Russian Chemical Reviews **68** (3) 183 – 201 (1999) © 1999 Russian Academy of Sciences and Turpion Ltd

UDC 547.222.127

Mechanism of the directing influence of functional groups and the geometry of reactant molecules on peroxide epoxidation of alkenes

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Abstract. The influence of steric and electronic factors on the reactivity and the stereochemical outcome of epoxidation of cycloalkenes and prochiral alkenes by alkyl hydroperoxides, peroxy acids, oxaziridines, dioxiranes and dimethyl-α-peroxy lactone is analysed comparatively and generalised. The distinctive features of the directing influence of functional groups on the stereochemistry of the epoxide ring closure in the series of ionic, radical and molecular reactions are demonstrated. Some variants alternative to known reaction mechanisms are proposed. The bibliography includes 114 references.

I. Introduction

Stereochemical regularities of the epoxidation of alkenes by peroxide reagents have been the subject of detailed studies,[1–8] because reactions of this type are widely used in asymmetric synthesis and for the preparation of a number of polyfunctional compounds of specified structures. In the last two decades, the knowledge of the stereochemistry of epoxidation has become much deeper due to the understanding of the role of stereoelectronic microeffects in the transition state[2,5–9] and long-range macrostereochemical effects at the stage of coming together and coordination of reactants.[10–13]

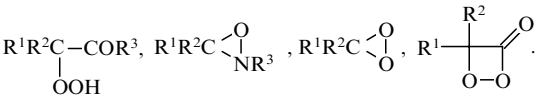
Thus it was found that the rate of epoxidation of aliphatic compounds by peroxy acids depends on the length and conformation of the hydrocarbon chain of the molecule.[1,2] The dependence of the rate constants for epoxidation (k_{epox}) on the number of carbon atoms in the molecule of the peroxy acid RCO_3H or alkene is a broken curve (alternation effect).[10] When the size of the peroxy acid molecule increases, the rate and contribution of epoxidation decrease; simultaneously, the loss of active oxygen in the alkene-induced decomposition of the peroxy acid becomes more significant.[2,11,12] The rate of epoxidation of the first double bond in the diallyl dicarboxylates $H_2C=CHCH_2OCO.(CH_2)_nCOOCH_2CH=CH_2$ markedly decreases at $n > 2$, although the electron-withdrawing influence of the ester group rapidly decays with an increase in n.[13]

The k_{epox} is substantially influenced by the solvation of functional groups far removed from the reaction centre. This solvation, like the increase in the size of the molecule, results in the loss of rotational degrees of freedom of reactant molecules and thus decreases the probability of their efficient collision.[2,13]

The requirements for the spatial compatibility of reactants become more rigorous with an increase in the size of the substituents surrounding the CO_3H group up to the point when the steric factor becomes more significant than the electronic factor. *cis*-Alkenes better fit in the 'niche' of the shielded peroxy-acid site. As a consequence, the $k_{cis}:k_{trans}$ value becomes relatively high. An increase in the number of alkyl substituents at the double bond decreases the reaction rate.[14]

The stereo- and regioselectivity of epoxidation are largely associated with the influence of alkyl substituents and functional groups in the alkene (OH, COOH, $CONH_2$, C=O, SiR_3, *etc.*) on the epoxidising reagent and with the geometry of the reactant molecules.[2,6–8,15] However, the features of the stereochemical influence of substituents and the stages responsible for this influence are still not quite clear. In particular, they have not yet been identified for the set of epoxidising reagents presented below.[1,2,4,5,16]

ROO^-M^+, $ROOH-Cat$, RCO_3H, $(CF_3)_2C(OH)OOH$,



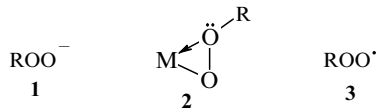
In this review, we attempt to generalise the accumulated data and to reveal new aspects concerning the mechanism of influence of the geometry of reactant molecules and the nature of functional groups on the rate, route and stereochemical outcome of epoxidation of alkenes with the above reagents. Using epoxidation by peroxy acids as an example, we describe systematically the general features of the behaviour of cycloalkenes and methylenecycloalkanes as functions of the strain and the degree of shielding of the double bond.

II. Epoxidation of alkenes with alkyl hydroperoxides

Epoxidation is normally carried out using alkyl hydroperoxide derivatives of types **1** – **3** shown below

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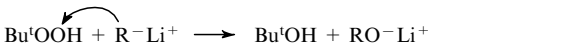
Received 5 January 1998
Uspekhi Khimii **68** (3) 206 – 226 (1999); translated by Z P Bobkova



1 **2** **3**

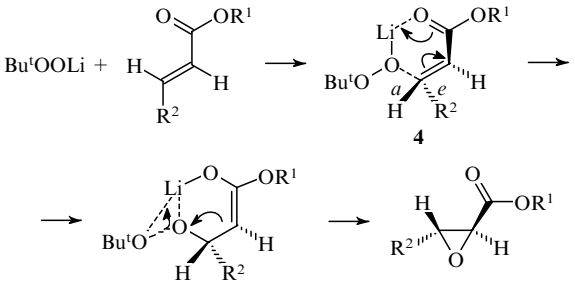
M is a transition metal in the highest oxidation state (Mo^{6+}, V^{5+}, Ti^{4+}, *etc.*).

Alkylperoxide anions **1**, like the hydroperoxide anion, oxidise polar C=C double bonds conjugated with a carbonyl group in chalcones, quinones, naphthoquinones,[17,18] α,β-unsaturated esters, sulfones, sulfoxyimines and amides[19–22] at moderate temperatures (−20 to 0 °C) with relatively high diastereoselectivity (20% – 100%). These reactions are catalysed by bases (NaOH, Na_2CO_3). The use of salts (ROOK and ROOLi), which are formed on treatment of ROOH with the corresponding metal hydrides or alkylmetals, is also efficient. It is of interest that the use of the Bu^tOOH – RLi oxidative system results in a side reaction, transfer of active oxygen to the carbanion, occurring in parallel with epoxidation.[19]



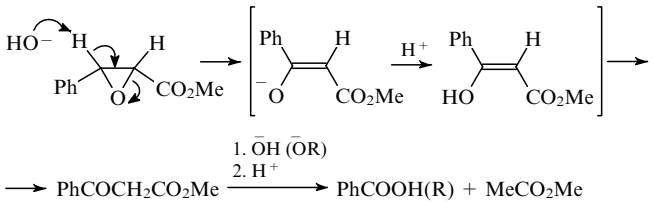
The regularities of the process have been studied most comprehensively in relation to epoxidation of α,β-unsaturated esters. This reaction is highly sensitive to steric restrictions, especially when the α- and β-positions in the substrate are substituted. The oxidation of *cis*-isomers is slower than that of *trans*-isomers. The reaction is completely stereospecific, except for oxidation of some sterically hindered esters of maleic acid. Di(*tert*-butyl) maleate is converted into the epoxide of di(*tert*-butyl) fumarate under the oxidation conditions.[19]

It is significant that epoxidation of α,β-unsaturated esters occurs diastereoselectively (the content of one isomer reaches 74%) only when lithium *tert*-butyl peroxide is used. When potassium *tert*-butyl peroxide is employed, the stereospecificity is lost. Apparently, the lithium cation, which has the most intense electromagnetic field among alkali metal cations, forms a stronger associative bond with the carbonyl oxygen atom in the substrate and thus stipulates the formation of cyclic transition state **4**. One of the two possible orientations of the unsaturated compound results in a more stable conformation of the transition state (TS) (with equatorial R^2); this ensures the predominant formation of one isomer.



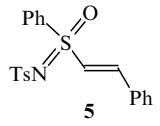
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The reaction is accompanied by several side processes, in particular, transesterification and a rearrangement of the α,β-epoxy ester. Thus epoxycinnamate can rearrange to give the ester of an oxo acid, which then undergoes the Claisen cleavage.



Di(*tert*-butyl) maleate does not undergo stereocontrolled epoxidation.[19] *N*,*N*-Dialkylamides of α,β-unsaturated acids undergo epoxidation with Bu^tOOLi with complete regio- and stereo-control and a small extent of side reactions. This method is relatively ineffective for secondary amides and totally ineffective for primary amides. As in the case of esters, oxidation of *cis*-amides occurs more slowly than that of the corresponding *trans*-isomers. The reaction rate depends appreciably on the size of the substituent at the β-position.

Phenyl *cis*-styryl sulfone is epoxidised according to the same rules as α,β-unsaturated esters. Epoxidation with potassium *tert*-butyl peroxide is not stereopecific (the ratio of *cis*- and *trans*-epoxides is 2 : 3), whereas treatment with lithium *tert*-butyl peroxide under the same conditions gives *cis*-epoxide as the only product in a high yield. The *trans*-isomer of this sulfone is epoxidised in a similar way. Asymmetric α,β-unsaturated sulfoxyimines **5** undergo epoxidation with 100% diastereoselectivity.



5

$(PhCH_2)_2NCH(R)CH{=}CHCOOMe$

6 (R = Alk)

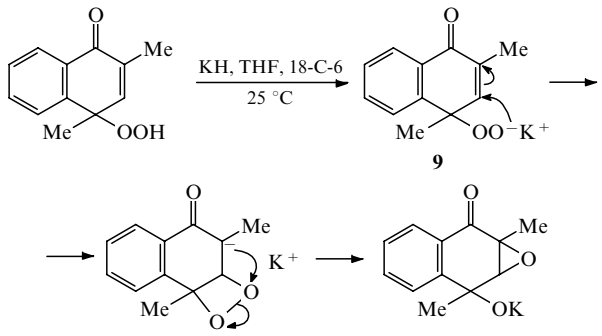
$RCH(OR')CH{=}CHSO_2R$ **7** (R = Alk, Ar; R′ = Alk)

$RCH_2CH{=}CHSO_2Ph$ **8** (R = Alk)

In this case, unlike the reactions described above,[19] the use of potassium *tert*-butyl peroxide in a THF – NH_3 mixture permits stereoselective epoxidation of unsaturated compounds **6**.[20] The ratio of *syn*- and *anti*-diastereoisomers amounts to 95 : 5.

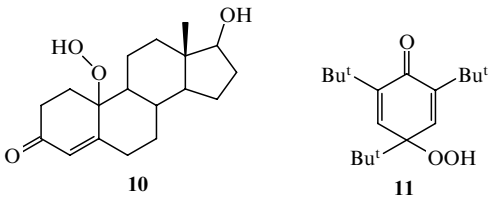
α,β-Unsaturated sulfones **7** undergo stereoselective epoxidation by Bu^tOOLi,[21] and analogous alkenyl sulfones **8** can be stereoselectively epoxidised by an alkaline solution of potassium *tert*-butyl peroxide.[22] In the latter case, the product of addition of alkyl hydroperoxide at the double bond was isolated, apart from the corresponding epoxide.

Intramolecular epoxidation of compound **9** simulates a stage of the biological oxidation of vitamin K.[23]



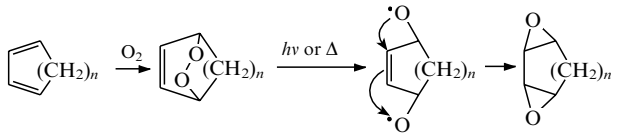
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The alkaline intramolecular epoxidation of cyclic α,β-unsaturated ketones **10** and **11** occurs in a similar way, yielding *cis*-epoxy alcohols.[24,25]

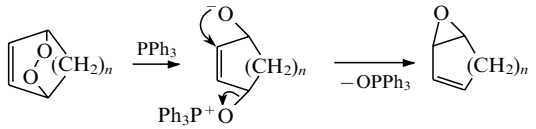


10 **11**

It can be easily understood that a coplanar arrangement of the *p* electrons of the peroxide anion and the π* (antibonding) orbital of the double bond in the substrate is a necessary stereochemical condition for epoxide ring closure in the ketones **9** – **11** (stereoelectronic factor). This is also true for a large number of other heterolytic and radical reactions involving not only π* orbitals[23–26] but also σ^*_{O-O}[1,27] and σ^*_{H-O}[28] type orbitals. In particular, this can be clearly seen in the case of photo or thermal isomerisation of *endo*-peroxides formed during oxygenation of cyclic 1,3-dienes by singlet oxygen.[26]



Similar stereoelectronic effects are involved in the deoxygenation of *endo*-peroxides with triphenylphosphine.[26]



The scheme of epoxidation of alkenes with alkylperoxyl radicals with the intermediate formation of β-peroxyalkyl radicals [1,27] is shown in Fig. 1.

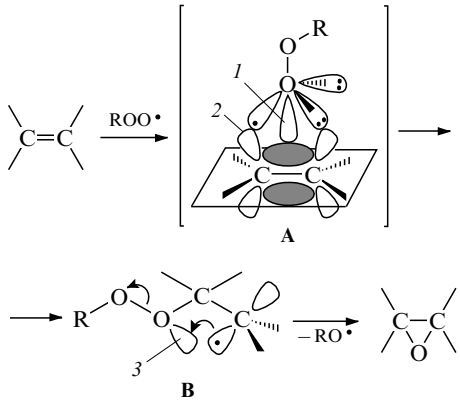
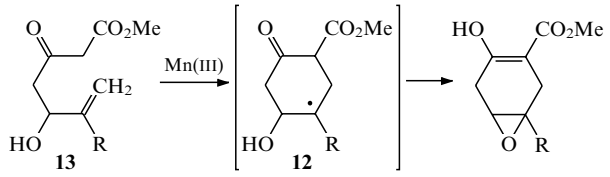
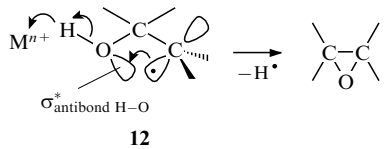


Figure 1. Epoxidation of alkenes with alkylperoxyl radicals: **A** is the donor–acceptor complex; **B** is the β-peroxyalkyl radical; (*1*) the σ^*_{O-O} orbital; (*2*) the π^*_{C-C} orbital; (*3*) the $\sigma^*_{\text{antibond } O-O}$ orbital.

