

THE PREFERENCE FOR SYN ELECTROPHILIC ATTACK IN ADDITIONS TO 3-SUBSTITUTED CYCLOHEXENES.

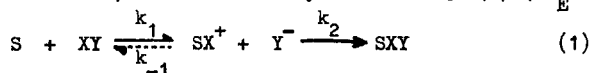
A NEW INTERPRETATION

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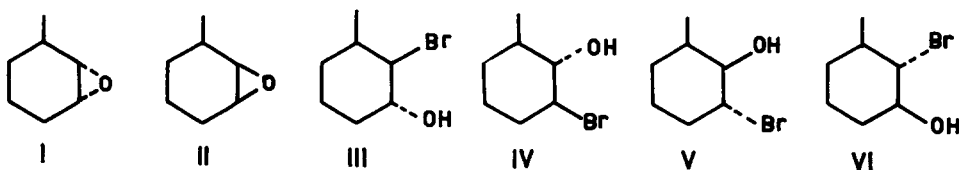
(Received in UK 9 August 1973; accepted for publication 24 August 1973)

The usual interpretation of electrophilic additions to alkenes involves an irreversible rate determining electrophilic step leading to a cationic intermediate, followed by a fast nucleophilic one giving the final adduct, as schematically shown in eq. (1) (Ad_E^2 mechanism).¹



This implies that the steric course of these reactions be determined in the first rather than in the second step. Evidence has however been accumulating in recent times indicating that in some types of additions the stereoselectivity, as well as the regiospecificity may rather be determined by steric and electronic factors during the nucleophilic step. These data concern mainly substituted cyclohexenes,²⁻⁶ and require that the electrophilic step be reversible and k_2 smaller than k_1 and k_{-1} . Some very recent results on bromine addition to acyclic alkenes in CF_3COOH have also been interpreted in similar terms.⁷

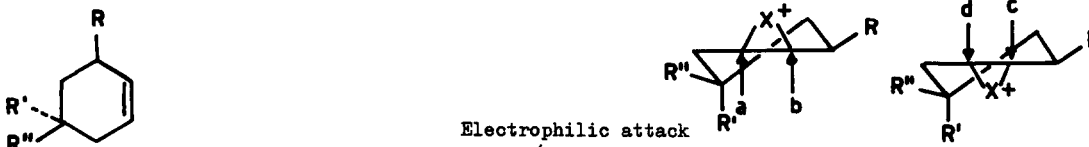
We have now investigated some additions to 3-methylcyclohexene under conditions that allow to distinguish between the direction of electrophilic and that of nucleophilic attack. The results are summarized in the Table (entries 1-3), which also includes other pertinent data on similar reactions. The mixtures of epoxides I and II obtained in run 2 and of bromohydrins III-VI, formed in runs 1 and 3 and in the reactions of I and II with HBr (entry 2, last two columns) were easily analyzed by g.l.p.c. The identification of these products was based on straightforward spectroscopic methods and will be discussed in the full paper.



The data in the Table constitute a fairly consistent set and suggest the following considerations.

1) The epoxidation with peroxyacids provides a rather good model for the irreversible electrophilic step when R is an alkyl group (compare entry 2 with 1, and 7 with 4-6). In the addi-

TABLE



R	R'	R''	Reagent	Electrophilic attack syn/anti ratio (relative to R)	Nucleophilic attack a/b ratio	c/d ratio
1) Me	H	H	BrOH/diox/H ₂ O ^a	50:50	94:6	66:34
2)			RCO ₃ H ^a	48:52	90:10 ^b	64:36 ^b
3)			NBS/DMSO/H ₂ O ^a	82:18	94:6	61:39
4) <i>t</i> -Bu	H	H	BrOH/diox/H ₂ O ^c	20:80	-	c≪d
5)			BrOAc/CCl ₄ ^c	21:79	91:9	15:85
6)			ClOH/Me ₂ CO/H ₂ O ^d	23:77	100:0	29:71
7)			RCO ₃ H ^e	10:90	100:0 ^{b,c}	22:78 ^{b,c}
8)			NBS/DMSO/H ₂ O ^c	82:18	95:5	17:83
9)			IN ₃ /MeCN ^f	85:15	-	-
10)			IOH/H ₂ O ^f	87:13	-	-
11) Me	Me	Me	Hg(OAc) ₂ /AcOH ^g	88:12	100:0	100:0
12) Me	H	<i>t</i> -Bu	Hg(OAc) ₂ /AcOH ^g	90:10	100:0	100:0
13) MeO	H	H	BrOH/diox/H ₂ O ^a	75:25	-	-
14)			RCO ₃ H ^a	37:63	100:0 ^{b,h}	10:90 ^{b,h}
15)			NBS/DMSO/H ₂ O ^a	95:5	-	-
16)			NBS/H ₂ O	90:10 ^a ;75:25 ¹	100:0 ¹	20:80 ⁱ

a) This work. b) Reaction of epoxide with HBr. c) Ref. 2. d) J.-C. Richer and C. Freppel, *Tetrahedron Letters*, 4411 (1969). e) J.-C. Richer and C. Freppel, *Can. J. Chem.*, 46, 3709 (1968). f) Ref. 6. g) Ref. 5. h) R.A.B. Bannard, A.A. Casselman, E.J. Langstaff, and R.Y. Moir, *Can. J. Chem.*, 46, 35 (1968). i) Ref. 3b.

