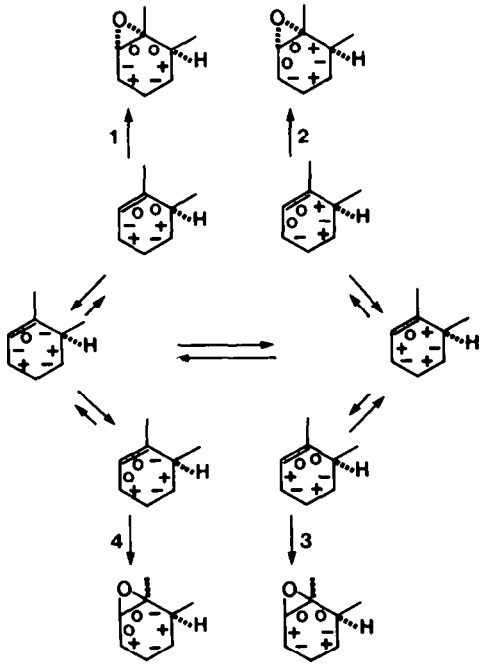


Fig 91

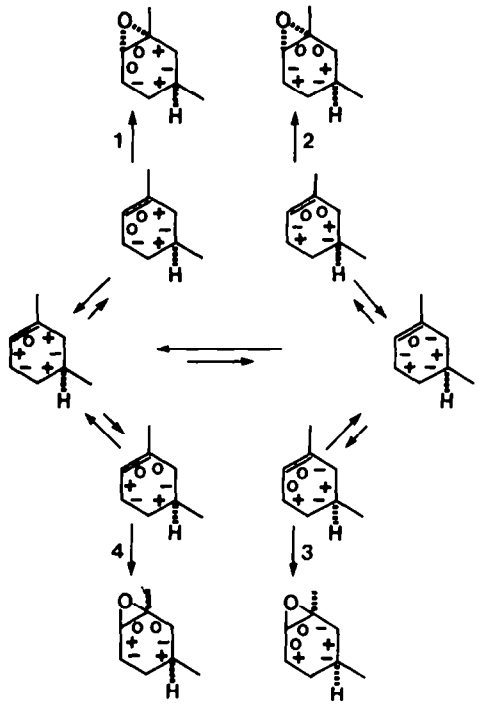


Fig. 92

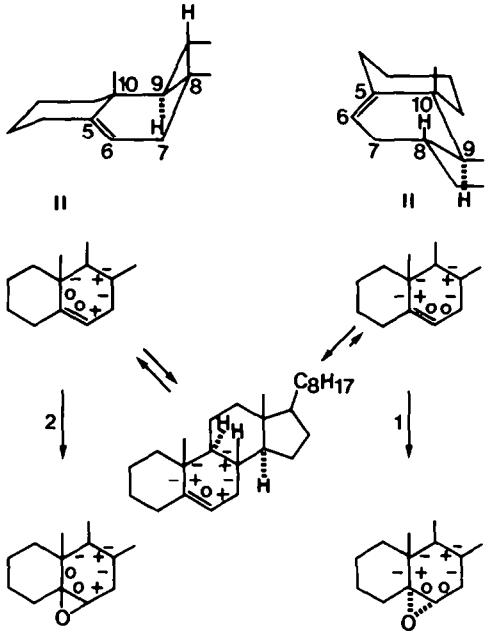


Fig. 93

raises the level of transition state of pathway 1 above that of pathway 2 which becomes the one of lowest energy.

Incidentally we may note that steric factors are usually overestimated in epoxidation. This is shown by the fact that removal of the 19-Me in cholesterol 3-acetate does not decrease the stereoselectivity of epoxidation, since with monoperphtalic acid in ether, the 19-nor-Δ^5 analogue yeilds 90% of α epoxide.[143] Apparently removal of the angular Me increases the stability of the 1.2-diplanar form of ring B favouring pathway 1 relative to pathway 2.

Let us note that epoxidation involving transition metal complexes, able to bind groups like OH's, may give results different to those found with common peracids.[144a] Moreover, the steric bulk of the active epoxidation complex may also play a part since it has been reported that the epoxidation of cholesterol with ferric acetylacetonate and hydrogen peroxide in acetonitrile yields 68% of β-epoxide and 17% of α-epoxide.[144b]

A few general conclusions may be drawn from the previous analyses. Firstly, owing to the usual existence of two equivalent low energy reactive cyclohexene conformers (either 1.2-diplanar or 1.3-diplanar) that lead to opposite steric results (Fig. 88–89 and 91–92, pathways 1.4 and 2.3 respectively) *syn*-additions to cyclohexenes cannot be expected, in general, to exhibit high stereoselectivity especially when compared to the analogous unsaturated 5- and 7-membered rings. Secondly, in quite a few cases, due to the small energy differences among the allowed pathways, the choice of experimental conditions may direct the reaction towards either one of the two possible isomers. This is especially true for catalytic hydrogenations and it has been shown several times that, depending on the catalyst nature, hydrogen pressure, acidity of the medium and solvent, addition of hydrogen can often be rendered more or less stereoselective on either side of a double bond provided, of course, that several low energy reactive conformers are available.[145] If there is only one low energy conformer available as in examples a and b of Fig. 94, the *syn*-addition to the cyclohexene is stereospecific, but such cases are fairly rare: the ethano bridge of the bicyclic compound of Fig. 94a,[146] as the lactone bridge of Fig. 94b[147] and c[148] prevents the formation of any 1.2-diplanar form other than the one shown. In the latter case the opening of the lactone again gives a conformational mobility to the ring and it is now possible (Fig. 94d) to take advantage of the directing influence of the allylic OH to obtain the *syn* epoxide as the exclusive product of reaction with metachloroperbenzoic acid in benzene-dioxane.[148]

As shown in Fig. 95,[147a] we may exploit the polar effects of the ester and 0-acylated OH group corresponding to the opening of lactone 94b, to highly stereoselectively orientate the addition of osmium tetroxide (and presumably other reagents) *anti* to the functional group.

From a practical standpoint, it is possible to increase the stereoselectivity of additions to cyclohexenes by taking advantage of electronic, steric, proximity or polar effects, the last effects often

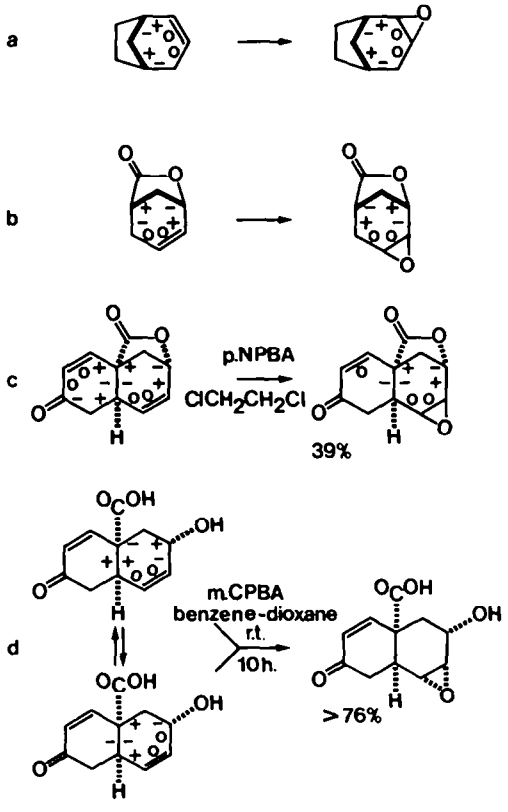


Fig. 94

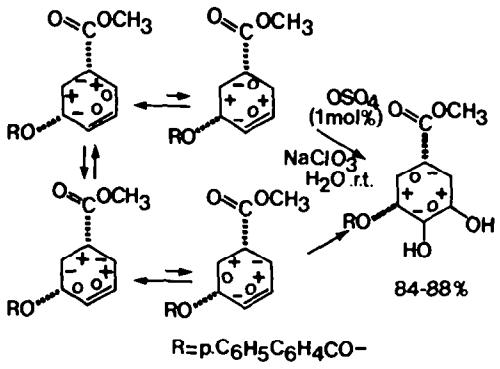


Fig. 95

being quite efficient to direct the addition. Alternatively, stereoselectivity of additions may also be enhanced by using bulky reagents: the bulkier the reagent the greater the stereoselectivity of the addition since steric interactions are now becoming the dominant factor and a selection of reactive forms of comparable energy appears possible. From this viewpoint it is interesting to compare a reaction not very sensitive to steric hindrance of the environment of the double bond,— such as peracid epoxidation, with another one very sensitive to the steric environment of the double bond, such as glycolation with osmium tetroxide. More precisely, we analyze briefly the addition of osmium tetroxide and peracids to the double bond of Δ^4-cholestenes. The unsaturated A ring of Δ^4 steroids is able to adopt either one of the four low energy 1,2-diplanar forms shown in Fig. 96 and either one of the low energy 1,3-diplanar forms of Fig. 97.

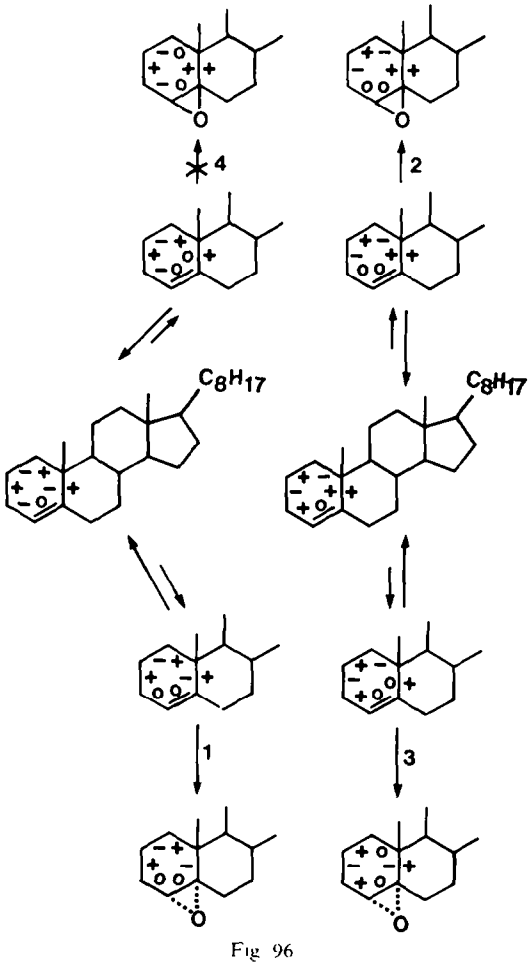


Fig. 96

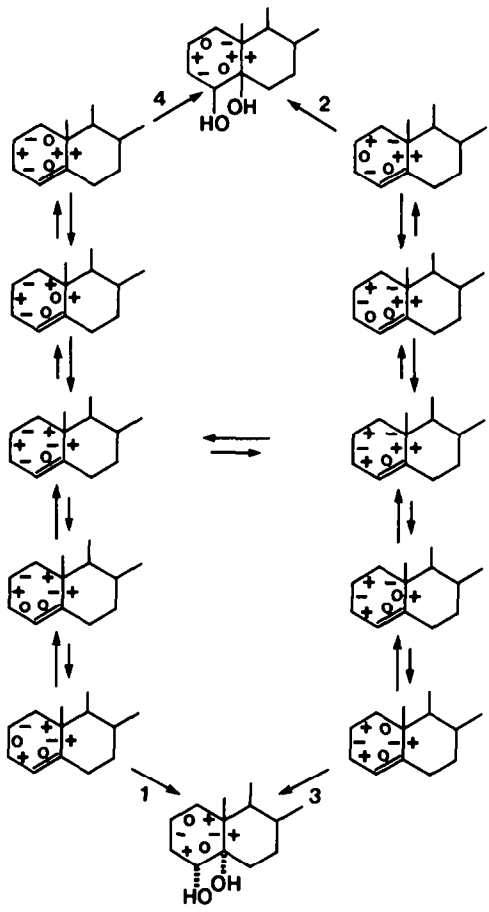


Fig. 97

From the picture given in Fig. 96 and 97 a few conclusions may be drawn, taking into account the following general assumptions. In the absence of steric hindrance or strong polar effects peracid epoxidation reflects, to some extent, the equilibrium of the reactive 1.2-diplanar conformers of lowest energy, whilst the outcome of glycolation with osmium tetroxide, even more than catalytic hydrogenation with palladium or platinum catalysts, depends to a large extent on the ease of complexation of the bulky reagent (or catalyst) with the double bond: preferential addition occurs on the reactive low energy conformation, which allows the least amount of steric compression during the reaction, from the initial reactive forms up to the primary final conformers. In other words the steric requirements of peracid epoxidation are only moderately sensitive to steric decompression whereas osmium tetroxide glycolation, and to a lesser degree catalytic hydrogenation, are extremely sensitive to steric decompression.

Now, with respect to Fig. 96 it can be concluded that peracid epoxidation of Δ^4 cholestene should give a mixture of epoxides with the α epoxide being the major product: the 1.2-diplanar forms corresponding to pathways 1 and 2 are presumably the main contributors to the reaction and the remaining 1.2-diplanar forms (pathways 3 and 4) may be neglected since formation of the epoxides requires not only a torsion angle sign change at the A, B rings' junction, but also, if molecular models are reliable, 1.3-diplanar conformers as the primary final forms. As, *quasi-trans* forms are generally more stable than the corresponding *quasi-cis* ones, it may be concluded that the transition state of pathway 1 is of lower energy than that of pathway 2 and therefore the α-epoxide ought to be the main isomer of the mixture.[149]

With regard to Fig. 97, pathways 1, 3, and 4 may contribute to the final result, while the 1.3-diplanar form corresponding to pathway 2 seems very strained and its contribution remains questionable. Although, here again the *quasi-trans* forms are of lower energy than the corresponding *quasi-cis* ones, the main pathway corresponds to the greater steric decompression which, from an

examination of models, is provided by β-addition of osmium tetroxide: pathway 4 corresponds to the transition state of lowest energy. Comparing these reactions, we may note that for epoxidation, osmylation and hydrogenation the ratios of α and β additions are respectively 61:39,[149] 24:76[150] and 45:55.[151a] Consonant with this conformational interpretation is the fact that the former results of glycolation are not strongly dependent on the presence of the angular methyl since in the 19-nor Δ^4 series, the corresponding results are comparable with a ratio of 11:89 for an α-:β-addition.[150]

Again for each one of these reactions, be it epoxidation, glycolation or catalytic hydrogenation the results are strongly dependent on the polar effects and, in this respect, dramatic reversals of selectivity have been noted in the literature.[149,150]

As an example, in the glycolation with osmium tetroxide of the Δ^4 olefin, the presence of a 3α or 6α-acetoxy[152] prevents the addition of the α side, the 4β 5β diol, the main product, being obtained in the former case with a 98% yield.[150] On the other hand the presence of a 3β-acetoxy group reverses the ratio of α and β diols, the ratio now being 87:13.[150]

These variations can be interpreted, according to our usual scheme, taking into account the destabilization of one of the reactive conformers by the inductive effect of the group. Apparently the *quasi-axial* orientation of these groups (pathways 3 and 4 for 3β and 3α acetate respectively) favours the addition to the corresponding 1.3-diplanar conformation.[153] Even for epoxidation it is not excluded that the reactive conformation may change from 1.2- to 1.3-diplanar in order to allow the polar group to be in a *quasi*-axial orientation: the nearly exclusive α epoxidation of 3β-chloro-Δ^4-cholestene[154] could be interpreted in that way.

There are many other interesting facets to *syn* additions to cyclohexenes, but they cannot be developed here. To sum up it may be said that it is possible to rationalize the steric outcome of *syn* addition to cyclohexenes in the following manner. When several reactive 1.2- or 1.3-diplanar forms of comparable energy are available, in the absence of steric or polar effects, the addition will usually lead to a mixture of isomers without any marked stereoselectivity. Now if any shift of such an equilibrium is allowed by steric, polar (inductive effects of various groups) electronic (maintenance of orbital overlap for conjugated olefins) or proximity effects (H-bond or groups able to orientate the reagent on their side) a higher selectivity of addition and sometimes a near specificity is to be expected. Experimental conditions may also play a part in the degree of stereoselectivity of additions to cyclohexenes, especially in solvent-dependent reactions, since the solvent is able to shift the equilibrium of conformers.[155]

Before closing this chapter we would like to briefly comment on a few selected examples of *syn*-additions to cyclohexenes, which take place with high stereoselectivity (Fig. 98 and 99). In Fig. 98 a few epoxidations are collected, the stereoselectivity of which originates from the polar effect of the ring substituents. In Fig. 98a epoxidation of the 4-cyanocyclohexene with perlauric acid in a variety of solvents leads to the preponderant formation of the *anti*-epoxide.[156] In Fig 98b (R = $SiMe_3$) allylic trimethylsilyloxy groups tend to prefer an axial orientation which may explain the outcome of peracid epoxidation.[157] As expected, preferential addition of peracids to the double bond occurs in Fig. 98c *anti* to the *cis*-substituted ester and acetate group.[158] Figure 99 gives simplified interpretations of peracid epoxidation involving various estrene derivatives.[159,160] In Fig. 99a epoxidation takes place mainly on the β side, giving the 5β, 10β-epoxide, presumably through the preferential pathway shown: the 1.2-diplanar forms of rings A and B, ensure the coplanarity of the conjugated system and this particular pathway appears as one of low energy, the more so as the 1.2-diplanar form of ring A relieves the steric interactions between hydrogens of carbons 1 and 11.[161]

The steric outcome of peracid epoxidation in example 99b (R = alkyl, hydroxyl, acyloxyl) could have been predicted from an examination of molecular models, using our usual hypotheses as to the *syn* addition of reagents to the 9–10 double bond. We present here a simplified treatment since the evaluation of the four different possible transition states is only qualitative. Two low energy forms are available for α addition and the one of lowest energy is shown on Fig. 99 (the other form, presumably of higher energy, can be neglected since it leads to a *quasi-cis* junction of rings B and C). Similarly two low 1.2-diplanar forms of low energy are available for β-addition and again, the second 1.2-diplanar form with the B, C *quasi-cis* ring junction is presumed to be of higher energy than the conformer shown in Fig. 99b and, for this reason, it is neglected. With this simplification the steric outcome of the reaction depends with respect to the B, C rings' junction, on the relative levels of the transition states of the two *quasi-trans* and *quasi-cis* 1.2-diplanar forms shown in Fig. 99. Now the reasoning is as follows: it is immaterial whether the A, B ring junction is of the *quasi-cis* or the *quasi-trans* nature

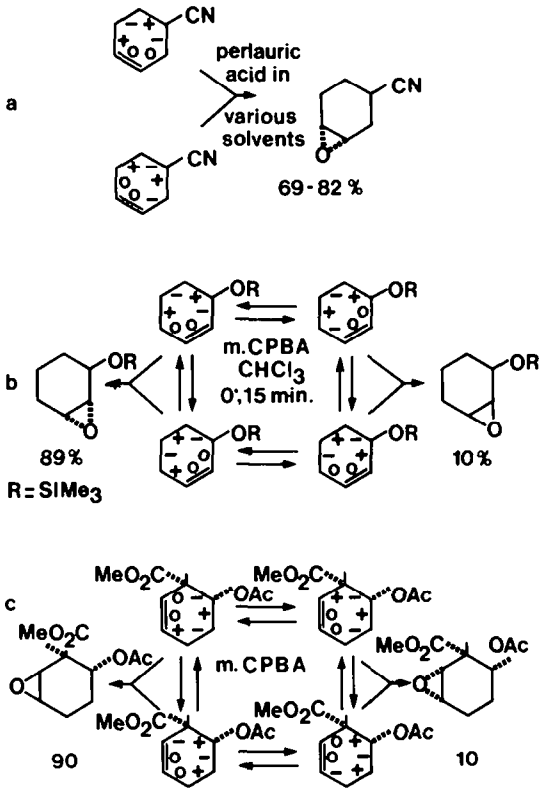


Fig. 98

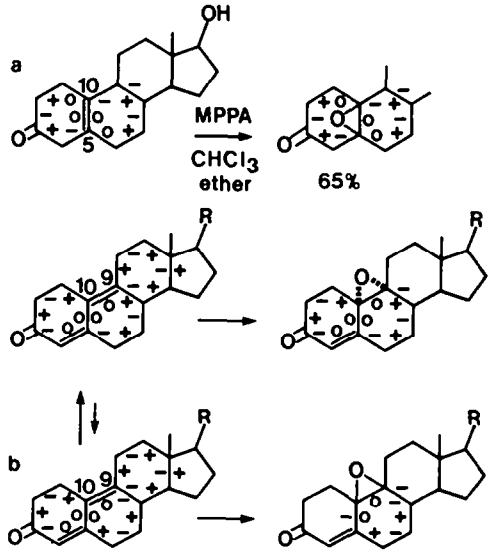


Fig. 99

due to the conformational mobility of ring A and the low energy expenditure involved in such a conformational change. However, due to the rigid half-chair form of ring C, the *quasi-trans* form at the B,C ring junction is certainly of much lower energy than the *quasi-cis* one. Since there is little conformational distortion from the initial reactive form up to the primary final one during the epoxidation, it may be concluded that the corresponding transition states follow the same trend; therefore, the energy of the transition state corresponding to the *quasi-trans* B,C 1,2-diplanar form

should be lower than that of the *quasi-cis* one; consequently α addition leading to 9α, 10α-epoxide, ought to be the main pathway. Experimentally it has been found that, when the 17β substituant is an OH (R = OH), Fig. 99b), the reaction of the Δ^9 conjugated double bond with *m*-chloroperbenzoic acid in chloroform at room temperature for two hours yields 74% of the 9α, 10α-epoxide;[160] with a 17β acyloxy group (R = OAc, OCOØ Fig. 99b), again the main product of epoxidation is the 9α, 10α-epoxide: R = OAc the ratio of 9α, 10α-to 9β, 10β-epoxides is 70:2, using paranitroperbenzoic acid in ether at room temperature.[162]

Syn-*Additions and cycloadditions to α, β-unsaturated enones*

There are relatively very few significant cycloadditions to cyclopentenones and cycloheptenones but we have no reason to believe that the addition to the conjugated double bond does not conform to the previously given rules; such additions should take place, specifically with respect to each low energy conformer, in the direction corresponding to the sequence of torsion angle signs of the conformer as shown in Fig. 100 for the cycloaddition of 1.3-butadiene to 2.4-dimethylcyclopentenone.[163] From the few data in the literature the reactive conformer of 2.4-dimethylcyclopentenone, at least in thermal Diels–Alder reactions, appears to be the envelope with the axial 4-Me.[163,164]

With respect to reactivity it has been found that, for Diels-Alder reactions of 1.3-butadiene with cycloalkenones, catalyzed by aluminium chloride, cycloheptenones are more reactive than cyclohexenones.[165]

Such a reactivity order is not unexpected for us if, in each case, the energy expenditure involved from the initial reactive low energy conformer up to the primary final form is taken into consideration. In contrast to the cyclohexene series, the direction of *syn*-additions and cycloadditions to the conjugated double bond of cyclohexenones may often be predicted; as in the case of cyclohexenes, the direction of addition is unambiguously determined for each low energy conformer of the 1.2-diplanar type and for the corresponding 1.3-diplanar forms. However, for cyclohexenones, as it was previously mentioned, (*see* Fig. 13) there are two pairs of 1.2- and 1.3-diplanar forms that correspond to each other and the two 1.2-diplanar forms that have the second zero torsion angle located between the ketone and the conjugated double bond are of lower energy than the other pair of 1.2-diplanar conformers with the second zero torsion angle β,γ to the ketone (*see* Figs. 13 and 101). Therefore, in the absence of steric or polar effects, the latter 1.2-diplanar forms may be neglected and we can reason only with the 1.2-diplanar forms of lowest energy, equienergetic with the half-chairs of cyclohexenones. The same reasoning applies to 1.3-diplanar forms of cyclohexenones that correspond to the two pairs of 1.2-diplanar forms; the 1.3-diplanar forms with the second zero torsion angle near the ketone are of lower energy than the others, with the second zero torsion angle far away from the ketone, and for this reason we may neglect the latter ones. Such a simplification is valid only in the absence of steric or polar effects and, in general, all 1.2- or 1.3-diplanar forms have to be taken into account to interpret or predict the steric outcome of additions.

In order to visualize these different low energy forms we analyze in Fig. 101 the addition of hydrogen to 3.5-dimethyl-cylohexenones with a Pd–C catalyst[166,167] reported to yield mainly the *cis* 3.5-dimethyl-cyclohexanone (95%) and a small amount of its *trans* isomer (5%).

There are four transition states corresponding to the pathways 1–4 in Fig. 101 and for each pathway a 1.3-diplanar reactive form corresponds to a 1.2-diplanar one. We surmise that the relative energies of these transition states are in the same order as the energies of the reactive 1.3-diplanar

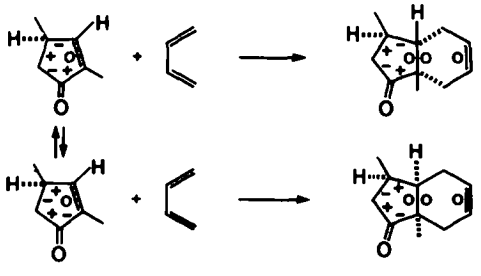


Fig. 100

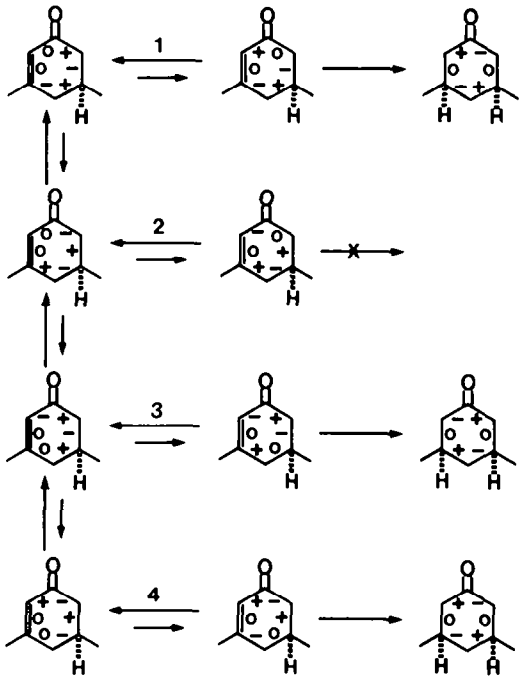


Fig. 101

forms presumably 1 < 2 < 3 < 4. If catalytic hydrogenation is supposed to take place through direct addition of hydrogen to the conjugated double bond, then the primary final forms are boats; starting with the reactive 1.3-diplanar forms and using our usual assumptions, it is clear that the main contribution comes from pathway 1 with minor contributions from pathways 3 and 4; this last pathway like pathway 1 gives rise to the saturated *cis* 3.5-dimethylcyclohexanone whereas pathway 3 leads to the *trans* isomer. Similarly, it would be expected that glycolation with osmium tetroxide would hydroxylate the conjugated double bond on the side opposite to the 5-Me. Another interpretation of glycolation of a sugar enone is given in Fig. 102.[168] Here the direction of addition appears to depend mainly on the anomeric effect of the bulky OR group at position 2. The axial orientation of this group defines the reactive 1.3-diplanar form corresponding to pathway 1 which appears to be the main contributor to the final result. [At least 68% of additions to the side opposite to the anomeric OR group].

Returning to catalytic hydrogenation, it may take place by direct addition of hydrogen to the conjugated double bond or by two successive additions, first of hydride ion through 1.4-addition to the enone followed by subsequent protonation of the enol or enolate, therefore a detailed discussion of the steric course of catalytic hydrogenation is deferred until the next chapter after the section devoted to the conjugated addition to enones. In the absence of steric or polar effects, catalytic hydrogenation of cyclohexenones taking place through direct addition of hydrogen to the double bond can be readily interpreted, as in example 101, taking into account the usual requirements of this reaction, already discussed in the preceding section concerning the catalytic hydrogenation of cyclohexenes. In Fig. 103, only the 1.3-diplanar form of lowest energy (pathway 1) has to be considered in order to interpret the steric result (> 90% of β-addition 169). The other pathway 2 involves a transition state of much higher energy (no boat is available for the primary final form). It is not surprising then that hydrogen addition occurs mainly on the β-side as expected from steric and conformational factors.

Cycloadditions to cyclohexenones are expected to exhibit the same stereoselectivity as *syn*-additions for analogous reasons. However, since all these cycloadditions probably occur stepwise there is a doubt as to the conformation of the primary final product: for this reason the torsion angles' sign sequence of the primary final forms in the examples of Figs. 104–106 are not given and we reason as if the relative energies of the transition states correspond to the relative energies of the initial

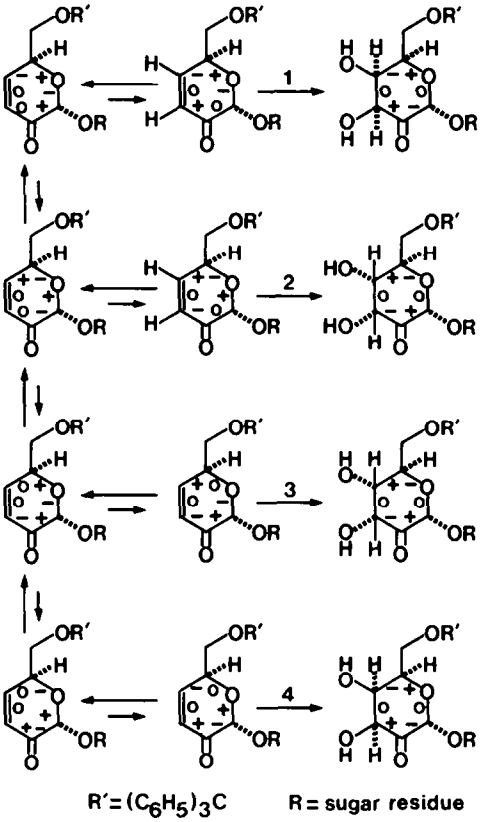


Fig. 102

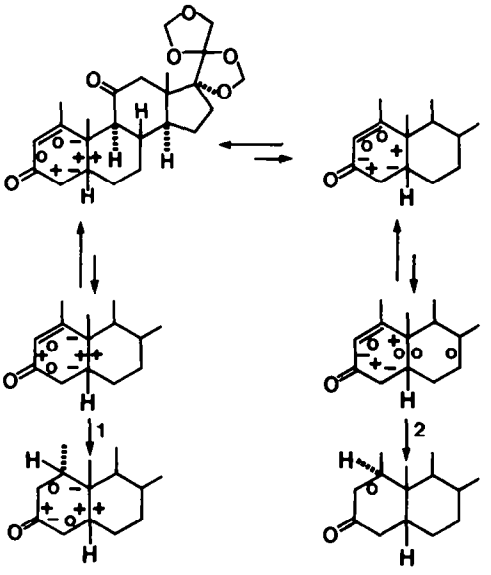


Fig. 103

reactive 1.2- or 1.3-diplanar forms. In Fig. 104, ynamine cycloadditions to 4-methyl-cylohexenone[170] occur with high stereoselectivity on the 1.2-diplanar form (or the corresponding 1.3-diplanar form), with the axial 4-methyl (Fig. 104a), whereas in the isomeric case of Fig. 104b, due to its axial orientation, the 5-Me prevents any substantial addition on its side.[171] Lewis acid catalyzed diene syntheses of Fig. 105a[172] are interpreted in the same manner: the addition is prohibited on the 1.3-diplanar form with the axial 5R'-alkyl since it has to occur on the same side. In Fig. 105b[173] the

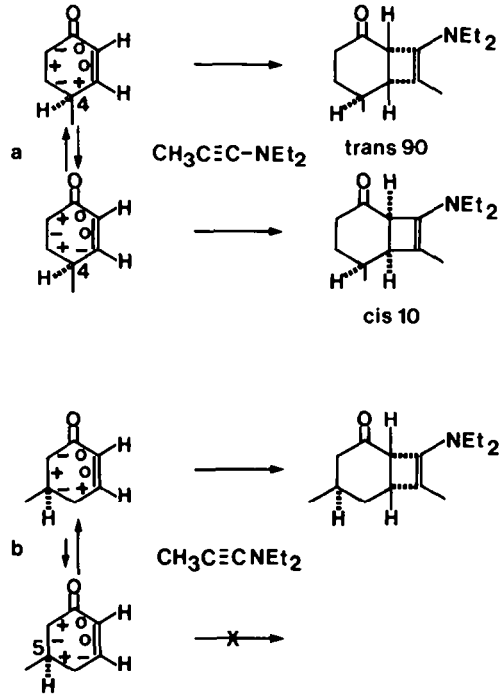
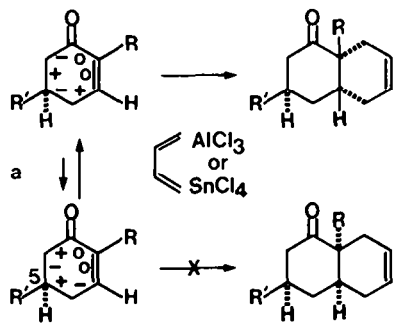


Fig. 104



R	R′	
H	CH_3	46
CH_3	CH_3	55
CH_3	iPr	40
CH_3	$(CH_2)_3OAc$	40

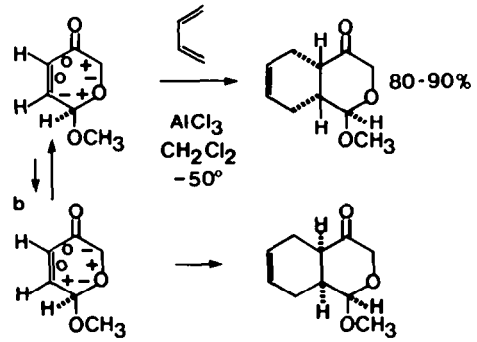


Fig. 105

anomeric effect of the 2-OMe group imposes the steric course of the cycloaddition since the axial orientation of the anomeric group defines the reactive 1.2-diplanar form of lowest energy. Again here the other two 1.2-diplanar forms may be neglected.