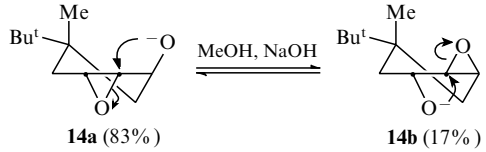
β-Hydroxy radicals **12** are generated during decarboxylation of β-hydroxy acids in the presence of lead tetraacetate and during oxidation of β-oxo esters **13** with manganese triacetate.[28]



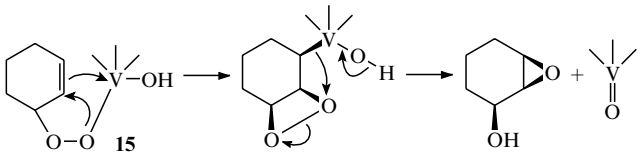
The epoxide ring closure occurring upon the oxidation of β-hydroxyl radicals by transition metal salts can be represented as follows:



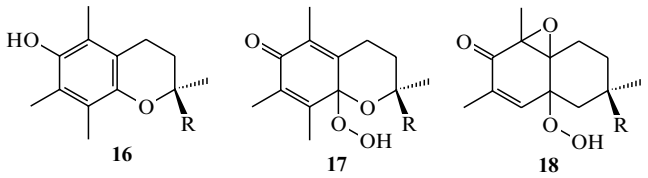
Isomerisation of α-hydroxy epoxide **14** in an alkaline medium occurs in a similar way.[29]



The generalisations made here can be invoked to interpret the mechanisms of some known reactions. Thus oxidation of alkenes with atmospheric oxygen on a vanadium catalyst [5,30] gives allyl hydroperoxides, which undergo intramolecular epoxidation. This affords epoxy alcohols only as *cis*-isomers, which has been confirmed by simulation of the stage of self-oxidation of cycloalkenyl hydroperoxides.[31] It is obvious that intramolecular *cis*-epoxidation rules out the possibility of the coplanar attack by the alkene π bond on the σ^*_{O-O} orbital and the mechanism typical of epoxidation of inorganic acids by peroxy esters.[5,7] Meanwhile, the structure of the substrate **15** is favourable for the nucleophilic attack by the outer peroxide oxygen atom on the π* orbital of the alkene activated by the catalyst.

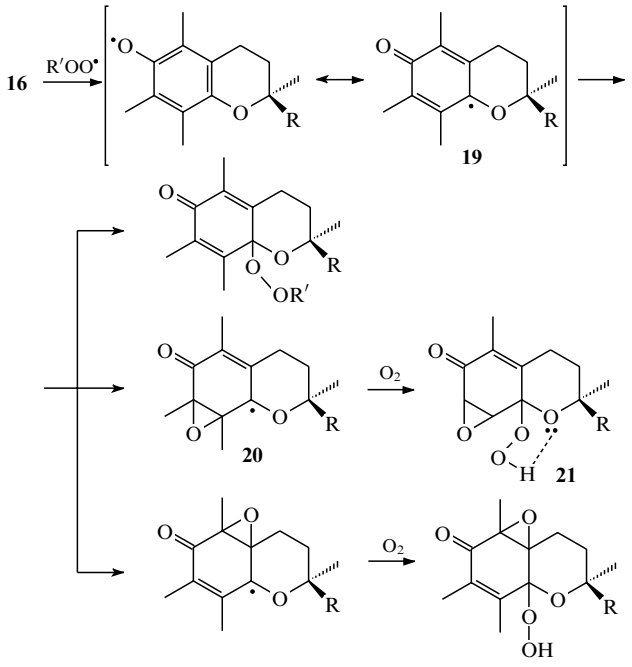


Yet another example of reaction the course of which can be predicted based on the above stereochemical regularity is oxidation of a biological antioxidant, vitamin E (D-α-tocopherol **16**).[32,33] It was reported [32] that the *tert*-butylperoxyl radical oxidises tocopherol **16** to give epoxy hydroperoxide **18** *via* the intermediate formation of hydroperoxide **17**.



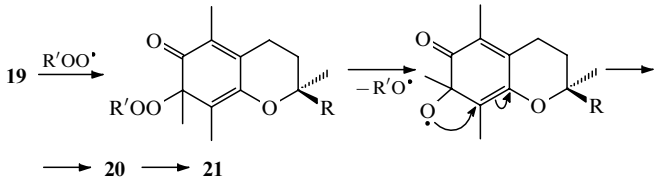
R = $CH_2[CH_2CH_2CH(Me)CH_2]_3H$.

When tocopherol **16** is oxidised by the radicals formed upon thermolysis of azobis-2,4-dimethylvaleronitrile in oxygen-saturated acetonitrile, the hydroperoxide **17** is formed in only small amounts and, judging by kinetic data, it is not an intermediate compound.[33] It was suggested that the reaction follows the scheme shown below:

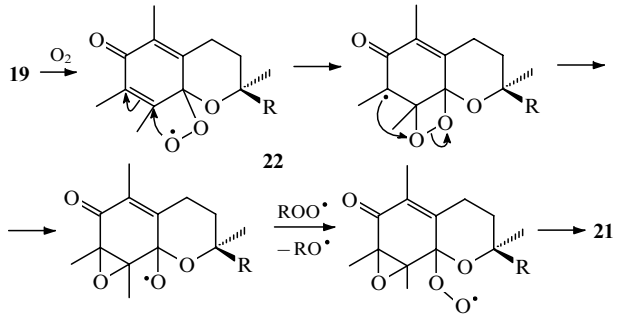


With allowance for the above-discussed stereoelectronic conditions for the closure of an epoxide ring, two ring formation mechanisms operating during the transformation of the radical **19**

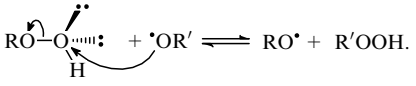
into **20** and then into the epoxide **21** can be conceived. In the case of direct attack by the alkylperoxyl radical R′OO• on the π bond, the following transformations occur:



In the case where the radical **19** captures a triplet oxygen molecule, a different sequence of transformations is possible.



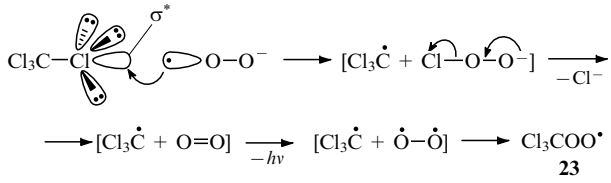
The epoxidation mechanism assuming the formation of the alkenylperoxyl radical **22** is possible in the case of either disproportionation of radicals or exchange interaction



One can expect that an equilibrium of this type in the reaction in question would be shifted towards the more stable hydroperoxide **21** having an intramolecular hydrogen bond.

It has been found that radicals formed from the superoxide ion ($O_2^{-\bullet}$) and polyhaloalkanes (CCl_4, $CHCl_3$, F_3CCCl_3, $PhCCl_3$, $Cl_2C=CCl_2$, *etc.*)[34,35] containing a halogen atom which can be homolytically eliminated possess epoxidising ability under mild conditions. For example, when CCl_4 is treated with potassium superoxide in acetonitrile in the presence of a phase transfer catalyst, the trichloromethylperoxyl radical $Cl_3COO^{\bullet}$ **23** acts a species of this type.

In our opinion, the mechanism of generation of this radical includes radical decomposition of polyhaloalkanes initiated by the superoxide ion to give singlet oxygen.

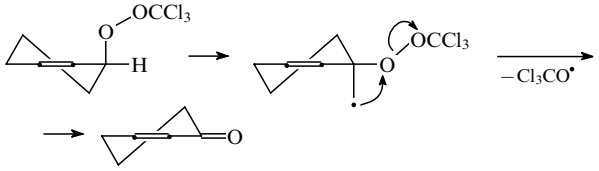


The fact that the yield of the epoxide does not depend on the concentration of $^3O_2$ indicates that the radical **23** is formed only from the initial compounds in a solvent cage.

The radical character of the process is confirmed by the loss of stereospecificity — *cis*-stilbene is mostly converted under these conditions into *trans*-stilbene oxide. Additives able to transform $Cl_3COO^{\bullet}$ into the anion inhibit the epoxidation.

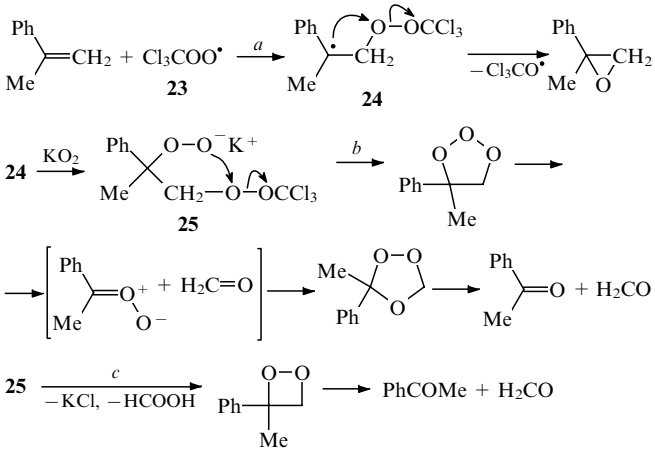
Oxidation of alkenes by radicals of the type **23** is a good model for the study of general, including stereochemical, regularities of the set of consecutive and competing transformations involved in epoxidation by alkylperoxyl radicals, oxometal complexes and triplet oxygen, which is usually accompanied by extensive oxidation of substrates with complete cleavage of the alkene double bond.[2,5,36]

In particular, attention is attracted by the fact that in addition to oxirane (yield 73%), epoxidation of cyclohexene in the CCl_4–KO_2 system gives cyclohex-2-enone (yield 9%), whereas 1-methylcyclohexene is oxidised only to the corresponding oxirane. This difference is undoubtedly due to the higher nucleophilicity of the double bond in the latter compound. However, the steric factor also cannot be ignored; indeed, the methyl group introduced in the cyclohexene molecule decreases its conformational mobility. The stereochemistry of radical oxidation of cyclohexene at the α-C–H bonds requires that the $Cl_3COO^{\bullet}$ radical **23** be inserted into the axial position; this should be followed (at the stage of formation of the carbonyl group) by ring inversion and migration of the substituents to the equatorial position.



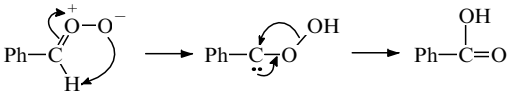
In addition to epoxides, the reaction affords products of complete cleavage of alkenes at the double bond (which are formed *via* a parallel route rather than in subsequent transformations). For example, acetophenone (19%) is formed in the oxidation of α-methylstyrene apart from the epoxide (73%). The highest yield of acetophenone is attained much earlier than that of the epoxide. It was found in special experiments that epoxide itself is not converted into acetophenone under the reaction conditions. It is also noteworthy that α-methylstyrene is oxidised more readily when taken as an equimolar mixture with styrene rather than in a pure state, although it is more nucleophilic.

The character of the observed transformations implies that in addition to the classical epoxidation of the alkene *via* β-peroxyalkyl radical **24** (pathway *a*),[2,36] transformations in this system include more extensive oxidation involving a second KO_2 molecule, yielding intermediate **25** and resulting in complete rupture of the alkene bond. This brings about the fundamentally important question of what is the route leading to the oxo compound. Indeed, this product could be formed either *via* the ozonide and then the Criegee intermediate (pathway *b*) or *via* dioxetane (pathway *c*).

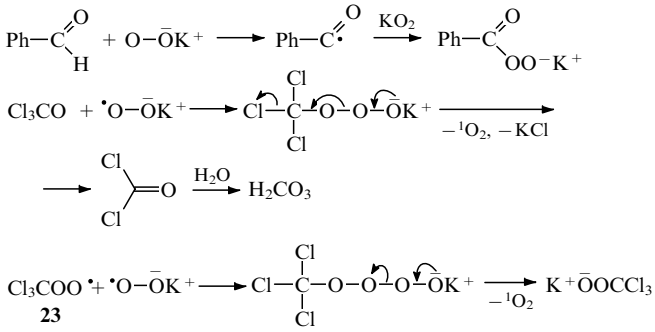


Pathway *b* is a result of the transfer of oxygen from the peroxide group R–O–O–R′ to the peroxyalkyl anion, by analogy with self-oxidation of peroxide compounds.[2] This seems more likely than pathway *c*, which assumes reversible nucleophilic substitution giving a strained dioxetane ring at an initial stage.

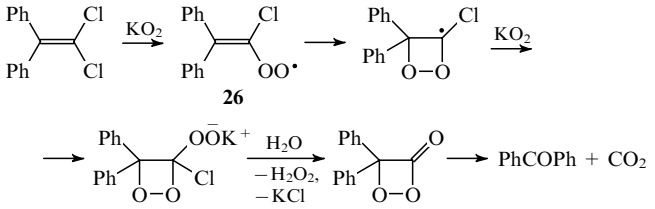
Pathway *b* involving the formation of a carbonyl oxide accounts for the fact that during oxidation of styrene, benzoic acid, formed in parallel with benzaldehyde, is accumulated in the reaction mixture.[35]



However, in the presence of KO_2, oxidation of aldehydes, in particular benzaldehyde, is also possible; this gives rise to the benzoylperoxide anion, the oxidative capacity of which exceeds that of the radical **23**. It is this fact that accounts for the promotory influence of styrene on the epoxidation of α-methylstyrene. The $Cl_3CO^{\bullet}$ radical formed in epoxidation is neutralised apparently by excess KO_2. The epoxidising radical **23** can be consumed in a similar way.



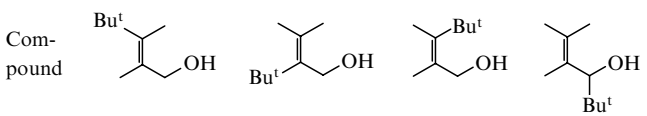
If the polyhalide molecule contains a double bond, cyclisation of the intermediate peroxyl radical **26** during the reaction becomes possible.[34]



Epoxidation of alkenes by peroxy esters of inorganic peroxy acids has been studied fairly comprehensively.[1, 2, 5, 7, 37, 38]

A peculiar feature of the ROOH – Cat epoxidising system (Cat is a transition metal complex) is that the hydroperoxide molecule enters the coordination sphere of the central atom as a nucleophile; this is accompanied by displacement of one ligand (acetylacetonate, OR, RCO_2, CO, *etc.*). Apparently, the alkene also participates in the ligand exchange. The rate of these reactions can be comparable with the epoxidation rate. Consequently, the overall rate of the process is controlled by the rate of diffusion and exhibits self-acceleration or, conversely, self-deceleration effects.[2, 39]

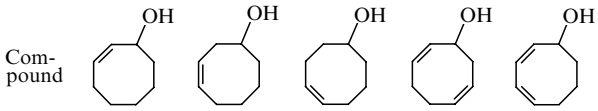
When the alkene contains a nucleophilic functional group (for example, an allylic hydroxy group), both the alkylperoxide fragment and this functional group get into the coordination sphere of the catalyst.[5, 7] Thus, the stereodirecting influence of the hydroxy group in alkenes on the attack by alkyl hydroperoxide is exerted at the stage of construction of a highly ordered multiligand donor–acceptor complex. It has been found that the stereoselectivity of formation of the corresponding oxiranes in the epoxidation of allylic alcohols decreases upon an increase in the degree of shielding of the hydroxy group.[40]



Compound				
ee (%)	> 95	85	25	5
Yield (%)	52	43	77	75

The geometry of the chiral environment of the catalytic center, which has a sort of matrix effect on the orientation of the prochiral double bond, is a crucial factor for the occurrence of stereocontrolled synthesis in the presence of the ROOH – Cat system. In particular, the Sharpless reagent ensures not only high diastereoselectivity but also enantiofacial selection caused by the ligand configuration (D- or L-tartrate). The strict spatial orientation of the molecular orbitals participating in the construction of the intermediate complex also makes a certain contribution to the matrix effect (stereoelectronic factor).

