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The Mechanism of the Acid-Catalyzed Ring Opening of Epoxides – A Reinterpretative Review*

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Summary

Summarizing all available evidence we may conclude that the acid-catalyzed ring opening of primary and secondary epoxides proceeds with WALDEN inversion by a S_N2 (or overall A-2) mechanism. A fractional positive charge at the reacting carbon atom may be postulated without taking recourse to the "borderline" S_N2 mechanism, for which clear evidence seems nonexistent. The entropy of activation and the solvent isotope effect merit reinterpretation as well. More work is needed to establish the mechanisms operating in the hydrolysis of tertiary and mono-aryl substituted epoxides.

In connection with recent work on the stereochemistry and mechanism of the acid-catalyzed reaction of epoxides with nitriles to give 2-oxazolines[1a] it became necessary to review the general field of the acid-catalyzed ring opening of epoxides. Since most of the reviews on epoxides are significantly dated[2–6] and contain incorrect material which continues to be cited, we have reviewed and reinterpreted one topic, namely the acid-catalyzed ring opening.

Three important aspects will be discussed as separately as possible: the observed orientation of ring opening in unsymmetrical epoxides such as propylene oxide, the observed stereochemistry, and the mechanism or kinetics of the ring opening.

Orientation of Epoxide Ring Opening

Ionic ring-opening reactions of epoxides proceed differently depending on whether the epoxide ring reacts in the neutral form, or as a protonated form or complex with a LEWIS acid.[2–6]

In the case of reactions where the epoxide reacts as a neutral or uncoordinated species, it has been well established that the nucleophilic reagent generally attacks almost exclusively the less branched carbon atom (*i.e.*, rate at primary > secondary > tertiary carbon atom) according to KRASUSKII's rule.[2–8] This is presumably due to steric reasons, and the mechanism of reaction is close to S_N2. In accordance with general practice, products resulting from compliance with KRASUSKII's rule will be termed "normal", while those resulting from additions violating it will be termed "abnormal".

Results are different, however, when the epoxide reacts in the protonated form or as a LEWIS acid complex. Here mixtures of "normal" and "abnormal" product are generally found. LONG and PRITCHARD investigated the reaction of propylene oxide with ^{18}O enriched water with perchloric acid as a catalyst. They found 74 percent opening at the secondary atom ("abnormal" product) and 26 percent opening at the primary carbon ("normal" product) to give the corresponding propane-1,2-diols (eq. 1).[9]

$$\underset{\diagup\,\diagdown}{\overset{O}{CH_3CH\,CH_2}} \xrightarrow{H_3O^{\oplus 18}} \underset{26\,\%}{CH_3\overset{OH}{\overset{|}{C}}HCH_2{}^{18}OH} + \underset{74\,\%}{CH_3\overset{{}^{18}OH}{\overset{|}{C}}HCH_2OH} \qquad (1)$$

For the reaction of propylene oxide with nitriles in the presence of sulfuric acid, ODA *et al.* found approximately 70 percent "abnormal" and 30 percent "normal" product,[1b] *i.e.*, a ratio very similar to the acid-catalyzed reaction with water.

In reactions with other acids and nucleophiles various ratios of "normal" to "abnormal" product are obtained, ranging roughly between 8 and 74 percent "abnormal" product.[2–6]

It remains to be explained why, in those cases where the epoxide reacts in a protonated or coordinated form, a mixture of "normal" and "abnormal" product is formed. This can be easily understood, as, *e.g.*, pointed out by PARKER and ISAACS,[6] if one assumes that the carbon atom at which the S_N2-type displacement takes place carries a significant positive charge in the transition state. This charge can be better stabilized at the more highly branched carbon atom as a consequence of the inductive effect. The ratio of "normal" and "abnormal" product is then the result of a balance of steric and electronic factors.

ADDY and PARKER have looked at the electronic factors in the reactions of propylene oxides suitably substituted at the methyl group.[10] For the acid-catalyzed ring opening with chloride ion as nucleophile, they found that electron-attracting substituents decrease the percentage of the "abnormal" product in the mixture, whereas electron-releasing substituents increase the percentage of "abnormal" product. Both "normal" and "abnormal" reactions are retarded by electron-withdrawing substituents, presumably due to the preliminary equilibrium between the epoxide and its conjugate acid.