The 1.3-dipolar addition of acetonitrile N-oxide to carvone has been described but the stereochemistry of the addition has not been ascertained.[174] On the basis of our usual reasoning the main adduct is suggested to be the one shown in Fig. 106.

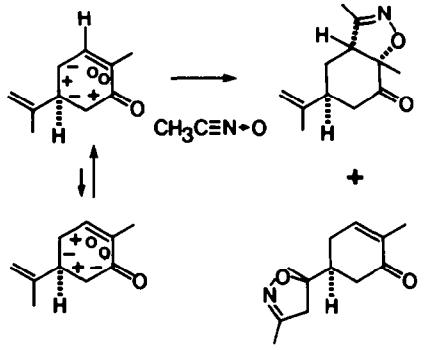


Fig. 106

VI. ALLYLIC REACTIONS

Under this heading are gathered a few allylic reactions, the common and controlling feature of which is the maintenance of orbital overlap during the whole course of the reaction.

The kinetic 1.2- and 1.4- additions of anions to conjugated cyclic enones is first examined, these reactions taking place without any shift of the allylic double bond. In another section the steric course of SN′ reactions, taking place with an allylic shift of the double bond, and involving 5-, 6- and 7-membered, unsaturated rings is dealt with.

(1) *Kinetic 1.2-additions of anions to conjugated enones*

1.2 Addition of anions to conjugated cyclic enones is a well documented field,[175] some aspects of which have already been investigated. Thus, the steric course of 1.2- addition of hydride ion and other anions to α,β-unsaturated cyclohexenones has been previously given an interpretation, using the hypothesis of maintenance of orbital overlap during the whole course of the reaction.[176] This assumption, implying that anion addition to the unsaturated ketone always takes place in the axial direction on the reactive conformation of the enone, appears in excellent agreement with most experimental studies. For this reason we briefly recall here the main rules to interpret or predict the steric outcome of the addition of anions, and especially hydride ions to conjugated cyclohexenones and we intend to devote more time to the extension of the reasoning to α, β-unsaturated 5- and 7-membered enones.

Kinetic 1.2-additions of hydride to α, β-unsaturated cyclohexenones

In the absence of steric or polar effects, the 1.2-addition to conjugated cyclohexenones of hydride ion from relatively small donors (mainly alkaline borohydrides or lithium aluminum hydride) may be interpreted by having recourse to the low energy reactive conformations of these unsaturated 6-membered rings, namely the 1.2-diplanar forms or the equienergetic half-chairs (Fig. 13). From the torsion angle signs sequence, before and after the ketone (clockwise motion!), the direction of kinetic 1.2-addition of hydride ion to α, β-unsaturated cyclohexenones is readily determined as shown in the example of Fig. 107[177] the main reduction products with common hydride donors (90–95%) corresponds to the 1.2-diplanar form with the 5-Me in the equatorial orientation; as for the minor reduction product, it may arise from the 1.3-diplanar form that corresponds to the preceding 1.2-diplanar form as illustrated in Fig. 107, (*quasi*-axial entry of the anion) or from the 1.3-diplanar form, numbered 5′ in Fig. 108, with the 5-Me in the *quasi*-axial orientation. In all the other 1.2- or 1.3-diplanar forms available (Fig. 108) the approach of the anion on the side of the 5-Me seems prevented

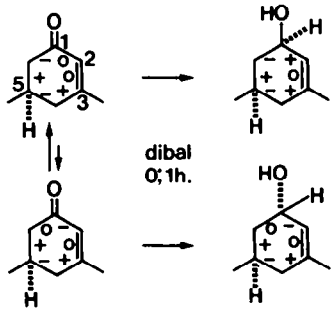


Fig. 107

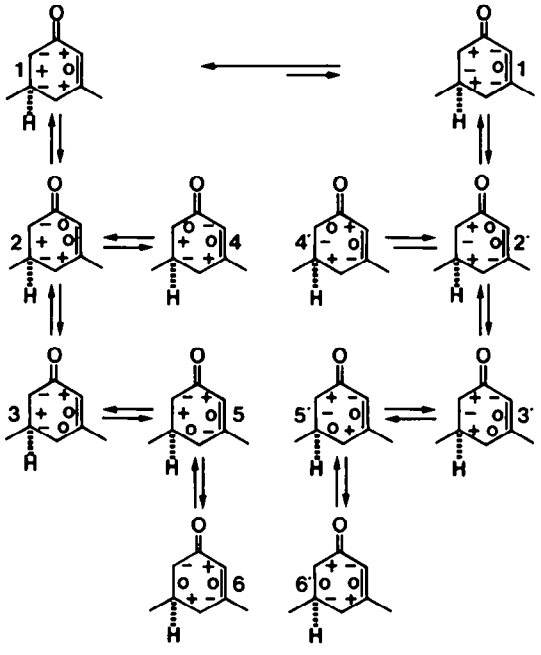


Fig. 108

owing to the strong steric 1.3 interactions of the *syn*-axial 5-Me with respect to the incoming hydride ion. In Fig. 108, all possible reactive forms of 3.5-dimethyl cyclohexenones have been drawn and to each reactive conformer corresponds a transition state. Fortunately a choice among all these transition states can be made, owing to notable energy differences between these various conformations and their corresponding primary final forms: 1.2- addition to enones can, most often be interpreted using only the forms of lowest energy, generally the 1.2-diplanar ones. For instance, in Fig. 109[178] electronic and polar effects favour the highly stereoselective addition of hydride ion to the 1.2-diplanar form on the side opposite to the oxymethylene bridge. Due to the rigidity of the unsaturated ring there is only one 1.2-diplanar form of lowest energy. Generally one has to take into consideration either the two inverted 1.2-diplanar conformers (examples of Fig. 110–112) or the 1.2- and 1.3-diplanar conformers that correspond to each other, as in Fig. 113. In Fig. 110[179] the steric outcome of hydride addition to the ketone is related to the 1.2-diplanar form of lowest energy. From this point of view, depending on the bulk of the R substituent, it may be either one of the two 1.2-diplanar forms of Fig. 110 for the following reason; when R is a small group, like Me or Et, the main reactive conformer, corresponding to the transition state of lower energy appears to be the one with the R group in the equatorial orientation; on the other hand, when R is a large group like isopropyl or phenyl, the main reactive conformer, that corresponds to the transition state of lowest energy may be the 1.2-diplanar form with the R group in the axial orientation.[180] In the latter case, approach of the

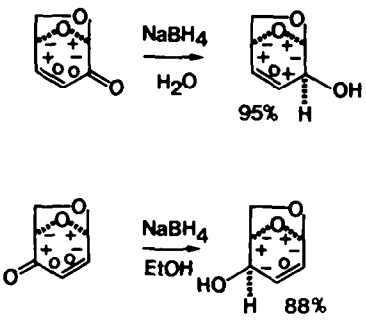


Fig. 109

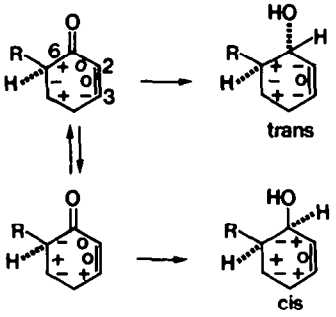


Fig. 110

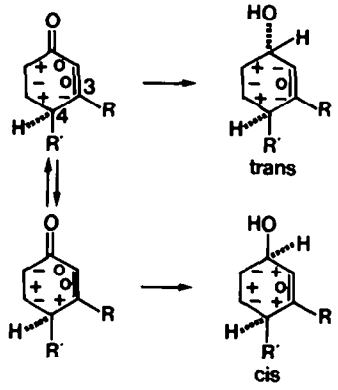


Fig. 111

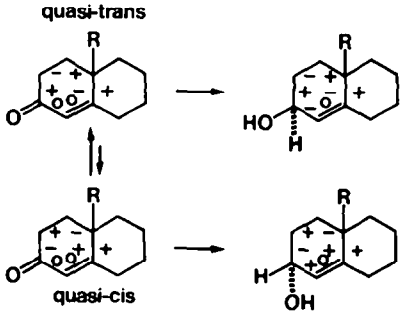


Fig. 112

incoming hydride ion to the ketone does not increase the steric compression between non-bonded atoms of the anion and those of the 6R group. Therefore stereoselectivity should vary with an increasing bulk of the hydride donor and favour the *cis*-isomer, arising from the conformer with the axial substituent at 6. For instance, it has been found that the reduction of 3-methyl-6-phenylcyclohexenone provides the *cis*-3-methyl-6-phenylcyclohexenol as the major isomer (63–74%), using aluminum hydride or lithium trimethoxyaluminum hydride in ether or tetrahydrofuran, whereas the stereoselectivity is lower (42–56%) using lithium aluminum hydride.[179] For comparison, let us note that when the 6R substituent is isopropyl the resulting *trans* to *cis* ratio of reduced 6-isopropyl cyclohexenols amounts to 2:1.[181]

The interpretation of the steric course of hydride addition to the ketone of Fig. 111 has to take into account the reactive conformer that involves the least amount of allylic strain[180] between the substituents of carbons 3 and 4. Already when the double bond is unsubstituted and the group at 4 is an isopropyl, the 1.2-diplanar conformer with the axial isopropyl group is presumably involved in the reduction since the ratio of the resulting *cis*, *trans* cyclohexenols is 75:25.[181] The latter conformer may become the main reactive form when both R and R′ groups at 3 and 4 are alkyls.[182]

Hydride addition to octalone of Fig. 112[183] or to the corresponding 3-oxo-Δ^4 steroids[184] may be interpreted with the help of *quasi-trans* and *quasi-cis* 1.2-diplanar forms of lowest energy. The transition state of the *quasi-trans* pathway is probably of lower energy than the one corresponding to the *quasi-cis* pathway and therefore the experimental result is what could have been expected: the 3βOH:3αOH ratio is around 9:1 when R = Me[183a] and around 4:1 when R = H.[183b]

As it was formerly mentioned[36] for the octalones as for the corresponding 3-oxo-Δ^4 steroids, there is less energy difference between *quasi-trans* and *quasi-cis* conformers in the nor-series (R = H) than in the normal series (R = Me). Therefore reduction of octalones of Fig. 112 (R = H) or 19 nor-3-oxo-Δ^4-steroids with sodium borohydride or lithium aluminum hydride should display a lesser degree of stereoselectivity than was found in the homologous series, which is in agreement with the experimental results of the literature.[183b, 185]

In the hydride addition to Δ^5-7-oxo-steroids of Fig. 113[186] the main product or reaction corresponds to the addition to the low energy 1.2-diplanar form, whilst the minor isomer presumably arises from the 1.3-diplanar form related to the preceding 1.2-diplanar form.

A similar interpretation may be given for the reduction with sodium borohydride or lithium aluminum hydride of 12-oxo-$\Delta^{9(11)}$-steroids[187] known to yield a mixture of isomers in which the major one, generally, corresponds to the expected α hydride addition to the low energy 1.2-diplanar form of ring C, the minor isomer arising from the related 1.3-diplanar form.

So far, only hydride ion addition to *transoid*-enones was considered, but, as shown in Fig. 114,[188] *cisoid*-enones obey also the previous rules and anion addition to such ketones are often highly stereoselective. The exocyclic double bond usually favours the addition of reagents to the low energy form of the ketone, the chair in the example of Fig. 114; the minor isomer, if formed at all, may arise from the addition to one of the twist forms. In both chair and twist forms there is a good maintenance of orbital overlap during the reaction and even bulky reagents like trisopropylaluminum favour the formation of *cis*-pulegol, obtained in 85% yields.[188]

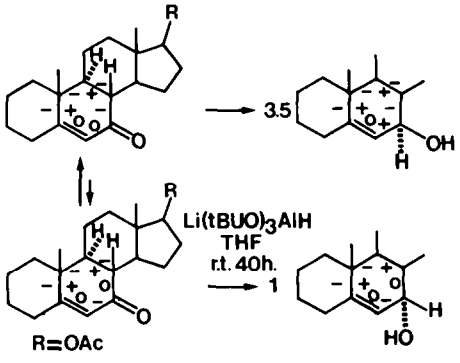


Fig. 113

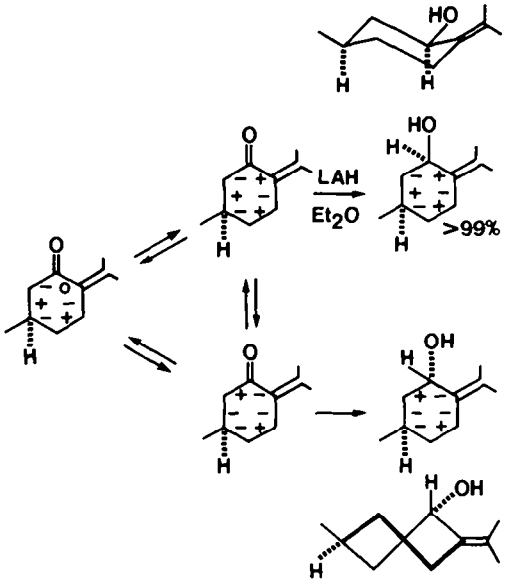


Fig. 114

For conjugated cyclohexenones that are part of a rigid framework, such as those of codeinone derivatives of Fig. 115,[189] the conformation of the ring may be forced to adopt a 1.3- or 1.4-diplanar form. Such forms are readily recognized in the X-ray diagrams of such compounds.[190a] In such cases, the addition of hydride ion or other small ions to the ketone follows the expected steric course corresponding to the sequence of torsion angles.[189,190]

Two main cases have to be discussed in the reduction of cyclohexadienones: those maintained in a rigid 1.4-diplanar form ought to be reduced stereospecifically whilst those that are taking part in a conformational equilibrium should yield a mixture of isomers. There are few reliable results in the literature since the dienols, thus obtained, are very acid sensitive and isomerize very readily during their isolation especially under the usual conditions of chromatographic separations.

A few interesting experimental results may be found in the hydride addition to 1.4- diplanar forms of cyclohexadienes, one double bond of which is replaced by a cyclopropane or an epoxide[191] but other factors to be discussed later on have, then, to be taken into account to rationalize the experimental results.

1.2-*Addition of other anions to conjugated ketones.* Increasing the volume of the anion involved with 1.2- addition to conjugated cyclohexenones with respect to that of hydride can bring a change in the stereochemistry of addition, since the approach to the ketone and the steric compression in the intermediate complex, at the moment of bond formation are not equivalent in these two cases. Using our general method, it is often possible to perform a qualitative interpretation or even a prediction of the outcome of 1.2-anion addition to conjugated cyclohexenones if steric, polar and stereoelectronic factors are carefully evaluated. Thus condensations in ether or benzene of the chloromagnesium enolate of tertiobutylacetate and the Reformasky reagent of ethyl bromoacetate with (−) piperitone

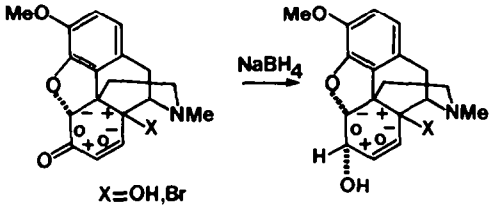


Fig. 115

and (+) pulegone (Fig. 116) are highly stereoselective, leading, in each case to a single β-hydroxy ester, the configuration of which can be readily predicted.[192]

Kinetic 1.2-additions of hydride ions to conjugated cyclopentenones and cycloheptenones

Arguments, similar to those used for conjugated cyclohexenones, may be presented to interpret the 1.2- additions of anions to conjugated cyclopentenones and cycloheptenones.

Cyclopentenones. Whenever the envelope form of the conjugated cyclopentenone is unique as in examples a,[94a] b,[193] c[193] of Fig. 117 a stereospecific addition of hydride ion is to be expected, whereas the reduction of conjugated cyclopentenones taking part in an equilibrium of envelope forms often leads to a mixture of isomeric cyclopentenols. The two envelope forms in 117b and c may interconvert through an intermediate enolate and, under isomerisation conditions a mixture can be expected,[193] but under non-isomerizing conditions each conformer ought to specifically yield the expected carbinol. Diisobutylaluminohydride reduction of the *cisoid*-enone of Fig. 117d yields a mixture of carbinols, the major isomer of which corresponds to the envelope form that allows the best orbital overlap of the ketone and the exocyclic double bond.[194]

The examples of Fig. 118[195 197] always involve a *quasi-trans*, *quasi-cis* equilibrium of envelope conformers, even if in the last two cases, b[196] and c,[197] the cyclopentenols corresponding to the *quasi-trans* envelope are reported to be the exclusive product of reduction.

The interpretation of examples a[198] and b[199] of Fig. 119 is somewhat more delicate. From the foregoing discussion it could have been anticipated that in both examples the main conformer ought to correspond to the envelope with the substituent at 4 in the axial orientation but, in fact, the main product of reduction corresponds to the minor conformer. To resolve this apparent contradiction we propose the following interpretation. Owing to the axial orientation of the substituent at 4, the addition of hydride ion on the side of this substituent is hindered relative to the other, less abundant, conformer and thus the reduction rate is more rapid for the minor reactive conformer than for the

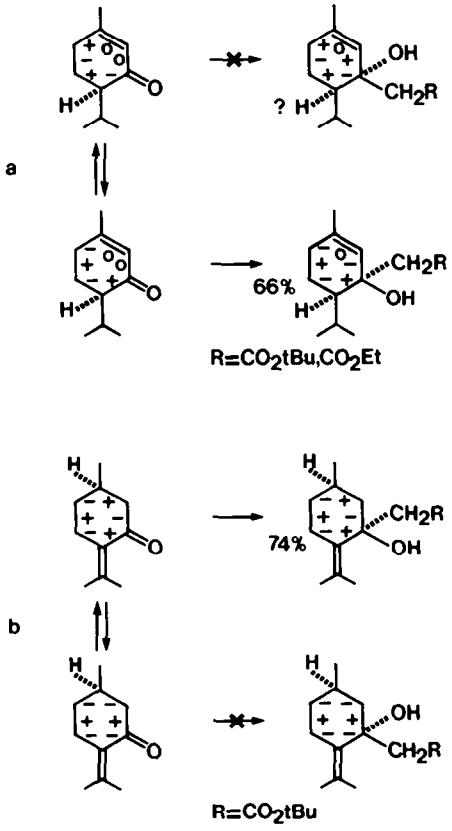


Fig 116

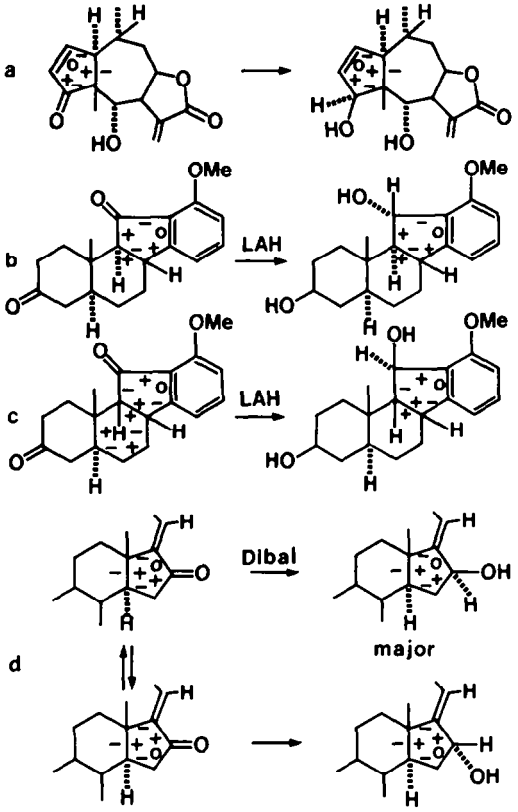


Fig. 117

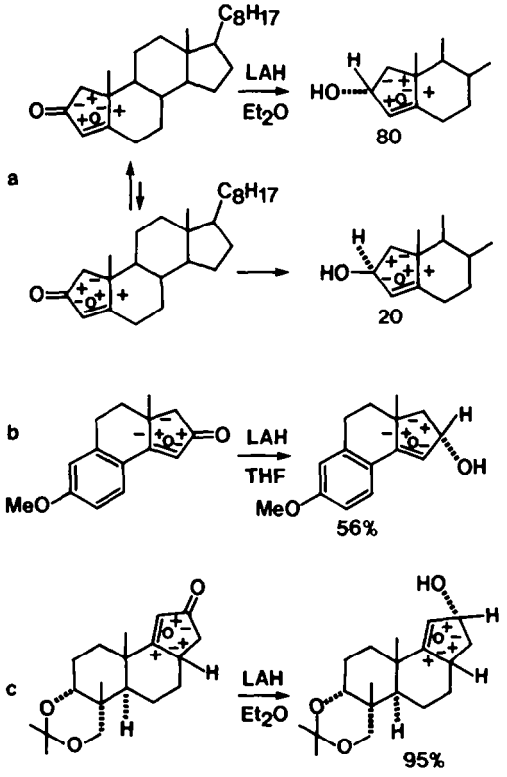


Fig. 118

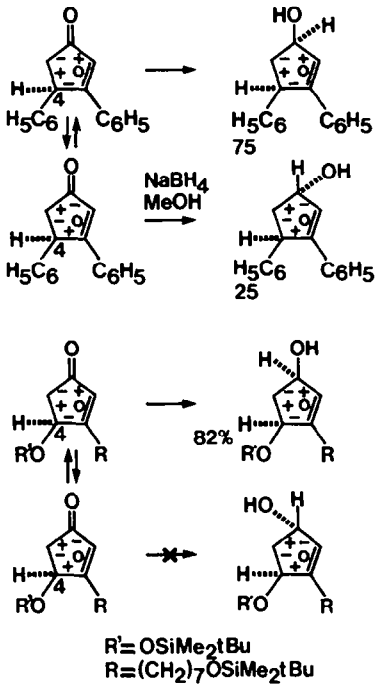


Fig. 119

other, which could explain the experimental results. In example b, the polar and steric effects of the axial dimethyltertiobutylsilyloxy group at 4 prevents or, at least, strongly delays the addition on its side of hydride, from lithium tri-s-butyl borohydride in tetrahydrofuran, to the ketone.

Cycloheptenones. Conjugated cycloheptenones able to adopt a low energy chair form are apparently reduced in a highly stereoselective manner insofar as the examples a and b[94a] of Fig. 120 may be considered as representative. In each case the reduced cycloheptenol is reported to be the exclusive product of hydride addition. In the conjugated cycloheptenones series the energy difference between twist and chair forms is very small (Fig. 16) and therefore interconversions between these forms may easily take place. Such an interconversion could explain the steric outcome of the reduction of Fig. 121,[200] in which hydride from sodium borohydride adds to the α, β epoxy ketone in the direction opposite to that found in Fig. 120b, for lithium aluminum hydride reduction of the corresponding unsaturated ketone. A chelation effect of the sodium cation of the borohydride to the epoxide oxygen could be among the factors responsible for this conformational change.

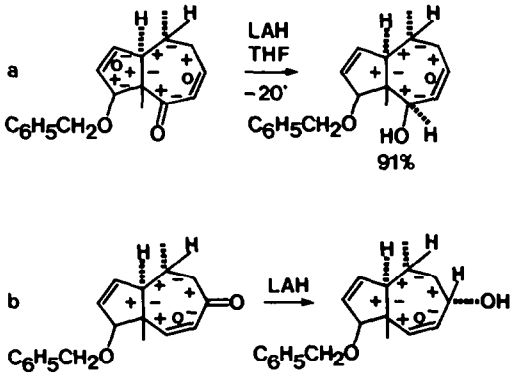


Fig. 120

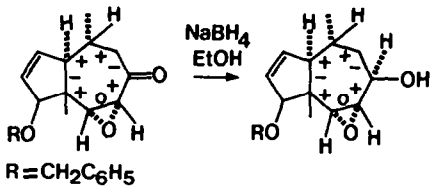


Fig. 121

Kinetic 1.2- addition of hydride ion to α, β-methylene and α, β-epoxy ketones

It was mentioned earlier that the geometry of the common unsaturated rings did not change much when one double bond was replaced by a 3-membered ring of a cyclopropane or epoxide. For instance, cyclohexene (Fig. 122a), norcarane (Fig. 122b, X = CH_2) and cyclohexene epoxide (Fig. 122b, X = 0) may be assumed to have similar low energy forms. Moreover, for the corresponding ketones namely norcaranone (Fig. 122d, X = CH_2) and cyclohexenone α, β-epoxide (Fig. 122d, X = 0) low energy conformations are presumably similar to those of the α, β unsaturated cyclohexenone shown in Fig. 13. In this respect it has already been pointed out in our previous publications[201,202] that we do not know exactly the extent of "conjugation" of the 3-membered ring with the ketone and therefore there might be some significant energy differences between the preferred conformations of conjugated cyclohexenones and those of the norcaranones or epoxy-ketones.

The presence of the epoxide ring imparts some peculiar features to the cyclic epoxy-ketones, owing to the ether-like inductive effect of the epoxidic oxygen and to its ability to chelate metallic cations in appropriate solvents,[203] which may have an orientating effect as to the direction of anion addition. Although it was suggested earlier that the direction of kinetic 1.2- hydride addition to the ketone of compounds of type 122d (X = CH_2, 0) takes place preferentially from the side of the methylene or oxygen of the 3-membered ring,[202] we feel, now that this suggestion is not always valid.[204] In fact, using the torsion angle notation and a few simple assumptions it is possible to qualitatively analyze the steric course of the kinetic reduction of cyclic α, β-methylene and α, β-epoxy-ketones of 5-, 6- and 7-membered rings.

Kinetic 1.2- addition of hydride ion to cyclic α, β-methylene ketones

Being accepted that the low energy forms of norcaranone (122d, S = CH_2) are similar to those of conjugated cyclohexenones and that the trigonal group is "conjugated" only to some extent with the ketone we can analyze the reduction of such derivatives. As shown in Fig. 123[205] the reduction of norcaranone, yielding a 3:7 ratio of *cis*- and *trans*-norcaranols respectively, may be interpreted in terms of the equilibrating half-chairs, 1.2- and 1.2-diplanar forms. If the contribution of these last forms is neglected we have to choose between the transition states that correspond to the two inverted half-chairs. Since for the transition state that yields the *trans* isomers there are two contributions, from the half-chair and from the equienergetic 1.2- diplanar form whereas for the other *cis* isomer the main contribution arises from the half-chair which in this case is of lower energy than the corresponding 1.2-diplanar form, we conclude that the former transition state will be of lower energy than the one that corresponds to the formation of the *cis* isomers.

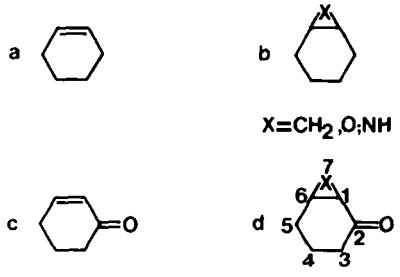


Fig. 122

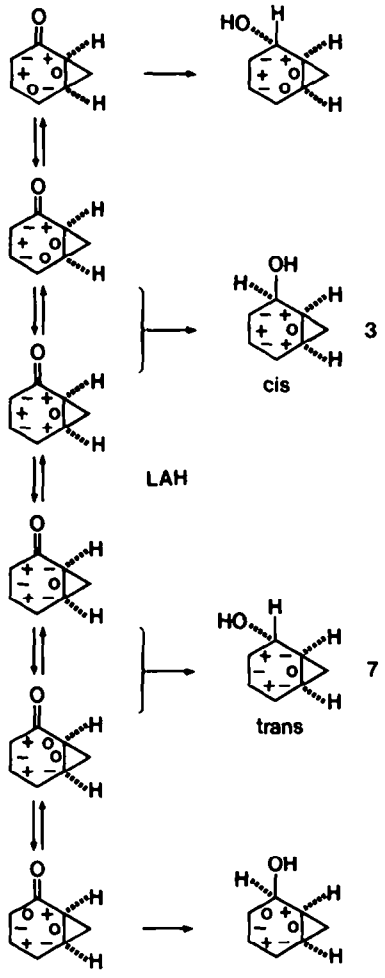


Fig. 123

As an empiric rule, in the absence of controlling steric or polar effects, the main direction of 1.2-hydride addition to the ketone corresponds to the half-chair form of lowest energy. Apparently conjugation is not the only controlling factor but it does contribute to the stereoselectivity of the reduction.

Comparing the reduction of the two isomeric 4-methylnorcaranones of Figs. 124 and 125[204] we notice that in each case the main product of reduction corresponds to the addition of hydride to the ketone from the same side as the axial hydrogen of the Me substituent on the half-chair conformation of lowest energy, with the 4-Me in equatorial orientation. Now in the reduction of the *cis* isomer of Fig. 124 a minor contribution from a 1.2-diplanar form with the axial 4-Me appears probable whilst in the *trans* isomer of Fig. 125, even such a minor contribution is probably very limited owing to the 1.3-steric interaction of the incoming hydride with the axial 4-Me. According to this simplified analysis, the stereoselectivity of reduction should be higher for the *cis* isomer of Fig. 124 than for the *trans* isomer of Fig. 125 which appears in agreement with the experimental results.[204]

A similar rationale may be offered for the interpretation of the reduction of Fig. 126.[206-208] In these examples there are less privileged forms than in the 6-membered series and therefore, at least, for the α, β-methylenecyclopentanones the main direction of hydride addition is easily predicted.

In the case of Fig. 126a[206] and b[207] the main direction of hydride addition to the ketone corresponds to the most stable conformation of bicyclo [3.1.0.] hexane [209] and probably of bicyclo [3.1.0.]hexenones. For Fig. 126b the steric course of hydride addition is the same whatever the reagent: lithium aluminum hydride in ether or sodium borohydride in methanol–water or in

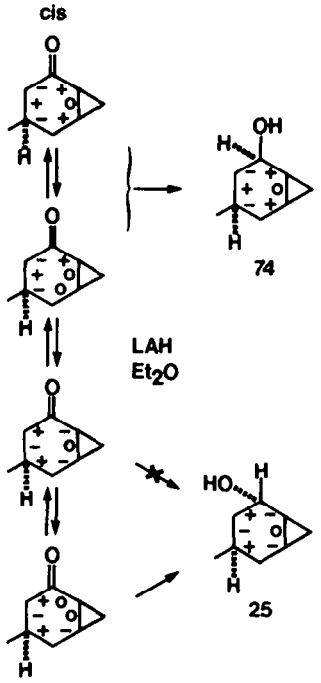


Fig. 124

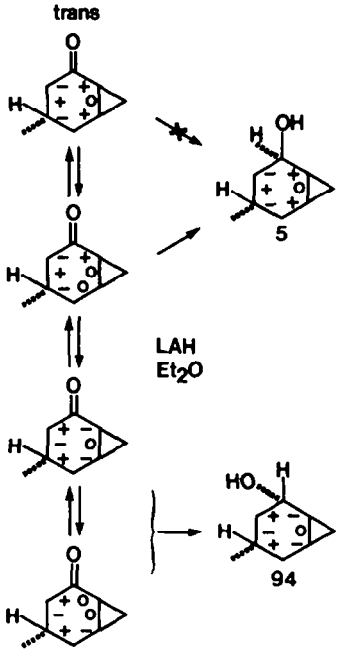


Fig. 125

hexamethylphosphoramide–water.[207] Again in Fig. 126c[208] hydride addition takes place mainly on the more stable conformer.