The extent to which a hydroxy group is involved in the epoxidation of cyclic alkenes and alkadienes is determined not only by its position relative to the double bond but also by the conformation of the molecule as a whole. This can be judged by examining the relative rates of epoxidation of the double bonds [Bu^tOOH, $VO(acac)_2$, C_6H_6, 40 °C] in the following sequence of substrates:[41]

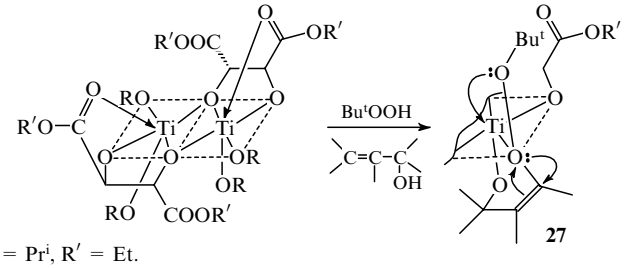


Compound					
k_{rel}	100	2.1	0.09	40	19

The introduction of a bulky trimethylsilyl group (*e.g.* at the 3-position) in the unsaturated alcohol molecule increases the stereoselectivity of epoxidation.[42]

The higher stereoselectivity observed in the presence of alkyl hydroperoxides and the greater versatility of these reagents compared to peroxy acids is due to the formation of a fairly strong donor–acceptor bond between the hydroxy group of alkenol and the central metal atom.

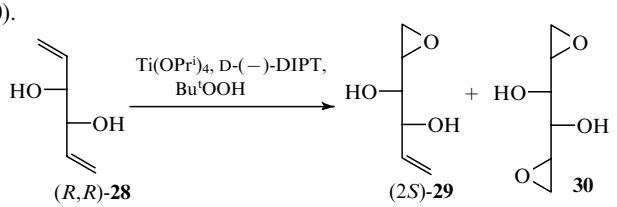
Detailed investigation of the Bu^tOOH – diethyl tartrate – Ti(IV) epoxidising system permitted the researchers[7, 39] to conclude that epoxidation occurs in binuclear complex **27** with six-coordinate titanium.



R = Pr^i, R′ = Et.

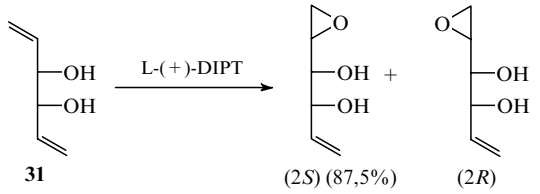
Change in the ligand nature, in particular, the use of titanium complexes containing chloride ions or amides of tartaric acid results in inverted stereoselectivity.[43]

It has been shown[44] that opposite enantiofacial selectivities are observed for allylic and homoallylic alcohols. This finding might suggest a synergistic effect of the two hydroxy groups in the optically active (1*R*,2*R*)-1,2-divinylethylene glycol **28**. However, epoxidation of this compound by Bu^tOOH led to an unexpected result,[40] namely, the inversion of enantioselectivity and enantiofacial selectivity was observed. Depending on the amount of the oxidant used, this reaction yielded either mono- (**29**) or di-epoxide (**30**).



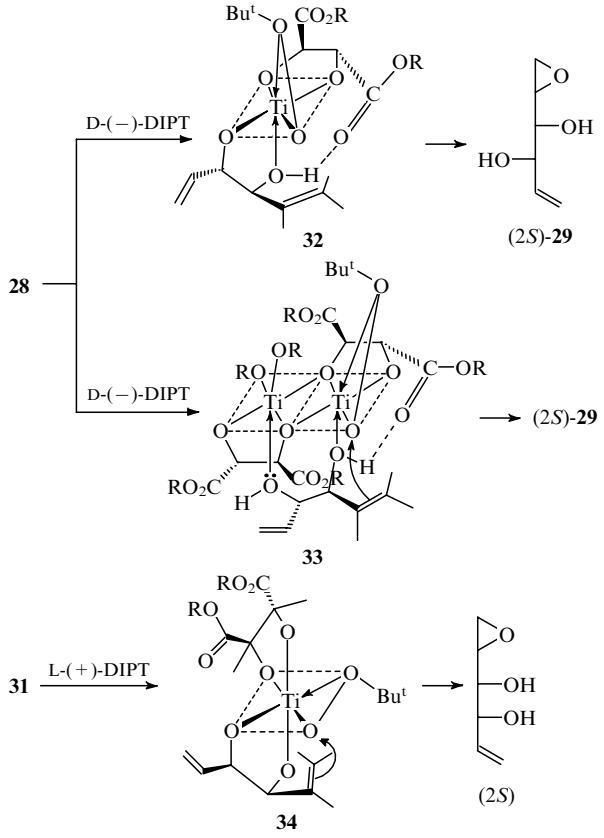
DIPT is diisopropyl tartrate

Diisopropyl L-(+)-tartrate [L-(+)-DIPT], which should have been used according to the empirical rule formulated by Rossiter and Sharpless,[44] proved to be inapplicable. However, epoxidation of the monobenzyl ether of glycol **28** occurred in conformity with this rule.[45] The *meso*-form of 1,2-divinylethylene glycol **31** was epoxidised in a similar way.



31 (2*S*) (87,5%) (2*R*)

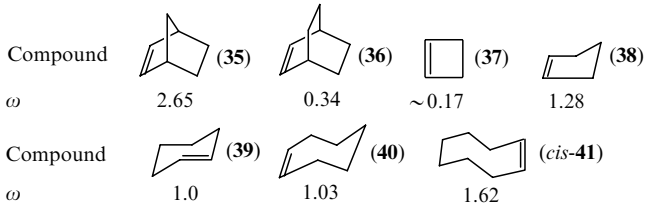
The result of the asymmetric epoxidation of the stereoisomeric glycols **28** and **31** was interpreted by assuming that the (*R*,*R*)-substrate **28** reacted as a monomeric (**32**) or dimeric (**33**) complex, in which the peroxide oxygen atoms are arranged as in the complex **27**, whereas the *meso*-form reacted in complex **34**, in which the oxygen atoms are arranged horizontally.



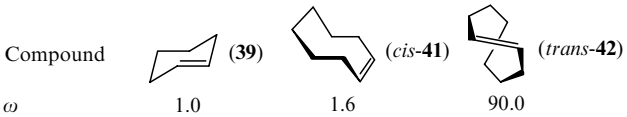
III. Specific features of epoxidation of cycloalkenes and methylenecycloalkanes with peroxy acids

Cycloalkene molecules are characterised by various types of strain: cisoid stretching or compression strain and out-of-plane, one-sided, torsional and transannular strain.[12,46–48] The three last mentioned types of strain are most typical of methylenecycloalkanes.[47,48] The real contributions of the components to the total strain can be estimated based on thermochemical data and quantum-chemical calculations.[12,46–49] Qualitative estimates can be made by comparing the relative rates of epoxidation (ω) of several cycloalkenes under conditions A and B.

A. Reaction conditions for cycloalkenes **35**–**40**: AcOOH, AcOEt, 25 °C.[47]



B. Reaction conditions for cycloalkenes **39**, **41** and **42**: PhCOOOH, THF, 20 °C.[46]



It can be seen that the reactivity of five- and six-membered rings increases in the sequence **39** < **38** < **35**. This was attributed to the increase in the cisoid compression strain and out-of-plane strain.[47,49]

The higher reactivity of the double bond of the norbornene fragment compared to that in the cyclopentene fragment is manifested when dicyclopentadiene is oxidised with peracetic and monoperoxyphthalic acids[50] and with geminal hydroxyalkyl hydroperoxides.[51]

The reaction of norbornene **35** is characterised, in addition to the typical *exo*-selectivity of the attack on the double bond, by a high rate of electrophilic addition, observed irrespective of the reagent used or the reaction mechanism. A certain contribution to the relatively high reactivity of norbornene is made by the out-of-plane deformation and hyperconjugation.[52] PMX calculations showed that the =C–H bonds in norbornene **35**, unlike those in cyclohexene **39** and bicyclo[2.2.2]octene **36**, are bent by 4.2° to the *endo*-region. In view of this result, which has been confirmed by *ab initio*[53] calculations, the preferred *exo*-attack by the electrophile is explained by the fact that in the *exo*-region, the π orbital of norbornene is turned outwards due to the repulsion from the occupied orbitals of the methylene bridge,[53,54] whereas in the *endo*-region, the orbital is shielded by the carbon skeleton of the molecule. In cyclopentene, this effect is less pronounced.[52]

The replacement of the *endo*-methylene bridge in norbornene **35** by an *endo*-ethylene bridge relieves the cisoid compression strain and, apparently, enhances shielding of the double bond, which results in a markedly lower reactivity of bicyclo[2.2.2]-octene **36**.

Upon replacement of the six-membered ring by an eight-membered ring, the system becomes more flexible and the reaction rate increases. Unlike other cycloalkenes, *cis*-cyclooctene **41** is readily converted into the epoxide on treatment with various oxidants including molecular oxygen. This leads to the conclusion that both the intermediate states and species and the epoxide formed from the cycloalkene **41** are highly conformationally stable.

trans-Cyclooctene **42** occupies a special place in the series of cycloalkenes.[46,55] It typically exists in a *twist*-conformation with highly pronounced out-of-plane torsional strain, favourable for *syn*-addition reactions. The electrophilic attack is directed only at one face of the double bond, which is rotated outwards due to twisting of the molecule.

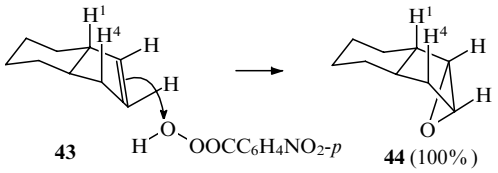
The general pattern of the electrophilic addition to double bonds in cycloalkanes is as follows: as the substrate becomes more strained, the formation of a cyclic transition state is facilitated, because this releases strain.[46,47,56] The more atoms incorporated in the transition state, the greater the decrease in the strain of the system; consequently, the reaction rates can differ by 2–3 orders of magnitude.[56] The fact that the rates of epoxidation of norbornene and cyclohexene differ by a factor of less than three attests to the formation of three-membered transition states in both cases.

It should be noted that in the case of typical 1,3-dipolar addition of phenyl azide (in CCl_4 at 25 °C) to *trans*-cyclooctene **42**, norbornene **35** and cyclohexene **39**, the relative reaction rates are 2.1×10^5, 5.7×10^3 and 1.0.

Apparently, the rate of epoxidation depends on the strain not only in the initial alkene but also in the final product, oxirane. It is the high conformational distortions in the latter in combination with steric shielding that account for the facts that 3,5-dibromocyclopentene and 3,6-dibromocyclohexene are much more difficult to epoxidise than their open-chain analogue, 1,4-dibromobut-

2-ene, and that cyclobutene **37** is much less reactive than cyclopentene **38**.[2]

An important factor governing the stereochemistry of epoxidation of cycloalkenes is the principle of the least conformational strain formulated by Toromanoff.[57] By means of dynamic conformational analysis of the probable transition states with allowance for the Curtin–Hammett principle, the researcher showed that insertion of the epoxide oxygen during the epoxidation of mono- and bicyclic alkenes follows predominantly the direction that ensures the least conformational distortions (thermodynamic control). However, the notion of conformational distortion is ambiguous and can comprise several components. The concepts of torsional,[10,58] hyperconjugative[59] and electrostatic[60] effects controlling the stereochemistry of epoxidation are being debated in the literature. It has been reported[57,61] that bicyclononene **43** reacts with peroxy acids to give exclusively *endo*-epoxide **44**.



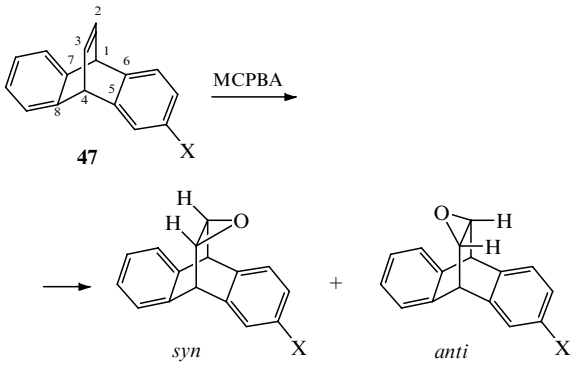
43 **44** (100%)

This reaction route is apparently facilitated by shielding of the double bond by the axial H^1 and H^4 atoms at the stage when the reactants approach each other, by the torsional strain in the transition state, which would have been generated by an attack by the peroxy acid from the side of these atoms and, finally, by stabilisation of the transition state formed in the case of the *anti*-attack by RCO_3H due to the interaction of the $C-H^1$ and $C-H^4$ σ bonds with the electron-deficient sites arising in the bicyclononene complex **43**. The latter type of interaction is involved in initial stages of classical rearrangements of carbenium ions of the type **45** and in the isomerisation of oxiranes **46** to oxo compounds,[62] associated with hydride shifts.



45 **46**

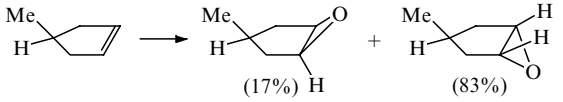
The combined action of all these factors in the reaction of bicyclononene **43** results ultimately in the generation of a conformationally more stable (see Section V) and, hence, energetically more favourable transition state. The $(\sigma-\delta+)$ type interaction (in the $\sigma-\sigma^*$ variant) has been invoked[63] to explain the stereochemical outcome of epoxidation of the bicyclo[2.2.2]octene derivative **47** by *m*-chloroperbenzoic acid (MCPBA).



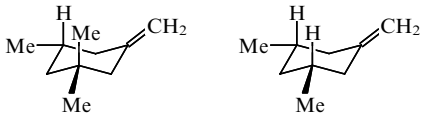
47

It was found that the proportions of the *syn*-isomer obtained with X = OMe, H, F and NO_2 are 48%, 50%, 58% and 77%, respectively. In other words, the introduction of an electron-withdrawing substituent (F, NO_2) decreases the σ-donor capacity of the C(1)–C(6) and C(4)–C(5) bonds and thus makes the *syn*-attack by the peroxy acid more favourable.

