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NUCLEOPHILIC SUBSTITUTION AT A SATURATED CARBON ATOM WITH RETENTION OF CONFIGURATION: THE REACTION OF TRANS-2-HALO-3-TERT-BUTYLOXIRANES WITH PHENOLATES

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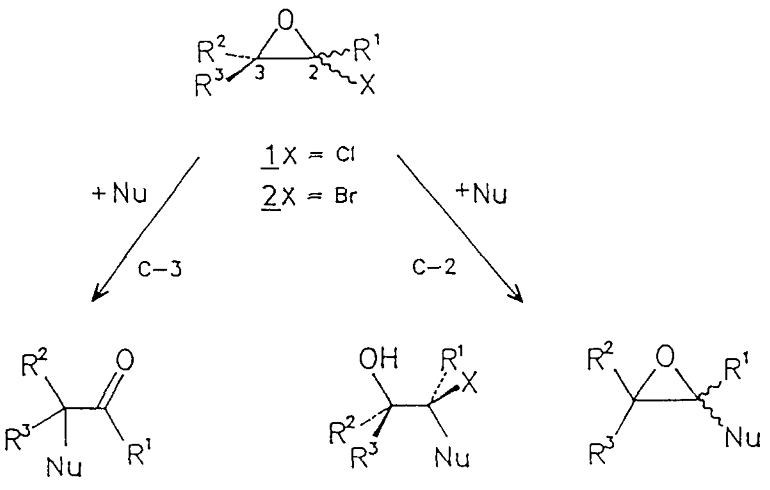
Abstract: *Whereas reaction of trans-2-chloro or 2-bromo-3-tert-butyloxirane with thiophenolate occurs at C-3 to give 2-phenylmercapto-3,3-dimethylbutanal, phenolates give substitution at C-2 with retention of the oxirane ring and retention of configuration with kinetics that indicate a bimolecular mechanism.*

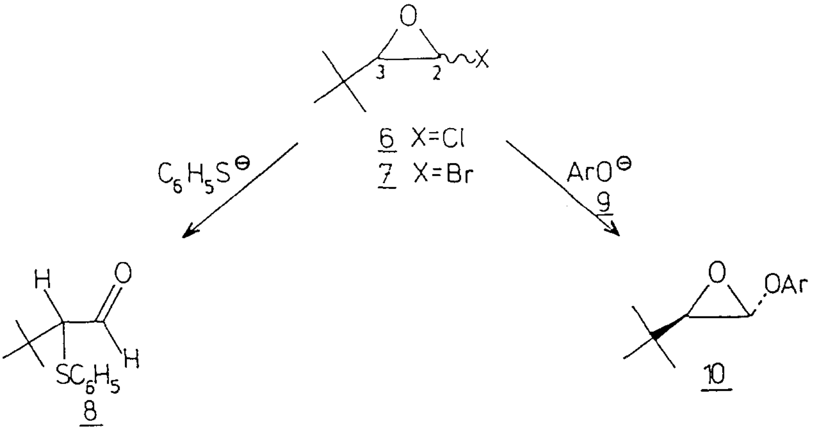
Alkyl-substituted 2-chloro- and 2-bromooxiranes, 1 and 2,[1] can be taken as model compounds for the study of the influence of electronic, steric, and strain energy effects on nucleophilic aliphatic substitution.[2] Compounds 1 and 2 provide two sites for nucleophilic attack: carbon atom 2 has the lower electron density and therefore should be the favored site of attack.

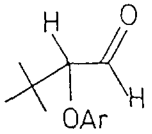


3 4 5

However, the reaction at atom C-3 occurs with release of strain energy leading to α-substituted carbonyl compounds 3.[3]

To shift the position of attack of nucleophiles from C-3 to C-2, steric crowding at C-3 was increased. Even with a *tert*-butyl group at C-3, halooxiranes 6 and 7[1,4] are still attacked by thiophenolate at this position giving the α-phenylmercaptoaldehyde 8. However, 6 and 7 react with phenolates 9 in CH_3CN at C-2 to give 2-aryloxy-oxiranes 10.