The interpretation of the reduction in the example of Fig. 127[210] implies that the transition state corresponding to the twist form of α, β- methylenecycloheptanone is of lower energy than the transition state corresponding to the chair: this could mean that the stability order of the preferred forms is the same as that of cycloheptenones (Fig. 16).

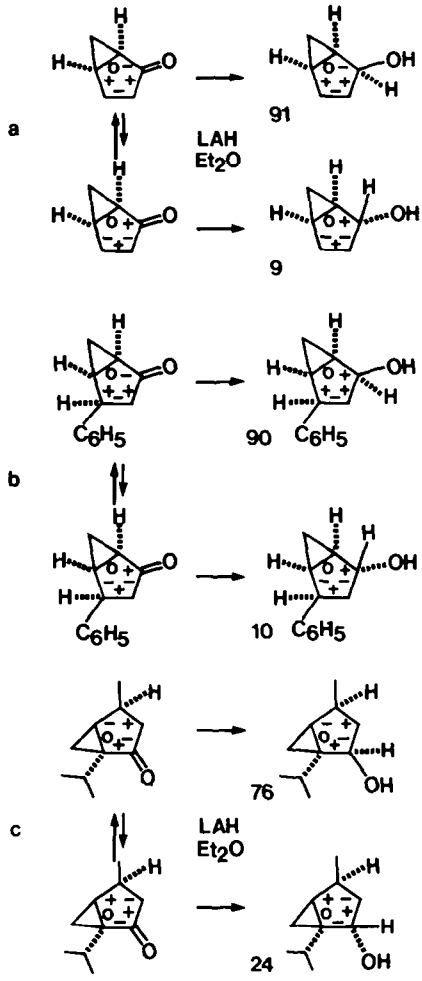


Fig. 126

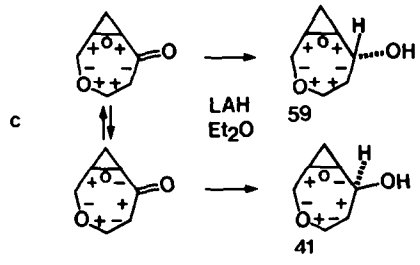


Fig. 127

1.2-*Addition of hydride ion to cyclic α, β- epoxyenones*

Epoxy-cyclohexenones. As it was already mentioned[202] the steric course of anion 1.2-addition to α, β-epoxy- and α, β-methylene ketones presents a few similarities. However, there are also some peculiar features for the former reaction due to the inductive effect of the epoxide and to the ability of the epoxide oxygen to bind metallic cations in appropriate solvents and, thus, to direct, under these conditions, the addition of small anions like hydride ion to the ketone.[203]

The interpretation of the steric course of the kinetic 1.2-addition of hydride ion to epoxides of α, β unsaturated cyclohexenones requires a careful evaluation of the main controlling factors: the

stability of the conformation allowing a favourable conjugation of the epoxide ring with the ketone[202] the inductive effect of the epoxide with respect to the reactive form and the ability of the epoxide in a given orientation (axial or bisectional) to chelate the metallic cation of the reducing agent (mostly sodium borohydride).

For many epoxy-ketones, in which the epoxide is "axial" on the 1.2-diplanar form of lowest energy, the experimental results may be predicted or interpreted through an evaluation of the relative importance of two main contributions: a major one from the 1.2-diplanar form, equienergetic with the half-chair and a minor one from the 1.3-diplanar form that corresponds to the preceding 1.2-diplanar conformation as shown in the example of Figs. 128 and 129, drawn from the steroid series.

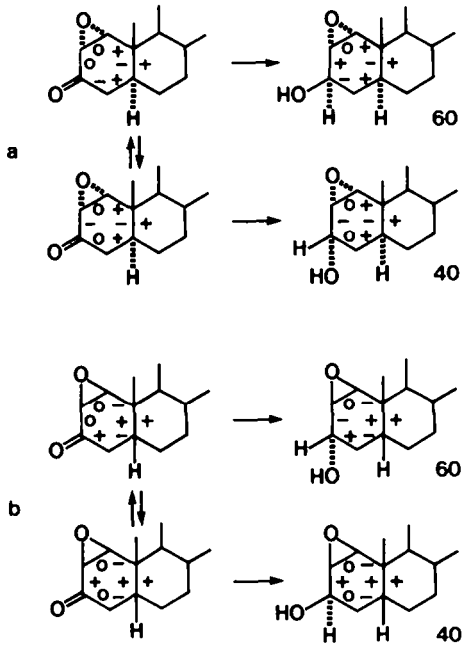


Fig. 128

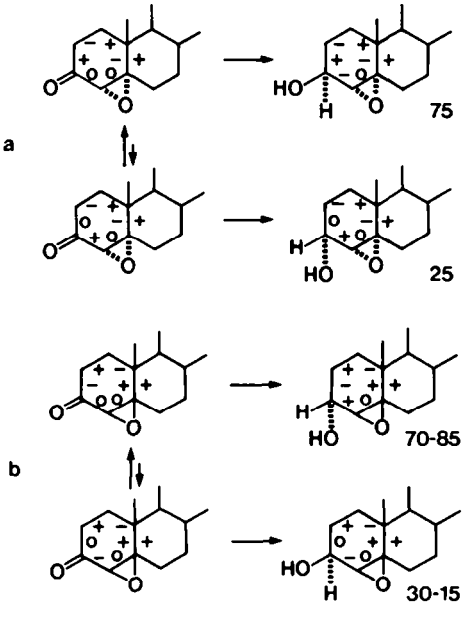


Fig. 129

The reduction of 1α, 2α-epoxy-5α-cholestan-3-one yields a 60:40 mixture of 3β and isomeric 3α-cholestanols.[211-212]

As explicited in Fig. 128a the main contribution derives from the 1.2-diplanar form of lower energy whereas the minor contribution comes from the corresponding 1.3-diplanar form. It should be remembered that in 1.3-diplanar forms the steric interactions are of the 1.4-type and not of the usual 1.3-type that occur in half-chairs on 1.2-diplanar forms. From that point of view the results of Fig. 128a appear reasonable since both the stability of the initial reactive conformations and the steric effects favour the 1.2-diplanar form over the 1.3-diplanar one. In this latter form the epoxide being in an axial orientation is able to control the direction of hydride addition to the ketone through its fully operative inductive effect.

Using similar arguments, the moderate stereoselectivity observed in the reduction of the isomeric 1β, 2β-epoxy-5β-cholestan-3-one[211b] can be explained as illustrated in Fig. 128b. In Fig. 129a[211] and b,[211,213] again the stereoselectivity of the reduction can be readily interpreted, the main isomer arising from the 1.2-diplanar from of lowest energy. In comparison with the examples of Fig. 128, there is a higher stereoselectivity of reduction in the examples of Fig. 129: this may be connected with the higher expenditure of energy required for the conversion of the 1.2-diplanar form into the corresponding 1.3-diplanar one respectively for the forms involved in Fig. 128 and 129.

So far we have dealt with keto-epoxides whose epoxide group was in the axial orientation on the preferred low-energy, 1.2-diplanar form. What happens when the epoxide has the bisectional orientation on the 1.2-diplanar form of lowest energy? Whenever the epoxide cannot adopt an axial orientation on the 1.2-diplanar form of lowest energy, one would expect the main controlling factors in the reduction of the ketone, to be the ability of the epoxide oxygen to chelate the metallic cation of the reducing agent and the stability of the conformer of lowest energy of the ring. The steric outcome of the reduction would thus depend on the relative importance of these controlling factors. In fact the results reported in the literature do not appear entirely reliable and further experimental work is required in order to ascertain, in a more quantitative manner, the effect of chelation (probably solvent- and reagent-dependent) and the nature of the reactive conformers.

Reduction of epoxy-cyclohexadienones and epoxy-quinones. There are few reliable examples concerning the kinetic reduction of cyclohexadienone-epoxides in the literature[214] and most of them can be readily interpreted, using our usual hypotheses. In Fig. 130[191] reduction of the dienone yields a 4:1 mixture of unsaturated diols, arising from further reduction of the epoxide. The major product of reduction comes, as expected, from the *quasi-cis* form of the unsaturated ring. As to the origin of the epimeric 3α-hydroxy diol, it remains obscure for the moment.

The steric course of epoxy-quinones reduction yielding, in general, a mixture of isomeric epoxy-ketols,[214] can be interpreted along similar lines. Very often the main component of the isomeric mixture corresponds to the 1.4-diplanar form with the epoxide in the axial orientation as in the example of Fig. 131,[214] in which for R = H the isomer ratio is 3.5:1.

Kinetic reduction of odd membered enone-epoxides. (a) Cyclopentenone-oxide: Pursuing the analogy between α, β-methylene (of Fig. 126) and α, β epoxy derivatives of cyclic-enones it could have been

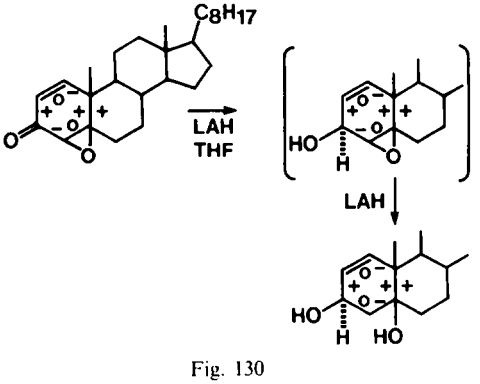


Fig. 130

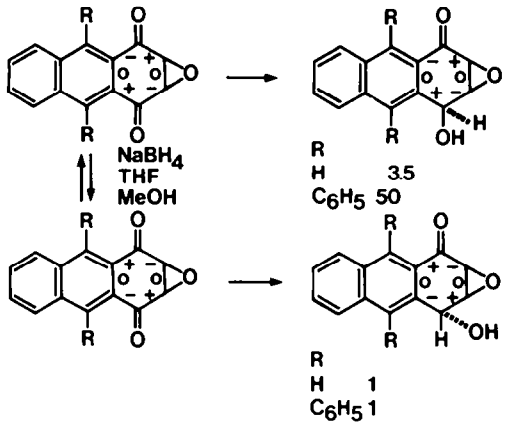


Fig. 131

expected that the reduction of epoxides of cyclopentenones would yield a major product of reduction arising from the more stable envelope form of the ring with the epoxide in the axial orientation as in the example of Fig. 132.[195] The origin of the minor product of reduction is not clear and we may note that the inductive effect of the "axial" epoxide and the preferred conformation tend to promote anion addition in the same direction.

(b) Cycloheptenone-oxide: An example of a kinetic reduction in the cycloheptenone epoxide series has been given in Fig. 121.[200]

(2) *Conjugate addition to cyclic enones*

Conjugate addition to cyclic enones plays an important part in the stereoselective creation of C–C bonds and is the first, stereochemically controlling step of several reactions of *cis*-addition like alkaline epoxidation[215] and cyclopropanation through sulfur ylides derivatives such as sulfonium and sulfoxonium ylides.[216]

In this section it is purposely intended to present a unified view of kinetic 1.4-addition of anions to cyclic enones taking into account the stereoelectronic requirement of orbital overlap, the conformational constraints implied in the least deformation of the initial reactive form during the reaction up to the primary final form, and the steric and polar effects of both substrate and reagent.

Since for enones that are not locked into a rigid conformation the steric outcome of anion conjugate addition depends, to a large extent, on the size of the reagent which is more or less rightly equated wth the size of the anion, we have first to make this point more explicit.

As a rule, the size of the reagent to be taken into consideration in the dynamic conformational analysis of conjugate additions to enones, may vary from small to large or even very large with all possible intermediates and, as expected, the bulk of the reagent and of the corresponding anion has a bearing on the relative energy levels of all possible transition states. As an example, conjugate

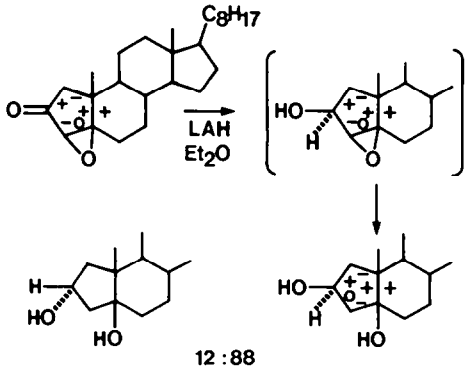


Fig. 132

addition of hydride ion to enones is a known reaction that may be performed using hydride from small or bulky donors. Among the small donors we may rank lithium or sodium in liquid ammonia and sodium borohydride in pyridine or in other solvents.[217]

Although the exact mechanism of enone 1.4-reduction by lithium in liquid ammonia in the presence of an alcohol is still debated,[218] the overall result may be interpreted as if the reaction takes place through 1.4-addition of hydride from a very small donor to the enone. Among the bulky donors are included complex hydrides[219] and hydrogen complexed with most of the transition metals used in catalytic hydrogenations and supposed to deliver first a hydride ion.[220] Therefore, in a general manner, we will distinguish the steric outcome of conjugate additions involving small anions (hydride from small donors, cyanides, hydroperoxides among others) or bulky anions and in the order of increasing size organo-metallic compounds, hydride from bulky donors, metallic enolates or enamines of substituted ketones or aldehydes and similar metallic species arising from other activating groups.

Since we assume the maintenance of orbital overlap during the course of anion 1.4-addition to the conjugated ketone, it means that in the primary final form of the product the entering group has always the axial orientation. Therefore, the sign sequence of torsion angles before and after the carbon undergoing the addition is readily determined and corresponds to those of the code (Fig. 8). In the conjugated cyclohexenones series, two opposite directions of additions are available for each reactive conformer (Fig. 30) whereas in the conjugated cyclopentenones series, only one direction of addition is allowed for each reactive conformer. Thus, for the odd membered series to each low energy reactive conformer corresponds only one direction of conjugate addition and the interpretation or prediction is particularly easy and, for this reason, conjugate addition to odd membered enones is treated first.

Conjugate addition to odd membered enones

Cyclopentenones. Assuming that cyclopentenones, although nearly planar, may readily adopt envelope conformations similar to those of cyclopentene but somewhat flattened around the ketone,[27] we have to consider only two cases:

(a) The cyclopentenone is locked into an envelope form and, in this case, the conjugate addition is stereospecific and takes place in the expected direction.

(b) The cyclopentenone may adopt either one of the two inverted envelope forms in equilibrium and the steric outcome of the addition depends on various factors, which are the size of the reagent to be added, the steric, polar and proximity effects that may affect or orientate the addition and influence the stereoselectivity by favoring one form rather than the other.

We examine successively these two cases and especially the last one that happens to be the most frequent.

A single envelope: stereospecificity. Owing to the rigid envelope form of ring D in the Δ^{15} androsten-17-one of Fig. 133 the results of conjugate addition of alcoholates (pathway 1)[221-224] alkaline hydrogen peroxide[222,223,225] (pathway 2) or cyanide anion (pathway 3)[223] are readily interpreted or predicted. Since there is only one low energy reactive envelope form and one corresponding low energy envelope for the primary final form, only the 15 β-direction of conjugate addition is consonant with our hypotheses. This direction of addition is implicit in the initial reactive form since the clockwise signs sequence at carbon 15 is 0, $-$. In the same manner, conjugate addition of the methylide of dimethyloxusulfonium to Δ^{15}-17-oxo steroids provides in 90% yield the 15β, 16β-methylene derivative.[226] For similar reasons, the conjugate addition of cysteine (R = cysteinyl residue in Fig. 134) in buffered alkaline medium,[227] and the alkaline epoxidation[228] of the cyclopentenone ring of tenulin and similar sesquiterpenes take place stereospecifically on the β side as expected. Again the lithium-ammonia reduction of the locked cyclopentenones of Figs. 135[222] and 136[229] yield the anticipated product of conjugate hydride addition. In 135 a, conformational and steric factors direct the conjugate hydride addition to the 17 β-side. Under non-isomerizing conditions, kinetic conjugate addition of hydride to the Δ^{16} unsaturated 15 ketone ought to occur on the 17α side as it was found for the catalytic hydrogenation.[222] The lithium ammonia reduction of the conjugated double bond in the rigid envelope form of the unsaturated 5-membered ring of example 136[229] affords, as expected, hydride conjugate addition on the same side as the hydroxymethyl group.

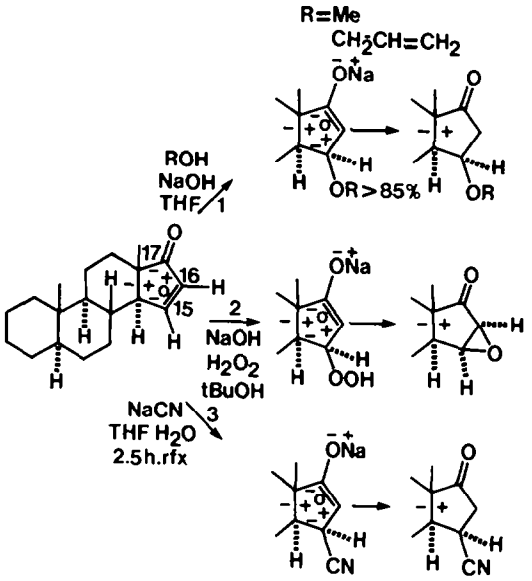


Fig. 133

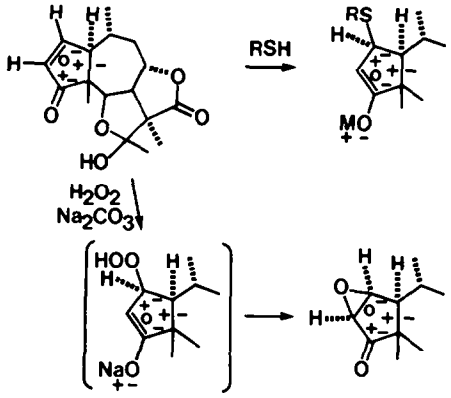


Fig. 134

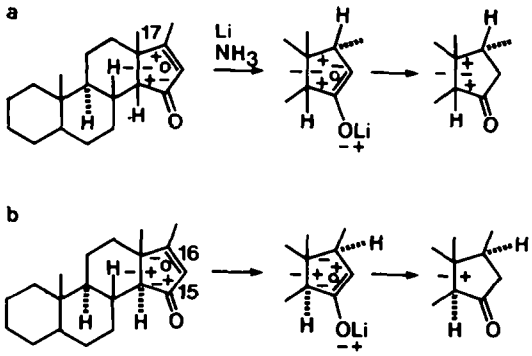


Fig. 135

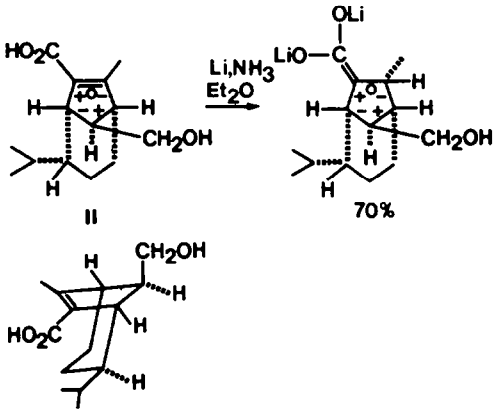


Fig. 136

Other examples of conjugate additions to a double bond conjugated with an exocyclic activating group are shown in Fig. 137[230-232]. In the first example (pathway 1 of Fig. 137) the conjugate addition of the Me anion is followed by the stereospecific alkylation of the kinetic enolate with methyl iodide.[230] The kinetic enolate can be trapped in excellent yield by various electrophiles, for instance by hydroperoxydes.[231] The 1.3-dipolar addition of phenyl azide to the Δ^{16} double bond (pathway 2, Fig. 137), which presumably, occurs stepwise through a dipolar intermediate, is also stereospecific and highly regioslective.[233]

Admittedly all the examples analyzed so far involve small or moderately bulky anions and we do not know whether the conjugate addition of very bulky anions to α,β unsaturated cyclopentenones always follows a stereochemistry that is in agreement with the torsion angle sign sequence.

Two envelope forms available: overall stereoselectivity resulting from stereospecificity to each form.

When two envelope forms are available for the cyclopentenones, as in the case of the *quasi-trans* and *quasi-cis* forms of the hydrindenone of Fig. 138, the conjugate addition is still stereospecific with respect to each envelope form but now the contribution of each form depends on the relative level of

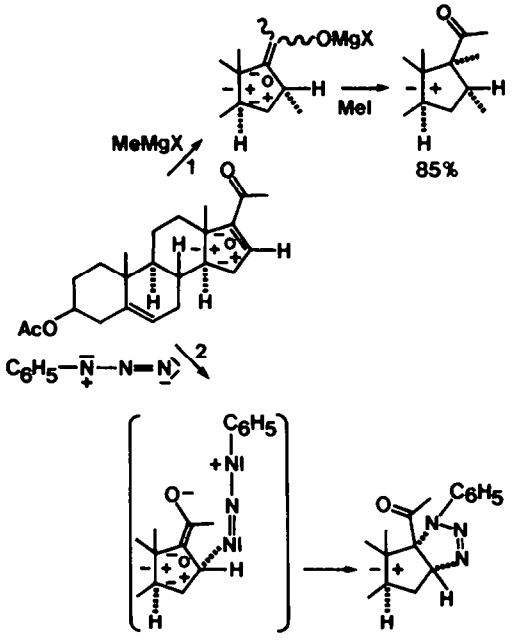


Fig. 137

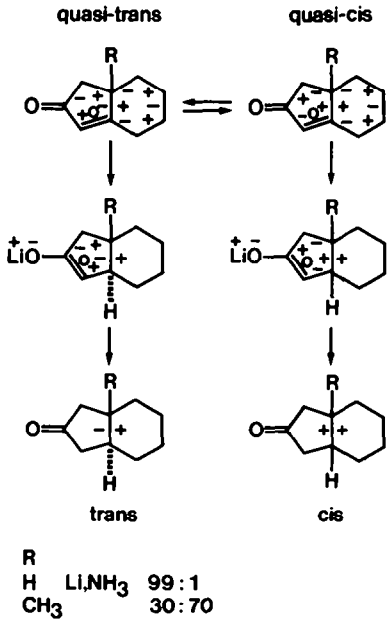


Fig. 138

the corresponding transition states: stereoselectivity appears only if the contribution of one envelope form is greater than that of the other. Thus for the hydrindenone of Fig. 138 the steric outcome of the kinetic conjugate addition depends on the size of the reagent and on the substitution of the rings, especially at angular positions. With respect to reagent size it can be said that the bulkier the reagent, the more *cis* product is obtained whether R is a hydrogen or an alkyl. With respect to substitution, there are already significant differences between the hydrindenone (R = H, Fig. 138) and its angularly methylated homologue (R = Me, Fig. 138) even in the conjugate addition of hydride ion from very small donors. For instance it has been reported that the *trans* hydrindanone (R = H, Fig. 138) is the almost exclusive product of reduction of the corresponding hydrindenone in the lithium-ammonia reduction,[234] whereas the *cis* isomer (R = Me, Fig. 138) is the major component of the mixture in the lithium ammonia reduction of the homologue.[235] Conjugate addition to hydrindenones, such as those of Fig. 138 (R = H, Me), of anions more bulky than hydride from small donors, (Me anion,[236] hydride from hydrogen complexed with transition metals[235,237]) usually gives mainly or exclusively the *cis*-hydrindanone. Such fused 5-membered rings are very sensitive to steric compression and since the *quasi-cis* form allows a better steric decompression of the intermediate substrate-reagent-complex than the *quasi-trans* form, we are led to believe that the transition state of the *quasi-cis* form is of lower energy than the other owing to comparatively reduced steric interactions.

quasi-trans and *quasi-cis* envelope forms are also available for conjugated cyclopentenones fused to seven membered rings as in Fig. 139 and, at least for lithium-ammonia reduction, the transition state corresponding to the *quasi-trans* envelope is of lower energy than the one that corresponds to the *quasi-cis* form.[238]

The knowledge of the relative stability of *quasi-trans* and *quasi-cis* forms may help to interpret a few experimental results as illustrated in the example of Fig. 140.[239] Starting from the low energy half-chair of the unsaturated cyclohexene ring, lithium-ammonia reduction may yield two primary *quasi-trans* and *quasi-cis* enolates and in the latter case, the 6-membered ring has to adopt a twist or boat form. Assuming the steric interactions to be comparable for both primary enolates, one is led to conclude that the relative stability of these angularly unsubstituted *quasi-trans* and *quasi-cis* forms is the usual one, therefore, the *quasi-trans* enolate should be the main reduction product, in agreement with the experimental result.[239] Kinetic protonation of the *quasi-trans* form ought to yield a *trans* junction of the rings, whereas kinetic protonation of the *quasi-cis* enolate would give the *cis*-hydrindanone.

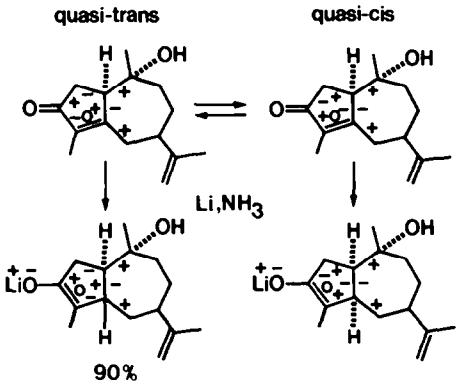


Fig. 139

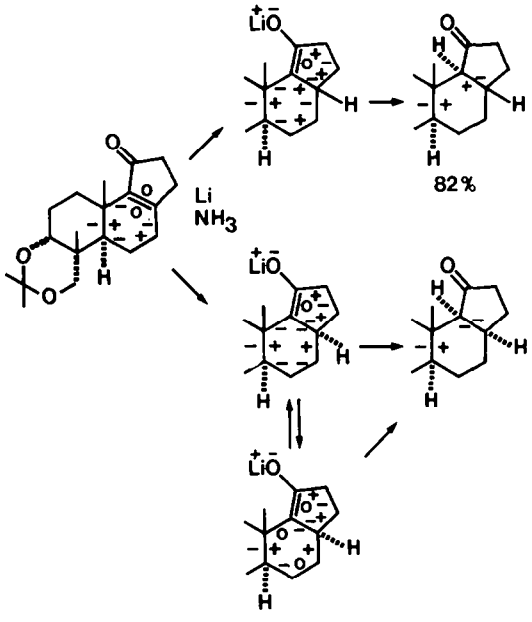
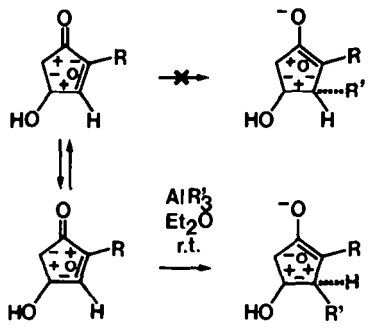


Fig. 140

Even for cyclopentenones for which two envelope forms are readily available, stereoselectivity is often observed in the conjugate addition of anions, due to attractive or repulsive effects. The development of synthetic method in the prostaglandins series has allowed a notable progress in the stereochemistry of 1.4-additions to substituted cyclopentenones[240] and there are many significant examples of attractive or repulsive effects, the last ones being often of steric or polar origin.

An example of the directive effect of an hydroxyl is shown in Fig. 141, featuring the 1.4-addition of a trialkylaluminum to a substituted cyclopentenolone,[241] the conjugate delivery of the alkyl group occurs almost exclusively on the side of the OH and, moreover, there is no reaction if the OH group is protected by pyranylation.

Polar substituents such as ethers, esters, cyano, acetate and silyloxy groups do have a strong, often determining influence on the stereoselectivity of 1.4-additions to cyclopentenones. An example showing the influence of the anomeric effect of an axial OMe on the steric course of conjugate addition of various anions to cyclic arylazoenes in carbohydrate series is given in Fig. 142.[242] For all the anions listed in Fig. 142 (D = deuterium, it comes from the conjugate addition of sodium borodeuteride) the addition occurs on the side opposite to the anomeric OMe.



R = $(CH_2)_6CO_2CH_3$
R' = $-C{\equiv}C(CH_2)_6H$

Fig. 141

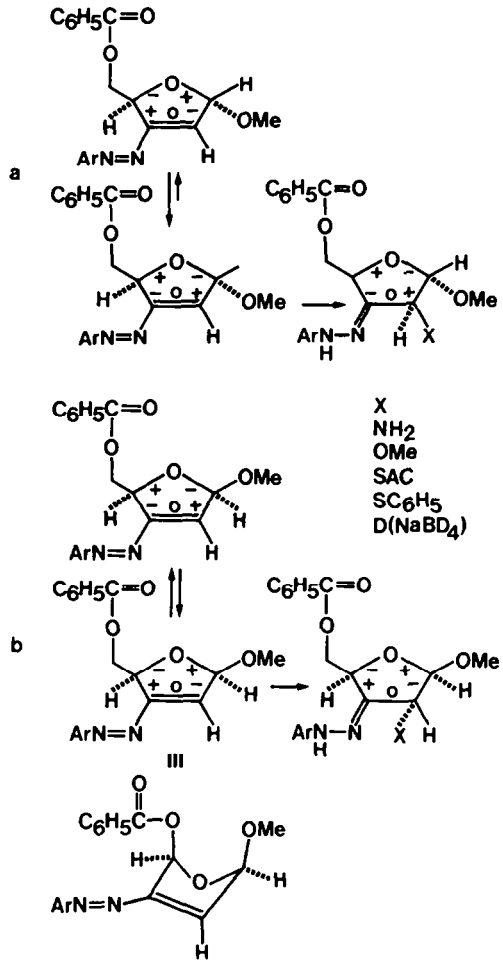


Fig. 142

The kinetic addition of malonate anion to the acetoxy cyclopentenone of Fig. 143a[243] places the malonate anti to the acetoxy group: here the conjunction of steric and polar factors controls the kinetic addition: in the preferred reactive form, there are no steric interactions between adjacent Me and acetoxy groups. Furthermore, the latter group has the axial orientation that is required to influence the addition in the *anti* direction. The thermodynamic product of *cis*-addition (Fig. 143b) can also be obtained under different experimental conditions and it should be noted that the reactive conformations are different for *cis* and *trans* additions.

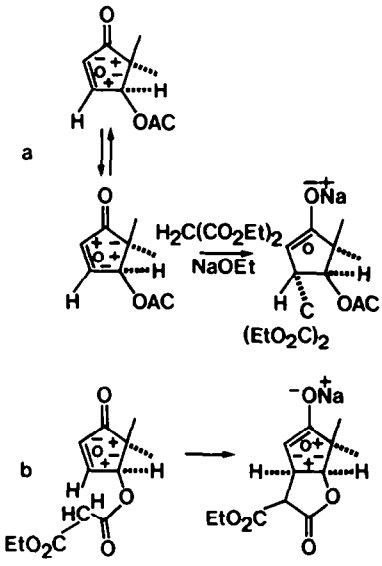


Fig. 143

Cycloheptenones. Let us first recall that anion conjugate addition to a cycloheptenone in one of its preferred forms (described in Fig. 16) yields an enolate, itself in one of the preferred forms of cycloheptene (described in Fig. 15) and, therefore, the path of lowest energy is likely to be one that involves the least amount of conformational distortion from the low energy form of cycloheptenone to the corresponding low energy form of cycloheptene.

Moreover, for cycloheptenones and cycloheptenes as well, twist and chair forms are of comparable energy whereas boats are of much higher energy than either twist or boat and thence may often be neglected in the analysis.