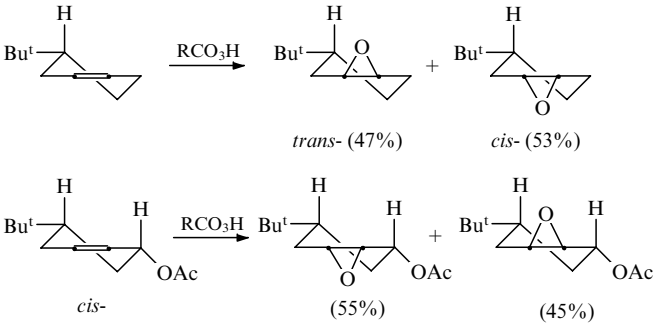
The presence of an alkyl substituent in the five-membered ring and in polycyclic molecules[6,50] can hamper the attack on the double bond from one side.



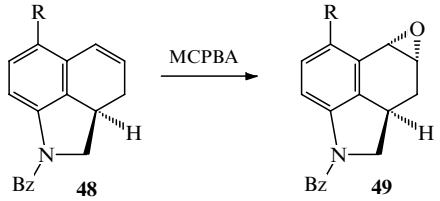
The presence of an axial methyl group at C(3) in 3,3,5-trimethyl-1-methylenecyclohexane decreases the proportion of the axial attack by RCO_3H on the double bond to 17% (compared to 64% observed for 3,5-dimethyl-1-methylenecyclohexane).[15]



However, in flexible systems, for example, in cyclohexene derivatives direct steric shielding can be removed or minimised due to the conformational mobility of the molecule,[29] because the most substantial steric restrictions are created by an axial substituent.



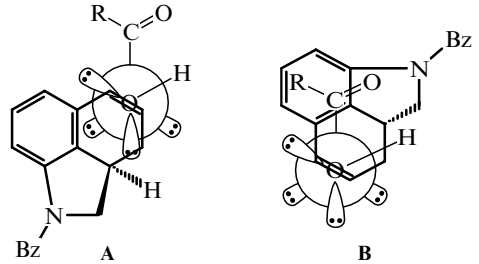
Alkene **48**, having a rigid alkenyl system, forms epoxide **49** with high diastereospecificity (93%–99%);[18] in this case, the *anti*-attack by the oxidant predominates.



48 **49**

R = H, Br, CN, OMe.

Conformational analysis of diastereoisomeric transition states (**A** and **B**, Fig. 2) permits the conclusion that *gauche*-structure **A**, leading to the *anti*-epoxide, is more favourable than eclipsed

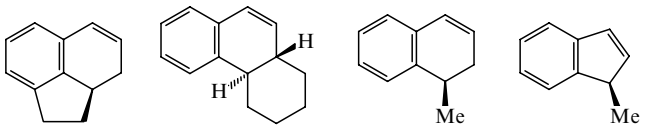


A **B**

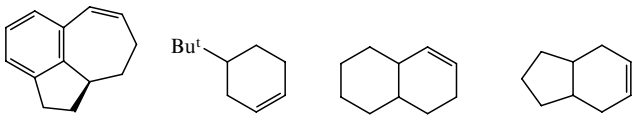
Figure 2. Newman projections of the transition state formed in the oxidation of the alkene **48** with *m*-chloroperbenzoic acid: **A** is the *gauche*-conformation; **B** is the eclipsed conformation.

structure **B**, in which the orientation of the benzamide group in one direction with the peroxy-acid fragment increases the torsional strain in the transition state. In the Newman projections, the line of sight of the observer is directed along the peroxide bond from the side of the attack of the alkene, the π bond passing through one of the two lone pairs of the active oxygen atom; this is a necessary condition for the occurrence of dative interaction at the stage of the epoxide ring formation.[2]

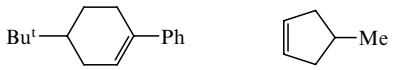
The composition of the products of epoxidation of two series of compounds, alicyclic compounds **50**–**54** with conformationally fixed styrene fragments, and more flexible structures, cyclohexene derivatives **55**–**58** and cyclopentene derivative **59**, by peroxy acids shows that high diastereofacial selectivity is manifested only in the series of compounds **50**–**54** (the ratio of *syn*- to *anti*-epoxides is given in parentheses). This may be explained by the conformational stability of the transition state with allowance for all factors which ensure this stability.



50 (1:99) **51** (1:99) **52** (15:85) **53** (50:50)

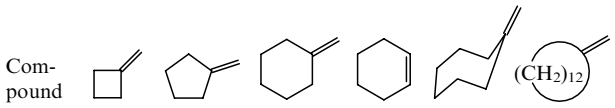


54 (82:18) **55** (40:60) **56** (45:55) **57** (40:60)



58 (50:50) **59** (76:24)

The regularities of epoxidation of methylene- and alkylidenecycloalkanes have been briefly considered.[64] The relative rates of epoxidation of monocyclic compounds with *exo*-double bonds by peracetic acid in ethyl acetate at 40 °C were determined.[12]



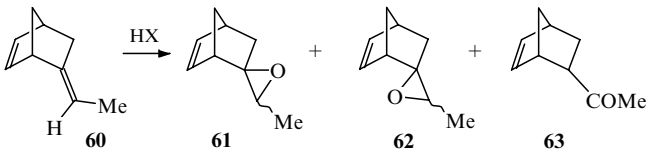
Compound						
k_{rel}	0.62	1.95	1.0	1.1	1.12	0.21

Terminal double bonds in aliphatic compounds are known to be substantially less reactive than symmetrically dialkyl-substituted bonds.[2, 14] In the series of alicyclic compounds, the relative reactivities of *exo*- and *endo*-double bonds are substantially affected by cyclic strain. This is indicated by kinetic and activation parameters. As noted above, more strained cycloalkenes are more reactive. However, methylenecyclobutane, which has the most strained molecule in the series of its analogues, is the least reactive compound. It may be expected that the rate of epoxidation would be correlated with the HOMO energy of the alkene, calculated by a quantum-chemical method: the higher this energy, the easier the interaction between the π orbital and the σ^*_{O-O} orbital of the peroxy acid. In the case of cycloalkenes, this correlation actually holds.[47] In fact, E_{HOMO} increases in parallel with the decrease in the ring size and with the enhancement of strain. In the series of methylenecycloalkanes, the opposite dependence is manifested.[10] Methylenecyclohexane is epoxidised at a lower rate and with a higher activation energy than more strained methylenecyclopentane, although the data of photoelectron spectra indicate that they have close π-ionisation potentials. However, the low reactivity of methylenecyclobutane correlates with the fact that it has the highest ionisation potential in the series of compounds under study.[10]

Nevertheless, the differences in the reactivity found in the series of medium rings (C_4–C_7) are relatively small, because in all these cases, a strained three-membered transition state is formed.

Methylenecyclododecane occupies a special place in this series. Its low reactivity is inconsistent with the views on the ring strain and leads to the conclusion that the reaction rate is also influenced by the probability of effective collision of the reactant molecules, which varies depending on the size of the molecules.[2, 10, 13]

Epoxidation of alicyclic compound **60** presents interest because this compound contains both norbornene and ethylidene fragments. The reaction with monoperoxyphthalic acid affords nearly equal amounts of compounds **61**–**63**, *i.e.* only the exocyclic double bond is involved in the reaction.[50]



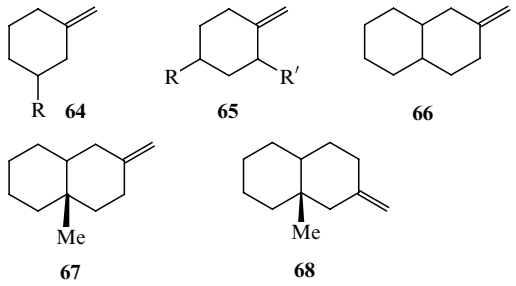
60 **61** **62** **63**

HX = $HOOCC_6H_4COOOH$.

The ratio of the epoxide **61** to the epoxide **62** is 1.9 after 1 h, and 0.9 after 2 h. When peracetic acid is used, this ratio does not change during the reaction and lies in the range 1.6–1.7.

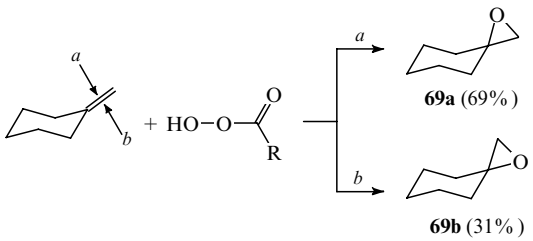
It was found in special experiments that the ketone **63** is formed only from the oxirane **61** during oxidation by monoperoxyphthalic acid. When peracetic acid is used, this isomerisation does not occur. This might be due to the lower acidity of the medium.

Study of epoxidation of substituted methylenecyclohexanes **64**–**68** revealed fine stereochemical features of this reaction.[15, 64–67]



64 **65** **66** **67** **68**

The addition of an oxygen atom to an alkene can be directed at either axial (*a*) or equatorial (*e*) positions. Epoxide **69a** in which the methylene group is equatorial is 0.6–1.1 kJ mol^{-1} thermodynamically more favourable than the product **69b**.



69a (69%) **69b** (31%)

The compositions of the isomeric epoxide mixtures formed from the alkenes **64**–**68** were determined using low-temperature ^1H NMR spectroscopy or stereochemical analysis of the alcohols formed upon hydride reduction of the epoxides.

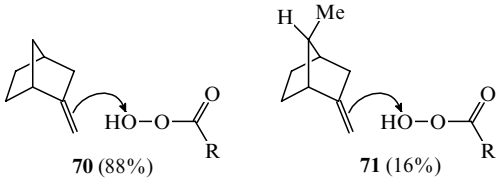
In the majority of cases, when peracetic, *m*-chloroperbenzoic and peroxyphthalic acids are used, the axial attack proved to be preferred. The inversion of the epoxidation stereochemistry was observed in the case of the alkene **68**, due to the shielding of the double bond by the methyl group, and in the case where the methylenecycloalkanes **64**–**68** were epoxidised with peroxybenzimidic acid ($C_6H_5CN + H_2O_2 + KHCO_3$). It has been reported [61]

that the change in the predominant direction of the attack in the latter case is due to the larger size of the peroxycarboimide group compared to the CO_3H group. It should also be noted that the presence of an active proton and a basic imide nitrogen atom in the peroxyimidic acid molecule changes significantly the solvation conditions and may be the reason for the change in the optimum spatial orientation of the reactants.

The predominance of the axial attack [66, 68] in the epoxidation of methylenecycloalkanes is mainly explained by hyperconjugation effects. The axial attack is facilitated by some stabilisation of the transition state attained due to interaction of the α-C–H bond electrons with electron-deficient sites, similar to what has been observed in the epoxidation of the bicycloalkene **43**.

The axial attack of the oxidant predominates in the epoxidation of methylenenorbornane **70**.[64, 69]

The introduction of a *syn*-7-methyl group in methylenenorbornane (compound **71**) results in inverted stereoselectivity. The selectivity of epoxidation of methylenenorbornane **70** is lower than that for norbornene (98%) because the double bond is further removed from the methylene bridge.



70 (88%) **71** (16%)

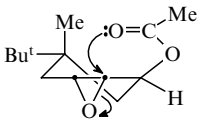
The increase in the size of the exocyclic group in the series $=CH_2 < =CHMe < =CMe_2$ increases the rate of epoxidation by a large factor.

Meanwhile, the rate of oxidation of the exocyclic double bond depends on the ring size and decreases in the order cyclohexane > cycloheptane > cyclopentane.

Electrophilic addition to alicyclic alkenes is typically accompanied by participation of neighbouring atoms and groups, in particular, by migration of C–C and C–H σ bonds.[70, 71] From the theoretical viewpoint, it is significant to distinguish the few cases in which the neighbouring nucleophilic groups directly participate in the transfer of active oxygen to the substrate.

The nucleophilic assistance of the *endo*-$CONH_2$ and *endo*-CH_2OH groups to the epoxidation of norbornene has been considered in a review.[2] Participation of this type of hydroxy group in the reaction has been noted in other studies.[1, 70, 71] In particular, 5-hydroxymethylbicyclo[2.2.1]hept-2-ene reacts with perbenzoic acid 30 times faster than its methyl ether and 40 times faster than the corresponding acetate.[70] Most often, however, the formation and opening of an epoxide ring in cycloalkenes occur as consecutive reactions.

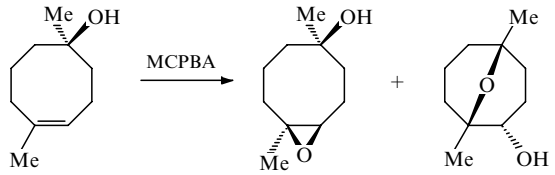
It is noteworthy that epoxy alcohol acetate **72** proved to be unstable on silica gel, its epoxide ring being cleaved, apparently due to participation of the neighbouring acetoxy group.



72

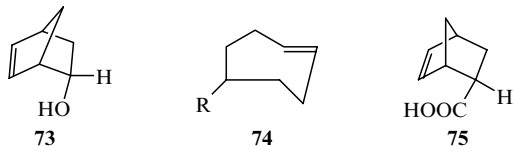
As noted above, the corresponding alcohol **14** exists in an alkaline solution of methanol in an equilibrium with its isomer. The exceptional instability of *trans*-2,3-epoxycyclohexanol acetate under conditions of epoxidation of cyclohex-2-enol with hexafluoro-2-hydroperoxypropan-2-ol has also been noted.[72] Epoxycyclohexane containing a *trans*-benzamide group in the α-position behaves in a similar way.[4]

Epoxidation of 1,5-dimethylcyclooct-4-en-1-ol is accompanied by partial transannular cyclisation.[73]



(40%) (29%)

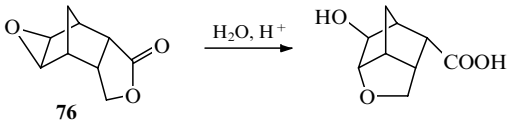
The hydroxy group at the 5-position of the compound **73** has no influence on the course of epoxidation.[74] However, cycloheptene derivatives **74** are epoxidised by *m*-chloroperbenzoic acid to give products of the transannular cleavage of the epoxide ring.



73 **74** **75**

R = CH_2OH, COOH.