tions of preformed ClOH, or BrOH, or BrOAc (entries 1,4,5 and 6), like in those of halogens in low polarity solvents, the electrophilic step is apparently irreversible, or at least $k_2 \gg k_{-1}$.^{1,4}

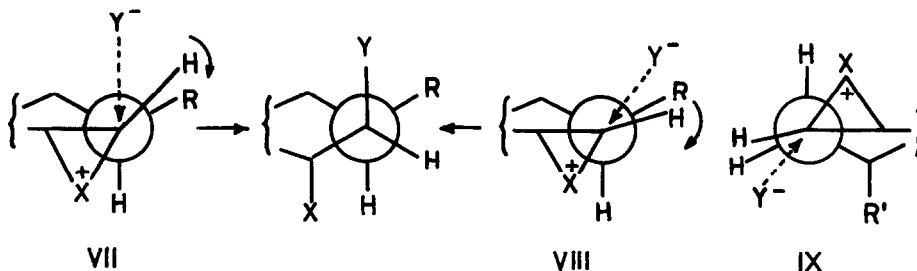
2) The use of NBS as the source of electrophilic bromine (entries 3 and 8) considerably changes the ratio of syn to anti attack, the former becoming largely predominant, independently from the size of the allylic substituent. The same is observed with other electrophiles, such as IOH (entry 10, in contrast with BrOH and ClOH), IN₃ (entry 9) and Hg(OAc)₂ (entries 11 and 12). Since this preference would be very difficult to explain on the basis of steric or electronic effects of R in the electrophilic step, the hypothesis of the reversibility of this step^{2,3a,4-6} and of k_2 being smaller than k_{-1} appears as rather soundly founded.

3) When the allylic substituent is CH₃O the steric course of epoxidation fails as a model

for the electrophilic step (compare entry 14 with those 13, 15 and 16) and the difference between the addition of preformed BrOH and the NBS reactions is less pronounced. However, even in this case the latter reactions give a higher percentage of syn attack than the former one. Possible reasons for this difference between polar and non polar substituents will be discussed elsewhere.⁸

4) The last two columns in the Table show the available data on the regioselectivity of the reactions of each of the two diastereoisomeric cationic intermediates with the nucleophiles and of the opening of the epoxides with HBr. The latter reaction provides a good model for the nucleophilic step. All the cis ions and cis epoxides exhibit the expected high prevalence of antiparallel attack, in accordance with the stereoelectronic preference and unhindered nature of pathway a. The regioselectivity of the attack on the trans ions depends on the nature of R, but very little on that of the reagent. When R is methyl (entries 1-3) the antiparallel path c predominates, but about 1/3 of the product arises through the parallel one d (or through antiparallel attack on the conformer with pseudoaxial R). The preference for path d is much higher when R is t-butyl (entries 5-8, unfavourable steric effect in path c) or methoxyl (entries 14 and 16, unfavourable inductive effect in path c). The reasons for the exclusive diaxial opening reported for the trans mercurinium ions (entries 11 and 12) are not clear.

5) The preference for nucleophilic attack on the cis ions, conditioning the prevalence of products derived from reversible electrophilic attack syn to the allylic group, has been attributed in the case of acetoxymercuration⁵ and of the reactions involving iodonium ions⁶ to an unfavourable torsional effect operating in the T.S. of the diaxial opening of the trans ions, involving eclipsing strain between the substituent and the vicinal H on the three-membered ring. This would require the rather peculiar geometry shown in VII for the bridged ions, which cannot be ruled out a priori for such species as mercurinium and iodonium ions. The fact that bromonium, chloronium and protonated epoxide analogues behave similarly casts some doubt on this interpretation, since all these species should have similar geometries (except for the C-X bond distances⁹), which would not be expected to differ much from that of free epoxides, for which Dreiding models and some structural evidence¹⁰ rather point to the geometry shown in VIII. Diaxial opening of the ring should therefore involve de-eclipsing and not eclipsing in the T.S. We rather believe that a purely steric effect of the pseudoequatorial allylic substituent could hinder the approach by the



nucleophile in the trans ion, if this takes place obliquely, that is in the direction of the breaking C-X bond, as shown in VIII, a not too unlikely hypothesis, also on the basis of some calculations on the approach of H^- to ethylene oxide.¹¹ This could account, without having to assume a torsional strain effect, for the substantial contribution of route d even when R_{is} is relatively small and not electronegative, like methyl, and for the fact that an axial substituent (R') in the homoallylic position does not seem to have any unfavourable effect on the opening of the cis ion through path a (entry 11 in the Table):⁵ an "oblique" approach would be less hindered than one parallel to R' , as shown in IX.

This work was supported by a grant from C.N.R.

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