We disagree, however, somewhat on the mechanism which causes the positive charge in the transition state. PARKER and coworkers claim that the positive charge is caused by a "borderline" S_N2 mechanism, where bond

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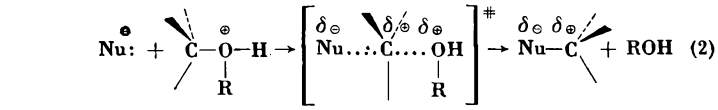
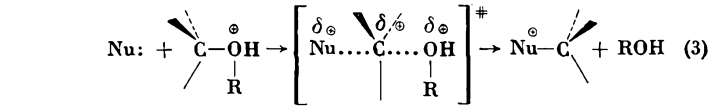
breaking has progressed further in the transition state than bond making. Evidence for and against this "borderline" mechanism will be discussed in reference to the mechanism of the reaction. For the moment, it is sufficient to state that we feel that the evidence for the "borderline" mechanism is not strong, and that the positive charge in the transition state may simply be a consequence of a *positive* leaving group leaving in a normal S_N2 reaction. In the transition state, the leaving group has only left partially, and it is reasonable to assume that part of the positive charge resides on the carbon atom in spite of the incoming nucleophile (eq. 2).



The positive charge at the carbon atom in the transition state plausibly will be larger when the attacking nucleophile is a neutral species which will end up positively charged at the end of the S_N2 displacement (eq. 3), than when the nucleophile is an anionic species which is becoming neutral during the reaction (eq. 2).



This may help to explain why there seems to exist a tendency for neutral nucleophiles such as H_2O and nitriles to give a higher percentage of "abnormal" product than negatively charged nucleophiles such as halide ions do.

It should be emphasized that these conclusions are restricted to the acid-catalyzed ring opening and to the comparison between attack at secondary ("abnormal") *versus* primary ("normal") carbon atom.

Stereochemistry of Epoxide Ring Opening

The very large majority of acid-catalyzed ring openings (as well as *all* neutral or basic ionic openings) proceeds with complete WALDEN inversion.[2–6] This fact is, of course, independent of any postulated detailed mechanism, but would exclude a limiting S_N1 mechanism.

The main exception is a group of compounds which possess an aryl or acyl group attached to the epoxide ring. Here the acid-catalyzed ring opening may proceed with neighboring group participation in a double-inversion mechanism resulting in overall retention.[6, 11]

A small number of cases are known where nonstereospecific ring openings are observed. Most of these reactions seem to go by a combination of the inversion- and double-inversion mechanism, although it cannot be excluded that some reactions may actually proceed through an open free carbonium ion by a S_N1 mechanism. It should be repeated that older data in many cases are suspect. In some cases it has been found that the starting material or the product may racemize or isomerize independent of the actual ring-opening step.[4,12] Criticism against the frequently postulated S_N1 mechanism has also been put forward by CHAN and WELLS.[13]

The Mechanism of the Epoxide Ring Opening

Having discussed the orientation and stereochemistry of the ring opening, we can now turn our attention to the kinetics and mechanism as a whole. In order to understand most of the presently held views it is necessary to briefly summarize the historical development.

Originally all epoxides, including ethylene oxide, were assumed to hydrolyze in acidic solution in a classic or limiting S_N1 mechanism, *i.e.*, by an unimolecular opening to give a free carbonium ion, followed by rapid reaction of the free carbonium ion with the nucleophile.[14] Soon this mechanism had to be abandoned, at first for primary carbonium ions and then also for secondary carbonium ions. First, it was realized that primary free carbonium ions are extremely unstable. Second, the observed stereochemistry always consisted of complete WALDEN inversion, whereas, with the S_N1 mechanism at least partial racemization would be expected (see, however, [40, 41]).

Unfortunately, at that time, the normal S_N2 mechanism could not be postulated either since it seemed to be in contradiction to other available evidence. LONG and PRITCHARD investigated the reaction of 10 epoxides in aqueous perchloric acid and found the rate constant k to be proportional to the HAMMETT acidity function h_0, rather than to $[H_3O^+]$.[9, 15] Using the ZUCKER-HAMMETT hypothesis[16] they reasoned that the transition state therefore could not contain a water molecule as a nucleophile, which excluded the S_N2 (or overall A-2) mechanism and indicated the S_N1 (or overall A-1) mechanism. Therefore, neither the limiting S_N1 nor the pure S_N2 mechanism seemed to fit the available data. The same mechanistic problem, complete inversion and k proportional to h_0, was also found in many other reactions, *e.g.*, in the acid-catalyzed oxygen exchange of 2-butanol observed by means of ^{18}O enriched water,[17] and in the acid-catalyzed racemization of optically active 2-butanol.[18]