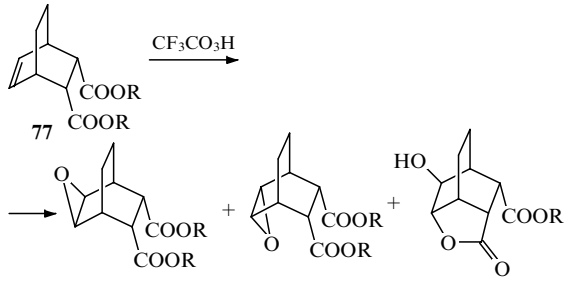
Epoxidation of the acid **75** of the norbornene series also affords initially the epoxy acid; however, due to the fast isomerisation to hydroxy lactone, the acid has not been isolated. Kinetic data rule out the possibility of participation of the carboxy group in the rate-determining step of transfer of the active oxygen to the alkene,[69] because the hydroxy group is more nucleophilic than the carboxy group.[76] In the case of lactone **76**, the cleavage of the epoxide ring during hydrolysis involves the hydroxy group rather than the carboxy group, because the latter is less nucleophilic.[76]



76

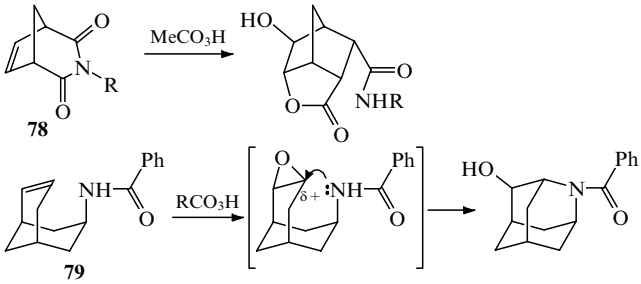
Unlike norbornene, bicyclo[2.2.2]octene derivatives are epoxidised without *exo*-stereospecificity, which is due to the lower strain and the higher conformational mobility of the cage.

endo-Acids and esters of the bicyclo[2.2.2]octene series **77** form *endo*- and *exo*-epoxides together with the lactones derived from the *exo*-isomer.[76]



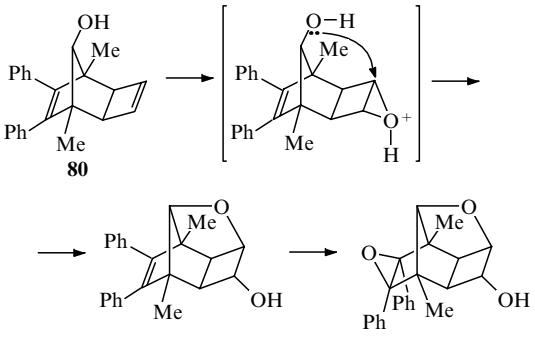
77

Oxidation of bicyclic imide **78** is accompanied by intramolecular cyclisation involving the oxygen atom of the carbonyl group,[77] as has been observed for *endo*-amides of the norbornene series.[2] In the oxidation of amide **79**, the structure of the intermediate epoxide is favourable for the intramolecular cyclisation involving the nitrogen atom to give an azaadamantane derivative.[78]

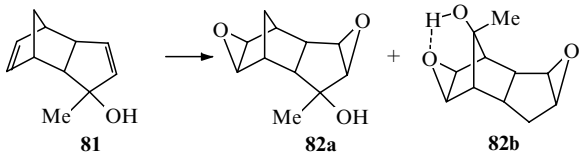


78 **79**

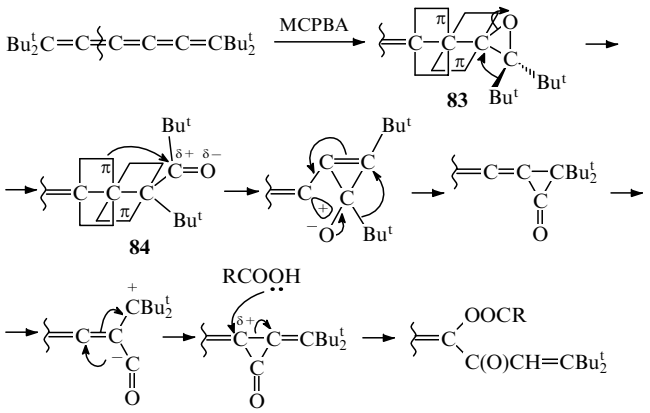
Epoxidation of diene **80** occurs chemoselectivity according to the following scheme:[79]



During epoxidation by monoperoxyphthalic acid, tricyclic dienol **81** partially isomerises, diepoxides **82a**,**b** being formed in a ratio of 65 : 35.[80]



Sterically hindered cumulenes, which are converted into cyclopropanones upon a rearrangement of intermediate oxiranes, represent a peculiar system as regards epoxidation by peroxy acids.[81] A probable mechanism for this reaction is shown below:

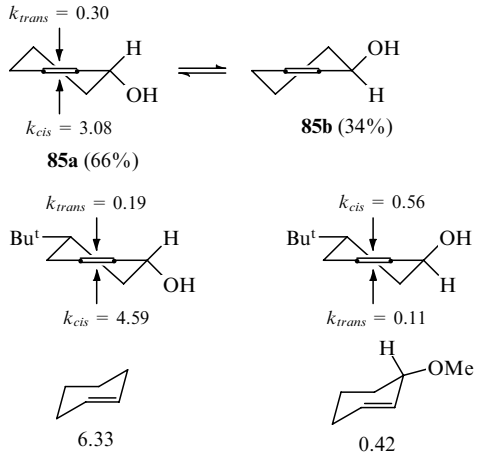


The formation of the intermediate epoxide **83** was not detected; therefore, the isomeric ketone **84** might also arise upon disproportionation of the alkene – RCO_3H complex in the transition state.

IV. Mechanism of the directing influence of functional groups during epoxidation of alkenes with peroxy acids

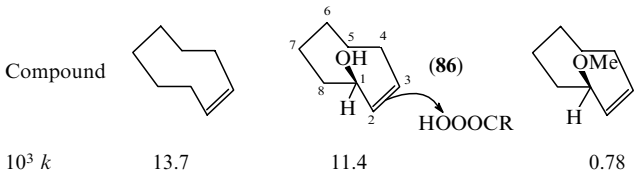
The stereodirecting influence of the hydroxy group in 2-, 3- and 4-alkenols on the attack by RCO_3H has been discussed in numerous publications.[1,2,6,82,83] Possible variants of the transition state geometry have been discussed. Stereochemical features of the epoxidation of cyclohex-2-enols have been considered.[29] It was found that the directing influence is exerted by a pseudo-equatorial (compound **85**) rather than axial hydroxy group.[29]

The relationship between the rate and the route of epoxidation and the structure of cyclohexenols is clearly illustrated by the scheme given below, in which $k_{epox} \times 10^3$ (perbenzoic acid, benzene, 5 °C) is resolved into components, k_{cis} and k_{trans}, with respect to the hydroxy group.



It is significant that in the epoxidation of $C_6 - C_9$ cycloalkenols with *m*-chloroperbenzoic acid, the direction of the attack by the reagent changes on passing from seven- to eight-membered ring; the yields of *cis*-epoxides from the above cycloalkenols are 95.0%, 61.0%, 0.2% and 0.2%, respectively.[41] When an alkyl hydroperoxide and a vanadium catalyst are used in this reaction, the coordination of the hydroxy group to the metal is so strong that it leads to a change in the conformation and ensures the *cis*-attack in the two latter cases.

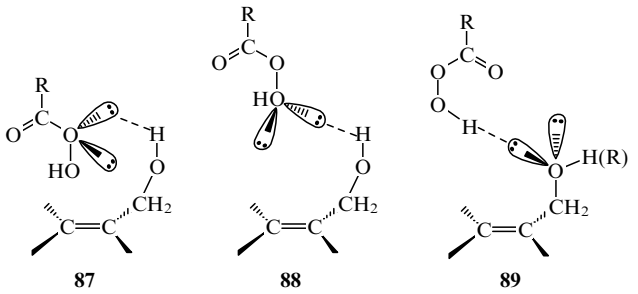
It is notable that not only *cis*-cyclooct-2-enol **86** but also its methyl ether are epoxidised by RCO_3H stereospecifically into the *trans*-position. However, the difference in the reaction rates (perbenzoic acid, benzene, 5 °C) implies active assistance from the hydroxy group of the cyclooctenol **86**.[29]



When cyclooctenol **86** occurs in a pseudo-chair conformation, electrophilic assistance to the peroxy acid comes, as in the case of cyclohexenol **85**, from the pseudo-equatorial OH group; however, in epoxycyclooctanol, unlike epoxycyclohexanol, this group gets into *trans*-position with respect to the oxirane ring. It was suggested that the rear attack by the peroxy acid is hampered by the hydrogen atoms at C(5) and C(8), similarly to the situation observed in the epoxidation of the bicycloalkene **43** and methylenecyclohexane.

The mechanism of interaction of the directing hydroxy group with a peroxy acid is not so unambiguous as that for alkyl hydroperoxides. It is clear that a peroxy acid is capable of forming hydrogen bonds with basic groups, including the hydroxy group. However, it is significant to elucidate not only the nature of these bonds but also the stage at which their role is manifested. On the one hand, a hydroxy group can be involved at the stage when the reactants approach each other and are coordinated; on the other hand, this group can stabilise the leaving RCO_2^- anion at the stage of decomposition of the alkene – peroxy acid activated complex.

Several schemes have been proposed describing the hydrogen bonds formed between allylic alcohols and peroxy acids, in particular, **87**,[2,6] **88**[73] and **89**.[2,78]



87 **88** **89**

Evaluation of the relative strengths of the hydrogen bonds and stereoelectronic analysis of the structures **87** – **89** lead to several conclusions. In conformity with the views on the acid – base properties of the reaction participants, the strength of the hydrogen bond must substantially decrease in the sequence **89** > **88** > **87**. Moreover, the formation of a hydrogen bond between an allylic hydroxy group and an RCO_3H molecule in the ground state according to the associate **87** pattern is relatively unlikely, because the *p* electrons of the O(2) atom are involved in conjugation and are difficult to displace. In addition, the corresponding *n* orbitals are arranged at an angle relative to the O – H bond of the alcohol. When the associates **88** and **89** are formed, the reaction sites ($\pi_{\text{bonding C-C}}$ and $\sigma^*_{\text{antibonding O-O}}$) are too far removed from each other for the epoxidation proper to occur. This rules out participation of the hydroxy group directly in the step of transfer of the active oxygen to the alkene.

The problem of efficiency of the directing action of the hydroxy group at the stage when the reactants approach each other was solved based on the data on epoxidation of cyclohexene containing an axial OR group (R = Me, Bz) in the allylic position.[74]

It was found that when *m*-chloroperbenzoic acid is used as the oxidant, the hydrogen bond formed between the acid and the OR group, similar to that in **89**, is not sufficiently strong to exert a *syn*-directing influence; steric effects of the OR groups induce predominantly *anti*-epoxidation. Only replacement of *m*-chloroperbenzoic acid by CF_3COOOH, which is the strongest peroxy acid having a relatively high pK_a value, results in *syn*-epoxidation. This mechanism for the assistance by the OR group is supported by the fact that replacement of the inert solvent (CH_2Cl_2) by a basic solvent (THF) capable of solvating CF_3COOOH changes the stereochemical outcome of epoxidation, which yields predominantly the *anti*-isomer. The hypothesis that the reactants approach each other through the formation of species like **87** and **88** seems even less likely.

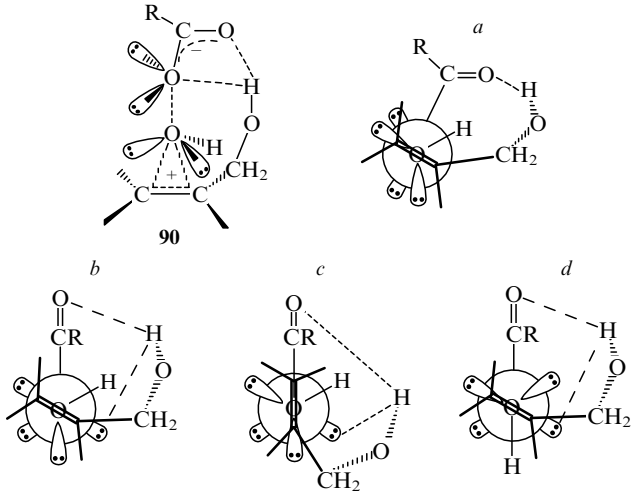
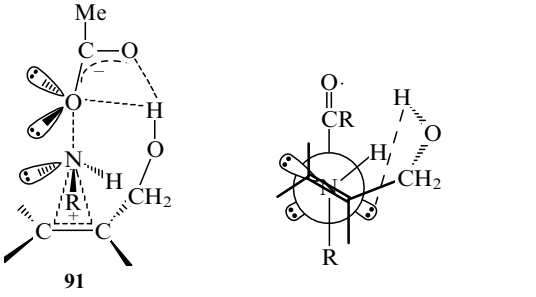


Figure 3. Activated complex **90** formed in the oxidation of allylic alcohols by peroxy acids; (*a*, *b*, *c*, *d*) are the Newman projections.

Orbital consideration and quantum-chemical calculations[2, 84] allow the conclusion that the directing influence of a hydroxy group is due to the interaction of the leaving anion of the acid with the hydrogen atom of the hydroxy group during decomposition of the activated complex **90** (Fig. 3).

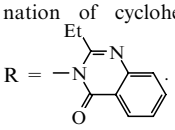
It can be seen from Fig. 3 that in this case we are dealing not with a classical hydrogen bond, formed as a hydrogen bridge between two proton acceptors, but with interaction of the proton with a delocalised negative charge in a fairly polarised intermediate complex. When constructing Newman projections *a* – *d* for the transition state **90**, we assumed that any of the two *p*-electron pairs of the active oxygen atom can participate in the formation of the oxirane ring.

Analysis of projections *a* – *d* with allowance for the Curtin – Hammett principle demonstrates that structures *b* and *d* are the most favourable. The actual occurrence of structure *b* is confirmed by a comparison of the epoxidation mechanism with the closely related mechanism of aziridination of cyclohex-2-enol by 3-acetoxyamino-2-ethylquinazolone.[85] The latter reacts more stereo- and regioselectively than peroxy acids. In our opinion, this is due to the more rigorous steric requirements imposed on the transition state. Unlike the peroxide oxygen atom in RCO_3H, nitrogen carries two substituents. This appreciably hampers the electrophilic attack on the alkene and makes it more strictly directed. In addition, the nitrogen atom has only one pair of *p* electrons. As a result, the optimum orientation of the reactants is attained only in structure **91** (Fig. 4), in which the bulkiest substituents occupy transoid positions and the NH group proton deflects from the plane of the O – C = O fragment.



91

Figure 4. Activated complex **91** and its Newman projection for aziridination of cyclohex-2-enol with 3-acetoxyamino-2-ethylquinazolone

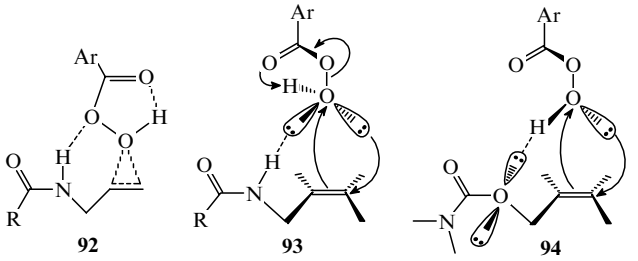


The transoid species *d*, which is energetically even more favourable, is sterically less strained than structure *b*; its acid proton participates in the stabilisation of the leaving RCO_2^- anion through interaction with both *p*-electron pairs of the O(2) atom. In structures *b* and *d* (Fig. 3) and **91** (Fig. 4), the allylic hydroxy group and the carboxy group are optimally removed from each other.