In Fig. 144,[244] owing to rigidly *trans*-fused A,B rings, the twist, chair and boat forms are the only three preferred forms of the cycloheptenone to be taken into consideration—the twist and the chair are both able to give rise to the β-epoxide which is nearly four times more abundant than its α isomer. The twist form of ring A cycloheptenone may give rise to a chair form of cycloheptene enolate. The latter is identical with the enolate that results from the conjugate addition of hydroperoxide anion to

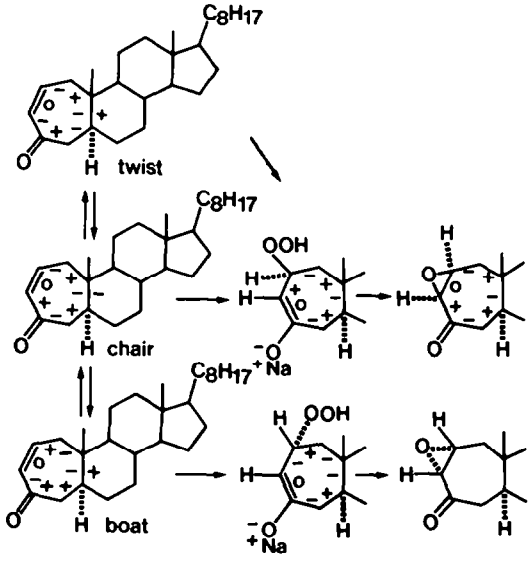


Fig. 144

the chair form of the cycloheptenone. Finally the boat form of cycloheptenone may give rise to a primary enolate in the twist form. The main formation of the β-epoxide, presumably through the chair form of cycloheptenone and the chair form of the primary enolate, is the more striking because, at least on models, the β side of the chair is more sterically hindered than the α side.

Again, three low energy conformations are available for the cycloheptenone ring in the example of alkaline epoxydation of Fig. 145.[200a] Twist, chair and boat forms all lead to the α-epoxide and we should, therefore, expect a highly stereoselective formation of the α hydroperoxide and, consequently, that of the α epoxide, in agreement with the experimental result.

In the general case of a conformationally mobile, substituted cycloheptenone, we have to consider six possible initial reactive forms or only four if we neglect boat forms; since to each of these reactive forms corresponds a transition state, we have to estimate the relative energy levels of all these transition states. Fortunately, a consideration of steric and polar factors usually allows one to discard a few pathways of high energy and to predict in a qualitative manner the steric outcome of conjugate addition. For instance, as shown in Fig. 146, there are six transition states corresponding to the six initial reactive forms (twist, chair and boat and their inverted conformers). It seems reasonable to admit that the forms with both Me's at 5 and 7 in the equatorial orientation are of lower energy than the similar forms with one Me or two in the axial orientation. Now if we neglect boat forms (pathways 3 and 6) and make the further assumption that the OR group at 4 preferentially adopts an axial orientation, we may discard pathways 1 and 5 and we are left with the low energy pathways 2 and 4 that fulfil all foregoing requirements. Since both pathways 2 and 4 yield the same product of conjugate addition the orientation of which is anti to the axial OR group at 4 and to the Me's at 5 and 7, we may conclude that the conjugate addition of the methyl anion should be fairly stereoselective as it seems to be.[245]

Conjugate addition to α,β-unsaturated cyclohexenones.[246] The conjugate addition of anions to α,β-unsaturated cyclohexenones has already been alluded to in the introduction and its steric course is, in general, readily interpreted with the torsion angle notation and our usual hypotheses. Broadly speaking, when only one low energy conformation is available, the conjugate addition not only of small but even of moderately bulky anions is stereospecific or, at least, highly stereoselective. If two low energy conformations are available the conjugate addition is more or less stereoselective and the outcome of the reaction depends on the size of the reagent and also of repulsive or attractive effects. Repulsive effects are mainly of steric or polar origin, whereas attractive effects are often connected with the presence of groups like OH that may orientate the addition of the reagent to one side of the enone.

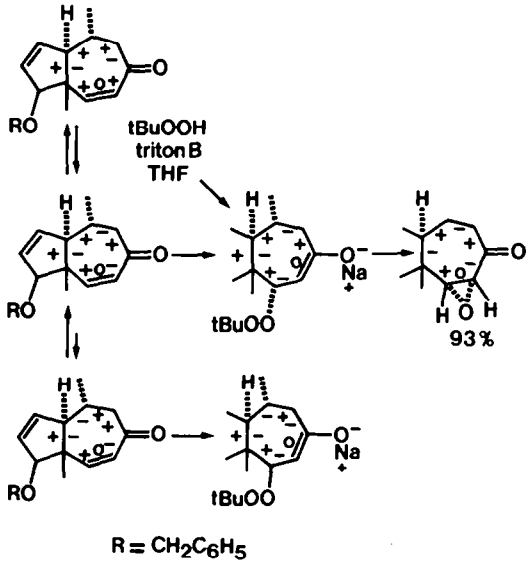


Fig. 145

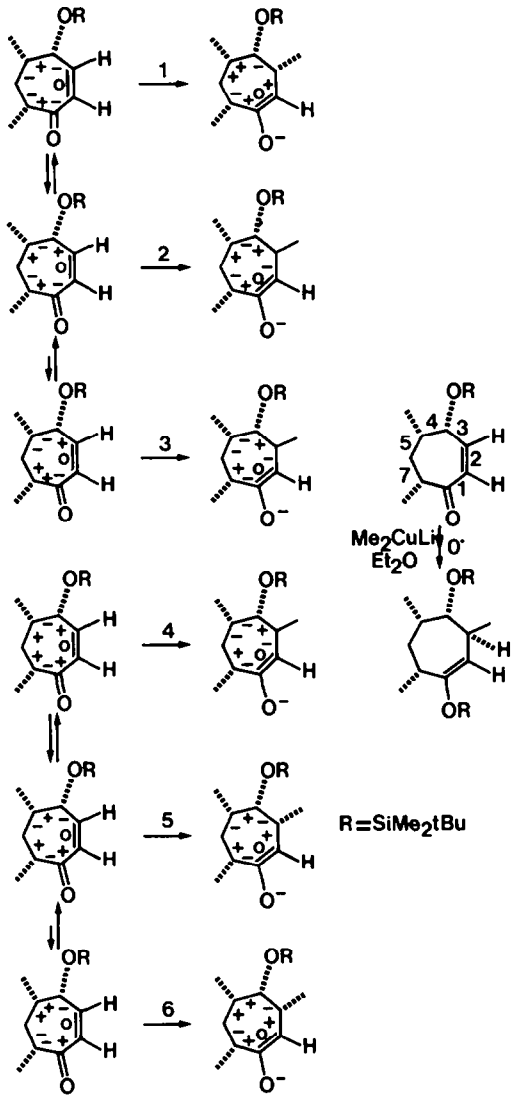


Fig 146

As it was emphasized earlier, we intend to give a unified view of this question taking into account the size of the reagent which is especially important when dealing with conformationally mobile derivatives of cyclohexenone.

(a) *One low energy conformation available.* Whenever only one low energy conformer of an α,β-unsaturated cyclohexenone, either the half-chair or the equienergetic 1.2-diplanar form, is available, the steric course of the kinetic conjugate addition of small or moderately bulky anions is easily interpreted or predicted. For instance, in the 1-oxo-Δ^2-5α-steroid of Fig. 147,[247] ring A can adopt either the low energy half-chair or the equienergetic 1.2-diplanar form. Although there are other preferred forms of cyclohexenones, we neglect them since they are of higher energy than the 1.2-diplanar form or the half-chair and we consider only the 1.2-diplanar form (the results are identical if we use the half-chair). As shown in pathway 1 of Fig. 147, conjugate addition of an anion R occurs with the least distortion of the initial reactive conformation. We start from a low energy 1.2-diplanar form to end up with a low energy 1.2-diplanar form. In pathway 2 starting from the same initial reactive 1.2-diplanar form as before we end up with a 1.3-diplanar form of higher energy than the corresponding 1.2-diplanar one and with a certain distortion of the initial conformation of the ring.

Moreover, since in 1.3-diplanar forms steric interactions are of the 1.4-type, we may expect a certain amount of steric hindrance to the conjugate addition to the 3β side (1.4-type steric interaction

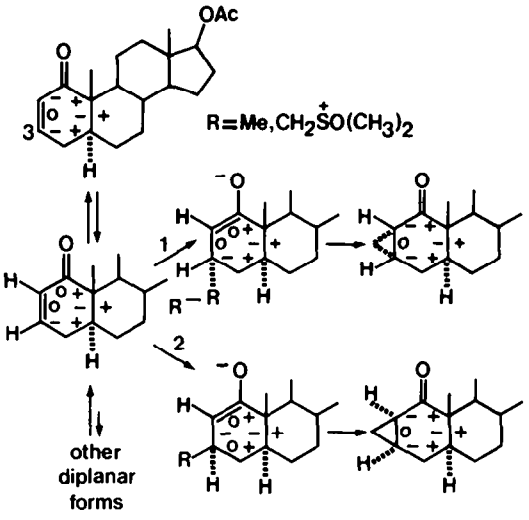


Fig 147

with the angular Me). Having admitted that most of the constraints of the transition state are already present in the initial reactive form and in the corresponding primary final one, provided the anion is small or moderately bulky we have to conclude in agreement with the experimental results,[247] that conjugate addition either of the Me anion from a Grignard reagent or of dimethyloxosulfonium methylide to the 1-oxo-Δ^2 unsaturated system of a 5α-steroid will take place mainly on the α side giving, respectively, the 3α-Me or the 2α, 3α-methylene. The same steric course is also expected for the conjugate addition of small anions like those of cyanide or hydroperoxide.

The above interpretation is similar to that given earlier for the conjugate addition of the Me anion to 3-oxo-Δ^1 steroids of the 5 α-series (Fig. 29): again there is only one low energy 1.2-diplanar form that may give rise to two primary final enolates and the path of least distortion involving 1.2-diplanar forms appears to correspond to the transition state of lower energy. In this series also we can generalize this result: conjugate addition of Me[6d] vinyl[248] anions, alkaline epoxidation[249] methylenation[247] all take place initially on the 1α side of the steroid. So far we had only examples of cyclohexenones which were part of *trans*-fused polycyclic compounds, but the reasoning applies to *cis*-fused cyclohexenones as well. In Fig. 148 we analyze the conjugate addition of anion R- to the 3-oxo-Δ^1 unsaturated system of a 5 β-steroid. The rigid junction of *trans*-fused B, C rings imparts a definite sequence of torsion angle signs to ring B and consequently to *cis*-fused ring A. There is only one low energy 1.2-diplanar form of ring A and, therefore, according to our reasoning of the two pathways available for the conjugate addition, the first should be of lower energy than the other: there

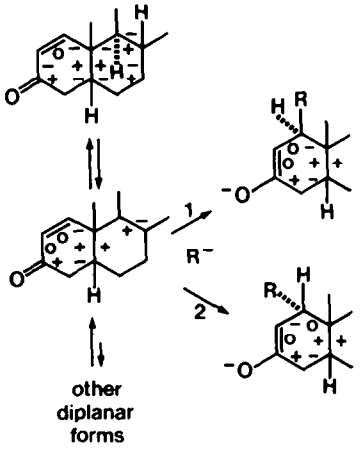


Fig 148

is less conformational distortion of the initial reactive form during the reaction from the initial reactive 1.2-diplanar form to the primary final 1.2-diplanar form of the enolate. Moreover, 1 α-addition on the other 1.3-diplanar form is probably disfavored by the folding of the *cis*-fused A, B rings. Again for compounds having the features of the 3-oxo-Δ^1-unsaturated steroids of the 5 β-series (A, B rings *cis*-fused), we may expect the conjugate addition of anions to the end of the unsaturated system to occur on the side of the proximate angular substituent, be it hydrogen or Me.[169]

In a synthesis of 1-α-methylcortisone, use has been made of the catalytic hydrogenation of a precursor, the 3-oxo-Δ^1-steroid of the 5β-series shown in Fig. 149;[169] the addition of hydrogen occurs, as expected, on the β side since steric and conformational factors control the addition in the same β direction. We do not know whether this catalytic hydrogenation takes place through direct hydrogen addition to the double bond or through initial 1.4-conjugate addition of hydride ion to the unsaturated ketone followed by protonation of the enol (or enolate). In any event, and whatever the mechanism, the initial reactive 1.2-diplanar form favours 1 β-addition of hydrogen. In a few cases, steric, polar or proximity effects may contribute to lower the energy difference between the transition states that correspond to the two primary kinetic enolates arising from the low energy 1.2-diplanar form. It may then happen, that the steric outcome of the conjugate addition depends not only on the size of the reagent, but also on the presence or absence of some functional groups in the molecule that undergoes the addition. Furthermore, in the case of sterically congested cyclohexenones, conjugate addition may stereoselectively involve either the 1.3-diplanar form of the primary enolate or even other preferred forms of higher energy but such cases are fairly rare.

It has been reported that the steric course of conjugate addition of various Grignard reagents, in the presence of cupric acetate, in tetra-hydrofuran to 1,1-dimethyl-*trans*-3 octal-2-one was highly dependent on the size of the reagent[250] as shown in Fig. 150a. The former octalone is comparable to the B, C rings of steroidal 4-6 dien − 3 ones of Fig. 150b and we could expect to have similar results of conjugate addition in both cases, at least for the 11-unsubstituted steroids (X = H, R = H) which is indeed the case.[251,252]

Let us first analyze the steric course of addition to the octalone of Fig. 150a: all the possible preferred forms of the bicyclic enone and all the corresponding products of conjugate addition have been drawn in Fig. 151. Only the half-chair and 1.2-diplanar forms of the octalone are able to give the conjugate addition *cis* to the nearby angular hydrogen of the adjacent carbon and for small or moderately bulky anion the pathway of lower energy corresponds to the addition of the R group anti to the angular hydrogen of the adjacent carbon; by analogy, this means that 7 α conjugate addition should be predominant for dienones similar to that of Fig. 150b, which is in agreement with the experimental kinetic results for small or moderately bulky anions (R = Me,[251] $CH_2S(O)Me$[252]).

To account for the near absence of stereoselectivity in the conjugate addition of the isopropyl anion to the octalone of Fig. 150a and the reversal of selectivity in the conjugate addition of phenyl anion as compared to Me we have to look again at the analysis of Fig. 151. There is no obvious steric reason why the conjugate addition of bulky anions should occur *cis* to the angular hydrogen of the carbon adjacent to the unsaturation, and it is even more true for the dienone of Fig. 150b since the α side appears sterically less hindered than the β side. A tentative explanation for the change in stereoselectivity of conjugate addition with bulky anions may lie in the different abilities of the primary 1.2-and 1.3-diplanar enolates to undergo deformations that allow either steric decompression or, at least, no further steric compression of the congested part of the molecule. From this point of view, anion conjugate addition involving the low energy pathway to the primary 1.2-diplanar

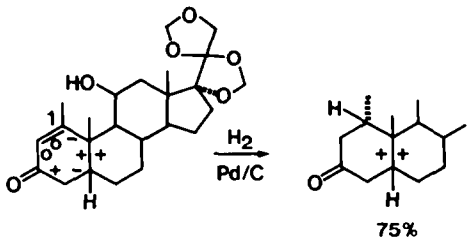


Fig. 149

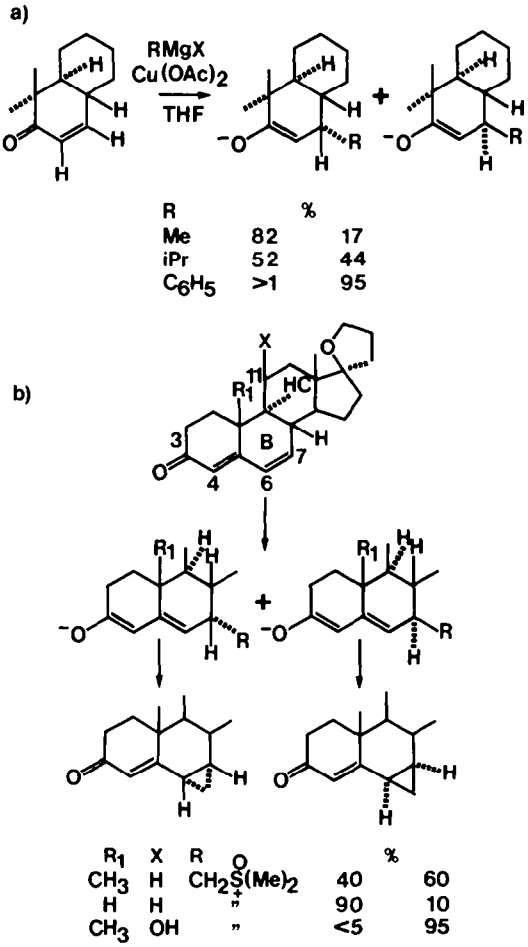


Fig 150

enolate presumably tends to increase non-bonded steric interactions which rigidifies still more the congested part of the molecule through a kind of reflex effect.[253,254] On the other hand, anion conjugate addition through the primary 1.3-diplanar enolate, thanks to the flexibility of such forms, does not increase non-bonded interactions on both sides of the molecule and apparently keeps the steric congestion within reasonable limits. More precisely looking at Fig. 151, it can be seen that there is no problem regarding the perpendicular approach of the anion, even a bulky one, to the end of the conjugated enone for half-chair and 1.2-diplanar forms. Between these last two forms, the one of lower energy appears to be the more favorable. In the corresponding primary 1.3-diplanar enolate, there is probably a steric interaction between the *quasi*-axial R group and the axial Me and such an interaction would be strong in the ideal 1.3-diplanar form but again a slight deformation of this flexible 1.3-diplanar form is able to reduce or minimize steric interactions of the 1.4 type.

Returning to Fig. 150b it should be noted that in the normal series (R_1 = Me, X = H) conjugate addition of Me Grignard provides mainly the 7α derivative.[251] In the 19 nor series (R_1 = H, X = H) conjugate addition of dimethyloxosulfonium methylide again yields mainly the 6α, 7α-methylene derivative, whereas in the normal series (R_1 = Me, X = H) there is a reversal of stereoselectivity and the 6β, 7β methylene derivative happens to be slightly more abundant than its isomer. Now, when a 11β OH is present in the steroidal 4.6-dien-3-one (R_1 = Me, X = OH) it controls the steric course of conjugate addition of Me[251] and methylide anions.[252] Besides, polar groups at position 17 may influence the steric course of conjugate addition to the 4.6-dien-3-one and thus modify the relative ratio of 7α- and 7β-isomers.

It is interesting to note that 1.1,4-trimethyl-*trans*-3-octal-2-one of Fig. 152[250] is reduced by lithium-ammonia, as expected, through a pre-1.2-diplanar transition state. Moreover catalytic

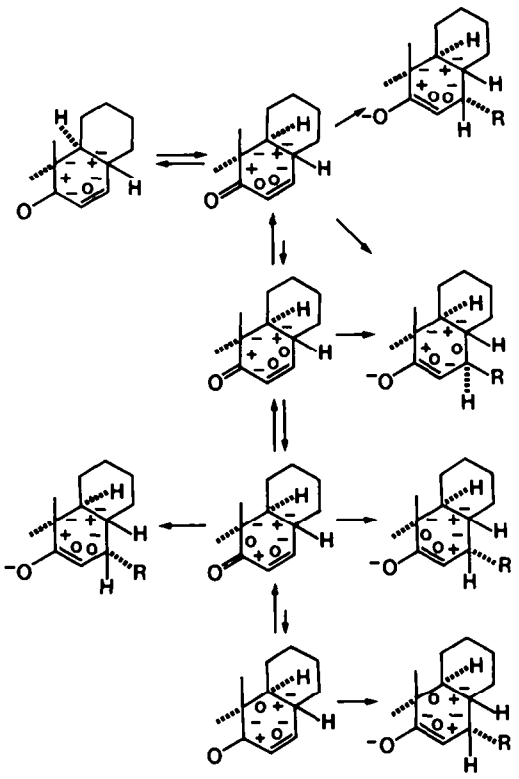


Fig. 151

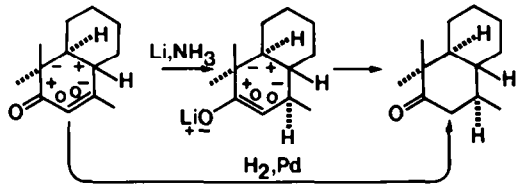


Fig. 152

hydrogenation also affords mainly the same compound of reduction as the one from lithium-ammonia, a result that could be taken as implying that this side of the molecule is the least hindered.

(b) *Two low energy forms are available.* When two low energy forms are available for α,β-unsaturated cyclohexenones the steric outcome of conjugate addition is very dependent on the size of the reagent and on the steric, polar and proximity effects. A review of the whole field is beyond the scope of this report and we prefer to show, with the help of a few significant examples, how the implementation of the dynamic torsion angle notation allows an interpretation or a prediction of the experimental results.

The first examples we analyze deal with the 1.4-addition of various anions from organometallic compounds to 4-substituted cyclohexenones (Fig. 153) and 1.4-addition of hydride ion from small donors to 3.4-disubstituted cyclohexenones (Fig. 154). It has been reported that the conjugate addition of anions such as methyl, ethyl, isopropyl, phenyl to 4-substituted cyclohexenones of Fig. 153 yields mainly the *trans*-isomer.[255-257] Already when the substituent and the added anions are Me's (R_1 = R = Me) the *trans* to *cis* ratio of isomers is 78 : 28 and the stereoselectivity increases with the size of both the substituent R_1 and the anion R.[256] Similarly methylenation of 4-alkyl-substituted cyclohexenones with dimethyloxosulfonium methylide yields mainly the *trans* derivative (R_1 = CH_2 – CO_2CH_3 ratio of *trans-cis*-methylene 85 : 15,[258] R_1 = Bu: only the *trans*-methylene is

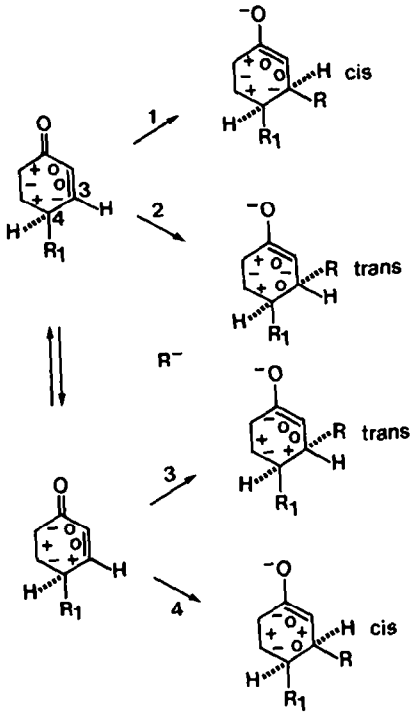
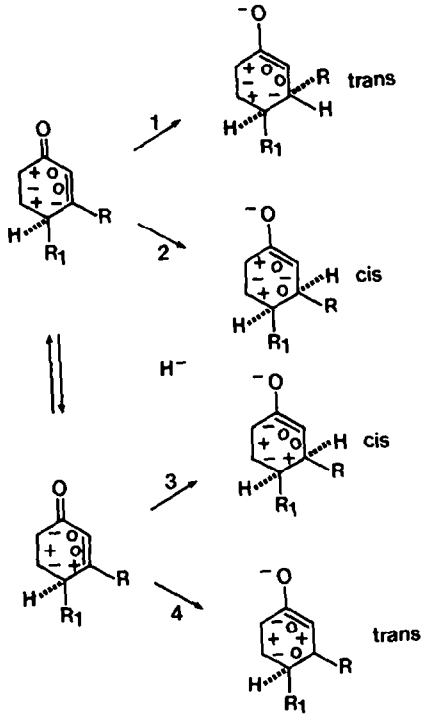


Fig. 153



R_1	R	trans:cis $NaNH_3$	Li,NH_3
Me	Me	99:1	84:16
Me	Et	92:8	
Et	Me		
Et	Et	77:23	70:30

Fig. 154

formed[259]). If we neglect the minor contributions of pathways 2 and 4 in Fig. 153, which seems reasonable, we have to admit that the pre-1.2-diplanar transition state of pathway 3 is of lower energy than the pre-1.2-diplanar transition state of pathway 1. Apparently gauche interactions between R_1 and the incoming anion R destabilize pathway 1 with respect to pathway 3.

For the cases of methylenation mentioned above, the same reasoning applies except for the addition to the 4-t-butylcyclohexenone. In this last case only pathways 1 and 2 are available if the bulky group is to remain equatorial and since pathway 1 is excluded for steric reasons (steric interaction of the 1.3 type between one Me of the t-Bu group and the incoming anion) the conjugate addition has to take place through pathway 2. If gauche interactions are, as we believe, responsible for the foregoing results then with small anions (hydride or deuteride from metal-ammonia reduction, or cyanide), that are less sensitive to such interactions, we should observe a reversal of the stereoselectivity that has been observed so far. Unfortunately there are no such clear-cut examples in the literature, we may however find an argument in favor of our proposal in the results of metal ammonia reduction of 3.4-dialkyl-cyclohexen-2-ones-1 which has been recently submitted to a detailed investigation:[260] the *trans*-isomer is largely dominant as shown in Fig. 154. Assuming again minor contributions from pathways 2 and 4 we are left with the transition state of the pre-1.2-diplanar pathway 1 of lower energy than that of the corresponding pathway 3. Moreover, whereas gauche interactions remain moderate between Me and Et groups, they are strong enough between two Et groups (R_1 = R = Et) to slightly destabilize pathway 1 and thus increase the percentage of *cis* derivative. We may invoke also the allylic strain between bulky R and R_1 groups, favoring an axial orientation of the R_1 substituent and thus increasing the *cis*-derivative. Indeed, if this is true when the substituents at 3 and 4 are bulky, then one would expect the main formation of the *cis* isomer by sodium or lithium in ammonia. In fact, it has been reported in the literature that the presence of one bulky group such as a phenyl at position 3 in Fig. 154 was sufficient to force the substituent at 4, be it Me or phenyl, to adopt the axial orientation and thus favor pathway 3: indeed, metal-ammonia reduction affords 94% of the *cis* disubstituted cyclohexanone when R is a phenyl and R_1 a Me and 98% of the *cis*-derivative when both groups are phenyls.[182] A similar interpretation may be given for the reduction of the cyclohexenone substituted at 3 by a carboxyl ($R = CO_2H$) and at 4 by a phenyl (R_1 = phenyl), affording only the corresponding *cis*-disubstituted cyclohexanone.[261]

Catalytic hydrogenation of 3.4-disubstituted cyclohexenones of Fig. 154, with a Pd-C catalyst, in various polar (dimethylformamide aqueous ethanol) or non-polar (carbon tetrachloride) solvents has been studied in the literature.[260] The steric outcome of such catalytic hydrogenations depends on the solvent and on the relative size of the substituents of the cyclohexenone. In carbon tetrachloride catalytic hydrogenation affords mainly the *cis*-isomer whereas in polar solvents it affords mainly the *trans*-isomer. The interpretation of these experimental results is delicate in view of the possible involvement of several competitive mechanisms of hydrogenation, therefore, we tentatively propose the following rationale which rests on the following assumptions:

(1) in polar solvents catalytic hydrogenation presumably involves the conjugate addition of an hydride ion to the enone followed by protonation of the resulting enol.

(2) hydride ion from hydrogen complexed by transition metals has to be considered as delivered from a bulky donor.

The results of catalytic hydrogenation in polar solvents should be comparable to those of metal ammonia reduction, but, in this case, with a lesser stereoselectivity owing to the relative bulk of the donor.

In non-polar solvents if catalytic hydrogenation proceeds by direct stepwise *cis*-addition of hydrogen to the double bond, we have to turn to the two pathways of Fig. 155 involving 1.3-diplanar forms. Pathway 2 is preferred since the steric decompression at the moment of intermediate complex formation and up to the primary final product (less gauche interaction) appears better than for pathway 1.

We analyze now the conjugate addition of anions to bicyclic enones of the $\Delta^{1(9)}$-octal-2-ones type, including the steroidal 4en-3-ones. As shown in Fig. 156 these octalones are able to adopt either the *quasi-trans* or the *quasi-cis* low energy 1.2-diplanar forms, and there are only two low energy pathways: pathway 1 corresponds to the *quasi-trans*-pre-1.2-diplanar transition state whereas pathway 2 corresponds to the *quasi-cis*-pre-1.2-diplanar transition state. Here the steric outcome of the kinetic conjugate addition depends on the size of the anion. When the anion is small (hydride from

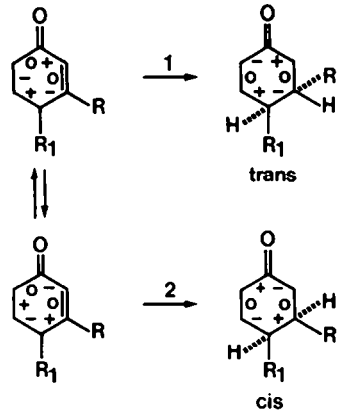


Fig. 155

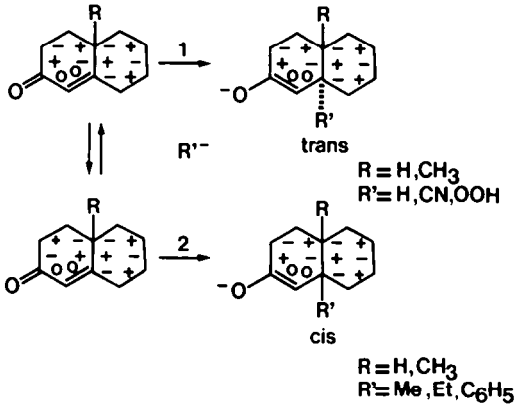


Fig. 156

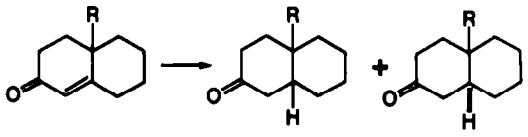
metal-ammonia, cyanide, hydroperoxide) the major *trans*-decalone of addition corresponds to the *quasi-trans* pathway 1 with eventually a minor contribution from the *quasi-cis* pathway 2.[262,263]

We have collected in Table 157 the results of the conjugate addition of hydride ions from various donors to such octalones and it is clear that the *trans : cis* ratios of the resulting decalones depend on the size of the hydride donor.[264]

When the anion to be added has the size of a Me from a Grignard reagent or a bigger size, steric compression factors control the conjugate addition to the octalone and favor the *quasi-cis* pathway 2 giving rise exclusively to the *cis* decalone.[265] The steric course of the conjugate addition of the dimethyloxosulfonium methylide to octalones is quite comparable to the conjugate addition of the Me anion and probably for the same reasons, only the *cis* decalone derivative is obtained.[259]

In the *quasi-cis* pathway the bicyclic system is folded and thus it offers a better accessibility to a bulky reagent but to explain the specificity of conjugate addition we have to look for other arguments relating to the increase or decrease of non-bonded interactions during the course of the reaction from the approach to the reactive conformation up to the primary final enolate. In the *quasi-trans* pathway the passage from the reactive *quasi-trans* form to the primary enolate increases the non-bonded interactions of the angularly introduced anion with the axial hydrogens of the adjacent ring owing to the fact that the double bond of the enolate closes the torsion angle of junction meta to it which correspond to an opening of the *trans*-fused adjacent ring.[34]

In the *quasi-cis* pathway the passage from the reactive *quasi-cis* form to the primary enolate does not increase the non-bonded interactions between the angularly introduced substituent and the axial hydrogens of the rings since the double bond of the primary enolate closes the torsion angle of junction which corresponds to a closing of the *cis*-fused adjacent ring.



	R=H	% cis	% trans
a	tBuOH, THF, Li, NH_3, -33°	<2	98
	tBuOH, HMPA, Na, THF, -33°	7	93
	tBuOH, HMPA, Na, 0°	6	94
b	TMB–Na, THF or $(MeOCH_2)_2$	30	70
c	tBu–C≡C–Li$(CuH)_3$	87	13
d	$Fe(CO)_5$, NaOH, H_2O, N_2, 20°, 36h.	37	63
e	H_2, Pd/C, EtOH	53	47
	" HCl	93	7
	H_2, PtO_2, EtOH	72	28
	R=Me		
f	Li, NH_3, THF, tBuOH -33°	<2	96
g	nPr–C≡C–CuH^-Li^+, THF, -20°, 24h	70	30
h	nBuCuH$^-Li^+$, ether, -40°, 2h	(7 : 3)	
i	H_2, Pd/C	93	7
j	H_2, 10% Pd/C, EtOH	80	20
k	H_2, 10% Pd/C, MeOH, AcOH	80	20

Table

Fig. 157

The steric decompression which is allowed by the folding of the *quasi-cis* conformer to the corresponding *cis* primary enolate may explain the remarkably high stereoselectivity of the conjugate addition of more or less bulky anions in various cases such as the one of Fig. 158 (see Fig. 6), that occurs nearly quantitatively: we briefly detail it.