Explanations of this apparent contradiction between the stereochemical evidence and the evidence of the HAMMETT acidity function have been given by BUNTON and LLEWELLYN,[17, 18] by PRITCHARD and LONG,[19, 20] and, by PARKER and ISAACS.[6] BUNTON claimed that the lifetime of the carbonium ion was not long enough for the leaving group to move sufficiently far away to make the carbon at the reaction center susceptible to attack from all directions, an effect termed "steric shielding".[17, 18] PRITCHARD and LONG rationalized the results on the basis that in the strained oxide ring, given ionizing conditions, a carbon oxygen bond did not have to stretch very far before a full energy maximum for the

process of bond breaking was reached.[19, 20] Finally, PARKER and ISAACS explained the acid-catalyzed ring opening of epoxides by a S_N2 type mechanism in which the reagent was further away than usual from the seat of attack, and the driving force of the reaction was provided more by transfer of electrons from carbon to oxygen than from nucleophile to carbon. In other words, bond breaking would be more important (*i.e.*, more nearly complete) in the transition state than bond making. They referred to this mechanism as "borderline S_N2".[6]

This type of transition state, where both partial bonds of the activated complex were longer than usual, also gave support to the concept of a fractional positive charge on the central carbon atom which would explain the observed product mixtures of "normal" and "abnormal" product.

These explanations all attempted to postulate a mechanism intermediate between limiting S_N1 and S_N2. Such a mechanism is also commonly referred to as a S_N2 mechanism with a good deal of S_N1 "character", and the corresponding transition state is referred to as a "loose" transition state (as opposed to tight).[21]

All these explanations were put forward in the heyday of the ZUCKER-HAMMETT hypothesis. In the meantime it has been shown that the ZUCKER-HAMMETT hypothesis is essentially invalid.[22–25] BUNNETT has introduced two new treatments of reactions in strongly acidic solution, the earlier one in terms of the (BUNNETT) ω-value,[23] the more recent one in terms of the "solvation variable" Φ.[24, 25] By a detailed analysis of over one hundred reactions, on which accurate literature data were available, BUNNETT showed that the reactions in strongly acidic medium do not fall neatly into the various categories according to the ZUCKER-HAMMETT hypothesis, but form a continuous series.

BUNNETT also found that many reactions, such as the acid-catalyzed O-exchange of 2-butanol[17, 26] and racemization of optically active 2-butanol,[18, 26] which on the base of the ZUCKER-HAMMETT hypothesis were formerly classified as proceeding by a S_N1 mechanism, had to be reclassified as proceeding by a S_N2 mechanism; in other words, a molecule of water was involved as nucleophile in the activated complex contrary to the ZUCKER-HAMMETT hypothesis.

It seems entirely reasonable, then, to reclassify the normal acid-catalyzed ring opening of epoxides proceeding with inversion as belonging essentially to the S_N2 or A-2 mechanism.

Using the data of LONG and PRITCHARD,[20] we have evaluated the BUNNETT solvation variable Φ for the perchloric acid-catalyzed ring opening of ethylene oxide. Plotting $(\log k + H_0)$ against $(H_0 + \log H^+)$, we obtained a Φ value of approximately 0.32, clearly indicative of the S_N2 or overall A-2 mechanism.[27]

The S_N2 mechanism is, of course, in agreement with all the kinetic data available on the acid-catalyzed ring opening. In all cases at constant pH, second order kinetics were found, being first order both in the epoxide and in the nucleophile.[4, 6]

The S_N2 mechanism is also in agreement with the negative value for the volume of activation observed by WHALLEY, who was one of the first persons to argue in favor of the S_N2 (A-2) rather than S_N1 (A-1) mechanism.[28]

At least two more criteria have in the past been used to support the "borderline" S_N2 mechanism. First, LONG, PRITCHARD and STAFFORD found that the values of the entropies of activation for three epoxides were intermediate (-4 to -6 cal mole^{-1} deg^{-1}) between those found for reactions of established A-2 mechanism (-21 to -25 cal mole^{-1} deg^{-1}) such as the hydrolysis of simple esters (*e.g.*, ethyl acetate) and lactones and those found for reactions of established A-1 mechanisms (generally $+6$ to $+13$ cal mole^{-1} deg^{-1}) such as the hydrolysis of acetals, ketals and *ortho* esters.[19, 29, 30]