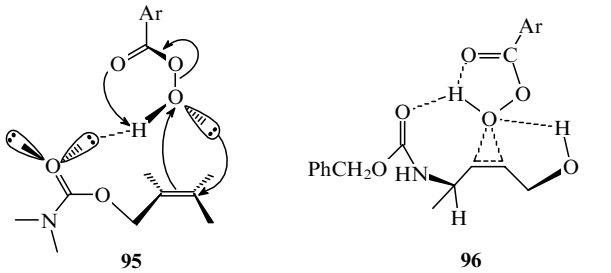
The close arrangement of the hydroxy and carboxy groups in the energetically unfavourable eclipsed conformation *a* diminishes or even completely rules out the possibility for assistance of the hydroxy group to the leaving RCO_2^- anion; in the case of planar structure *c*, the allylic hydroxy group is removed too far from the leaving anion.

The *syn*-directing effect is manifested in epoxidation of not only alkenols but also unsaturated carboxylic acids,[86, 87] amides,[88, 89] urethanes, urea derivatives,[6, 90] acetals, sulfones, sulfoxides,[6] sulfamides[91] and ketones of the aliphatic and aromatic series.[92] In some cases, concerted or competing action of two groups has been observed.[6, 89, 90]

Several variants have been considered for the mechanism of the directing influence of some groups, for example, those involving the formation of structures **92**,[89] **93**[90] and **94**–**96**.[6]

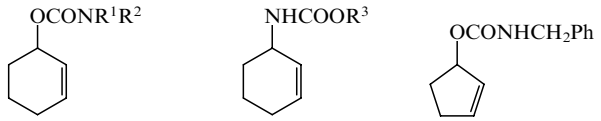


92 **93** **94**



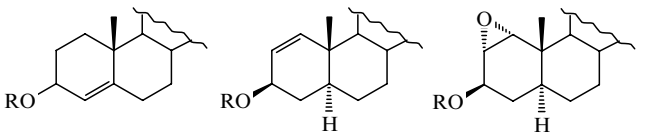
95 **96**

Kocovsky and Stary,[6] who studied a broad range of unsaturated (allylic and homoallylic) carbamates, amides, urethanes and esters, in particular, cyclohexene (**97**, **98**) and cyclopentene (**99**) derivatives and steroid type compounds **100**–**105**, including those differing in the position of the double bond, concluded that the stereodirecting influence exerted by the functional groups present in these substrates is due to involvement of the carbonyl oxygen atom, which carries the highest electron density into the hydrogen bond (see structure **95**).

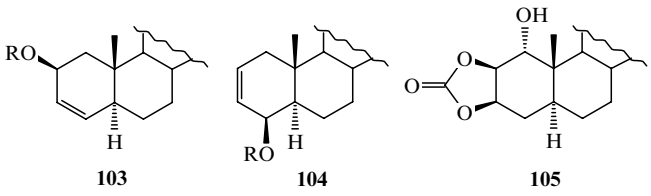


97 **98** **99**

R^1 = H, Me; R^2 = Me, CH_2Ph (**97**); R^3 = Alk, NH_2, EtO (**98**).



100a,b **101** **102**



103 **104** **105**

R = $PhCH_2NHCO$ (**100a**, **101**, **102**); R = Me_2NCO (**100b**, **103**, **104**).

The lower basicity of the carbonyl oxygen atom in esters compared to that in amides or carbamates accounts for the lower stereoselectivity of their epoxidation; however, *syn*-epoxidation of dimethyl *trans*-1,2-dihydrophthalate occurs to more than 90%.[93] The assumption that it is the carbonyl group that participates in the reaction was confirmed by the IR spectroscopy data obtained for *trans*- (**106**) and *cis*-hydroxy amides (**107**) used as model compounds. In the latter case, it was found that no intramolecular hydrogen bond is formed.

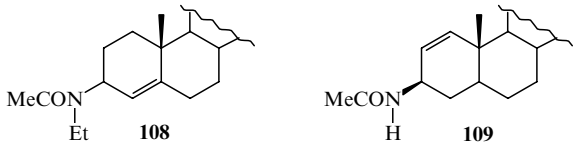


106 **107**

The directing influence of the carbonyl oxygen atom in the type **95** transition state, unlike that of the hydroxy group in the transition state **90**, appears most likely at the stage of coordination of the reactants. The two mechanisms acting through the transition states **90** and **95** are based on the formation of a hydrogen bond; however, they differ significantly regarding the stereochemical features and, hence, the general substrate selectivity. Thus allylic alcohol **101** (R = H) is converted into a mixture of *cis*- and *trans*-epoxy alcohols in a ratio of 3 : 1, whereas in the case of the corresponding *N*-benzylcarbamate, *cis*-epoxidation is prevented by the spatial shielding of the β-side, *trans*-epoxide **102** and compound **105**, resulting from intramolecular opening of the epoxide ring, being isolated as the major reaction products.

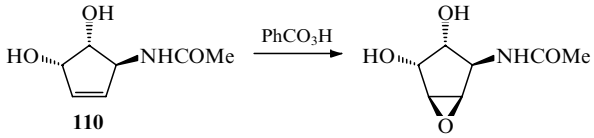
Carbamates **103** and **104**, like the corresponding alcohols (R = H), are mainly converted into *trans*-epoxides. The mere replacement of the benzyl group in the structure **100** by a phenyl group or the introduction of an additional substituent, for example, a methoxy group, into the carbamate **104** can result in the reversed stereoselectivity.[94] The *N*-ethylacetamide prevents epoxidation of amide **108**, which is consistent with the data reported in another publication.[95]

However, the acetamide group in the molecule **109** exerts a *syn*-directing influence exceeding that of a hydroxy group.[6]



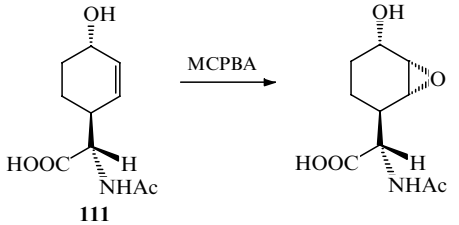
108 **109**

The competition of the acetamide and hydroxy groups[78] in amide **110** also results in the predominance of the stereodirecting influence of the former.[87]



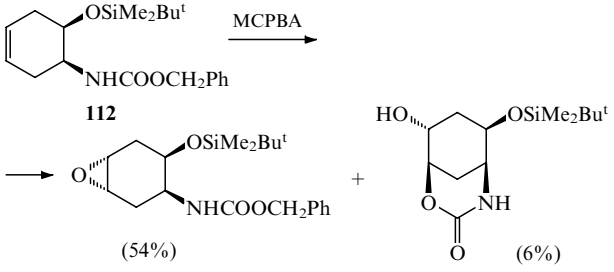
110

The distant acetamide and allylic hydroxy groups in the molecule of acid **111** exert a concerted influence.[96]



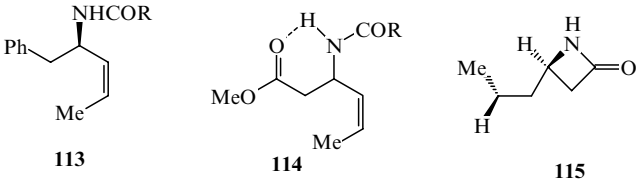
111

The trialkylsilyloxy group in *cis*-cyclohexylcarbamate **112** stipulates the *trans*-attack by a peroxy acid. The reaction product undergoes partial intramolecular cyclisation.[97]



112 (54%) (6%)

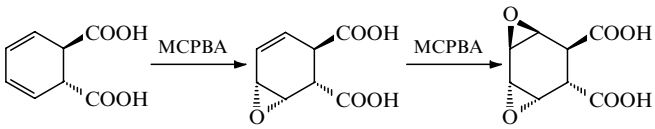
Acyclic allyl *Z*-amides **113** are epoxidised by peroxy acids and *tert*-butyl hydroperoxide in the presence of $Mo(CO)_6$ with a high *threo*-selectivity (75% – 95%).[87] The corresponding *E*-isomers are less sensitive to this reagent and to the influence of the amide group, the yield of the *threo*-isomer amounting to 60% – 78%. The general regularity is violated in the case of amides **114**. The low stereoselectivity of the reaction, in which the *erythro*-isomers slightly predominate in the reaction products, is apparently due to the unfavourable structure of the major conformation, which is fixed by an intramolecular hydrogen bond. In the case of amide **115**, participation of the carbonyl group in the orienting influence is relatively unlikely; nevertheless, the stereoselectivity of epoxidation is fairly high. This is apparently accounted for by the directing influence of the NH group, which has been postulated by Davies and Whitham.[87] This type of electrophilic assistance to the epoxidising agent is also preferable for the toluenesulfamide group.[88]



113 **114** **115**

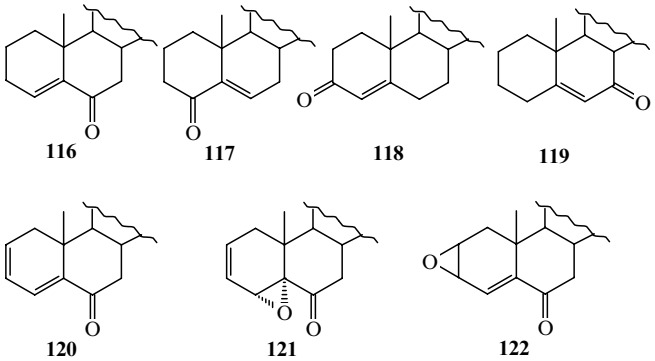
R = CCl_3, Ph, OMe, NHPh.

An α-carboxy group exerts a strong orienting influence on the attack by RCO_3H. Oxidation of both *trans*-1,2-dihydrophthalic acid and dimethyl *trans*-1,2-dihydrophthalate affords only mono- and diepoxides with *cis*-arrangement of the neighbouring epoxy and carboxy groups even in a basic solvent (ethyl acetate),[86] capable of solvating carboxy groups. It still remains unclear how the carboxy groups affect the course of the process, either similarly to a homoallylic hydroxy group or in accordance with the transition state **95**.



The *syn*-stereoselectivity of epoxidation of *trans*-5-*tert*-butylcyclohex-2-enecarboxylic acid in inert solvents is not very high (54% – 79%). Meanwhile, the epoxidation of the corresponding methyl ester affords predominantly the *trans*-isomer irrespective of the solvent used.[98] Apparently, the *tert*-butyl substituent diminishes the coordination mobility of the ring and hampers the formation of the conformation optimum for the carbonyl group to be involved in the active oxygen transfer.

It has been reported[92] that the carbonyl group in α,β-unsaturated steroid ketones **116** – **119** and dienone **120** influences the rate and regioselectivity of their epoxidation by MCPBA *via* the formation of a hydrogen bond.

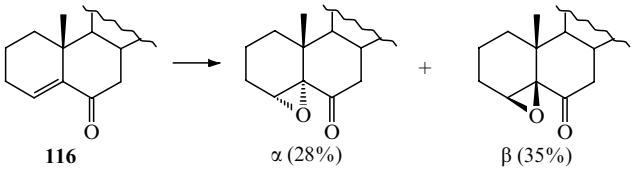


116 **117** **118** **119**

120 **121** **122**

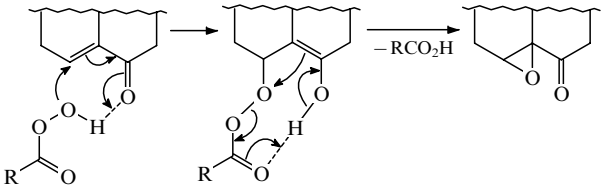
The mere fact that these compounds do undergo epoxidation seems quite unexpected, because the double bond conjugated with a carbonyl group is usually inert to peroxy acids. Moreover, when the dienone **120** is oxidised in a non-polar solvent (benzene), the epoxidation involves the α,β-double bond rather then the remote double bond. In a polar solvent (acetonitrile), the efficiency of participation of the carbonyl group of the ketone **120** in the formation of the hydrogen bond decreases, the yields of the isomeric monoepoxides **121** and **121** becoming comparable. The *S-cis*-ketones **116** and **117** react with an oxidant faster and give the oxiranes in higher yields (63% and 51%) than the *S-trans*-isomers **118** and **119** (the yields of the corresponding oxiranes are 8% and 27%).

In this connection, it is pertinent to consider the possible epoxidation mechanisms. Stereoelectronic analysis shows that in this reaction, there are no stereochemical prerequisites for the mechanism based on the transition state **95**. The RCO_3H molecule, associated with the carbonyl group through a hydrogen bond, is unable to attack the π electrons of the alkenyl fragment. Therefore, if the classical epoxidation mechanism is realised, the carbonyl group of a cycloenone can render assistance only at the stage when the reactants approach each other, thus increasing the probability of their efficient collision. However, epoxidation of the ketone **116** affords α- and β-oxiranes in comparable amounts, although, by analogy with the epoxidation of the methylenebicycloalkane **68** and alkyl-substituted cycloalkenes,[6,15] one could have expected that the methyl substituent would shield the β-side and promote the formation of the α-isomer.



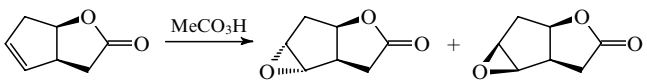
116 α (28%) β (35%)

The geometry of the molecules of the cycloenones **116**, **117** and **120** and the whole set of the available experimental data suggest that the process follows a mechanism including a nucleophilic attack on the antibonding π^*_{C-C} orbital and 1,4-addition of RCO_3H.



The structure of the *S-trans*-isomers **118** and **119** excludes the possibility of a similar synchronous nucleophilic addition of RCO_3H. In addition, the formation of only α-oxirane (27%) from the ketone **119** is evidence supporting the ordinary epoxidation mechanism, which assumes the electrophilic attack by the peroxy acid on the less shielded side of the double bond.

A fairly unusual effect of the nature of the solvent on the stereochemistry of epoxidation of 2-hydroxycyclopent-4-enylacetolactone has been observed.[99]



The ratio of the *cis* to *trans* isomers in the resulting epoxides changes from 8.1 in acetic acid and 4.0 in hexane to 0.89 in benzene and 0.67 in CCl_4. Since the carbonyl oxygen atom in the lactone is far removed from the double bond, its association with the peroxy acid molecule cannot influence significantly the epoxidation route. Apparently, solvation of the ester group, which determines the character of shielding of the double bond and the conformational stability of the diastereoisomeric transition states, is the

crucial factor governing the stereochemical outcome of the reaction. The pronounced difference between the reaction outcomes in inert solvents, for example, in hexane and benzene, indicates that the process stereochemistry depends substantially on the structural features of the solvent cage.