Owing to the rigid *trans*-fused C, D rings, the torsion angle signs sequence of ring C is readily determined. Since *quasi-trans*-fused rings are usually more stable than *quasi-cis* ones for octalones of the B, C rings type we attribute the corresponding (*quasi-trans*) signs to ring B half-chair. Now, conjugate addition to angular position 19 probably requires *quasi-cis*-fused A, B rings which allows one to complete the signs sequence of ring A and account for the steric course of this conjugate

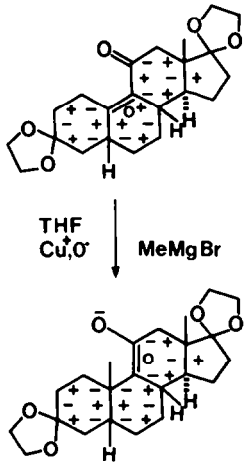


Fig. 158

addition, the realization of which requires the compatibility of deformation of the three A, B and C rings during the reaction.

Substitution on the rings of the octalone or structural modifications may alter the relative energy differences between the *quasi-trans* and the *quasi-cis* pathways and, by way of consequence, change the usual course of the conjugate addition. Such changes are particularly noticeable when small reagents like hydride from metal ammonia is used in the conjugate addition. For instance, as shown in Fig. 159a[266] metal-ammonia reduction of 4-alkyl-10 methyl $\Delta^{1(9)}$-octalone affords, besides the major *trans*-decalone, some *cis*-decalone, the amount of which increases with the size of the 4-alkyl. It should be noted that the production of the *cis* decalone occurs only when the 4-alkyl is *trans* to the nearby angular Me; indeed, when the 4-alkyl is *cis* to the angular Me only the *trans* decalone results from the metal-ammonia reduction. In 159b, metal-ammonia reduction of the 1-methyl-4-isopropyl $\Delta^{1(9)}$-octal-2-one, affords exclusively the corresponding *cis*-decalone.[266]

The foregoing experimental results are readily interpreted with the help of the *quasi-trans* and *quasi-cis* pathways of Fig. 156. It is clear that a 4-alkyl *cis* to the angular substituent is equatorial on the *quasi-trans* 1.2-diplanar form of the unsaturated ring and therefore its presence would rather stabilize this *quasi-trans* form and consequently the *quasi-trans* pathway. On the other hand, a 4-alkyl *trans* to the angular substituent (as in Fig. 159a and b) is axial on the *quasi-trans* 1.2-diplanar form but equatorial on the corresponding *quasi-cis* form. Therefore, the *quasi-trans* pathway is destabilized with respect to the *quasi-cis* and the degree of destabilization increases with the size of the 4-alkyl (or aryl). That the effect of a substituent is more spectacular in the octalone series, without angular Me (Fig. 159b), than in the corresponding 10-Me series of Fig. 159a is not unexpected.

Barring any particular effect of the 1-Me of the octalone of Fig. 159b, on the steric course of the reduction the explanation could be the following. It has been shown that the energy difference between *quasi-trans* and *quasi-cis* form of steroidal 4-en-3-ones was much higher in the normal series than in the 19-nor series;[36] by analogy, we believe that there is the same energy difference between the corresponding 10 methyl $\Delta^{1(9)}$-octal-2-one and the $\Delta^{1(9)}$-octal-2-one. Let us note, in passing, that

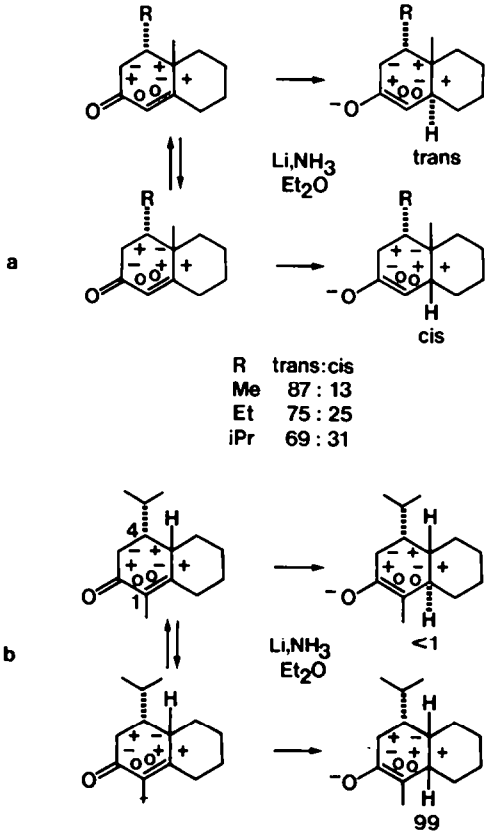


Fig. 159

catalytic hydrogenation of the 1-methyl-4-isopropyl $\Delta^{1(9)}$-octal-2-one of Fig. 159b provides also the *cis*-decalone as the only product of hydrogenation.[266a] Again the interpretation of this result points to the destabilization of the *quasi-trans* form and the ready availability of the *quasi-cis* pathway of low energy.

Similarly, (Fig. 160), the presence of a bulky substituent at position 4, *cis* to the angular substituent of a 10-methyl-$\Delta^{1(9)}$-octal-2-one has a stabilizing effect on the *quasi-trans* reactive form and on the corresponding *quasi-trans* pathway; lithium ammonia reduction and catalytic hydrogenation afford the same *trans*-decalone.[267] The presence of substituents on the saturated ring of the octalone may also influence the steric course of reduction by metal-ammonia if they have the proper orientation. For instance, as illustrated in Fig. 161,[268] an 8-Me substituent of a $\Delta^{1(9)}$-10-methyl-octal-2-one does not modify the steric outcome of lithium-ammonia reduction with respect to the unsubstituted octalone if it is *trans* to the angular Me (Fig. 161a), only the corresponding *trans* decalone is obtained. However, if the 8-OMe is *cis* to the angular Me (Fig. 161b), then the same conditions of reduction afford, besides the major *trans*-decalone, a small amount of the corresponding *cis*-decalone. In this last case, catalytic hydrogenation with Pd-C in 95% ethanol yields 65% of the *trans*-decalone and 35% of the *cis*-isomer: the selectivity is similar to that of the metal ammonia reduction but weaker since the hydride donor is more bulky. A tentative interpretation of these results is given in Fig. 161c, but in order to grasp the arguments, the reader has first to be reminded about the rules concerning the transmission of deformations from one ring to the other in *cis*-and *trans*-decalins and in the corresponding *quasi-cis*-and *quasi-trans*-octalins.

Whilst compatible deformations are, in general, readily apparent when the various rings of a polycyclic system are in the chair or half-chair form, it is no longer the case when the polycyclic structure involves rings which cannot be in chair form and are thus forced to adopt flexible forms either twists or boats.

To analyze the steric course of conjugate addition to enones in such systems, incorporating non-chair conformations for one of the rings, one has to apply the formerly given rules of transmission of distortions.

cis-Fused rings. The deformations are similar at the junction of two rings: to a closure (or flattening) of the torsion angle of junction corresponds a closure of the adjacent torsion angle of junction and to an opening an opening.

trans-Fused rings. The deformations are opposite: to a closure of a torsion angle of junction corresponds an opening of the adjacent torsion angle of junction and vice versa.

Contribution of an isolated olefinic bond inside a ring to the distortion of an adjacent ring.

It has been stated by Bucourt that the introduction of a double bond inside a chair form of a 6-membered ring opens the torsion angle that is located *para* to it and closes the torsion angle located *meta* to it.[269] Therefore, it is clear that the introduction of an olefinic bond in a ring has a bearing on the distortion on the contiguous fused ring and, accordingly, on the increase or decrease of steric compression between groups of the molecule in the ground state and during the course of a reaction. The more so, that closing a torsion angle relieves 1.3-diaxial non-bonded interactions between axial groups by widening the distance between the involved axial groups whereas the opening of a torsional

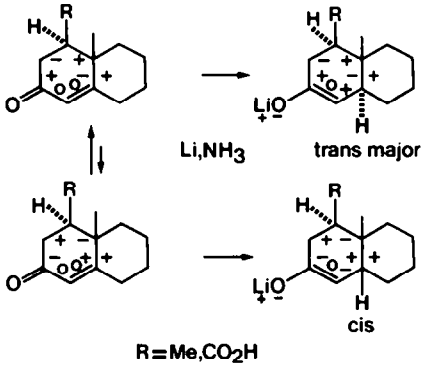


Fig. 160

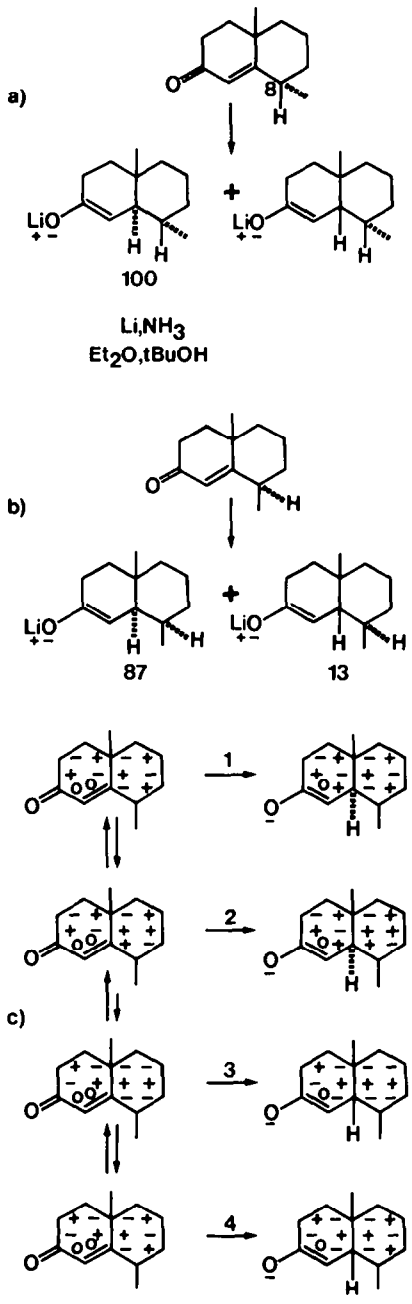


Fig. 161

angle is just exerting the reverse effect: the distance between 1.3-diaxal group decreases somewhat which increases the internal steric compression of the molecule.

Moreover to evaluate compatible distortions, especially at rings junction, one has to keep in mind the average values of the torsion angles of the twist and boat forms.[270] In this respect, boats may be distinguished from the corresponding twist forms.

Boat forms are usually acceptable at rings junction since their average torsion angle (around 54°) does not introduce distortions in the other ring but one has to be cautious in the evaluation of 1.4 steric interactions (bowsprit-flagpole), which tends to destabilize this type of conformation.

Twist forms, although usually of lower energy than the corresponding boats are not always suitable to minimize conformational distortions arising in the ground state or during the course of a reaction. The reason for this unsuitability may be traced to the presence of the small torsion angle of

the twist form whose low value (around 31°) causes either a severe closure of the contiguous torsion angle of junction (in the case of *cis*-fused rings) or a strong opening of the adjacent torsion angle of junction (in the case of *trans*-fused rings), resulting in distortions of the ring too strong to be achieved with a minimum expenditure of energy and, therefore, hardly compatible with a low energy ground state conformation. With respect to the small (around 31°) and large (around 65°) torsion angles of twist forms, we may summarize the compatibility requirements at the junction of two rings as indicated below:

Fused rings:

Trans. The torsion angle of junction is hardly compatible with the small torsion angle of a twist form but it is compatible with the large torsion angle.

Quasi-trans. The torsion angle of junction is hardly compatible with the large torsion angle of the twist form but it is compatible with the small torsion angle.

Cis and quasi-cis. The torsion angle of junction is hardly compatible with the small torsion angle but it is compatible with the large torsion angle of a twist form.

These rules appear valid not only for static conformational analysis but they can also be used for dynamic conformational analysis. Thus the conjugate addition of an anion to a 10-methyl-1(9)-octal-2-one may lead to the corresponding *trans* or *cis*-decalone enolates (Fig. 161) and compatibility of deformations at the rings junction is required for the ground state conformation of the initial reactive octalone and also for the primary enolates conformers of the corresponding *trans* and *cis* decalones. With respect to these last two forms we sum up in Figure 162 the distortions induced on the torsion angles at the junction of the rings, by the formation of the primary enolate double bond (in Fig. 162 C means closure and O means opening of the torsion angle). Taking into account the foregoing considerations it is possible to interpret most of the results of metal-ammonia reduction of octalones into *cis* decalone and in this respect Fig. 162 is very helpful.

Let us return now to the interpretation of the results shown in Fig. 161b. In the chair form of the saturated ring of the octalone, there is a 1.3-*syn*-axial interaction between the angular Me and the Me substituent at 8.

To relieve this steric interaction the molecule may adopt either one of the two flexible forms shown in Fig. 161c, one with the 8-methyl in the bisectional orientation (sequence − −) and the other with the 8-Me in the equatorial orientation. Now, according to the previously given rules, the twist form, whose large angle is at the ring junction, is mainly compatible with a *quasi-cis* form of the unsaturated ring, whilst the twist form, whose small angle is at the ring junction, appears mainly compatible with a *quasi-trans* form of the unsaturated ring. If all four forms of Fig. 161c contribute to the final result, the *trans*-octalone ought to be the major product, since pathway 1 presumably still gives the main contribution, and the small amount of *cis*-decalone reflects the involvement of the *quasi-cis* forms (pathways 3 and 4) and specially of the "*quasi-cis*-twist" form of pathway 3. When such a *quasi-cis* form is favored by a bulky substituent as seems to be the case for 6 β-or 7 α t-butyl-10-methyl-1(9)-octal-2-ones, metal ammonia reduction can be expected to afford a good amount of the *cis* decalone, as was shown to be the case.[271] The interpretation of the major formation of the *cis*-decalone is given in Fig. 163. The bulky t-Bu tends to adopt an equatorial orientation on the twist forms (pathways 1 and 2), but less favorably, a bisectional one which we exclude on steric grounds (pathway 3).

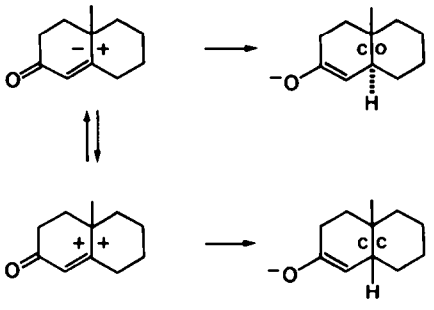


Fig. 162

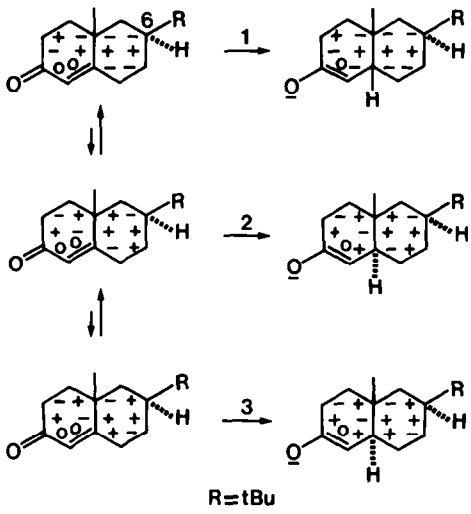


Fig 163

The large torsion angle of junction of the twist form in the saturated ring of pathway 1 is only compatible with a *quasi-cis* form of the unsaturated ring, whilst the small torsion angle of junction of the twist form in pathway 2 is compatible with a *quasi-trans* form. The twist form of pathway 3 also has a small torsion angle at the junction of the rings and, therefore, this third pathway is also of the *quasi-trans* type. There is no ready evaluation of the energy levels of the corresponding transition states. We believe two factors at least favor pathway 1 over pathway 2. The distortions induced by the twist form on the unsaturated ring seem to affect less the initial reactive form in pathway 1. Moreover, the *quasi-cis* pathway appears to better accommodate the steric compression connected with the presence of a bulky group on the saturated ring.

Not all interpretations require as much sophistication as this last example. The exclusive formation of a single epoxide corresponding to the *quasi-trans* pathway in the alkaline epoxidation of nootkatone of Fig. 164b[272] is expected using steric arguments and the shift of the *quasi-trans*, *quasi-cis* equilibrium of the reactive forms (Fig. 164c). In the *quasi-cis* form, the 4-Me is axial which destabilizes this form in the ground state with respect to the *quasi-trans* form; furthermore, the approach of the hydroperoxide anion is hindered on the *quasi-cis* reactive 1.2-diplanar form by the 1.3 *syn*-axial interaction of the incoming anion with the axial 4-Me. Therefore, the result appears reasonable, even if it is the reverse of that usually observed for the analogous unsubstituted octalones of Fig. 164a: however, because of the known reversibility of the first step in the alkaline epoxidation, the results of Fig. 164a cannot be considered as truly kinetic.

A similar interpretation (Fig. 165) may be offered for the metal-ammonia reduction of 2α-cyano, 2β-methyl-4-cholesten-3-one, yielding 97% of the 5β derivative,[273] but, here, steric and polar factors drive the reaction through the *quasi-cis* pathway. The 1.3-*syn*-axial interaction between the axial 2β-Me and the angular 19-Me in the chair form of ring A, destabilizes the *quasi-trans* form with respect to the *quasi-cis* form in which the steric interaction has disappeared and the 2α-cyano group, now axial, can wield its inductive effect.

In the example of Fig. 166a, the unsaturated ring of the bridged octalone is forced by the ethano-bridge into the *quasi-cis* form and it is no surprise that metal ammonia reduction yields mainly the *cis* compound.[274] The same argument may be used to explain the stereoselective *cis*-addition to the bridge of the Me anion to the dienone of Fig. 166b:[274] the dienone presumably selectively exists in the *quasi-cis* form. What is surprising here, is that the other isomer is formed at all: real molecules are much more flexible than the molecular models that are presently used to represent them.

Polar effects. We turn now to other aspects of conjugate additions to cyclohexenones and similar enones of 6-membered rings. It has been shown many times that polar effects could influence the steric course of conjugate addition to conformationally mobile cyclohexenones. Thus, conjugate addition to 4-trimethylsilyloxy-cyclohexenone of anions from organo-metallic compounds provides in

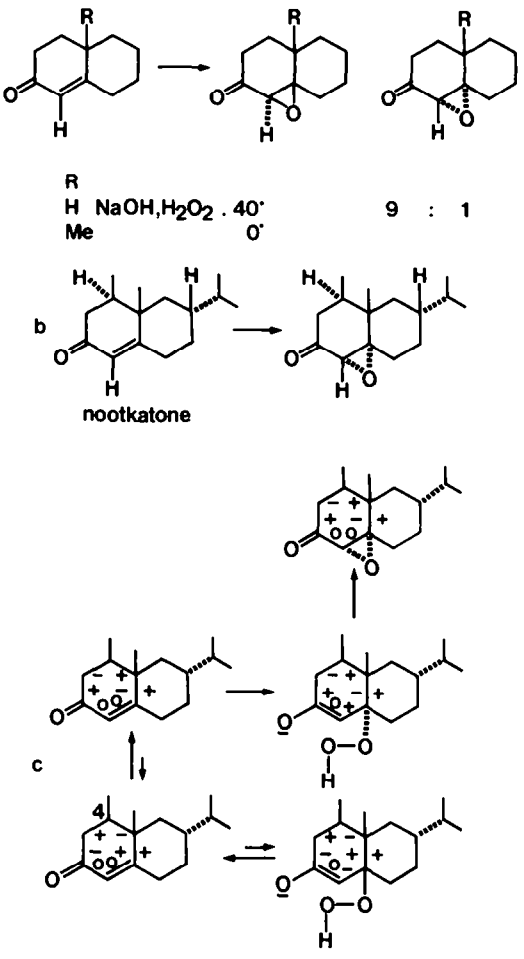


Fig. 164

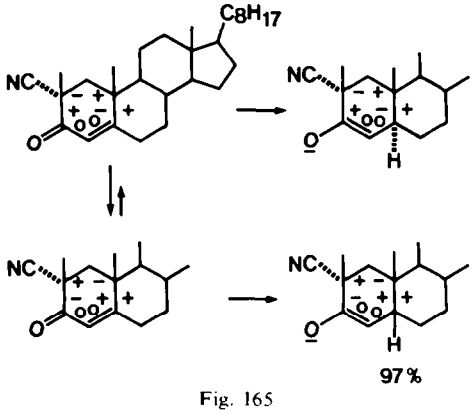


Fig. 165

excellent yield the cyclohexanone substituted *trans* to the 4-trimethylsilyloxy group as shown in Fig. 167:[275] conjugate addition apparently takes place exclusively anti to the polar group.

Other significant examples of polar effects have been observed in the carbohydrate series[276,277] and we present in Fig. 168[276] one of them. The addition of anions from organo-metallics or from substituted 1.3-dithiolan occurs *anti* to the anomeric OMe. In Fig. 168a the anomeric effect and the equatorial orientation of the 5 Me contribute jointly to the steric course of the reaction. In Fig. 168b, however, the two effects are in opposition and the anomeric effect still controls the conjugate addition.

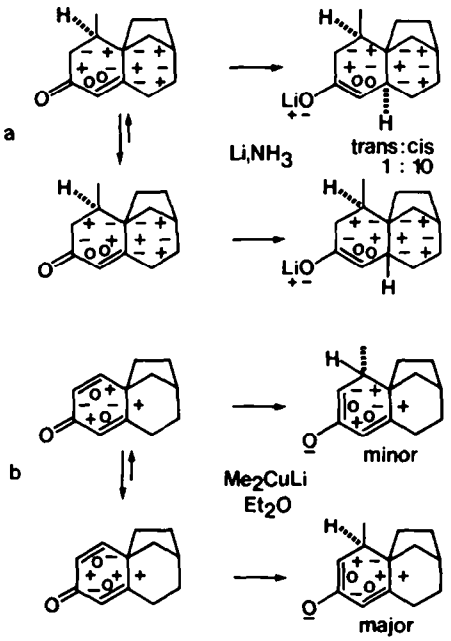


Fig. 166

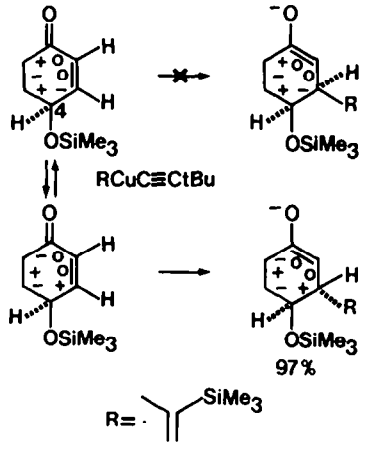


Fig. 167

1.4 *Addition to cross-conjugated dienones.* Much of what has been said about the steric course of conjugate addition to enones can be repeated for cross-conjugated dienones of 6-membered rings. Thus, the bicyclic analogues of steroidal 1.4-dien-3-ones of Fig. 169[266a] may exist as *quasi-trans*, *quasi-cis* 1.4-diplanar forms (boats) in equilibrium, the *quasi-trans* form being often the more stable. Therefore, with small and moderately bulky anions, conjugate addition occurs stereoselectively on the α side:[278] the alkaline epoxidation of the steroidal trienedione of Fig. 170[279] as the addition of the methylide of trimethyloxosulfonium[279,280] occur on the α-side.

The replacement of a double bond of a dienone by a cyclopropane would not be expected to greatly alter the geometry of the ring, but steric effects may shift the equilibrium of *quasi-trans*, *quasi-cis* forms towards either one depending on the orientation of the cyclopropane and its degree of substitution. It has been reported that lithium-ammonia reduction of the homologous dienone of Fig. 171[281] yields exclusively the *cis*-derivative: the conformational equilibrium has been shifted to the *quasi-cis*-isomer owing to the steric hindrance of the dimethylcyclopropane bridge on the β side of the

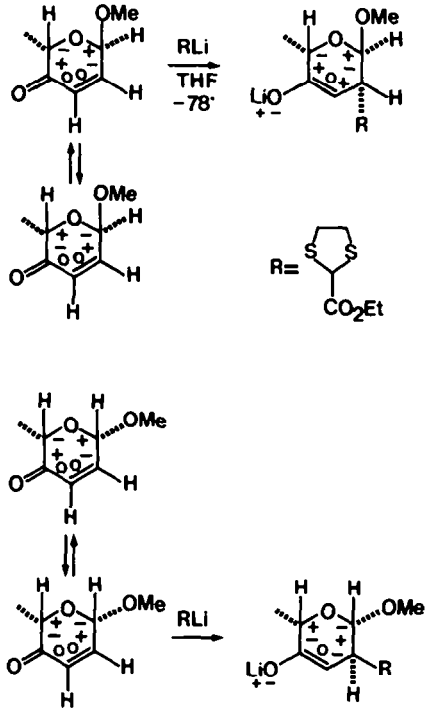


Fig. 168

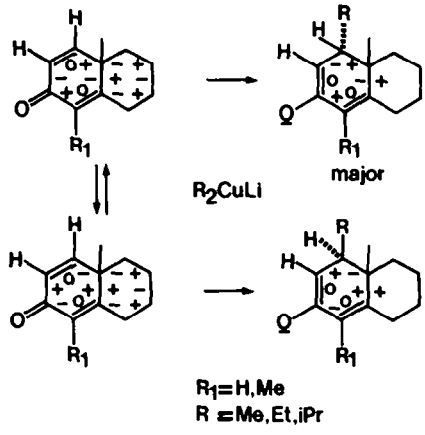


Fig. 169

A ring and the corresponding transition state is probably the one of lower energy. Even without any substitution, the β orientated 1.2-methylene bridge of Fig. 171b[282] shifts the equilibrium of conformers towards the *quasi-cis* one as evidenced by the results of lithium-ammonia reduction.

Before closing this chapter, we analyze a few examples of conjugate additions to 6-membered ring enones, the initial reactive form of which is the 1.3-diplanar one.

In the case of Fig. 172,[283] the conjugate addition of the Me anion in dioxane places the Me mostly anti to the methylene bridge as could have been expected from steric and electronic considerations: the methylene in the main reactive conformation is axial (sequence + 0 −) and conjugated with the double bond.

Another example of conjugate addition to a 1.3-diplanar unsaturated lactone is analyzed in Fig. 173.[284] Since in pathway 2 there is a 1.3-*syn*-axial interaction between the incoming anion and the

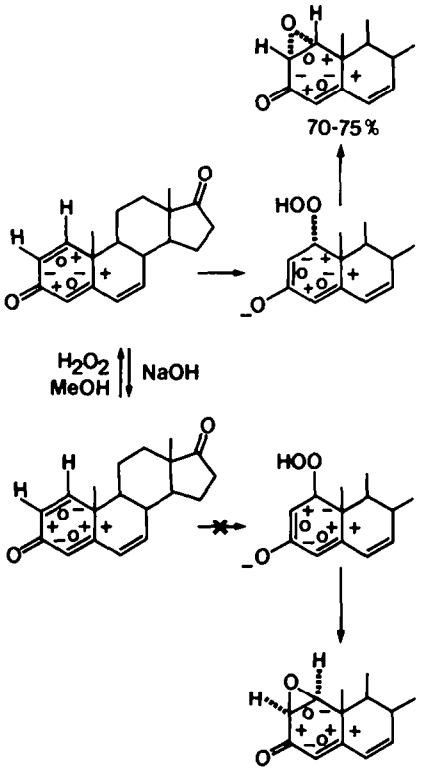


Fig 170

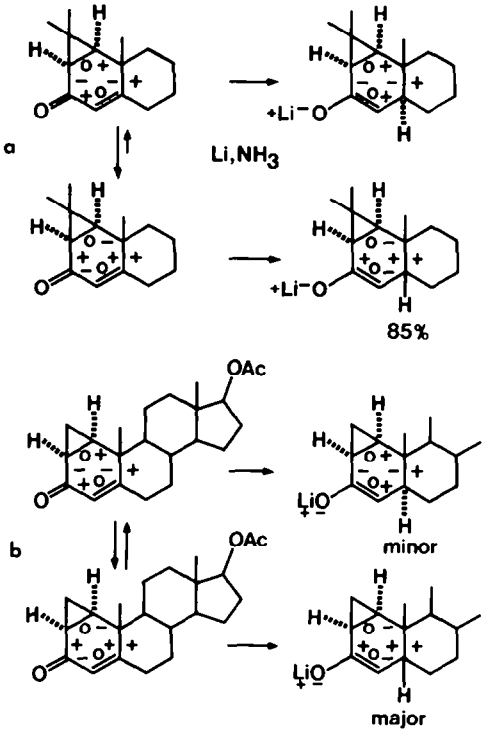


Fig 171

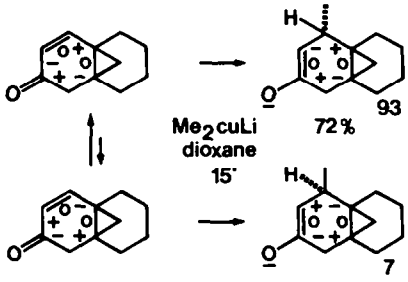


Fig. 172

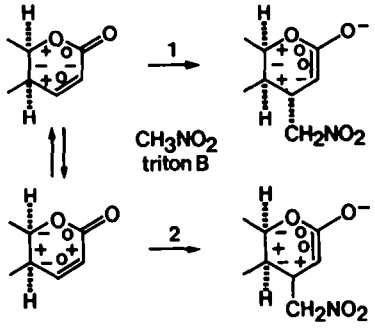


Fig 173

axial Me which may hinder the approach of the anion whereas there is no such hindrance in pathway 1, we would expect the kinetic product of conjugate addition to correspond to pathway 1: therefore, and provided it is the kinetic addition product, we would attribute the corresponding configuration to the unique product of addition isolated in 88% yield.

(3) *Allylic displacements*

In this section we envisage the steric course of a few reactions of displacements which occur with an allylic shift of the double bond as illustrated in the following examples.

At the outset, let us emphasize that we are concerned here only with concerted displacements of the S′ types (S_N2' and S_Ni'). More precisely, we assume that concertation has to do with the timing of bond breaking and bond forming and that, in the ideal case, there is a perfect synchronization between the two events. However, the prevalent view nowadays is, that for most concerted reactions, bond breaking and bond making are not occurring in a synchronous fashion but rather stepwise.[44] Still the reaction is considered as being concerted in as much as there is no interception of discrete intermediates by the solvent or by nucleophiles present in the medium. By the same token, reactions that proceed through successive addition and elimination are not considered as being concerted. In this respect, allylic displacements involving certain organo-metallic derivatives, especially organo-copper derivatives, have to be interpreted with caution since they may take place through addition-elimination[285] even if the final result corresponds to a seemingly concerted allylic displacement. Thus it is hard to believe that the reaction of the $\Delta^{9(11)}$-unsaturated 5α, 10α-steroidal epoxide of Fig. 174[286] with the bulky anion of lithium diphenylcuprate takes place by a direct displacement at 11β, owing to the *syn*-axial interaction of the incoming anion with the angular methyl. A mechanism implying an addition followed by a transfer appears more plausible.[286] For the same reason, allylic displacements with lithium aluminum hydride have also to be viewed with caution, even though the overall results are, generally, in agreement with those expected from a concerted reaction.