An alternative explanation, however, is that ring-opening reactions of epoxides proceeding by a S_N2 mechanism may have more positive entropies of activation than the same mechanism occurring in an open chain compound.[30] It is well known that transition states, where rings are formed, can have unusually small or negative entropies of activation.[31] The reverse should hold true for ring-opening reaction. But, on an even more fundamental basis, we would like to quote HAMMETT: "The prospect of detecting stoichiometric involvement of the solvent in the formation of a transition state in solution by way of the entropy of activation is not (therefore) good."[25a]

The second criterion used by PRITCHARD and LONG to support the "borderline" S_N2 mechanism for the acid-catalyzed epoxide ring opening is the solvent isotope effect k_{D_2O}/k_{H_2O}.[29, 32]

For the acid-catalyzed reaction of three epoxides they found values 1.9 and 2.2, whereas the values for the base-catalyzed reaction were quite small, k_{D_2O}/k_{H_2O} varying from *ca.* 1.0 to 1.1. This was interpreted as being in agreement with A-1 and A-2 mechanisms, respectively. A theoretical interpretation has been given by BUNTON and SHINER.[33] Once again, the evidence in favor of the A-1 mechanism seems quite tenuous from the present point of view. Since a pre-equilibrium is involved in the acid-catalyzed reaction, it seems rather difficult to estimate accurately the various factors involved.[34]

The observed solvent isotope effect might also be caused partially by differences in the interactions between solute and solvent (solvation). We would like to close these comments once again by quoting HAMMETT: "The hope, which at one time seemed bright, for a simple correlation of the solvent isotope effect with the mechanism of the reaction involving proton transfer or with the stoichiometric involvement of the solvent in the transition state has proved vain."[25b]

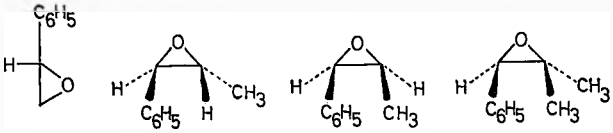
We cannot, of course, *a priori* exclude a "borderline" S_N2 mechanism with a "loose" transition state, but at

present very little if any evidence seems to exist in favour of it.[35] It should be realized that the need for this mechanism in the acid-catalyzed ring-opening of epoxides historically arose entirely from the apparent contradiction between the stereochemical evidence and the kinetic data based on the ZUCKER-HAMMETT hypothesis.

The Acid-Catalyzed Hydrolysis of Tertiary Epoxides and (Mono-) Aryl Epoxides

So far we have dealt with the hydrolysis of primary and secondary epoxides. Clear evidence for the mechanisms operating in tertiary epoxides as well as in (the possibly related[36]) (mono) aryl-substituted epoxides has only recently been forthcoming.

AUDIER, DUPIN and JULLIEN have investigated the acid-catalyzed hydrolysis of a series of styrene oxides **1** to **4** increasingly substituted at the β-carbon atom.[38] They showed by mass spectrometry that the incoming water attacks the 3 compounds **1** to **3** almost exclusively ($> 95\%$) at the benzylic α-carbon. In the case of the epoxide **4** with 2β-methyl groups they found *ca.* 45% attack at the benzylic and 55% attack at the aliphatic carbon. Optically active (+)-S-styrene oxide (**1**) was found to give completely racemic diol on acid-catalyzed hydrolysis. The *trans*-epoxide **2**, similarly, gave equal proportions of inverted and retained product. Both these compounds, therefore, react irrefutably by a S_N1 (or overall A-1) mechanism.[39]



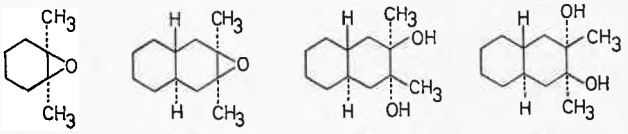
1 **2** **3** **4**

The *cis* epoxide **3**, on the other hand, reacted *ca.* 100 times slower than the *trans* isomer **2** and gave mainly (80%) inverted product. Epoxide **4** exhibited a similar rate of reaction as compound **3**, and both compounds were regarded to hydrolyze predominantly ($\geqslant 60\%$) by the S_N2 or A-2 mechanism, the changeover in mechanism being caused by the destabilization of the benzylic cations derived from epoxides **3** and **4** due to the *cis* C_6H_5/CH_3 interactions.