A similar type of dependence of the enantioselectivity on the solvent nature is displayed in the epoxidation of a number of cyclohexene derivatives by dimethyldioxirane.[4] It might be this factor that is responsible for the enantioselectivity of some enzyme-catalysed reactions[98] and for the difference between the yields of glycols in epoxidation of diallyl dicarboxylates[13] and phenylcyclohexene[62] in solvents with close basicities — tetrahydrofuran and diethyl ether.

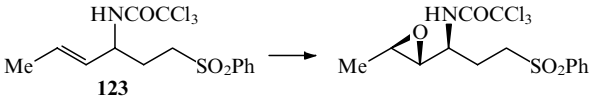
V. Complementarity of reactants as a factor of stereodirected epoxidation

As shown above, the presence in the alkene of a functional group capable of association with an epoxidising agent (ROOH, RCO_3H) is not always a sufficient condition for an efficient directing influence. Spatial compatibility of the reactants favourable for the reaction is also needed. This is ensured, on the one hand, by an appropriate molecular geometry and the environment of the reaction sites and, on the other hand, by a coplanar arrangement of the vacant and occupied orbitals which overlap during the reaction (stereoelectronic factor).

In cycloalkenes and, especially, in polycycloalkenes, the optimum direction of the attack by the oxidant is provided by the rigidly fixed structure of the carbon framework.[8, 64]

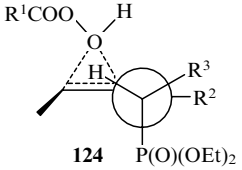
In alkenes, which are normally characterised by relatively low barriers to the rotation around σ bonds, stereodirected epoxidation can be attained in those cases where the two diastereoisomeric transition states of the reaction have substantially different energies. According to the Curtin–Hammett principle, the reaction proceeds *via* the more favourable transition state. This transition state often arises upon transformation of the most stable conformation with a transoid arrangement of the bulkiest substituents.

The simultaneous influence of bulky groups such as SiR_3 or $OSiR_3$ and the corresponding functional group results in a single diastereoisomer being formed in an almost quantitative yield.[42, 100] Only one diastereoisomer is produced, for example, in the epoxidation of amide **123**,[101] which contains a bulky sulfonyl group in addition to the directing amide group.



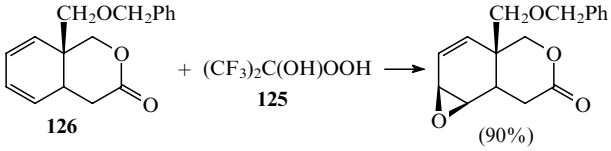
123

In some cases, the stereoselectivity of the reaction can be ensured without the formation of a hydrogen bond with the peroxy acid but only due to the ordinary spatial shielding of one side of the π bond by bulky groups such as SiR_3 in a fixed conformation of the alkene.[42] This can account for the *erythro*-selectivity of epoxidation of alkenylphosphonates.[102] The bulky phosphonate group and the peroxy acid occupy transoid positions in the transition state **124** formed in this reaction.



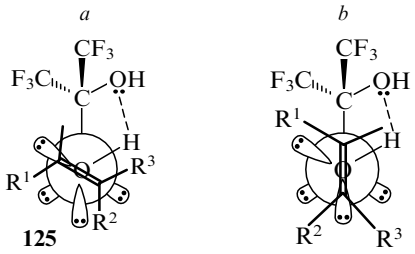
124

The factors that govern the mutual arrangement of the reactants in space can be judged from a comparison of the stereochemical outcome of epoxidation of alkenes by peroxy acids and by hexafluoro-2-hydroperoxypropan-2-ol **125**.[72] Whereas cyclohex-2-enol reacts with *m*-chloroperbenzoic acid to give *cis*- and *trans*-epoxycyclohexanols in 93 : 7 ratio, the reaction with hydroperoxide **125** yields only the *cis*-isomer. Furthermore, on treatment with the hydroperoxide **125**, cyclohex-2-en-1-ol acetate is converted into the corresponding *cis*-epoxide by 80%, whereas the use of *m*-chloroperbenzoic acid results in a mixture of *cis*- and *trans*-isomers of epoxycyclohexyl acetate in a ratio of 2 : 3. Hexafluoro-2-hydroperoxypropan-2-ol oxidises bicyclic diene **126** to give only one monoepoxide. Other oxidants, namely, peroxy acids, ROOH–Cat and singlet oxygen combined with trimethyl phosphite, react with the diene **126** to give all four isomers of monooxirane.



126

The specific behaviour of the hydroperoxide **125** can be explained by the fact that its molecule, unlike RCO_3H, is tetrahedral, the hydroperoxide group occupying a vertex of the tetrahedron which has two bulky trifluoromethyl groups at the base (Fig. 5). Shielding of the peroxide site restricts the sphere of the attack on the alkene and imposes stringent steric requirements on the transition state caused by the torsional strain between the substituents in the hydroperoxide and the alkene.



125

Figure 5. Newman projections of the transition state formed in the oxidation of alkenols with hexafluoro-2-hydroperoxypropan-2-ol (**125**); (*a*) spiro structure; (*b*) eclipsed conformation.

Of the two transition state structures *a* and *b* (see Fig. 5), possible due to the presence of two lone electron pairs at the active oxygen atom, spiro structure *a* is preferred, in which the pseudo-axial electron pair in relation to the five-membered chelate ring of the hydroperoxide participates in ring formation.

Epoxidation of the cycloalkene **126** involves the double bond removed further from the benzyloxymethyl substituent. The *syn*-orientation of the oxidant with respect to the substituent ensures the formation of the most favourable transoid conformation of the transition state (Fig. 6 *a*). The *anti*-orientation would result in *gauche*-conformation (Fig. 6 *b*).

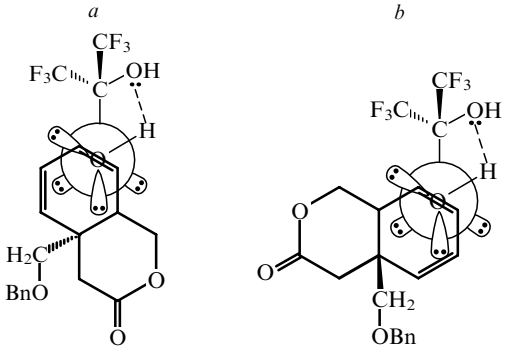


Figure 6. Newman projections of the transition state formed in the oxidation of the diene **126** by hexafluoro-2-hydroperoxypropan-2-ol (**125**); (*a*) transoid conformation; (*b*) *gauche* conformation.

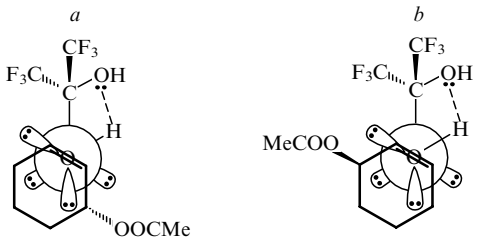


Figure 7. Newman projections (*a* and *b*) of the transition state formed in the oxidation of cyclohex-2-enol acetate with hexafluoro-2-hydroperoxypropan-2-ol (**125**).

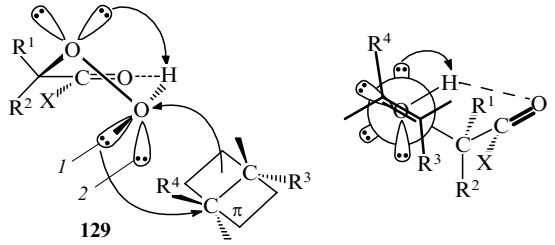


Figure 8. Transition state **129** formed in the oxidation of alkenes by the hydroperoxide **127** and its Newman projection: (*1*) equatorial lone pair of the oxygen atom; (*2*) axial lone pair of the oxygen atom.

From this standpoint, it becomes clear why acylated cyclohex-2-enol is converted into the *syn*-epoxide. Evidently, conformation *a* is more stable than conformation *b* (Fig. 7).

Epoxidation of the same alkene by a peroxy acid affords mostly the *anti*-epoxide. When cyclohex-2-enol is epoxidised by hexafluoro-2-hydroperoxypropan-2-ol, the role of complementarity is enhanced by the directing influence of the hydroxy group, thus making this reagent more selective than peroxy acids.

The stereochemistry of the epoxidation of alkenes by α-hydroperoxides **127** and α-hydroperoxy nitriles **128** has been described in reviews.[1,2]



127 **128**

R^1 = Me, R^2 = Ph; X = OR^3, NR_2, Alk.

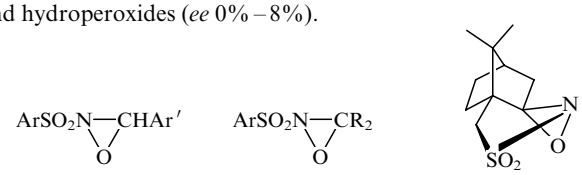
The hydroxy group in cyclohex-2-enol has a *syn*-directing influence on epoxidation. However, unlike peroxy acids, the hydroperoxide **127** (X = OR) oxidises *trans*-stilbene more easily than *cis*-stilbene and oxidises *trans*-β-methylstyrene more easily than cyclohexene.

Interpretation of the *trans*-selectivity should be sought in a comparison of the electronic and steric features of the transfer of active oxygen from the hydroperoxide **127** to the alkene with those for peroxy acids. The latter are known to be characterised by low energies of the O–O bond and high mobility of the OOH-group proton. The RCO_3H – alkene transition state is extended along the reaction coordinate, and, in conformity with the Bell–Evans–Polanyi principle, its structure is closer to the final products than to the initial compounds. This means that loosening of the peroxide bond in RCO_3H starts at an early stage of insertion of the alkene π orbital into the antibonding σ^*_{O-O} orbital before the O–H bond is cleaved. The proton transfer does not limit the overall rate of the process.[1,2] In addition, in the case of peroxy acids, there is no torsional strain, involved in the transition state with hexafluoro-2-hydroperoxypropan-2-ol and the hydroperoxides **127**. This accounts for the low sensitivity of the RCO_3H molecule to the alkene structure; the *cis*-alkene is epoxidised slightly more readily than the *trans*-isomer,[14] which can be easily explained by the higher thermodynamic stability of the latter isomer.

Regarding the α-hydroperoxides **127**, it should be noted that they are several orders of magnitude weaker oxidants than peroxy acids.[2] The peroxide proton in the hydroperoxides **127** is substantially less active than that in RCO_3H. Therefore, the α-hydroperoxide–alkene transition state **129** is compact and the intramolecular proton transfer on the leaving alkoxy anion is necessarily included in the step determining the overall rate of the process (Fig. 8). This, in turn, places certain steric demands on the orientation of the OH group in the hydroperoxide **127**. On the one hand, this group tends to be coplanar with the axial lone electron pair of the neighbouring peroxide oxygen atom and, on the other hand, it tends to escape the eclipsed position with respect to the bulky substituents at the alkene double bond. These requirements are satisfied in the case where the coplanar alkene π bond and chelated hydroperoxide molecule approach each other with the R^3 substituent of the alkene being removed from the eclipsed position with respect to the OH group (under the π-bond plane) and the R^4 substituent being located above the plane. This determines the *trans*-selectivity of the reaction.

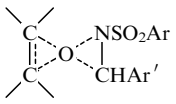
In the case of *cis*-alkene, the substituents R^3 and R^4 should be directed below the plane of the chelated hydroperoxide; this increases the strain in the transition state due to the interaction of these groups with R^2. If the transition state had a spiro structure in which the alkene π plane passed through the n_a orbital of the active oxygen atom, the shift of the proton into the axial position and its interaction with the leaving alkoxy anion would be hampered. In this connection, it is noteworthy that the transition state formed in the epoxidation of alkenes by hexafluoro-2-hydroperoxypropan-2-ol **125** has a spiro structure (see Fig. 6 *a*). In this case, the problem of the proton transfer to the leaving alkoxy anion is eliminated because the process is synchronous.

The complementarity factor, which determines the direction of the attack on the electrophilic site of the alkene, becomes significant when substituted oxaziridines are used as epoxidising agents.[103–107] Diastereoisomeric 2-sulfonyloxaziridines **130**–**132** epoxidise alkenes containing no directing functional groups with higher enantioselectivity (*ee* 12%–65%) than chiral peroxy acids and hydroperoxides (*ee* 0%–8%).



130 **131** **132**

Based on kinetic and thermodynamic parameters, correlation analysis of the effects of substituents present in the phenyl groups of oxaziridines, a synchronous mechanism of epoxidation of alkenes including transition state **133** has been proposed. In accordance with this mechanism, the oxaziridine ring and the π bond are coplanar, the process stereochemistry being controlled by the configuration of substituents.[104–107]



133

Similar conclusions have been drawn from quantum-chemical calculations.[108] Experimental data cited above[103–107] can be interpreted in a different way by invoking general theoretical views on the stereoelectronic features of reactions of this type, in particular, epoxidation of alkenes by hydroperoxides[1,2,5] and dioxiranes.[4,109,110]

The oxidising capacity of oxaziridines is due most of all to the N–O bond, which is similar to the peroxide bond. The nitrogen atom is less electronegative than oxygen but the E_{N-O} value in the oxaziridines **130**–**132** decreases owing to the strong electron-

withdrawing influence of the SO_2 group. The difference between the O–N and O–C bond energies results in the loosening and rupture of the O–N bond at the stage of oxygen transfer to the substrate occurring somewhat ahead of the O–C bond cleavage. The asynchronous cleavage of bonds is apparently a general feature of small rings similar to oxaziridine, in particular, dioxirane and dioxetane.

The nucleophilic attack by the alkene π electrons on the oxygen atom of the oxaziridine ring is directed at the antibonding orbital of the O–N bond along its axis (transition state **134**, Fig. 9). In the initial interaction event, transfer of the π-electron density on the oxygen atom loosens the N–O bond and, simultaneously, the axial lone electron pair of oxygen n_a interacts with the π^* orbital of the alkene. As in the case of hydroperoxides, the combination of two types of interaction — donor-acceptor and dative interaction — is a necessary condition for the synchronous formation of the C–O bonds in the oxirane ring.