Allylic displacements in the odd and the even membered series are successively treated, using our usual hypotheses. In this respect, the assumed maintenance of orbital overlap during the whole course of the reaction implies that the entering and leaving groups have, both, to be in the axial orientation in the transition state.[287] As a consequence of this hypothesis, usually the leaving group has to be axial or *quasi*-axial on the initial reactive conformation and the newly formed bond, resulting from the

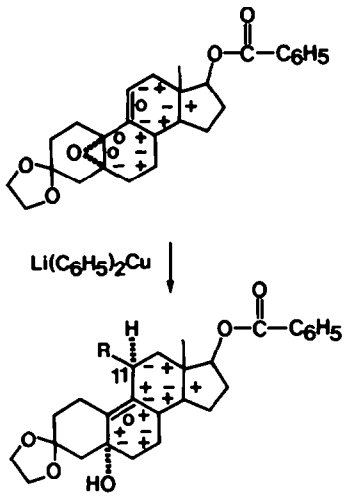


Fig. 174

addition of the entering group to the double bond that is displaced, has also to be in an axial or *quasi*-axial orientation. These simple assumptions allow to rationalize a large body of experimental results, scattered in the literature and at the same time, they show that, in quite a few cases, the mechanisms of allylic reactions are much more complex than could have been expected up to now. There are relatively few reliable results concerning S′ displacement reactions in the odd membered unsaturated series, whilst in the even membered series some of the older results have to be considered with suspicion due to the fact that configuration assignments were not well established and analytical methods were far from being satisfactory and accurate.

Allylic displacements in odd membered unsaturated rings. (a) *Cyclopentene derivatives.* There are very few significant examples of allylic displacements concerning cyclopentene derivatives. Fortunately, in general, there are only two envelope forms in equilibrium for substituted cyclopentenes and only one that has the leaving group in the proper axial orientation, therefore, it is fairly easy to interpret or predict the steric course of the reaction. Thus, as shown in Figs. 175a and b, we have analyzed the steric course of allylic displacements for *trans* (Fig. 175a) and *cis* (Fig. 175b)

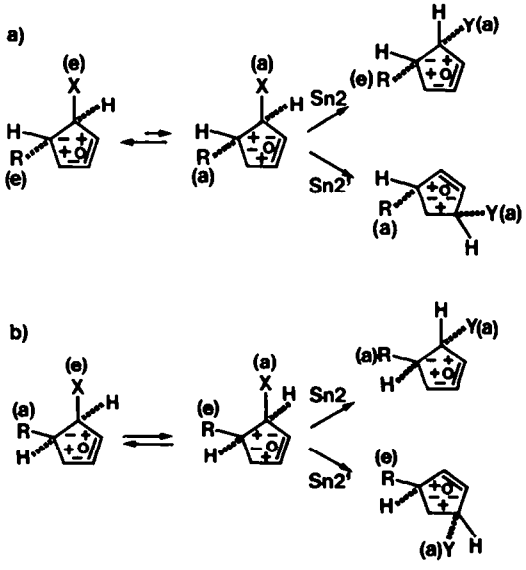


Fig. 175

disubstituted cyclopentenes where X is the leaving group, R a substituent and Y the entering nucleophilic group.[288]

For the *trans*-disubstituted cyclopentene of Fig. 175a, the initial reactive form has both substituents X and R in the axial orientation, and whereas S_N2 displacement causes a complete inversion of the torsion angles, equivalent to a conformational inversion, S_N2' displacement may take place without much conformational distortion, the direction of the entering axial group Y being *anti* to that of the leaving group X.

For the *cis*-cyclopentene of Fig. 175b, the initial reactive form has the R-substituent equatorial and the leaving group X axial. Again S_N2 displacement involves a complete inversion of the envelope, whereas S_N2' reaction can occur without much distortion of the unsaturated ring. Therefore, in this latter case, also the axial nucleophile Y ought to come *anti* to the leaving group X and we may assume that *anti* stereochemistry is a general feature of allylic displacements for such cyclopentene derivatives. Now, if the cyclopentene derivative is not able to undergo a conformational inversion of its reactive envelope form, only S_N2' displacements may occur. The following evidence may be given in support of this preference: it has been found that treatment with sodium methoxide in methanol of the 17α-halo-16 oxo-steroids of Fig. 176 afforded mainly the corresponding 15β-methoxylated ketone with loss of the 17α-halogen.[237] The interpretation of this result involves the formation of the intermediate Δ^{15}-enolate of the ketone and the subsequent allylic displacement of the axial 17α-halogen by methoxyde ion, taking place in the expected *anti* fashion. For conformationally mobile cyclopentene derivatives we expect S_N2' displacements to be competitive with S_N2 ones, but, as is always the case, the relative ratio of these types of displacements may vary with the substrate and the experimental conditions.

(b) *Cyclopentadiene monoepoxide*. The lability of this unsaturated epoxide and its easy isomerization under the experimental conditions either of hydrolysis[289] or organo-metallic anion addition[290] prevents any definite conclusion to be drawn as to the steric course of allylic displacements. Hydrolytic opening of the unsaturated epoxide apparently gives rise to the four possible diols,[289] although only two are expected if the controlling mechanisms were of the S_N2 types (Fig. 177, R = OH). The outcome of addition of anions from organo-metallics to cyclopentadiene epoxide

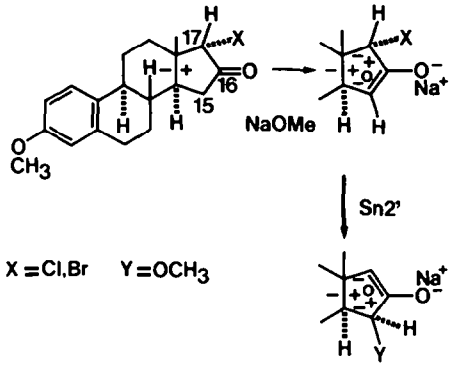


Fig. 176

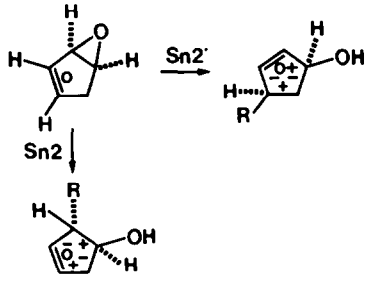


Fig. 177

depends to a large extent on the experimental conditions and the nature of the metal of the reagent. For instance, with ethyl magnesium bromide in ether a mixture of addition products is obtained: one of the products corresponds to an allylic displacement and has the expected *syn*-relationship of the ethyl with respect to the OH, arising from the opening of the epoxide (Fig. 177, S_N2' R = Et) and another one corresponds to a *cis*-1.2-opening of the epoxide: the vicinal Et and OH being *cis* to each other. When the same reaction is performed with added hexamethylphosphoramide in the medium, both *cis* and *trans* products of 1.2-opening of the unsaturated epoxide are formed in nearly equivalent amounts.[291] On the other hand, organolithium derivatives in ether, apparently promote mainly S_N2 opening of the unsaturated epoxide.[292] So, subtle electronic effects are involved in these results and more experimental work is needed in order to ascertain the factors that control the steric course of such competitive reactions.[293]

(c) *Cycloheptene derivatives.* To our knowledge, there is no significant example of allylic displacements in the cycloheptene series. As far as the steric course of allylic displacements is concerned, a few differences of reactivity between 5- and 7-membered unsaturated rings may be anticipated. On the one hand, cycloheptenes are able to adopt several initial reactive conformations and they are more mobile conformationally than cyclopentenes. On the other hand, as shown in Fig. 178, displacements of either S_N2 or S_N2' types are able to occur with a low expenditure of energy since they involve the passage from a low energy form (chair or twist) to another low energy form (chair or twist) with a small distortion of the initial reactive form. More precisely, it is clear from Fig. 178 that the preferred reactive forms of cycloheptene may give rise to *anti* (chair and boat) or *syn* (twist) allylic displacements: S_N2 reactions are, in this series, quite competitive with their S_N2' counterpart since they do not involve a conformational inversion of the ring as was the case for cyclopentene derivatives of Fig. 175. Accordingly, displacements in the cycloheptene series may give rise to competitive S_N2 and S_N2' displacements, depending on the substrate and experimental conditions. As for allylic S_N2' displacements, their steric outcome is also dependent on the substrate and experimental conditions and may result in *syn* or *anti* entry of the anion with respect to the leaving group.

(d) 1.3-*Cycloheptadiene monoepoxide.* The same conclusions apply for allylic displacements of 1.3-cycloheptadiene monoepoxide (Fig. 179) that are susceptible to take place with a *syn* or *anti* stereochemistry. Here again, S_N2 displacements are competitive with allylic S_N2' displacements and the results depend on the substrate and experimental conditions.[294]

Allylic displacements in even membered unsaturated rings. (a) *Cyclobutenes.* The few results of the literature[295-296] support a *syn* stereochemistry for S_N2' displacements in the cyclobutene series as

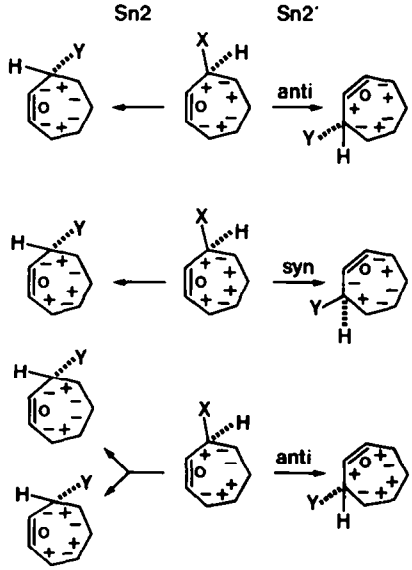


Fig. 178

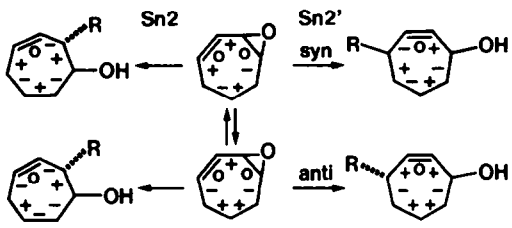


Fig. 179

illustrated in Fig. 180. Apparently in the example of 180b, the exclusive reaction is that of S_N2' allylic displacement, occurring in nearly quantitive yield.[295] We feel that here, the torsion angle notation is useful as a mnemonic device but we do not see clearly which interpretation to give to these results: here again, subtle electronic factors are involved.

(b) *Cyclohexenes.*[297,298] Numerous theoretical[299] and experimental[300] studies have been recently devoted to nucleophilic displacements of the S_N2' and S_N' types, occurring with an allylic shift of the double bond. The general view now, is that the stereochemistry of these reactions appear much more complex than had previously been thought.

Electronic, steric and polar factors, as well as experimental conditions, are involved in the steric outcome of the reaction that occurs with *syn* or *anti* delivery of the incoming nucleophile with respect to the leaving group. In the cyclohexene series, S_N2' reactions appear only stereoselective and take place competitively with the corresponding S_N2 displacements.

We do not intend to review the abundant literature pertaining to this subject. Rather, with the help of a few selected, significant examples, we want to underline the importance of a few conformational factors which, in our opinion, play a part in the steric outcome of such allylic displacements.

Without losing sight of the possibility of competing S_N2 displacements, let us first analyze, in the light of our usual assumptions, the conformational requirements of concerted S_N2' reactions.

As a simplification, we admit that the products of allylic displacements the most likely to be formed are those of the low energy pathways, corresponding to the least amount of conformational distortion from the initial reactive form up to the primary final one.

As illustrated in Fig. 181 (*cis* R, X), when both substituent and leaving group are *cis* on the cyclohexenic ring, the preferred pathway of low energy ought to be the *syn*-pathway since there is no

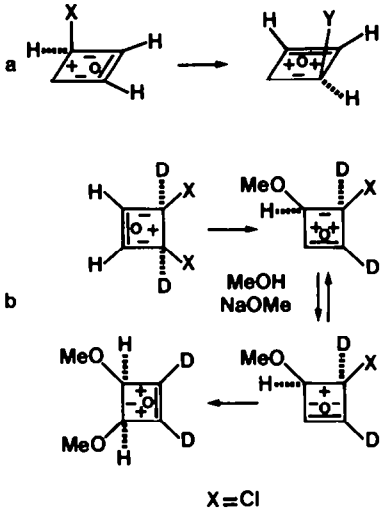


Fig. 180

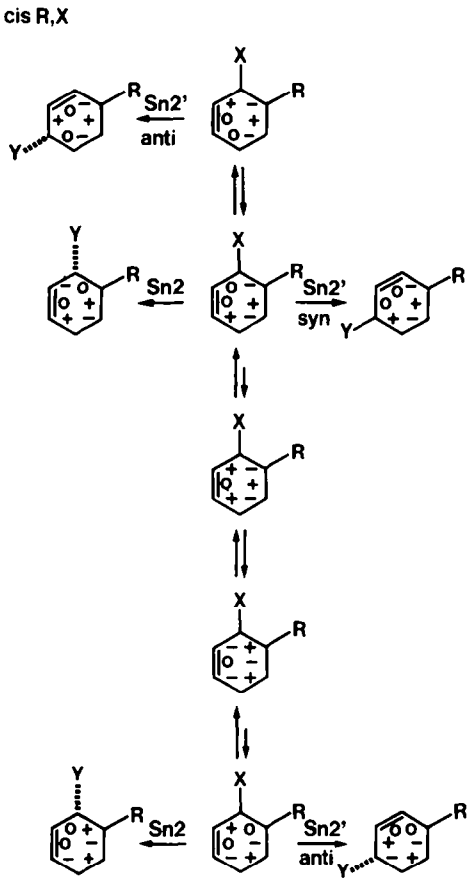


Fig. 181

conformational distortion from the initial reactive form (1.2-diplanar) up to the corresponding primary final one (again 1.2-diplanar). The anti pathways are not excluded, however, since presumably their corresponding transition states do not differ much in energy from the one that corresponds to the *syn*-pathway. Moreover, S_N2 displacements may also be competitive. Taking all this into account, we may say that if the conformational factors were controlling the allylic displacements, the main product of reaction ought to correspond to a syn S_N2' reaction.

Since, in practice, the experimental conditions and the nature of the nucleophile strongly influence the steric outcome of such reactions,[300] we are led to believe that a mixture of products of the S_N2' and S_N2 types are likely to be formed. In this mixture the main compound ought to correspond to the *syn* S_N2' type of reaction.

Reasoning along similar lines in the *trans* series of Fig. 182 (*trans* R, X), the conclusion is again that the *syn* S_N2' pathway for allylic displacements ought to correspond to the main product of the reaction if the controlling factor is of conformational nature. However, in this latter series, we cannot ignore the bulk of the R-substituent. When R is a t-Bu group, it is unlikely to be in the axial orientation on the chair form; the only alternatives that allow the t-Bu group to be in the equatorial or *quasi* equatorial orientation and the leaving group to be axial or *quasi*-axial are the 1.3-diplanar form and the boat shown at the bottom of Fig. 182. The former 1.3-diplanar reactive form appears more likely than the corresponding boat, but whatever the initial reactive conformation (1.3-diplanar or boat) the steric course of the S_N2' displacement is anti with respect to the leaving group. A competition of S_N2 and S_N2' displacements in the reactions of Fig. 182 appears likely.

Other examples of displacement reactions are analyzed in Fig. 183 in the isomeric *trans* and *cis* disubstituted cyclohexenic derivatives. Now the nature of the substituent (R = t-Bu in Figs. 183a and b) prevents any conformation inversion and only one initial reactive conformation of low energy is available for the displacements. In the *trans* series of Fig. 183a, the *syn* S_N2' pathway appears preferred. In the *cis* series of Fig. 183b, the anti S_N2' pathway and the S_N2 pathway are competitive.

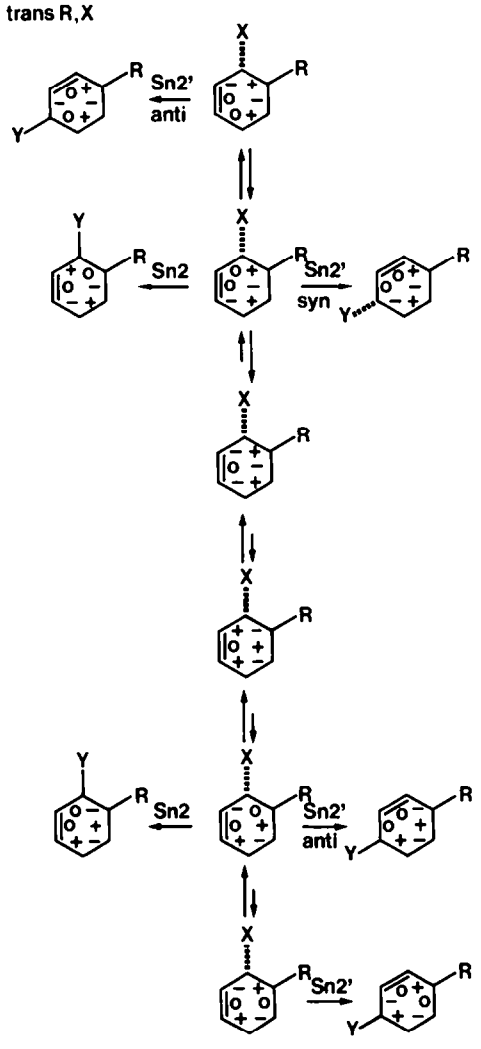


Fig. 182

We present now a few examples drawn from the literature[301-309] of S_N2' reactions of unsaturated 6-membered rings: the interpretation of the *syn* displacements of Fig. 184[301-303] is straightforward and, therefore, we do not comment on these examples. In Fig. 185[304-305] are presented a few examples of anti allylic displacements in the 14-bromo-codeine series. The conformation of the unsaturated ring is intermediate between the boat and the 1.3-diplanar form and the allylic displacement leads to a 1.3-diplanar form with the expected *anti* stereoselectivity. The rigidity of the unsaturated ring limits the conformational changes and thus favours the *anti* pathway in both cases.

In Fig. 186, the equatorial leaving group is displaced *anti* by the anion of methyl lithium.[306] Apparently, under the experimental conditions of this last reaction, there is no involvement of the inverted half-chair form with both Me substituent and leaving group axial, presumably *syn*-axial interactions with the axial Me and the incoming Me anion prevents this last pathway to be operating. A few examples of allylic displacements by lithium aluminum hydride or deuteride are shown in Fig. 187. In the example a[307] and b[308] the stereochemistry of the reaction is *syn* as expected; for 187a it is worth noting that even tributylstannane is able to promote an allylic rearrangement. In the last examples c and d of Fig. 187,[309] the leaving group is the allylic anomeric OMe of unsaturated sugars and the addition of deuteride ion occurs according to the expected modes: *syn* (187c: leaving group axial on the half-chair form of the unsaturated ring) and *anti* (187d: leaving group axial on the 1.3-diplanar form).

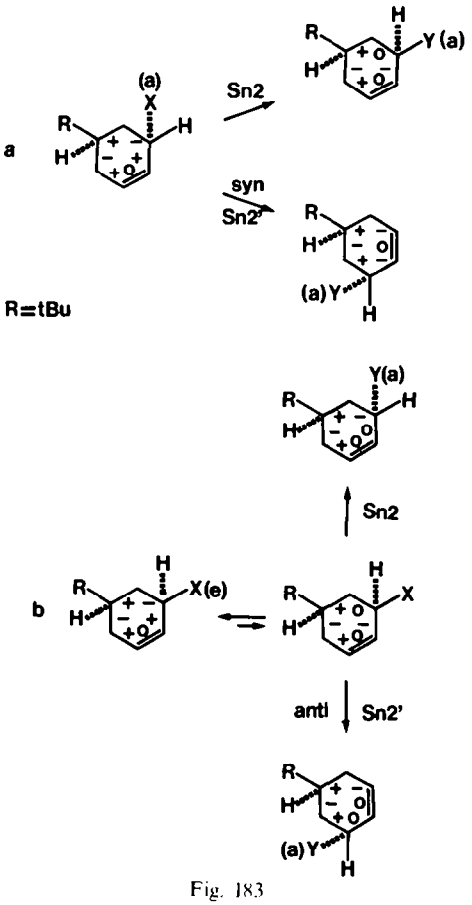


Fig. 183

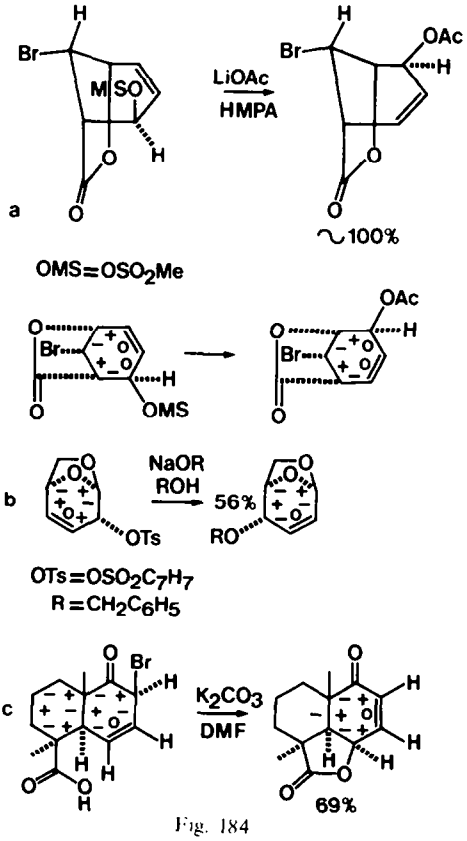


Fig. 184

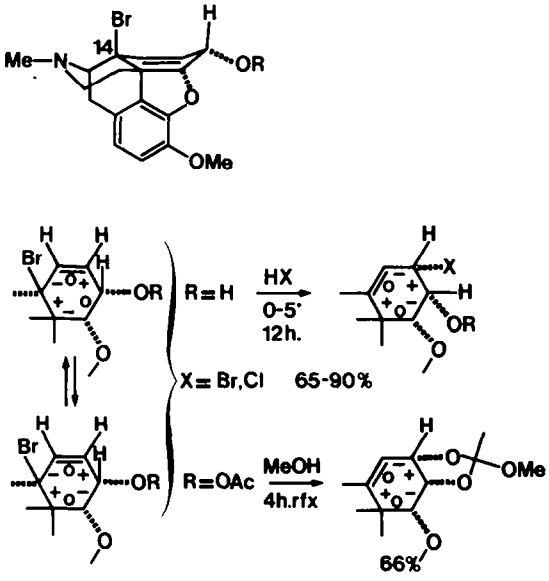


Fig 185

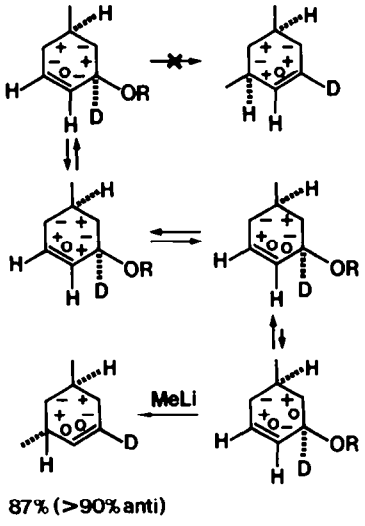


Fig 186

(c) *Cine-substitution of α-halo-ketones.* A few reactions of α-halo ketones taking place with migration to the α′ position either of the halogen or of an anion able to displace the halogen, can be interpreted as concerted allylic displacements occurring through the enol or enolate double bond. Again, in such displacements, depending on the orientation of the halogen the kinetically added nucleophile may come with respect to the halogen, either *syn*, as in Fig. 188a[310], or *anti*, as in Fig. 188b.[311] The latter case is one of the first authentic examples of an allylic displacement taking place with an anti addition of the acetate ion with respect to the leaving bromide. The primary kinetic 2α-acetoxy derivative isomerizes, under ordinary experimental conditions, into the more stable 2β-acetoxy-equatorial isomer.

Analogous allylic displacements have been observed with vinylogous halo-ketones, such as 6β-bromo-3oxo-Δ^4-steroids.[312] In the latter case, the allylic shifts involve two double bonds (one of which is an enol or an enolate double bond) but we believe, that again, conformational effects control the steric course of the kinetic reaction.

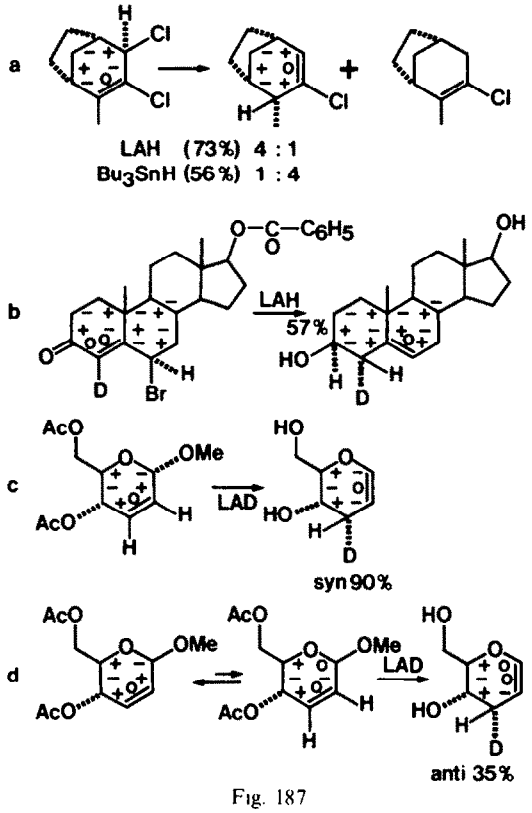


Fig. 187

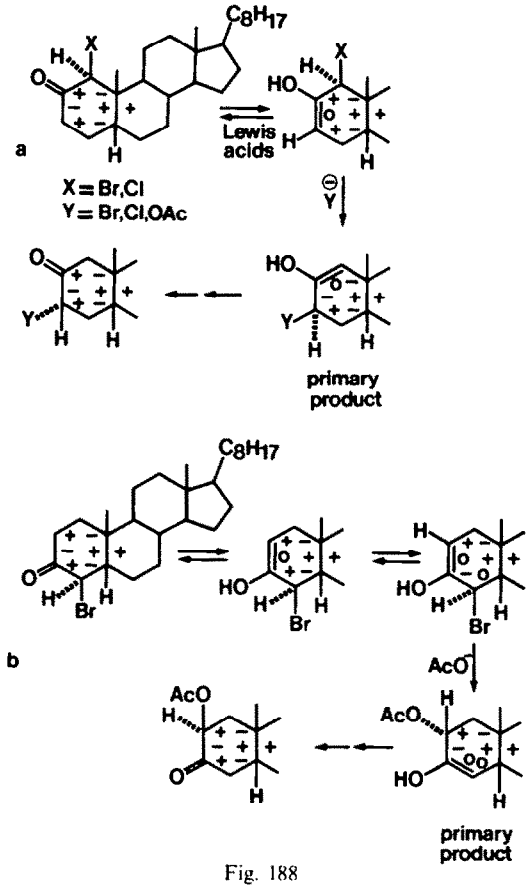


Fig. 188

Allylic displacements of α,β-unsaturated epoxides.[313] The stereochemistry of allylic displacements involving α,β-unsaturated epoxides is of interest in as much as it could be a useful tool in synthesis. With respect to the steric course of the reaction we have to distinguish between homoannular and hetero-annular unsaturated epoxides. In the first case the double bond and the epoxide are in the same ring whilst, in the second case, the double bond and the epoxide are in two separate contiguous rings.

(a) *Homoannular unsaturated epoxides.* The monoepoxide of 1.3-cyclohexadiene is an example of homoannular unsaturated epoxide; the ring has necessarily one of the two possible 1.3-diplanar forms of Fig. 189, the one with the epoxide axial (as shown in the figure, the sequence if + 0 −) and the other with the epoxide in the bisectional orientation. According to our previous hypotheses, the form with the axial epoxide is expected to be the reactive one in displacements since in the transition state, the displaced bond has to be in the axial orientation[314] and it is clear that the *anti* pathway 1, corresponding to the addition of the anion *anti* with respect to the allylic bond of the epoxide that is breaking, is of lower energy than the *syn* pathway 2. S_N2 displacement is also a pathway of low energy that may be competitive with allylic displacements and, indeed, this seems to be the case (Fig. 190). From the other 1.3-diplanar form with the epoxide in the bisectional orientation, only the *syn* pathway 3 is compatible with the stereoelectronic requirements of the transition state, although it appears of much higher energy than pathway 1. Therefore, *anti* allylic addition of nucleophiles to cyclohexadiene-monoepoxide seems favored over the alternative *syn*-addition. As shown in Fig. 190, hydrolysis of cyclohexadiene-monoepoxide by water in acidic or dihydrogenphosphate buffered solution[315] or methyl-lithium addition to cyclohexadiene-monoepoxide[316] occurs in agreement with the foregoing considerations.

The addition of various anions to unsaturated epoxides of steroids intermediates has been shown to be of the following types: *anti*, as in the example of Fig. 191[318] or *syn*, in the example of Fig. 192.[318]

(b) *Displacements involving α,β-epoxy-ketones.* A few cine-substitutions, involving the enol or enolate double bond of α,β-epoxy ketones, may be interpreted as resulting from an allylic displacement at the end of the enolate double bond by a nucleophile. Such reactions apparently do

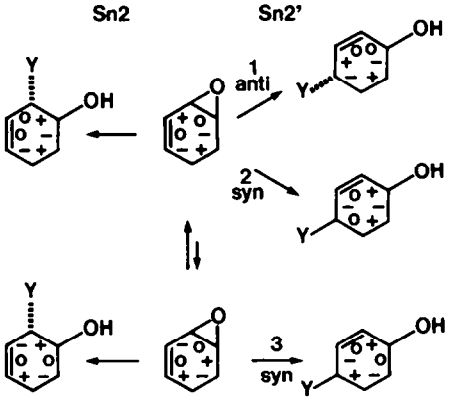


Fig. 189

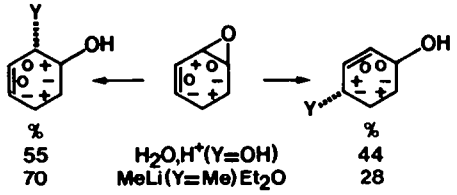


Fig 190

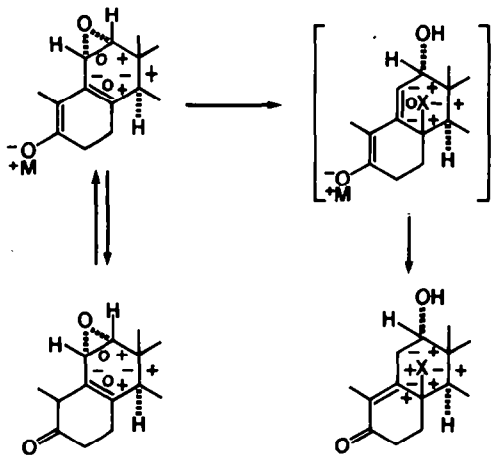


Fig. 191

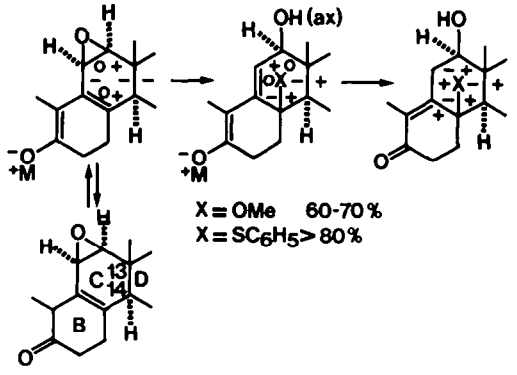


Fig 192

obey the rules previously given for allylic displacements of unsaturated epoxides. For instance, in Fig. 193a,[319] through the Δ^3-enolic form of the ketone, fluorhydric acid treatment of the 1α,2α-epoxy-3-oxo-steroid of the 5α-series, allows an allylic *anti* displacement of the enol epoxide by fluoride ion that introduces the halogen at position 4β, on the same side as the angular Me. In Fig. 193b[320] acid treatment of the steroidal 3-oxo-4β,5β-epoxide, again through an *anti* allylic displacement of the corresponding enol epoxide, stereoselectively yields the 2α-substituted derivative (X = F, OAC, OH Fig. 193b). We feel that it becomes possible now to use the stereoselectivity of this type of reactions in synthetic work.

(c) *Heteroannular unsaturated epoxides.* The steric course of allylic displacements involving heteroannular epoxides may be readily interpreted and often predicted even if the compatibility of deformations between the rings concerned by the allylic shift of the double bond, is a strict requirement. For example the allylic addition of hydride or deuteride[321] or hydroxide ions[322] to the unsaturated epoxide of Fig. 194 takes place, as expected from a simple conformational analysis, on the same side as the breaking bond of the epoxide.