On the other hand, one might argue that the observed stereochemistry shows that epoxide **3** and, by analogy, also compound **4** react at least 40% by the S_N1 or A-1 mechanism.

CARR and STEVENSON have recently shown[42] that the acid-catalyzed hydrolysis of tetramethylethylene oxide, contrary to earlier reports,[43] leads to *ca.* 99% pinacol. Their interpretation is that the reaction does not proceed with intermediacy of a kinetically free carbonium ion, as is implied in many contemporary reviews on the subject,[44, 45] since it has been shown that the carbonium ion derived from pinacol gives *ca.* 30% pinacalone under similar reaction conditions (besides *ca.* 70% pinacol).[48]

An A-2 mechanism for the hydrolysis of tertiary epoxides is in agreement with the stereochemistry observed in the few examples of ditertiary[49] epoxides examined.[41] Thus both epoxides **5** and **6** have been reported to give the corresponding *trans* diols.[52, 53] In the case of compound **6** the product contained the diaxial (71%) and the diequatorial (23%) diols, **7** and **8**, respectively, with no *cis*-diol being detectable.



5 **6** **7** **8**

PRITCHARD and SIDDIQUI, on the other hand, in a recent kinetic reinvestigation of the acid-catalyzed hydrolysis of epichlorohydrin, propylene oxide and isobutylene oxide came to the conclusion that while the first two compounds react according to the A-2 mechanism, isobutylene oxide reacts according to the A-1 mechanism.[54] They cited the following arguments in favour of the A-1 mechanism: the fact that substitution occurs exclusively at the tertiary carbon atom,[9] the analogy to the case of the styrene oxide **1**, a faster rate by a factor of 110 with respect to propylene oxide, an entropy of activation *ca.* 13 units more positive than for propylene oxide and epichlorohydrin. Additional hypotheses, on the other hand, had to be invoked in order to rationalize the suspiciously low value of the volume of activation, $\Delta V^{\neq}$ (-9.2 cm^3 mole^{-1}), for an A-1 case.

On the other side of the case, *i.e.*, against the A-1 mechanism and for the A-2 mechanism, one might cite: the analogy of isobutylene oxide to tetramethylethylene oxide which seems to react by the A-2 mechanism, the observed stereochemistry in the hydrolysis of the epoxides **5** and **6**,[41] the facts that attack occurs in *ca.* 70% at the secondary carbon atom of propylene oxide and propylene oxide reacts *ca.* 6 times faster than ethylene oxide[15] while both epoxides react by the same A-2 mechanism, and the perilous nature of the use of the entropy of activation as a mechanistic argument in the present context.[25a]

Clearly, more work is needed to firmly establish the mechanisms operating in the acid-catalyzed hydrolysis of tertiary and mono-aryl epoxides.

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8 A very small number of reactions clearly violate KRASUSKII's rule, *e.g.*, the reactions with sodium cyanide and sodium acetylide.[6]

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26 ω-Values for these two reactions are 0.82 and 1.82.[23] After BUNNETT, a ω-value between -2.5 and 0 indicates water does not enter; a ω-value of 1.2 to 3.3 means water enters as nucleophile in the rate determining step. The values of the solvation variable for these two reactions are 0.13 and 0.17.[24] After BUNNETT a Φ value smaller than 0 indicates that water does not enter, a Φ value of $+0.22$ to $+0.56$ means that water enters as nucleophile in the rate determining step.

27 Unfortunately the data were not published as such but only in a graph from which they are difficult to read with great accuracy.

28 J. KOSKIKALLIO and E. WHALLEY, *Trans. Faraday Soc. 55* (1959) 815; see also W. J. LENOBLE and M. DUFFY, *J. Physic. Chem. 68* (1964) 619.

29 See also N. S. ISAACS and K. NELAKANTAN, *Can. J. Chem. 46* (1968) 1043.

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31 H. E. O. NEAL and S. W. BENSON, *J. Physic. Chem. 71* (1967) 2903.

32 J. G. PRITCHARD and F. A. LONG, *J. Amer. Chem. Soc. 78* (1956) 6008.

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34 PARKER and ISAACS[6] have already pointed out that the observed isotope effect for the acid-catalyzed reaction could equally well support the *A*-2 mechanism because of the greater amount of conjugate acid of the epoxide formed in D_2O in the pre-equilibrium.