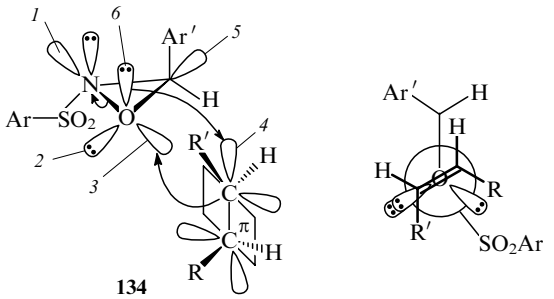


Figure 9. Transition state **134** formed in the epoxidation of alkenes with ozxaziridines and its Newman projection;
(*1*) σ^*_{N-O}; (*2*) equatorial lone pair of the oxygen atom (n_e); (*3*) σ^*_{N-O}; (*4*) π^*; (*5*) σ^*_{C-O}; (*6*) axial lone pair of the oxygen atom (n_a).

The localisation of excess electron density at the nitrogen atom creates conditions for the overlap of the partially occupied σ^*_{N-O} orbital (or the nitrogen *n* orbital) with the vacant σ^*_{C-O} orbital, which, in turn, induces loosening of the C–O bond.

It is clear that the angle between the attack on the alkene π bond and the plane of the oxaziridine ring is about 180° – 109° = 71°, the most significant restrictions hampering the approach of the reactants and construction of the transition state being caused by the carbon atom and its substituents rather than by the substituents at the nitrogen atom in the epoxidising agent. Therefore, the epoxidation transition state **134** in which the ring formation involves the *cis*-alkene and the axial lone electron pair of oxygen seems to be the least sterically hindered.

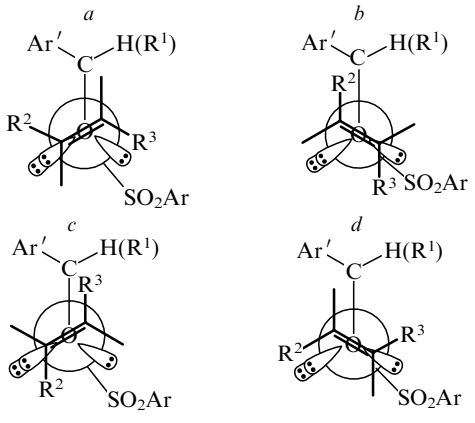
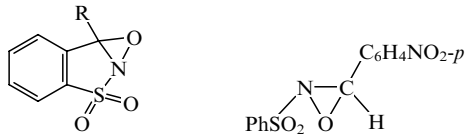


Figure 10. Newman projections (*a*–*d*) of the transition state of epoxidation of *trans*-alkenes with sulfonyloxaziridines.

The best transition state for the epoxidation of *trans*-alkenes should be chosen out of the four possible structures *a*–*d* (Fig. 10) (in the Newman projections, the observer looks along the O–N bond from the side of the alkene attack).

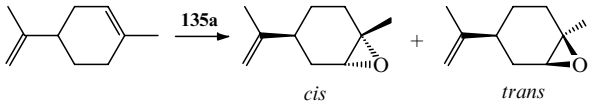
Analysis of the stereochemical outcome of epoxidation of *trans*-stilbene with (*R*,*R*)-(+)-sulfonyloxaziridines **135a**–**d** shows that the (*R*,*R*)-(+)-oxirane is formed with *ee* 34.9%. Hence, the reaction occurs mainly *via* transition state *a*. Indeed, transition state *b* is sterically much more strained and transition states *c* and *d* would lead to the (*S*,*S*)-oxirane.



135a–**d** **136**

R = Me (**a**), Bu^n (**b**), Bu^i (**c**), Bu^t (**d**).

Our conclusions are also consistent with other experimental data.[105–108] Thus epoxidation of (*R*)-(+)-limonene by sterically shielded oxaziridine **135a** is 20.7 times slower than that by oxaziridine **136**.[104] This reaction is fairly *cis*-selective (60%–74%), the selectivity increasing with an increase in the size of the group R.



Note for comparison that oxidation of limonene by *m*-chloroperbenzoic acid yields the isomers in 1 : 1 ratio. It is also noteworthy that the rates of limonene epoxidation by the oxaziridines **135a**–**c** are related as 1 : 0.93 : 0.3, and the compound **135d** barely enters into this reaction.

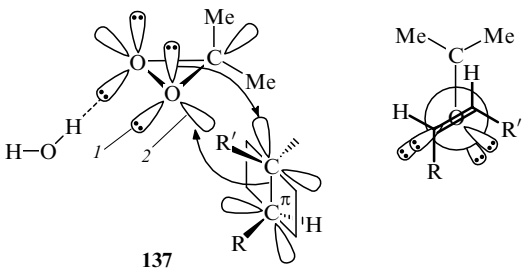
The replacement of the oxaziridine **136** by its analogue containing a nitro group in the *ortho*-position rather than in the *para*-position decreases the rate of epoxidation of 1-methylcyclohexene by a factor of more than 6.[107]

To summarise the foregoing, we can conclude that the reaction in question occurs by an S_N-type mechanism assuming the formation of a spiro transition state. The fact that the bonds in the oxaziridine ring are cleaved asynchronously induces some charge separation. The negative charge on the nitrogen atom is highly delocalised due to the electron-withdrawing influence of the SO_2 group. The buffer function of this group markedly decreases the sensitivity of the reaction to the polar influence of the substituent X in the $XC_6H_4SO_2$ group. Hence, the Hammett constants of the reaction (ρ) found upon variation of substituents in the benzene nucleus at the carbon atom and in the sulfamide moiety of the sulfooxaziridine molecule are nearly equal and amount to 1.07 and 1.09, respectively.

Dioxiranes are very close to oxaziridines regarding the character of their reactions with alkenes.[4, 109, 110] In the case of dimethyldioxirane, the reaction is highly sensitive to steric restrictions caused by the interaction of the methyl groups with the substituents at the double bond. Branched alkenes, *trans*-4,4-dimethylpent-2-ene and *trans*-2,2,5,5-tetramethylhex-3-ene, are epoxidised much more slowly than *trans*-hex-3-ene. In the series of ordinary dialkyl-substituted alkenes, *cis*-isomers are an order of magnitude more reactive than the corresponding *trans*-alkenes.

Based on the kinetic and thermodynamic parameters, it was concluded that the reaction proceeds *via* a bimolecular complex having a spiro structure.[110]

By analogy with the transition state **134**, it can be assumed that the attack by the alkene is directed at the antibonding σ^*_{O-O} orbital of the dioxirane along the peroxide bond, the π-electron plane passing through the pseudo-axial non-bonding orbital of oxygen as has been shown in the structure **137** (Fig. 11).



137

Figure 11. Transition state **137** formed in the epoxidation of alkenes with dioxiranes and its Newman projection; (*1*) n_e of oxygen, (*2*) σ^*_{O-N}.

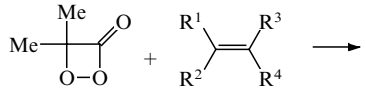
The loosening and rupture of the O – O bond in dioxirane at an initial stage of its reaction with the alkene occurs ahead of the C – O bond cleavage, a partial negative charge being created on the leaving oxygen atom. Unlike oxaziridine, dioxirane is unable to delocalise the excess charge and in the transition state **137**, the leaving anion is solvated, which is typical of the S_N-type reactions. It is due to this fact that the allylic hydroxy group has a directing influence on the oxidant during epoxidation of cyclohex-2-enol.[4] It has also been found that admixtures of water in acetone catalyse the process.[109] The decrease in the effect of water admixtures in the case of epoxidation of low-reactivity alkenes by dioxiranes is, apparently, due, as in the case of epoxidation by peroxy acids,[1,2] to the ability of the oxidant to undergo self-oxidation to give singlet oxygen in media favourable for the formation of hydrogen bonds. Reactive alkenes normally suppress decomposition of the epoxidising agent thus increasing the rate of formation and the yield of oxiranes. Chiral dioxiranes, prepared from chiral ketones and oxone ($KHSO_5$), epoxidise alkenes with a substantial asymmetric induction (up to 87%).[111]

Correlation analysis and thermodynamic parameters point to a common character of electron density distribution in the transition states formed when dioxiranes, oxaziridines and peroxy acids are used as epoxidising agents.

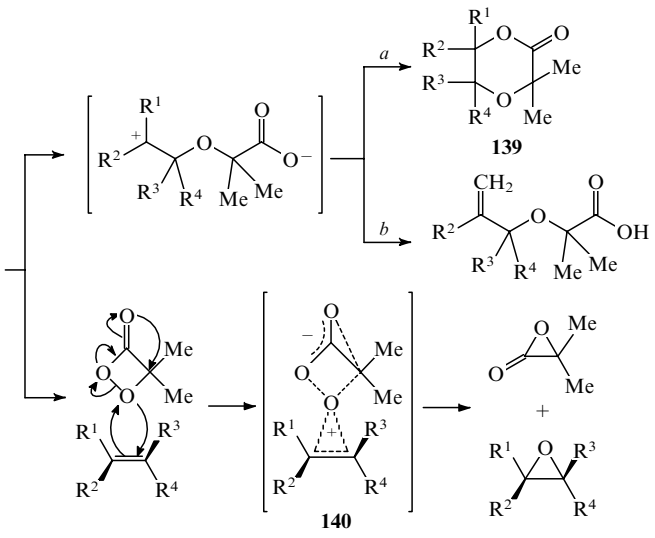
Epoxidation of di-, tri- and tetrasubstituted alkenes by dimethyl-α-peroxy lactone **138**, the structure of which is similar to that of dimethyldioxirane, is controlled by absolutely different stereochemical factors.

First, attention is attracted by the high *trans*-selectivity of epoxidation by peroxy lactone **138**. *cis*-But-2-ene is virtually not epoxidised; instead, it is converted into cycloaddition product **139**. However, *trans*-but-2-ene is transformed only into the epoxide. As the number of alkyl substituents at the double bond increases, the overall rate of the process increases, indicating that the alkene acts in this reaction as a nucleophile. Simultaneously, the contribution of cycloaddition, which is known to be highly sensitive to steric restrictions, diminishes. In the case of tetraalkyl-substituted alkenes, cycloaddition hardly occurs. Yet another characteristic feature of this process is the relatively high polarity of the intermediate complex. This is indicated by the fact that it can be efficiently neutralised by methanol, acting as a carbocation trap.

The formation of the oxirane ring implies a concerted mechanism for the electron density redistribution in transition state **140**, which, judging from experimental data, is conformationally stable only for *trans*-alkene, as in the epoxidation of α,β-unsaturated carbonyl compounds **4**.[112]

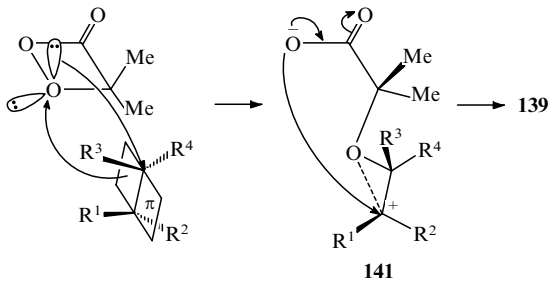


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(*a*) Cycloaddition; (*b*) ene reaction, R^1 = Me.

It turns out that the *cis*-orientation of substituents in the alkene, which is favourable for the reactants to come together, prevents the formation of a planar, conformationally stable transition state **140** with delocalised charges. In this case, zwitter-ionic transition state **141** with sterically non-hindered rotation around the σ-bonds, needed for 1,4-dioxane ring closure, becomes more preferable.



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The principle of complementarity of reactants underlies the asymmetric epoxidation of simple, non-functionalised alkenes by oxometal complexes containing Schiff's bases, porphyrins or other oxygen- and nitrogen-containing compounds as ligands.[112–114] The geometry of the environment of the reaction site determines the predominant orientation of the prochiral alkene at the stage when the reactants approach each other. For example, epoxidation of a number of alkenes with an oxygenated manganese complex gives the corresponding oxiranes in very high optical yields (92% – 98%).[112] However, detailed consideration of reactions of this type is beyond the scope of our review.

VI. Conclusion

Conformational analysis of the diastereoisomeric transition states (TS) with allowance for the stereoorbital conditions for the closure to give an oxirane ring is an efficient method for substantiation and prediction of the route and the stereochemical outcome of epoxidation of alkenes with various peroxide reagents. The integral stereocontrolling factor in these reactions is the conformational stability of the TS, which is determined, in its turn, by the spatial compatibility (complementarity) of the reactants, torsional strain, influence of the neighbouring functional groups, hyperconjugation and other effects.

The directing influence of allylic and homoallylic hydroxy groups in the case of alkyl hydroperoxides, which require metal complex catalysis, is attained at the stage of construction of a multiligand complex and the formation of a donor-acceptor bond between the OH group and the central atom. When epoxidation is carried out by an epoxy acid, the role of these groups is to stabilise the carboxylate anion, which is eliminated at the stage of decomposition of the transition state, whereas carbonyl groups in alkenyl-containing amides, esters, carbamates and urethanes exert a similar stereoeffect due to the formation of a hydrogen bond with RCO_3H at the stage of coming together and coordination of the reactants.

Epoxidation of α,β-unsaturated *S-cis*-ketones of the steroid type occurs apparently by a non-classical mechanism assuming 1,4-addition of the peroxy acid.

The stereochemistry of the non-catalysed epoxidation involving active alkyl hydroperoxides is largely determined by the formation of more compact transition states than those in the case of peroxy acids and by the substituents attached to the sp^3 hybridised carbon atom of the C–OOH group.

Some general regularities of the formation of planar transition states and spiro structures were established. The spiro type TS, which are less sterically strained, are formed in the epoxidation of alkenes with RCO_3H and $(CF_3)_2C(OH)OOH$. Under these conditions, the stage of transfer of the active oxygen to the substrate does not depend on the rate of proton transfer. Meanwhile, the epoxidation of alkenes with α-hydroperoxy-derivatives of esters is controlled by the transfer of the OOH group proton on the axial pair of *p* electrons of the neighbouring oxygen atom. The orientation of molecular orbitals participating in this process induces the formation of a planar transition state and requires a transoid configuration of the alkene molecule.

trans-Selectivity is also typical of other epoxidation reactions involving the formation of planar TS, in particular, those using dimethyl-α-peroxy lactone as the epoxidising reagent and in the alkaline alkyl-peroxide oxidation of α,β-unsaturated esters. In the latter case, the reaction occurs stereoselectively because of the two possible conformations of the cyclic transition state, the more stable conformation with an equatorial orientation of the bulkiest substituent in the alkene molecule is formed preferentially.

cis-Selectivity is an indication of a spiro configuration of the compact transition states formed in epoxidation of alkenes with oxaziridines and dimethyldioxirane. The process stereochemistry is controlled by the substituents at the carbon atom in these heterocycles; in the case of oxaziridines, this ensures a fairly high enantioselectivity.

The overall effect of various types of strain in cycloalkenes and methylenecycloalkanes stipulates the predominance of the epoxidation pathway that relieves the strain in cycloalkene and results in the formation of the transition state and the oxirane with the least conformation distortion.

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