Extension. Although it will not be developed here since it is beyond the scope of this report, it is possible to apply the foregoing rules to successfully interpret the steric course of a few allylic reactions

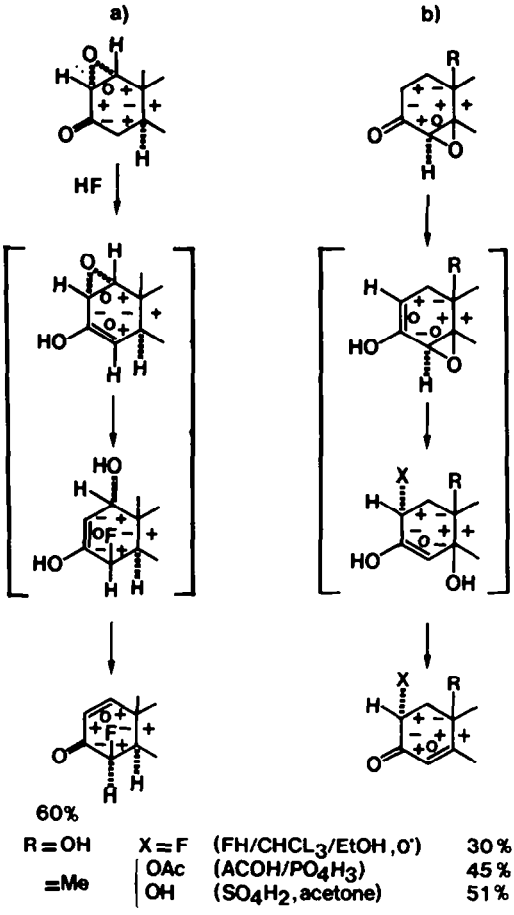


Fig. 193

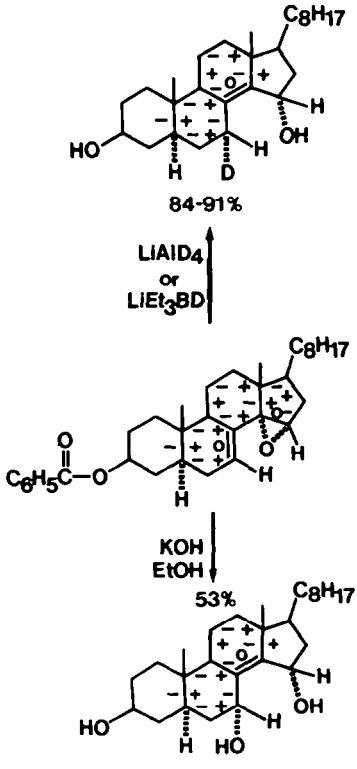


Fig. 194

of 6-membered unsaturated rings, that take place with an allylic shift of the double bond, namely the Wolff-Kishner reduction of unsaturated ketones,[323] the photosensitized peroxidation of allylic double bonds[324] and the ene-synthesis.[325]

CONCLUSION

Although limited for the time being to cyclic compounds, the dynamic conformational analysis of reactions with the help of the torsion angle notation appears as a very powerful tool to interpret or predict the steric course of many reactions involving 5-, 6- and 7-membered unsaturated rings; at the same time it gives a unifying view of the factors that determine the stereochemistry of a given reaction.

The method should prove useful in the planning of synthetic work since the stereoselectivity or stereospecificity of a reaction can be readily evaluated.

Finally, it is our belief that it may be of great help to most organic chemists to valorize their experimental results through a better analysis of all the parameters that may influence the steric course of a reaction and its mechanism.

Acknowledgements The author expresses his heartfelt thanks to Prof. J. Boissier, Head of Pharmaceutical Research, and Dr. G. Nomine, Head of Chemical Research, for the authorization to publish this work and to Dr. R. Bucourt, Head of Research, Roussel Laboratories, for many fruitful discussions and his constant encouragement.

REFERENCES

[1]R. Bucourt, *The torsion angle concept in conformational analysis.* In *Topics of Stereochemistry* Vol. 8, p. 159. (Edited by E. L. Eliel and N. L. Allinger), Interscience, New York (1974).

[2]E. Toromanoff and R. Bucourt, *Tetrahedron Letters* 3523 (1976); see Ref. 2 for the basic assumptions.

[3]J. P. Girard, J. P. Vidal, R. Granger, J. C. Rossi and J. P. Chapat, *Ibid.* 943 (1974).

[4]The initial reactive form is the preferred form of lowest energy that satisfies the stereoelectronic requirements of the reaction and the primary final form is the preferred form that directly derives from the initial reactive form using the basic assumptions stated in Ref. 2, including the principle of least conformational distortion during the course of a reaction.

[5]J. B. Hendrickson and R. K. Boeckman, Jr., *J. Org. Chem.* **36,** 2315 (1971).

[6a]H. M. Mori, *Chem. Pharm. Bull.* **10,** 386 (1962); [b]R. Wiechert, U. Kerb and K. Kieslich, *Chem. Ber.* **96,** 2765 (1963); [c]B. Pelc, *Coll. Czech. Chem. Commun.* **29,** 3089 (1964); [d]C. C. Bolt and F. J. Zeelen, *Rec. Trav. Chim.* **92,** 1267 (1973).

[7]E. Toromanoff, *Bull. Soc. Chim. Fr.* 1445 (1966). *Ibid* 708 (1962).

[8]The primary kinetic enolate may be trapped namely by O-acylation, O-silylation or O-phosphorylation or intercepted *in situ* with electrophilic reagents such as methyl iodide or benzoyl peroxide. See H. O. House, *Modern Synthetic Reactions.* Benjamin, New York (1972).

[9a]P. R. Andrews, E. N. Cain, E. Rizzardo, G. D. Smith, *Biochem.* **16,** 4848 (1977); [b]For a discussion of this question, see B. Ganem, *Tetrahedron* **34,** 3361 (1978).

[10a]Ref. 1, p. 183; [b]J. L. Marshall, L. G. Faehl, C. R. McDaniel and N. D. Ledford, *J. Am. Chem. Soc.* **99,** 321 (1977); [c]P. W. Rabideau, *Accounts Chem. Res.* **11,** 141 (1978).

[11]E. Toromanoff, *Bull. Soc. Chim. Fr.* 1190 (1968)

[12]This wording is probably more in agreement with the results of various *ab initio* computations about the direction of anion addition to the carbonyl or imine double bond: H. B. Buergi, J. M. Lehn and G. Wipff, *J. Am. Chem. Soc.* **96,** 1956 (1974); V. Kala and J. Kuthan, *Coll. Czech. Chem Commun.* **43,** 3064 (1978), see also J. E. Baldwin, *Chem. Commun.* 738 (1976).

[13]*Conformational Analysis* (Edited by E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison), pp. 273, 291. Interscience, New York (1965).

[14]The concept of overlap control has already been used several times in the literature, to interpret the steric course of various reactions involving conjugated enones as in the following cases: (a) Alkaline epoxidation: H. E. Zimmerman, L. Singer and B. S. Thyagarajan, *J. Am. Chem. Soc.* **81,** 108 (1959). (b) Lithium-ammonia reduction of substituted octalones: G. Stork and S. D. Darling, **82,** 1512 (1960); **86,** 1761 (1964).

[15]For 6-membered ring epoxides the overall result corresponds to the Fuerst-Plattner rule: A. Fuerst and Pl. A. Plattner, *abstract papers 12th Intern. Congress Pure and Appl. Chem.*, p. 409. New York (1961).

[16]R. Bucourt *et al.*, unpublished work.

[17]Chemists have to be aware of the fact that molecular models in current use do not always permit the building of a conformation that corresponds to the X-ray crystal structure. For instance, the inverted quasi-*cis* half-chair of 2β-acetoxy-3-oxo-Δ^4-steroids cannot be built with Dreiding models although such a form exists in the crystal: see Y. Osawa and J. O. Gardner, *J. Org. Chem.* **36,** 3246 (1971); W. L. Duax, C. Eger, S. Pokrywiecki and Y. Osawa, *J. Med. Chem.* **14,** 295 (1971).

[18]D. Coussedière, Thèse, C.N.A.M., Paris (9 January 1973).

[19]*Experientia* **16,** 521 (1960).

[20]For the basic features of the torsion angle notation the reader should consult, besides the review by R. Bucourt (1), the following publications: *Bull. Soc. Chim. Fr.* 1262, (1963); 2080 (1964).

[21]This statement is an over-simplification since, not only the signs, but also the absolute values of torsion angles are involved in the relative stability of a given conformation and its reactivity. However, in the first approximation of the method that is given in this report, we assume that small variations of the absolute value of the torsion angles do not alter much the characteristic properties and the behaviour of the slightly distorted form with respect to the undistorted one.

[22]G. M. Kellie and F. G. Riddel, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. 8, p. 236. Interscience, New York (1974).

[23]Even through small variations of torsion angles there may be an infinity of conformations, but the important point, already underlined in Ref. 21, is that all these conformations belong to the same type and are endowed with the same characteristic properties.
[24]P. de Clercq, M. Samson, D. Tavernier, D. van Haver and M. Vandewalle, *J. Org. Chem.* **42,** 3140 (1977).
[25]B. Fuchs, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. 10, p. 1. Interscience, New York (1978).
[26a]N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.* **94,** 5734 (1972); [b]O. Ermer and S. Lifson, *Ibid.* **95,** 4121 (1973).
[27]Cyclopentenone itself appears planar, or nearly so, according to physical measurements of the microwave spectrum by D. A. Chadwick, A. C. Legon and D. J. Millen, *Chem. Commun.* 1130 (1969), *J. Chem. Soc.* Faraday 2, 302 (1979), or of the I.R. by T. H. Chao and J. Laane, *J. Mol. Spectrosc.* **48,** 226 (1973). This does not imply that substituted cyclopentenones do not depart from planarity: cyclopentenones *trans*-fused to another ring are necessarily non-planar. Finally, even for planar cyclopentenones, a conformational bias may exist during the passage to a non-planar form of cyclopentene, cyclopentane or cyclopentanone.
[28]G. Favini, G. Buemi and M. Raimondi, *J. Mol. Struct.* **2,** 137 (1968).
[29a]E. M. Philbin and T. S. Wheeler, *Proc. Chem. Soc.* 167 (1958); [b]Ref. 1, p. 186; R. Bucourt and D. Hainaut, *Bull. Soc. Chim. Fr.* 4562 (1967).
[30a]J. B. Hendrickson, *J. Am. Chem. Soc.* **89,** 7036, 7047 (1967); [b]D. E. Bocian, H. M. Pickett, R. C. Roundsand, H. L. Strauss, *Ibid* **97,** 687 (1975); D. E. Bocian and H. L. Strauss, *Ibid.* **99,** 2866, 2876 (1977); [c]J. Casanova and B. Waegell, *Bull. Soc. Chim. Fr.* 911 (1975); [d]J. Dale, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. 9, p. 233. Interscience, New York (1976).
[31a]N. L. Allinger, M. T. Tribble and M. A. Miller, *Tetrahedron* **28,** 1173 (1972); [b]M. Saint-Jacques, C. Vaziri, D. A. Frenette, A. Goursot and S. Fliszar, *J. Am. Chem. Soc.* **98,** 5759 (1976).
[32a]S. Kabuss, H. Friebolin and H. Schmid, *Tetrahedron Letters* 469 (1965); [b]R. Knorr, C. Ganter and J. D. Roberts, *Angew. Chem. Int. Ed.* **6,** 556 (1967); [c]W. Tochtermann, *Topics in Current Chemistry* Vol. 15, p. 338. Springer–Verlag, Berlin (1970); [d]F. H. Allen and J. Trotter, *J. Chem. Soc.* (**B**), 721 (1970); [e]E. A. Noe and J. D. Roberts, *J. Am. Chem. Soc.* **93,** 7261 (1971); [f]M. Saint-Jacques and C. Vaziri, *Can. J. Chem.* **49,** 1256 (1971); [g]N. L. Allinger and T. T. Sprague, *J. Am. Chem. Soc.* **94,** 5734 (1972); [h]K. L. Servis, E. A. Noe, N. R. Easton and F. A. Anet, *Ibid.* **96,** 4185 (1974). [i]J. Kao and Tai-Nang Huang, *Ibid.*, **101,** 5553 (1979).
[33a]R. W. Kitchin, T. B. Malloy, Jr. and R. L. Cook, *J. Mol. Spectrosc.* **75,** 429 (1979); [b]A. T. McPhail and K. D. Onan, *Tetrahedron Letters* 1229 (1975); From the X-ray data the cycloheptenone has the twist-chair form. [c]N. C. Cohen 1978, unpublished results.
[34]Ref. 1, p. 205.
[35a]Ref. 1, p. 195; [b]H. Christol and Y. Pietrasanta, *Bull. Soc. Chim. Fr.* 1030 (1967).
[36]R. Bucourt, N. C. Cohen and G. Lemoine, *Ibid.* 903 (1975).
[37]For a discussion see: D. N. Kirk and M. P. Hartshorn, *Steroid Reaction Mechanisms*, p. 163. Elsevier, New York (1968).
[38]Examples in Ref. 13, p. 171.
[39]For an early formulation see J. Valls and E. Toromanoff, *Bull. Soc. Chim. Fr.* 758 (1961).
[40]E. Toromanoff, *Ibid.* 3357 (1966).
[41a]F. Bohlmann, E. Winterfeldt, P. Studt, H. Laurent, G. Borochewski and K. M. Kleine, *Chem. Ber.* **94,** 3151 (1961); [b]Y. Arata, *Chem. Pharm. Bull.* **13,** 907 (1965).
[42]R. T. La Londe, N. Muhammad and C. F. Wong, *J. Org. Chem.* **42,** 2113 (1977).
[43]C. Weissman, H. Schmid and P. Karrer, *Helv. Chim. Acta* **45,** 64 (1962).
[44a]Cyclo-addition, R. B. Woodward and T. J. Katz, *Tetrahedron* **5,** 70 (1959); J. C. Little, *J. Am. Chem. Soc.* **87,** 4020 (1965); D. I. Rawson, B. K. Carpenter and H. M. R. Hoffmann, *Ibid.*, **101,** 1786 (1979); B. B. Snyder, D. J. Rodini, R. S. E. Conn and S. Scalfon, *Ibid.* **101,** 5283 (1979); [b]Epoxidation, B. Plesnicar, M. Tasevski and A. Azman, *Ibid.* **100,** 743 (1978); A. Azman, J. Kollec and B. Plesnicar, *Ibid.* 101, 1107 (1979); [c]Methylenation; B. Zuranskii and W. Kutzelnigg, *Ibid.*, **100,** 2654 (1978); [d]Catalytic hydrogenation; R. R. Schrock and J. A. Osborn, *Ibid.* **98,** 2143 (1976); J. M. Brown and P. A. Chaloner, *Chem. Commun.* 321 (1978); Ref. 37, p. 81.
[45]The reactive entity of peracid epoxidation is assumed to be ^{+}OH for the sake of simplicity. According to Ref. 44*b*, the mechanism of peracidepoxidation could be different from that suggested by P. D. Bartlett, *Rec. Chem. Progr.* **11,** 47 (1950).
[46a]H. B. Henbest and J. J. McCullough, *Proc. Chem. Soc.* 74 (1962); [b]G. M. Kauffmann, *Dissert. Abstr.* **27,** 1417B (1966); [c]G. Bernath and M. Svoboda, *Tetrahedron* **38,** 3747 (1972).
[47]H. C. Brown, G. J. Lynch, W. J. Hammar and L. C. Liu, *J. Org. Chem.* **44,** 1910 (1979).
[48]P. D. Bartlett, *Organic Chemistry, An Advanced Treatise* (Edited by Gilman), Vol. 3, p. 9. Wiley, New York (1953).
[49a]D. W. Emerson, A. P. Craig and J. W. Potts, Jr. *J. Org. Chem.* **32,** 102 (1967); [b]D. W. Emerson and T. J. Korniski, *Ibid.* **34,** 4115 (1969); [c]J. W. A. M. Janssen and H. Kwart, **42,** 1530 (1977).
[50]H. J. Reich, S. Wollowitz, J. E. Trend, F. Chow and D. F. Wendelborn, *Ibid.* **43,** 1697 (1978).
[51a]E. W. Garbisch Jr., S. M. Schildcrout, D. B. Patterson and C. M. Sprecher, *J. Am. Chem. Soc.* **87,** 2932 (1965).
[51b]B. Rickborn and J. H. H. Chan, *J. Org. Chem.* **32,** 3576 (1967); [c]N. Garti and S. Siegel, *Ibid.* **41,** 3922 (1976); [d]S. Siegel, M. Foreman, R. P. Fischer and S. E. Johnson, *Ibid.* **41,** 3599 (1976).
[52]A. Hassner, H. W. Pinnick and J. M. Ansell, *Ibid.* **43,** 1774 (1978); I. J. Westerman and C. K. Bradsher, *Ibid.*, **44,** 727 (1979).
[53]P. Scheiner, *Tetrahedron* **24,** 349 (1967); J. Bourgois, M. Bourgois and F. Texier, *Bull. Soc. Chim. Fr.* **11,** 486 (1978).
[54]D. L. J. Clive and G. Chittattu, *Chem. Commun.* 484 (1977); for other examples see K. C. Nicolaou and Z. Lysenko, *J. Am. Chem. Soc.* **99,** 3185 (1977).
[55]J. P. Marino and J. S. Farina, *J. Org. Chem.* **41,** 3213 (1976).
[56]B. Ganem, *J. Am. Chem. Soc.* **98,** 104 (1976).
[57]B. Rickborn and R. P. Thummel, *J. Org. Chem.* **34,** 3583 (1969). Our interpretation differs in part from that given by the authors.
[58]G. Teutsch and R. Bucourt, *Chem. Commun.* 763 (1974).
[59]L. A. Paquette, A. E. Fristad, C. A. Schuman, M. A. Beno and G. A. Christoph, *J. Am. Chem. Soc.* **101,** 4645 (1979).
[60]J. K. Whitesell and A. M. Helbling, *Chem. Commun.* 594 (1977).
[61]D. K. Murphy, R. L. Alumbaugh and B. Rickborn, *J. Am. Chem. Soc.* **91,** 2649 (1969).
[62]R. C. Fahey, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), p. 237. Interscience, New York (1968).
[63]I. C. Ambidge, S. K. Dwight, C. M. Rynard and T. T. Tidwell, *Can. J. Chem.*, **55,** 3086 (1979), for a recent discussion about mercurinium ions.

[64]W. A. Smit, N. S. Zefirov, F. Bodrikov and M. K. Krimer, *Accounts Chem. Res.* **12,** 282 (1979).
[65]E. Toromanoff, *Tetrahedron* **35,** 893 (1979).
[66]G. Nominé, D. Bertin and A. Pierdet, *Ibid.* **8,** 217 (1960).
[67]V. Prelog, L. Ruzicka and P. Wieland, *Helv. Chim. Acta* **28,** 2501 (1945).
[68]T. Nambara and J. Fishman, *J. Org. Chem.* **27,** 2131 (1962).
[69]W. C. Agosta and S. Wolff, *J. Am. Chem. Soc.* **98,** 4316 (1976).
[70]T. G. Traylor, *Accounts Chem. Res.* **2,** 152 (1969).
[71]H. C. Brown, J. H. Kawakami and S. Ikigama, *J. Am. Chem. Soc.* **92,** 6914 (1970).
[72]The following letters correspond to those of Fig. 53. [a]H. C. Brown, R. Liotta and L. Brener, *J. Am. Chem. Soc.* **99,** 3427 (1977); [b]T. G. Traylor and A. W. Baker, *J. Am. Chem. Soc.* **85,** 2746 (1963); [c]A. S. Hussey and Y. Takeuchi, *J. Org. Chem.* **35,** 643 (1970); [d]Ref 53; [e]H. Kwart and R. K. Miller, *J. Am. Chem. Soc.* **78,** 5678 (1956).
[73]J. A. Marshall and W. R. Snyder, *J. Org. Chem.* **40,** 1656 (1975).
[74]N. C. Cohen, 1978, unpublished results.
[75a]R. A Finnegan and P. J. Wepplo, *Tetrahedron* **28,** 4367 (1972); [b]K. Jankovsky and J. Y. Daigle, *Can. J. Chem.* **49,** 2594 (1971); Epoxides configurational assignments have to be reversed.
[76]R. Hanselaer, M. Samson and M. Vandewalle, *Tetrahedron* **34,** 2393 (1978).
[77]R. D. Clark and G. D. Untch, *J. Org. Chem.* **44,** 248 (1979).
[78]A. Horeau, E. Lorthioy, J. P. Guetté, *C.R. Acad. Sci.* 269C, 558 (1969). The same explanation may be given for the stereoselective bromoacetate alkylation of the substituted cyclopentenone enolate in the following example: G. H. Posner, M. J. Chapdelaine and C. M. Lentz, *J. Org. Chem.* **44,** 3661 (1979).
[79]M. Pesaro and J. P. Bachmann, *Chem. Commun.* 203 (1978).
[80]Ken'ichi Takeda, H. Minato, T. Terasawa, M. Ishikawa and C. Yanaihara, *J. Chem Soc.* (C), 2095 (1966).
[81]J. Vasilevskis, J. A. Gualtieri, S. D. Hutchings, R. C. West, J. W. Scott, D. R. Parrish, F. T. Bizzaro and G. F Field, *J Am. Chem. Soc* **100,** 7423 (1978).
[82a]P. Caramella and G. Cellerino, *Tetrahedron Letters* 229 (1974). [b]P. Beltrame, P. L. Beltrame, P. Caramella, G Cellerino, R. Fantechi, *Ibid.* 3545 (1975). [c]E. J. McAlduff, P. Caramella and K. N. Houk, *J. Am. Chem. Soc.* **100,** 107 (1978).
[83a]Epoxidation: E. J. Corey and R. Noyori, *Tetrahedron Letters* 311 (1970); J. J. Partridge, N. K. Chadha and M. Uskokovic, *J. Am. Chem. Soc* **95,** 7171 (1973). [b]Glycolation: L. Gruber, I. Tömöskózi, E. Major and G. Kovacs, *Tetrahedron Letters* 3729 (1974).
[84a]F. Jrrevere, K. Morita, A. V. Robertson and B. Witkop, *J. Am. Chem. Soc.* **85,** 2824 (1963); [b]Y. Fujimoto, F. Jrrevere, J. M. Karle, I. L. Karle and B. Witkop, *Ibid.* **93,** 3471 (1971).
[85]A. K. Bose, G. Spiegelman and M. S. Manhas, *Ibid.* **90,** 4506 (1968); see also H. Vanderhaeghe and J. Thomis, *J. Med. Chem.* **18,** 486 (1975).
[86a]H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.* 1958 (1957); [b]R. Albrecht and C. Tamm, *Helv. Chim. Acta* **40,** 2216 (1957).
[87a]H. B. Henbest and B. Nicholls, *J. Chem. Soc.* 227 (1959); [b]M. R. Johnson and B. Rickborn, *J. Org. Chem.* **34,** 2781 (1969).
[88a]W. C. Baird Jr., B. Franzus and J. H. Surridge, *J. Am. Chem. Soc.* **89,** 410 (1967); [b]G. Büchi and H. Wüest, *J. Org. Chem.* **44,** 547 (1979).
[89a]J. A. Staroscik and B. Rickborn, *Ibid.* **37,** 738 (1972); [b]R. Perraud and P. Arnaud, *Bull. Soc. Chim. Fr.* 1540 (1968).
[90]H. B. Henbest, B. Nicholls, W. R. Jackson, R. A. L. Wilson, N. S. Crossley, M. B. Meyers and R. S. McElhinney, *Ibid.* 1365 (1960).
[91]G. Berti, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger) p. 93, review and discussion p. 130 and fg. Interscience, New York (1972).
[92]H. Boyle, W. Cocker, D. H. Grayson and P. V. R. Shannon, *Chem. Commun.* 395 (1971).
[93a]P. Kok, P. de Clercq, M. Vandewalle, J. P. Declercq, G. Germain and M. Van Meerssche, *Tetrahedron Letters* 2063 (1979).
[94]*Stereoselective Synthesis of Natural Products* (Edited by W. Bartmann and E. Winterfeldt). Excerpta Medica, Amsterdam, Oxford (1979); [a]P. A. Grieco, p. 121. [b]M. A. Vandewalle, P. de Clercq, M. Demuynck, P. Kok, G. Rozing and E. Scott, p. 130
[95]Examples are given later.
[96]L. Dolejs, A. Mironov and F. Sorm, *Coll. Czech. Chem. Comm.* **26,** 1015 (1961).
[97a]J. Bascoul, C. Reliaud, A. Guinot and A. Crastes de Paulet, *Bull. Soc. Chim. Fr.* 4074 (1968); [b]S. K. Pradhan and V. M. Girijavallabhan, *Steroids* **13,** 11 (1969).
[98]J. F Brunke, R. Böhm and H. Wolf, *Tetrahedron Letters* 3137 (1976).
[99]H. Schmidt and H. Kägi, *Helv. Chim. Acta* **33,** 1582 (1950).
[100]C W. Shoppee and G. H. T. Summers, *J. Chem. Soc.* 2528 (1952).
[101]E. Toromanoff, *C.R. Acad. Sci.* **286C,** 385 (1978).
[102]J. Iriarte, J. J. Ringold and C. Djerassi, *J. Am. Chem. Soc.* **80,** 6105 (1958).
[103]W. S. Johnson, A. D. Kemp, R. Pappo, Jr., J. Ackerman and W. F. Johns, *Ibid.* **78,** 6312 (1956).
[104]A. C. Chosh, B. G. Hazra and W. L. Duax, *J. Org. Chem.* **42,** 3091 (1977); A. C. Chosh, B. G. Hazra, H. C. Dalzell and R. K. Razdan, *J. Org. Chem.* **43,** 4795 (1978).
[105]A. C Chosh, B. G. Hazra, L. Karup-Nielsen, M. J. Kane, D. Hawke, W. L. Duax and C. M. Weeks, *Ibid.* **44,** 683 (1979).
[106]A. J. Birch and K. A. M. Walker, *J. Chem. Soc.* (C) 1894 (1966).
[107]J. Ficini, A. Guingant and J. d'Angelo, *J. Am. Chem. Soc.* **101,** 1318 (1979).
[108]E. J. Corey and D. S. Watt, *Ibid.* **95,** 2303 (1973).
[109]P A. Grieco and K. Hiroi, *Tetrahedron Letters* 3467 (1974).
[110]C. Girard and J M. Conia, *Ibid.* 3327 (1974).
[111]G. Buchi, W. Hofheinz and J. V. Paukstelis, *J. Am. Chem. Soc.* **88,** 4113 (1966).
[112]E. Kh. Kazakova, L. N. Surkova, Z. G. Isaeva and S. Sh. Bikeev, *Dokl. Akad. Nauk. SSSR* **236,** 363 (1977); *Chem. Abstr.* **88,** 22197. p. (1978).
[113]M. L. Mihailovic, J. Forsek and L. Lorenc, *Chem. Comm.* 916 (1978).
[114]Frl. G Eggart, P. Keller, C. Lehmann and H. Wehrli, *Helv. Chim. Acta* **51,** 940 (1968).
[115]Y. Yamada, H. Nagaoka and M. Kimura, *Synthesis* 581 (1977).
[116]W. S Johnson, R. Pappo and W. F. Johns, *J. Am. Chem. Soc.* **78,** 6339 (1956).
[117]R. T. Dean and H. Rapoport, *J. Org. Chem.* **43,** 4138 (1978).
[118]M. R Demuth, P. E. Garrett and J. D. White, *J. Am. Chem. Soc.* **98,** 634 (1976).
[119]A. L. Campbell, H. N. Leader, C. L. Spencer and J. D. McChesney, *J. Org. Chem.* **44,** 2746 (1979).