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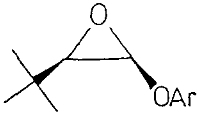

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a Ar= C_6H_5
b Ar= m-MeO-C_6H_4
c Ar= p-Cl-C_6H_4

It is remarkable that in the attack of 9 at C-2, halide ion is still the preferred leaving group giving compounds with the structure 5, although ring opening to alcohols of type 4 would relieve the oxirane strain energy. This reaction shows additional interesting features: Both *cis*- and *trans*-6 or 7 give *trans*-10.[5] *Trans*-6 or 7 react much faster than the corresponding *cis*-compounds.[6]

We have investigated the origin of the retention of configuration in the nucleophilic substitution of *trans*-7 by 9b in CH_3CN to give 10b[7]. 10b is not the product of thermodynamic control as neither 11b nor 12b, both prepared independently, gave 10b under the reaction conditions. Initial ring opening of *trans*-7 to an alkoxide ion, the anion of alcohol 4, and subsequent closure of the oxirane ring by expulsion of halide ion in an S_N2 process should lead to inversion at C-2.[8] Intermediate formation of an oxirene[9] should rapidly lead to a ketene resulting in esters of 3,3-dimethylbutanoic acid. Evidence against a single electron transfer mechanism[10] is provided by the second order kinetics (see below) which excludes a chain mechanism, the absence of rate retardation on addition of p-dinitrobenzene, and the lack of CIDNP signals. Under pseudo-first order conditions, increase in concentration of 9b led to a slight decrease in reaction rate (Table runs 1-3). On first sight this might be taken as evidence for an S_N1 process. However, this is largely a result of rate retardation through an increase in ionic strength. This negative salt effect was also observed on addition of lithium perchlorate.[11] For an S_N1 mechanism of this charge type, a positive salt effect should be observed. The negative salt effect is evidence against an S_N1 process[12] and indicates that in the rate-determining step charge dissipation is occurring. Similar results have been obtained for reactions of phenolates with n-butyl bromide in dimethylsulfoxide.[13] It appears that phenolate ion pairs are much less reactive than the free anions[13], so we added a crown ether to generate the free anion. The association constants for Na^+ and crown ethers in aprotic solvents are high[14] and we assume that the concentration of free phenolate ion is approximately equal to the concentration of crown ether. The influence of an increase in the effective nucleophile concentration, not masked by the negative salt effect, can be observed in runs 4-6. There, at constant ionic strength, the rate constant increases linearly with crown ether concentration suggesting that the reaction is first order in free phenolate. This concentration dependence and the negative salt effect point at a bimolecular, S_N2 type reaction. Furthermore, it was found that *trans*-6 reacts with 9b about 1700 times slower than *trans*-7. This large reactivity difference between chloro- and bromo-compound signifies that breaking of the carbon-halogen bond is important in the rate determining step. However, a normal S_N2 reaction path cannot be taken. Not only does the bulky *tert*-butyl group block nucleophilic attack at C-3, but also attack at C-2 opposite to the halogen. Thus, a stereochemical course different from the Walden inversion process normally observed in bimolecular nucleophilic aliphatic substitution has to be followed in this reaction.

Table. Effects of Concentration of Nucleophile and Crown Ether on the Rate Constants for the Reaction of *trans*-7 (2.5×10^{-3}M in CH_3CN) with 9b to give 10b

run	9b $[\times10^2/M]$	15-crown-5 $[\times10^2/M]$	T $[^\circ C]$	k_{obsd} $[\times10^4/s^{-1}]$
1	1.0	-	25	14.4 ± 0.4
2	5.0	-	25	6.46 ± 0.52
3	10.0	-	25	4.65 ± 0.06
4	10.0	1.0	25	12.1 ± 0.3
5	10.0	2.5	25	102 ± 2
6	10.0	5.0	25	302 ± 9

Further work is in progress to investigate whether the reaction of *trans*-7 with 9b is indeed an example of the long-sought bimolecular nucleophilic aliphatic substitution with retention of configuration.[15,16]

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5. *cis* -*trans* relationship can best be seen from $^3J_{HH}$ (in Hz): *cis*-6: 3.0; *cis*-7: 3.1; 12b: 2.6; *trans*-6: 1.2; *trans*-7: 1.35; 10b: 0.88.
6. For the reaction of 7 with 9b the factor is about 80.
7. On a preparative scale, 98% 10b can be isolated from *trans*-7.
8. Formation of *trans*-10b through an S_N1 step of such an anion (4 is an α-haloether) is difficult to reconcile with the large Br/Cl reactivity ratio (vide infra).
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