35 In reactions other than the acid-catalyzed ring-opening of epoxides there exists good evidence for the differentiation between "loose" and "tight" transition states.[21]

36 It is well established that an α-aryl group exerts a facilitating polar effect on both the S_N2 and the S_N1 reactions, especially on the latter. As a rough rule, one α-phenyl group equals two α-alkyl groups for the purpose of determining the relative importance of the two mechanisms.[37a]

37 C. K. INGOLD, *Structure and Mechanism in Organic Chemistry*, 2nd edition, Cornell University Press, Ithaca (N. Y.) 1969, (a) p. 437, (b) p. 525.

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39 The individual stereoisomeric diols were shown to be stable under the reaction conditions.

40 As is well known, the stereochemistry of S_N1 reactions can range (in the absence of neighboring group participation) from 100% inversion to 100% racemization.[37b,42] – The only observation in favour of a change in mechanism then remains the slower rate of hydrolysis of epoxides **3** and **4** as compared with epoxides **1** and **2**. Mechanistic arguments based upon relative rates alone, however, are notoriously fraught with pitfalls. The authors themselves admit that the relative hydrolysis rates of the epoxides under consideration are poorly understood.[38b]

41 The fact that the S_N1 mechanism can lead to predominant, if not exclusive, inversion can make it difficult to decide between the S_N1 and the S_N2 mechanism in a solvolysis reaction. (A solvolysis reaction is a kinetically first-order nucleophilic displacement reaction in which the displacing nucleophile is a molecule of solvent *irrespective* of the mechanism.[25c,37])

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43 Y. POCKER, *Chem. & Ind.* (London) 1959, 332.

44 See footnote 14 in reference 42.

45 An alternative explanation could possibly be that the carbonium ions derived from the acid-catalyzed S_N1 reactions of tetramethylethylene oxide and pinacol are *conformationally* different. Conformationally different carbonium ions (or ion pairs) as, *e.g.*, derived from *cis*- and *trans*-4-*tert.*-butylcyclohexyl tosylate[46] or *cis*- and *trans*-9-chlorodecaline[47] are known to lead to different product compositions.

46 S. WINSTEIN and N. J. HOLNESS, *J. Amer. Chem. Soc. 77* (1955) 5562.

47 A. F. BOSCHUNG, M. GEISEL, and C. A. GROB, *Tetrahedron Letters No. 50* (1968) 5169; R. C. FORT, Jr., R. E. HORNISH and G. A. LIANG, *J. Amer. Chem. Soc. 92* (1970) 7558.

48 C. A. BUNTON, T. HADWICK, D. K. LLEWELLYN and Y. POCKER, *J. Chem. Soc. 1958*, 403.

49 The stereochemistry of the acid-catalyzed hydrolysis of a number of mixed tertiary-secondary and tertiary-primary epoxides, including a large number of 4,5-, 5,6-, 7,8- and 9,11-epoxysteroids,[50] has been reported. In all cases, inversion of stereochemistry was observed, obtaining *trans* diols when using an epoxide derived from a cyclic olefin. Although it is likely that in some of the cases attack by water occurred, at least partially, at the tertiary carbon atom, this aspect was not investigated and, therefore, no conclusions with respect to *A*-1 or *A*-2 mechanism are possible.[51] The reactions have also generally been carried out for preparative purposes only, without a complete analysis of the crude product compositions.

50 S. COFFREY (ed.), *Rodd's Chemistry of Carbon Compounds*, 2nd edition, Vol. II/D, Elsevier Publ. Co., New York 1970, p. 111–4, and references cited therein.

51 See, however: C. W. DAVEY, E. L. MCGINNIS, J. M. MCKEOWN, G. D. MEAKINS, M. W. PEMBERTON, and R. N. YOUNG, *J. Chem. Soc. C 1968*, 2674, where an *A*-1 mechanism is postulated.

52 S. NAMETKIN and N. DELEKTROSKY, *Ber. dtsch. chem. Ges. 57B* (1924) 583; obviously the configuration assigned by these authors has to be reversed.

53 H. B. HENBEST, M. SMITH and A. THOMAS, *J. Chem. Soc. 1958*, 3293.

54 J. G. PRITCHARD and I. A. SIDDIQUI, *J. C. S. Perkin II 1973*, 452.