[120]W. Cocker, P. V. R. Shannon and P. A. Staniland, *J. Chem. Soc.* (C), 41 (1966).
[121a]H. Kuczynski and K. Piatowski, *Roczniki. Chem.* **31**, 59 (1957); [b]P. J. Kropp, D. C. Heckert and T. J. Flautt, *Tetrahedron* **24**, 1385 (1968); [c]A. Arbuzov, A. N. Vereschagin, S. G. Vul'fson and Z. G. Isaeva, *Izv. Akad. Nauk. SSSR.* Ser. Khim. 1966 (1968), *Chem. Abstr.* **70**, 11813p (1969); [d]W. Cocker and D. H. Grayson, *J. Chem. Soc.* Perkin I, 1217 (1975).
[122]W. Cocker, P. V. R. Shannon and P. A. Staniland, *Ibid.* (C), 485 (1967).
[123]T. Sasaki, S. Eguchi and Y. Yamada, *J. Org. Chem.* **38**, 679 (1973).
[124]A. Aumelas, E. Casadevall and A. Casadevall, *Tetrahedron* **34**, 2481 (1978).
[125]The exact nature of the complex is not known.
[126]*Steroid Hydrogenation* by R. L. Augustine in Fried–Edwards, *Organic Reactions in Steroid Chemistry*, Vol. I, p. 111. Van Nostrand, Reinhold, New York (1972).
[127]H. O. House, *Modern Synthetic Reactions*, p. 16. *Benjamin, New York, Amsterdam* (1965).
[128]Reviews: R. L. Augustine, *Catalytic Hydrogenation*, M. Dekker, New York (1965; M. Volpin, *Russ. Chem. Rev.* **38**, 273 (1969).
[129]The *cis* stepwise addition of two hydrogens has already been postulated: A. S. Hussey and Y. Takeuchi, *J. Am. Chem. Soc.* **91**, 672 (1969), and Ref. 37, p. 81.
[130]For an estimation of the energy of this form of cyclohexane, see Ref. 1, p. 180.
[131]S. Siegel, M. Dunkel, G. V. Smith, W. Halpern and J. Cozort, *J. Org. Chem.* **31**, 2802 (1966); see also A. S. Hussey and Y. Takeuchi, *Ibid.* **35**, 643 (1970).
[132]S. Siegel and G. S. McCaleb, *J. Am. Chem. Soc.* **81**, 3655 (1959).
[133]C. A. Brown and H. C. Brown, *J. Org. Chem.* **31**, 3989 (1966).
[134]Y. Watanabe, Y. Mizuhara and M. Shiota, *Ibid.* **31**, 3785 (1966).
[135a]W. J. Wechter, *Chem. & Ind.* 294 (1959); [b]S. Wolfe, M. Nussim, Y. Mazur and F. Sondheimer, *J. Org. Chem.* **24**, 1034 (1959); [c]J. E. Herz and L. A. Marquez, *J. Chem. Soc.* (C), 2243 (1969).
[136]J. R. Lewis and C. W. Shoppee, *Ibid.* 1365 (1965).
[137]D. F. Morrow, T. P. Culbertson and R. M. Hofer, *J. Org. Chem.* **32**, 361 (1967).
[138]P. M. Curry Jr., *Tetrahedron Letters* 1841 (1971).
[139]S. Y. Lwo, *J. Org. Chem.* **30**, 2212 (1965). We assume the epoxidation of 4-methylcyclohexene to be similar to that of 2,4-dimethylcyclohexene.
[140]For a discussion see Ref. 91, p. 112.
[141a]M. Mousseron-Canet, B. Labeeuw and J. C. Lanet, *Bull. Soc. Chim. Fr.* 2125 (1968); [b]K. D. Bingham, T. M. Blaiklock, R. C. B. Coleman and G. D. Meakins, *J. Chem. Soc.* (C), 2330 (1970); [c]U. M. Dzhemilev, N. S. Vostrikov, A. M. Moiseenkov and G. A. Tolstikov, *Izv. Akad. Nauk. S.S.S.R., Ser Khim.* 913 (1979), *Chem. Abstr.* **91**, 108141q (1979).
[142]G. S. Bylina, U. M. Dzhemilev, N. S. Vostrikov, G. A. Tolstikov, A. M. Moiseenkov, A. V. Semenovkii and S. S. Shavanov, *Izv. Akad. Nauk. S.S.S.R. Ser. Khim.* 447 (1978); *Chem. Abstr.* **89**, 43949w (1978).
[143]R. Villiotti, C. Djerassi and H. J. Ringold, *J. Am. Chem. Soc.* **81**, 1235 (1959).
[144a]G. A. Tolstikov, U. M. Dzhemilev, V. P. Yur'ev, S. R. Rafikov, *Dokl. Akad. Nauk S.S.S.R.* 208, 376 (1973); *Chem. Abstr.*, **78**, 159 (1973); [b]M. Tohma, T. Tomita and M. Kimura, *Tetrahedron Letters* 4359 (1973).
[145]W. Carruthers, *Some Modern Methods of Organic Syntheses*, p. 317. Cambridge University Press (1971).
[146]R. R. Sauers, H. M. How and H. Feilich, *Tetrahedron* **21**, 983 (1970). The bicyclo [3.2.1] octene-2 can be considered either as an ethano bridged cyclohexene or a methylene bridged cycloheptene. In either case epoxidation is stereospecific but the steric results are opposite. For heterocyclic analogues see the following references: F. Sweet and R. K. Brown, *Can. J. Chem.* **46**, 2289 (1968); F. Shafizadeh, C. W. Philpot and N. Ostojic, *Carbohydrate Res.* **16**, 279 (1971).
[147a]B. M. Trost, J. M. Timko and J. L. Stanton, *Chem. Commun.* 436 (1968). [b]R. G. Harrison, B. Lythgoe and P. W. Wright, *Tetrahedron Letters* 3649 (1973).
[148a]S. Danishefsky, P. F. Schuda, T. Kitahara and S. J. Etheredge, *J. Am. Chem. Soc.* **99**, 6066 (1977). [b]S. Danishefsky, T. Kitahara, P. F. Schuda and S. J. Etheredge, *Ibid.* **98**, 3028 (1976').
[149]Y. Houminer, *J. Chem. Soc.* Perkin I, 1663 (1975).
[150]J. R. Bull and J. Floor, *Ibid.* Perkin I, 724 (1977).
[151a]F. Sondheimer and D. Rosenthal, *J. Am. Chem. Soc.* **80**, 3995 (1958); [b]M. C. Dart and H. B. Henbest, *J. Chem. Soc.* 3563 (1960); [c]A. W. Burgstahler and I. C. Nordin, *J. Am Chem. Soc.* **83**, 198 (1961); [d]S. Nishimura and K. Mori, *Bull. Chem. Soc. Jap.* **36**, 318 (1963).
[152]J. R. Bull and J. A. Harpur, *S. Afr. J. Chem.* **30**, 175 (1977); *Chem. Abstr.* **88**, 23260r (1978).
[153]This is only a conjecture since no accurate evaluation of polar effects is presently available.
[154]W. G. Young, R. E. Ireland, T. I. Wrigley, C. W. Shoppee, B. D. Agashe and G. H. R. Summers, *J. Am. Chem. Soc.* **81**, 1452 (1959).
[155]We expect more examples to come to light over the next few years.
[156]H. B. Henbest, *Proc. Chem. Soc.* 159 (1963).
[157a]C. G. Chadvarian and C. M. Heathcock, *Synth. Comm.* **6**, 277 (1976). [b]R=Me, G. Bellucci, G. Berti, R. Bianchini, G. Ingrosso and E. Mastrorilli, *Gazz. Chim. Ital.* **106**, 955 (1976).
[158]T. Mah, H. M. Sirat and E. J. Thomas, *J. Chem. Soc.* Perkin I, 2255 (1979).
[159]J. Perez-Ruelas, J. Iruarte, F. Kincl and C. Djerassi, *J. Org. Chem.* **23**, 1744 (1958).
[160]J. Farkas and J. M. Owen, *J. Med. Chem.* **9**, 510 (1966).
[161]R. R. Sobti, J. Bordner and S. G. Levine, *J. Am. Chem. Soc.* **93**, 5589 (1971).
[162]D. Bauer, T. Iizuka, K. Schaffner and O. Jeger, *Helv. Chim. Acta* **55**, 852 (1972).
[163a]I. N. Nazarov and I. V. Torgov, *Izv. Akad. Nauk. S.S.S.R., Ser. Khim.* 901 (1953); [b]I. N. Nazarov and L. D. Bergelson, In *Chemistry of Steroid Hormones*, pp. 592, 598. *Acad. Sci. S.S.S.R. Ed.* Moscow (1955).
[164]R. E. Ireland, W. J. Thompson, N. S. Mandel and G. S. Mandel, *J. Org. Chem.* **44**, 3583 (1979); see Ref. 4.
[165]F. Fringuelli, F. Pizzo, A. Taticchi and E. Wenkert, *Synth. Comm.* **9**, 391 (1979).
[166]R. K. Boeckmann Jr. and R. Michalak, *J. Am. Chem. Soc.* **96**, 1623 (1974).
[167]S. Masamune, G. S. Bates and P. E. Georghiou, *Ibid.* **96**, 3686 (1974).
[168]S. David, A. Lubineau and J. M. Vatele, *Chem. Commun.* 536 (1978).
[169]D. Bertin and J. Perronnet, *Bull. Soc. Chim. Fr.* 2782 (1964).
[170]J. Ficini, A. Eman and A. M. Touzin, *Tetrahedron Letters* 679 (1976): 55% yield.
[171]J. Ficini and A. M Touzin, *Tetrahedron Letters* 1447 (1974): 50% yield.

[172a]T. Harayama, H. Cho and Y. Inubushi, *Chem. Pharm. Bull.* **25,** 2273 (1977); [b]T. Harayama, M. Takatani and Y. Inubushi, *Ibid.* **27,** 726 (1979); [c]W. Oppolzer and M. Petrzilka, *Helv. Chim. Acta* **61,** 2755 (1978).
[173]S. A. Sisk and R. C. Hutchinson, *J. Org. Chem.* **44,** 3501 (1979); for a similar interpretation: J. L. Primeau, R. C. Anderson and B. Fraser-Reid, *Chem. Commun.* 6, (1980).
[174]C. Y. Shiue, R. G. Lawler and L. B. Clapp, *J. Org. Chem.* **41,** 2210 (1976).
[175]Many results are scattered in the literature.
[176]E. Toromanoff, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. 2, p. 157. Interscience, New York (1967).
[177a]Y. Yamamoto and H. L. Sham, *J. Am. Chem. Soc.* **101,** 1609 (1979); [b]G. Asato, *Dissert. Abstr.* **22,** 2186 (1962).
[178a]P. Koell, T. Schultek and R. W. Rennecke, *Chem. Ber.* **109,** 337 (1976). [b]J. Pecka and M. Cerny, *Coll. Czech. Chem. Comm.* **43,** 1720 (1978).
[179]N. C. Danh, C Arnaud and J. Huet, *Bull. Soc. Chim. Fr.* 1071 (1974) see table II, p. 1072.
[180]F. Johnson and S. K. Malhotra, *J. Am. Chem. Soc.* **87,** 5492 (1965).
[181]A. K. Macbeth and J. S. Shannon, *J. Chem. Soc.* 2852 (1952).
[182]S. K. Malhotra, D. F. Moakley and F. Johnson, *Tetrahedron Letters* 1089 (1967) see Ref. 6.
[183a]H. B. Henbest and J. McEnte, *J. Chem. Soc.* 4478 (1961). [b]J. A. Marshall and W. I. Fanta, *J. Org. Chem.* **29,** 2501 (1964).
[184]J. L. Luche, L. Rodriguez-Hahn and P. Crabbe, *Chem. Comm.*, 601 (1978).
[185]Ref. 176, p. 173.
[186a]D. Baldwin and J. R. Hanson, *J. Chem. Soc.* Perkin I, 1940 (1975). [b]E. Chicoye, W. D. Powrie and R. O. Fennema, *Lipids* **3,** 551 (1968), *Chem. Abstr.* **70,** 47684m (1969).
[187a]T. Dahl, Y-H. Kim, D. Levy and R. Stevenson, *J. Chem. Soc.* (C), 2723 (1969). [b]A. Bowers, E. Denot, M. B. Sanchez, F. Neumann and C. Djerassi, *Ibid.* 1859 (1961).
[188]E. H. Eschinasi, *J. Org. Chem.* **35,** 2010 (1970).
[189a]K. Abe, M. Onca and S. Okuda, *Chem. Pharm. Bull.* **17,** 1847 (1969). [b]B. Bognar, S. Makleit, J. Knoll, S. Berenyi and G. Horvath, *Chem. Abstr.* **84,** 135889b.
[190a]C. C. Chiang, W. H. De Camp, D. Y. Curtin, I. C. Paul, S. Shifrin and U. Weiss, *J. Am. Chem. Soc.* **100,** 6195 (1978); [b]*N.M.R. Study:* S. Okuda, S. Yamaguchi, Y. Kawazoe and K. Tusda, *Chem. Pharm. Bull.*, **12,** 104 (1964).
[191]E. M. Burgess, *J. Org. Chem.* **27,** 1433 (1962); hydride addition mainly takes place as expected, from the α side.
[192]M. Perry and Y. Maroni-Barnaud, *Bull. Soc. Chim. Fr.* 3581 (1969).
[193]W. S. Johnson, N. Cohen, E. R. Habicht, Jr., D. P. G. Hamon, G. P. Rizzi and D. J. Faulkner, *Tetrahedron Letters* 2829 (1968).
[194]B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.* **100,** 3435 (1978).
[195]R. Heckendorf and Ch. Tamm, *Helv. Chim. Acta.* **50,** 1964 (1967).
[196]R. A. Packer and J. S. Whitehurst, *J. Chem. Soc.* Perkin I, 110 (1978).
[197]J. E. McMurry, A. G. M. Ksander, J. M. Husser and M. A. Johnson, *J. Am. Chem. Soc.* **101,** 1330 (1979).
[198]J. L. Swenton, J. A. Hyatt, T. J. Walker and A. L. Crumrine, *Ibid.* **93,** 4808 (1971).
[199]M. Gill and R. W. Rickards, *Chem. Commun.* 121 (1979).
[200a]Y. Ohfune, P. A. Grieco, C. L. J. Wang and G. Majetich, *J. Am. Chem. Soc.* **100,** 5946 (1978); [b]G. J. Quallich, R. H. Schlessinger, *Ibid.* **101,** 7627 (1979); [c]Discussion: P. Kok, P. J. de Clercq and M. E. Vandewalle, *J. Org. Chem.* **44,** 4553 (1979).
[201]E. Toromanoff, *C.R. Acad. Sci.* **264,** 1881 (1967).
[202]E. Toromanoff, *Bull. Soc. Chim. Fr.* 2457 (1968).
[203]L. Pierre and H. Handel, *Tetrahedron Letters* 2317 (1974).
[205a]F. Roquet et A. Sevin, *Bull. Soc. Chim. Fr.* 895 (1974); [b]J. L. Pierre and P. Chautemps, *Tetrahedron Letters* 4374 (1972).
[205a]J. H. H. Chan and B. Rickborn, *J. Am. Chem. Soc.* **90,** 6406 (1968); [b]W. G. Dauben and G. H. Berezin, *Ibid.* **85,** 468 (1963).
[206]M. Hanack and H. Allmendiger, *Chem. Ber.* **97,** 1669 (1964).
[207]C. Cueille, R. Jullien and M. Derieux, *Bull. Soc. Chim. Fr.* 306 (1972).
[208]C. M. Holden, J. C Rees, S. P. Scott and D. Whittaker, *J. Chem. Soc.* Perkin II, 1342 (1976).
[209]M. S Mastryukov, E. L Osina, L. V. Vilkov and R. L. Hilderbrandt, *J. Chem. Soc.* **99,** 6855 (1977).
[210]L. A. Paquette, R. W. Begland and P. C. Storm, *Ibid.* **92,** 1971 (1970).
[211]Discussion and Rererences: [a]M. Weissenberg, D. Lavie and E. Glotter, *Tetrahedron* **29,** 353 (1973); [b]M. Weissenberg and E. Glotter, *J. Chem. Soc.* Perkin I, 568 (1978).
[212]E. Glotter and P. Krinsky, *J. Chem. Soc.* Perkin I, 413 (1978).
[213]D J. Collins, *Ibid.* 3919 (1959).
[214]A. Defoin and J. Rigaudy, *Bull. Soc. Chim. Fr.* II-110 (1979).
[215a]Ref. 91, p. 166; [b]R. Curci, F. di Furia and M. Meneghin, *Gazz. Chim. Ital.* **108,** 123 (1978).
[216]B. M. Trost and L. S. Melvin, Jr., *Sulfur Ylides*, Vol. 31, p. 77. Academic Press, New York (1975).
[217]For instance see, H. Schechter, D. E. Ley, E. B. Robertson, Jr., *J. Am. Chem. Soc.* **78,** 4984 (1978).
[218]Review: D. Caine, *Org. React.* **31,** 1 (1976).
[219]H. C. Brown and S. Krishnamurthy, *Tetrahedron* **35,** 567 (1979); examples of conjugate addition to enones p. 586.
[220a]H. B. Henbest, W. R. Jackson and I. Malunowicz, *J. Chem. Soc.* (C), 2469 (1967). [b]R. L. Augustine, *Ann. New York Acad. Sci.* **145,** 19 (1967).
[221]E. Cantrall, R. Littell and S. Bernstein, *J. Org. Chem.* **29,** 64 (1964).
[222]A. R. van Horn and C. Djerassi, *J. Am. Chem. Soc.* **89,** 651 (1967).
[223]I M. Clark, W. A. Denny, E. H. R. Jones, G. D. Meakins, A. Pendlebury and J. T. Pinhey, *J.t.S.* Perkin I, 2765 (1972).
[224]J. E. T. Corrie, *J. Chem. Res.* (S), 9. 1979.
[225]C. Djerassi, G. von Mutzenbecker, J. Fajkos, D. H. Williams and H. Budzikiewicz *J. Am. Chem. Soc.* **87,** 817 (1965).
[226]O. Schmidt, K. Prezewowsky, G. Schulz and R. Wiechert, *Chem. Ber.* **101,** 939 (1968).
[227]I. H. Hall, K. H. Lee, E. C. Mar, C. O. Starnes and T. G. Waddell, *J. Med. Chem.* **20,** 333 (1977).
[228a]T. G. Waddell, A. M. Austin, J. W. Cochran, K. G. Gerhart, I. H. Hall and K. H. Lee, *J. Pharm. Sci.* **68,** 715 (1979); [b]I. H. Hall, *Ibid.* **68,** 537 (1979)
[229]A. Sakurai and S. Tamura, *Agr. Biol. Chem. Tokyo* **30,** 793 (1960).
[230a]J. Cairns, C. L. Hewett, R. J. Logan, G. McGarry, R. G. Roy, D. F. M. Stevenson and G. F. Woods, *J. Chem. Soc.* Perkin I, 1594 (1978); [b]R. E. Schaub and M. J. Weiss, *J. Med. Chem.* **10,** 789 (1967).

[231]U. Kerb and R. Wiechert, *Liebigs Ann.* **752,** 78 (1971).
[232]Other examples of anion addition to such enones: Ref. 37, p. 194.
[233]B. Green and D. R. Liu, *Tetrahedron Letters* 2807 (1975).
[234]Ref. 218, pp. 33, 34.
[235]R. Fraisse-Jullien, C. Frejaville, V. Toure and M. Derieux, *Bull. Soc. Chim. Fr.* 3725 (1966).
[236]C. Frejaville and R. Jullien, *Tetrahedron Letters* 2039 (1971). R. D. Clark and C. H. Heathcock, *J. Org. Chem.* **41,** 1396 (1976).
[237]W. F. Johns, *Ibid.* **28,** 1616 (1963).
[238]E. Piers and K. F. Cheng, *Can. J. Chem.* **48,** 2234 (1970).
[239]B. M. Trost, Y. Nishimura, K. Yamamoto and S. S. McElvain, *J. Am. Chem. Soc.* **101,** 1328 (1979).
[240a]P. de Clercq, M. de Smet, K. Legein, F. Vanhulle and M. Vandewalle, *Bull. Soc. Chim. Belg.* **85,** 503 (1976); [b]P. de Clercq, D. van Haver, D. Tavernier and M. Vandewalle, *Tetrahedron* **30,** 55 (1974); [c]M. Samson, P. de Clercq and M. Vandewalle, *Tetrahedron* **33,** 249 (1977).
[241]T. Pappo and P. W. Collins, *Tetrahedron Letters* 2627 (1972).
[242]P. M. Collins, J. R. Hurford and W. G. Overend, *J. Chem. Soc.* Perkin I, 2163 (1975).
[243]A. Ichihara, J. Morita, K. Kobayashi, S. Kagawa, H. Shirahama and T. Matsumoto *Tetrahedron* **26,** 1331 (1970).
[244]M. Ephritikine, J. Levisalles and G. Teutsch, *Bull. Soc. Chim. Fr.* 4355, (1971) (H_2O_2, NaOH, dioxane 14h).
[245a]J. D. White and Y. Fukuyama, *J. Am Chem. Soc.* **101,** 226 (1979); [b]G. Stork and V. Nair, *Ibid.* **101,** 1315 (1979); [c]In a similar way one can interpret the results reported by C. H. Heathcock, T. C. Germroth and S. Lindsay-Graham, *J. Org. Chem.* **44,** 4481 (1979).
[246]For a recent review of organocuprate conjugate addition see G. H. Posner, *Org. React.* **19,** 1 (1972).
[247]D. E. Evans, G. S. Lewis, J. P. Palmer and D. J. Weyell, *J. Chem. Soc.* (C), 1197 (1968) (>60% 2α, 3α methylene).
[248]H. Mori and R. Oh-Uchi, *Chem. Pharm. Bull.* **23,** 980 (1975).
[249]P. Striebel and C. Tamm, *Helv. Chim. Acta* **41,** 1730 (1958).
[250]J. A. Marshall and N. H. Andersen, *J. Org. Chem.* **31,** 667 (1966). [251]J. A. Campbell and J. C. Babcock, *J. Am. Chem. Soc.* **81,** 4069 (1959).
[252]G. E. Arth, G. F. Reynolds, G. H. Rasmussen, A. Chen and A. A. Patchett, *Tetrahedron Letters* 291 (1974).
[253]C. Sandris and G. Ourisson, *Bull. Soc. Chim. Fr.* 1524 (1958).
[254]J. F. Biellmann, R. Hanna, G. Ourisson, C. Sandris and B. Waegell, *Ibid.* 1429 (1960).
[255]Tuyet Long Thi Ngoc and H. Rivière, *C.R. Acad. Sci.* **267C,** 776 (1968).
[256]H. Rivière and J. Tostain, *Bull. Soc. Chim. Fr.* 568 (1969).
[257]Ngoc-Tuyet Luong Thi and H. Rivière, *Tetrahedron Letters* 1579 (1970).
[258]J. A. Marshall and R. H. Ellison, *J. Org. Chem.* **40,** 2070 (1975).
[259]F. Roquet and A. Sevin, *Bull. Soc. Chim. Fr.* 888 (1974).
[260]A. Pons, J. C. Milhavet and J. P. Chapat, *Ibid* II-381 (1979).
[261]F. E. Ziegler and M. F. Condon, *J. Org. Chem.* **36,** 3707 (1971).
[262]Under kinetic conditions cyanide anion yields mainly the *trans*-substituted decalone: W. Nagata, M. Yioshioka and S. Hirai, *Tetrahedron Letters* 461 (1962).
[263]K. E. Harding, R. C. Ligon, Chung-Ye-Tseng and Tsi-Chien-Wu, *J. Org. Chem.* **38,** 3478 (1973). For alkaline epoxidation, even if the initial kinetic product is the enolate of the *trans*-substituted hydroperoxydecalone, the reversibility of the reaction leads to a mixture in which the *cis* derivative is the major component.
[264]The following references correspond to the letters of the Table: [a]H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan and J. F. Simeone, *J. Am. Chem. Soc.* **92,** 2800 (1970). [b]S. A. Darling, O. N. Devgan and R. E. Cosgrove, *Ibid.* **92,** 696 (1970); [c]H. O. House and J. C. Dubose, *J. Org. Chem.* **40,** 788 (1975); [d]R. Noyori, I. Umeda and T. Ishigami, *Ibid.* **37,** 1542 (1972); [e]R. L. Augustine, *Ibid.* **23,** 1853 (1958); [f]H. Wehrli, C. Lehrmann, P. Keller, J. J. Bonnet, K. Schaffner and O. J. Jeger, *Helv. Chim. Acta* **49,** 2218 (1966); 151a; [g]R. K. Boeckman Jr. and R. Michalak, *J. Am. Chem. Soc.* **96,** 1623 (1974); [h,i]S. Masamune, G. S. Bates and P. E. Georghiou, *Ibid.* **96,** 3686 (1974); [j]=151a; [k]J. T. Gerig and J. D. Roberts, *Ibid.* **88,** 2791 (1966).
[265]A. J. Birch and M. Smith, *Proc. Chem. Soc.* 356 (1962); M. Fetizon, M. Golfier and N. Lafont, *C.R. Acad. Sci.* **254,** 3376 (1962); J. A. Marshall, W. I. Fanta and H. Roebke, *J. Org. Chem.* **31,** 1016 (1966).
[266a]E. Piers, W. M. Phillips-Johnson and C. Berger, *Tetrahedron Letters* 2915 (1972); [b]W. Reusch, K. Grimm, J. E. Karoglan, J. Martin, K. P. Subrahamanian, Yock-Chai Toong, P. S. Venkataramani, J. D. Yordi and P. Zoutendam, *J. Am. Chem. Soc.* **89,** 1953 (1977).
[267a]C. J. V. Scanio and R. M. Starrat, *Ibid.* **93,** 1539 (1971) R=Me. [b]D. L. Boger, *Tetrahedron Letters* 17 (1978), R=CO_2H.
[268]D. Caine and T. L. Smith, Jr., *J. Org. Chem.* **43,** 755 (1978).
[269]Ref. 1, p. 206
[270]For more details see: Ref. 1, p. 173.
[271]H. O. House and M. J. Lusch, *J. Org. Chem.* **42,** 183 (1977).
[272]G. W. Shaffer, E. H. Eschinazi, K. L. Purzycki and A. B. Doerr, *Ibid.* **40,** 2181 (1975).
[273]P. Beak and T. L. Chaffin, *Ibid.* **35,** 2275 (1970).
[274]J. A. Marshall and S. F. Brady, *Ibid.* **35,** 4068 (1970).
[275]R. K. Boeckman Jr and M. Ramaiah, *Ibid.* **42,** 1581 (1977).
[276]H. Paulsen, K. Koebernick and H. Koebernick, *Tetrahedron Letters* 2297 (1976).
[277a]T. Sakakibara and R. Sudoh, *J. Org. Chem.* **40,** 283 (1975); T. Sakakibara, M. Yamada and R. Sudoh, *Ibid.* **41,** 736 (1976); T. Sakakibara and R. Sudoh, *Ibid.* **42,** 1746 (1977); T. Sakakibara, R. Sudoh and T. Nagakawa, *Bull. Chem. Soc. Jap.* **51,** 1189 (1978); [b]P. M. Collins, D. Gardiner, S. Kumar and W. G. Overend, *J. Chem. Soc.* Perkin I, 2596, 2611 (1972).
[278]M. Kocor and W. Kroszczynski, *J. Indian. Chem Soc.* **55,** 1179 (1978); *Chem Abstr.* **91,** 193506e (1979); 1α addition of nitromethane anion.
[279]E. L. Shapiro, T. L. Popper, L. Weber, R. Neri and H. L. Herzog, *J. Med. Chem.* **12,** 631 (1969).
[280]G. W. Krakower and H. A. van Dine, *J. Org. Chem.* **31,** 3467 (1966).
[281]E. Piers, W. de Waal and B. W. Britton, *Chem. Comm.* 188 (1968), *Can. J. Chem.* **47,** 4299 (1969).
[282]R. Wiechert, O. Engelfried, U. Kerb, H. Laurent, H. Müller and G. Schulz, *Chem. Ber.* **99,** 1118 (1966).
[283]J. A. Marshall and R. A. Ruden, *J. Org. Chem.* **37,** 659 (1972).
[284]M. A. Adams, A. J. Duggan, J. Smolanoff and J. Meinwald, *J. Am. Chem. Soc.* **101,** 5364 (1979).
[285]This addition-elimination could involve first a displacement with configurational inversion and formation of a copper-carbon bond, followed by an alkyl transfer with allylic shift, as suggested in Ref. 286.
[286]G. Teutsch and A. Belanger, *Tetrahedron Letters* 2021 (1979).

[287]The same hypothesis has also been used for the interpretation of SN′ reactions (private communication from Professor R. M. Magid (1978)).
[288]E. Toromanoff, *Tetrahedron* **36,** 893 (1980).
[289]D. L. Whalen and A. M. Ross, *J. Am. Chem. Soc.* **96,** 3678 (1974).
[290]G. A. Crosby and R. A. Stephenson, *Chem. Commun.* 287 (1975).
[291]G. Stork, *results presented at a seminar in Romainville* (22 May 1970).
[292]G. Stork, C. Kowalski, G. Garcia, *J. Am. Chem. Soc.* **97,** 3258 (1975).
[293]For the opening of cyclopentadiene epoxide with organocuprates see: J. P. Marino and J. S. Farina, *J. Org. Chem.* **41,** 3213 (1976). The absence of compounds resulting from the 1.4-*cis* opening of cyclopentadiene epoxide is intriguing
[294]J. P. Marino and D. M. Floyd, *Tetrahedron Letters* 675 (1979). The opening of 1 3 cycloheptadiene epoxide yields a mixture of derivatives corresponding to *syn* and *anti* conjugate additions.
[295]W. Kirmse, F. Scheidt and H. J. Vater, *J. Am. Chem. Soc.* 100, 3945 (1978).
[296a]D. L. Garin and K. L. Cammack, *Chem. Commun.* 333 (1972); [b]W. T. Brady and A. D. Patel, *J. Org. Chem.* 38, 4106 (1973); [c]K. E. Harding, J. W. Trotter and L. M. May, *Ibid.* **42,** 2715 (1977). It is tempting to speculate about a *cis* mechanism for these SN′ reactions involving cyclobutanone enolates but the steric course of these cine-substitutions has not been ascertained.
[297]Reviews of SN′ reactions: [a]R. D. de Wolfe and W. G. Young, *The Chemistry of Alkenes* (Edited by S. Patai), p. 688 and seq. Interscience, New York (1964). [b]F. G. Bordwell, *Accounts Chem. Res.* **3,** 281 (1970). [c]R. A. Sneen, *Ibid.* **6,** 46 (1973).
[298]E. Toromanoff, *C.R. Acad. Sci. Paris* **284c,** 113 (1977); *Tetrahedron* **34,** 1665 (1978).
[299a]K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Jap.* **40,** 2018 (1967); [b]W. Drenth, *Rec. Trav. Chim.* **86,** 318 (1967); [c]N. T. Anh, *Chem. Commun.* 1089 (1968); [d]C. L. Liotta, *Tetrahedron Letters* 523 (1975); [e]R. L. Yates, N. D. Epiotis and F. Bernardi, *J. Am. Chem. Soc.* **97,** 6615 (1975).
[300a]P. S. Aumeer, T. B. H. McMurry, *Chem. Commun.* 641 (1971); [b]T. Masamune, H. Matsui and M. Fujii, *Bull. Chem. Soc. Jap.* **45,** 1812 (1972); [c]C. R. Johnson, R. W. Herr and D. M. Wieland, *J. Org. Chem.* **38,** 4263 (1973); [d]W. Clark Still, *Tetrahedron Letters* 2115 (1976); [e]H. L. Goering and V. D. Singleton Jr., *J. Am. Chem. Soc* **98,** 7854 (1976). A. Kreft, *Dissert. Abstr.* 76 30–389 (1976); [f]G. Stork and A. F. Kreft III, *J. Am. Chem. Soc.* **99,** 3850, 8373 (1977); [g]G. Stork and A. F. Kreft III, *Ibid.* **99,** 3851, 8373 (1977); [h]G. Stork and A. R. Schoofs, *Ibid.* **101,** 5081 (1979); [i]D. E. Cane, P. P. N. Murthy, *Ibid.* **99,** 8327 (1977); [j]S. Godtfredsen, J. P. Obrecht and D. Arigoni, *Chimia* **31,** 62 (1977); [k]A. A. Dobbie and K. H. Overton, *Chem. Commun.* 722 (1977); [l]T. Oritani and K. Overton, *Ibid.* 454 (1978); [m]R. M. Magid and O. S. Fruchey, *J. Am. Chem. Soc.* **99,** 8368 (1977); [n]O. S. Fruchey, *Dissert. Abstr. Int. B,* **38,** 5939 (1978); [o]R. M. Magid and O. S. Fruchey, *J. Am. Chem. Soc.* **101,** 2107 (1979); [p]J. J. Uebel, R. F. Milaszewski and R. E. Arlt, *J. Org. Chem.* **42,** 585 (1977); [q]A. R. Pinder and W. D. Saunders, *J. Chem. Soc.* Perkin I, 282 (1978); [r]C. Georgoulis and G. Ville, *J. Chem. Res.* (S), 248 (1978); [s]C. Gallina and P. G. Ciattini, *J. Am. Chem. Soc.* **101,** 1035 (1979).
[301]N. Ikota and B. Ganem, *Ibid.* **100,** 351 (1978).
[302]J. Pecka, J. Stanek, Jr. and M. Cerny, *Coll. Czech. Chem. Comm.* **39,** 1192 (1974).
[303]S. C. Welch, C. P. Hagan, D. H. White, W. P. Fleming and J. W. Trotter, *J. Am. Chem. Soc.* **99,** 549 (1977).
[304]K. Abe, Y. Nakamura, M. Onda and S. Okuda, *Tetrahedron* **27,** 4495 (1971).
[305]K. Abe, M. Onda and S. Okuda, *J. Chem. Soc.* Perkin I, 316 (1973).
[306]Y. Tanigawa, H. Ohta, A. Sonoda, S. I. Murahashi, *J. Am. Chem. Soc.* **100,** 4610 (1978).
[307]C. W. Jefford, A. Sweeney and F. Delay, *Helv. Chim. Acta* **55,** 2214 (1972).
[308]A. Viger, S. Coustal and A. Marquet, *Tetrahedron* **34,** 3285 (1978).
[309]B. Fraser-Reid, S. Y-K. Tam and B. Radatus, *Can. J. Chem.* **53,** 2005 (1975).
[310]J. Y. Satoh, C. A. Horiuchi and A. Hagitani, *Chem. Letters* 995 (1972).
[311]J. Y. Satoh and T. T. Takahashi, *Chem. Comm.* 1714 (1970).
[312]R. D. Burnett and D. N. Kirk, *J. Chem. Soc.* Perkin I, 1830 (1973).
[313]E. Toromanoff, *Tetrahedron* **34,** 1461 (1978).
[314]The epoxide being as shown, (axial above the mean plane of the molecule), the torsion angle sequence is: + 0 −.
[315]D. L. Whalen, *J. Am. Chem. Soc.* **95,** 3432 (1973).
[316]D. M. Wieland and C. R. Johnson, *Ibid.* **93,** 3048 (1971); For the conjugate addition of organocuprates, see the following references:
[317a]J. Staroscik and B. Rickborn, *Ibid.* **93,** 3046 (1973); [b]J. P. Marino and N. Hatanaka, *J. Org. Chem.* **44,** 4467 (1979).
[318]W. S. Knowles and Q. E. Thompson, *J. Am. Chem. Soc.* **79,** 3212 (1957).
[319]U. Kerb, G. Schulz and R. Wiechert, *Angew Chem.* Int. Ed. **7,** 893 (1968).
[320a]M. Neeman, T. Mukai, J. S. O'Grodnick and A. L. Rendall, *J. Chem. Soc.* Perkin I, 2300 (1972); [b]P. T. Julian, V. Georgian and H. C. Printy, *J. Am. Chem. Soc.* **91,** 1960 (1969) see footnote 13; [c]M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanamoto, T. Koga, M. Inuzuka and T. Furuta, *Tetrahedron* **21,** 733 (1965).
[321]E. J. Parish and G. J. Schroepfer, *Tetrahedron Letters* 3775 (1976).
[322]M. Tsuda, E. J. Parish and G. Schroepfer, Jr., *J. Org. Chem.* **44,** 1282 (1979).
[323]E. Toromanoff, unpublished results (1979).
[324]E. Toromanoff, *Tetrahedron* **36,** 207 (1980).
[325]E. Toromanoff, unpublished results (1979).