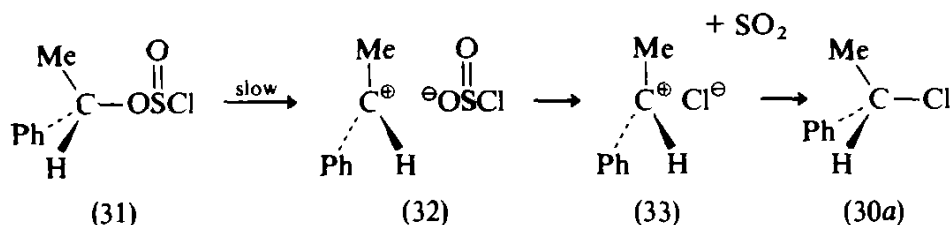


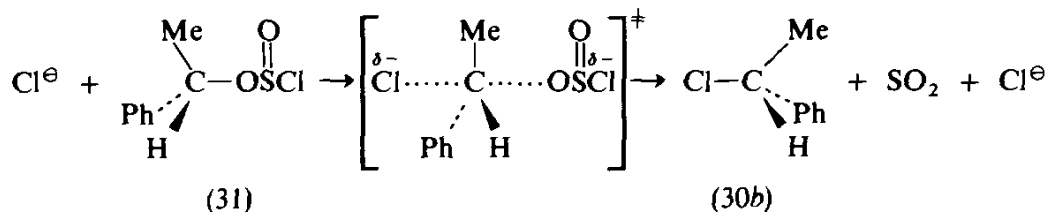
The reaction has been shown to follow a second order rate equation,  $\text{rate} = k_2[\text{ROH}][\text{SOCl}_2]$ , but clearly cannot proceed by the simple  $\text{S}_{\text{N}}2$  mode for this would lead to inversion of configuration (p. 87) in the product, which is not observed.

Carrying out the reaction under milder conditions allows of the isolation of an alkyl chlorosulphite,  $\text{ROSOCl}$  (31), and this can be shown to be a true intermediate. The chlorosulphite is formed with retention of configuration, the  $\text{R}-\text{O}$  bond not being broken during the reaction. The rate at which the alkyl chlorosulphite intermediate (31) breaks down to the product,  $\text{RCl}$  (30a), is found to increase with increasing polarity of the solvent, and also with increasing stability of the carbocation  $\text{R}^{\oplus}$ : an ion pair,  $\text{R}^{\oplus}\ominus\text{OSOCl}$  (32), is almost certainly involved. Provided collapse of the ion pair to products then occurs rapidly, i.e. in the intimate ion pair (33) within a solvent cage (*cf.* p. 90), then attack by  $\text{Cl}^{\ominus}$  is likely to occur on the same side of  $\text{R}^{\oplus}$  from which  $\ominus\text{OSOCl}$  departed, i.e. with retention of configuration:



Whether the breaking of the  $\text{C}-\text{O}$  and the  $\text{S}-\text{Cl}$  bonds occurs simultaneously, or whether the former occurs first, is still a matter of debate.

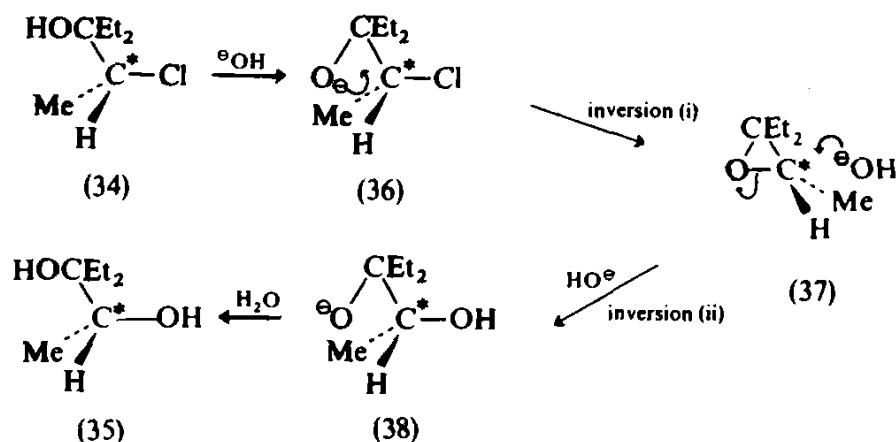
It is interesting that if the  $\text{SOCl}_2$  reaction on  $\text{ROH}$  (29) is carried out in the presence of pyridine, the product  $\text{RCl}$  is found now to have undergone inversion of configuration (30b). This occurs because the  $\text{HCl}$  produced during the formation of (31) from  $\text{ROH}$  and  $\text{SOCl}_2$  is converted by pyridine into  $\text{C}_5\text{H}_5\text{NH}^{\oplus}\text{Cl}^{\ominus}$  and  $\text{Cl}^{\ominus}$ , being an effective nucleophile, attacks (31) 'from the back' in a normal  $\text{S}_{\text{N}}2$  reaction with inversion of configuration:



#### 4.4.6 Neighbouring group participation: 'retention'

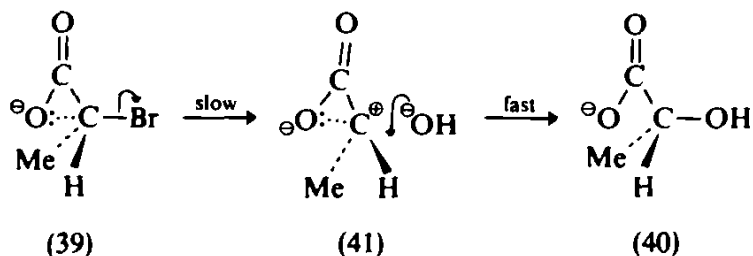
There are also some examples of retention of configuration in nucleophilic displacement reactions where the common feature is an atom or group—close to the carbon undergoing attack—which has an electron

pair available. This *neighbouring group* can use its electron pair to interact with the 'backside' of the carbon atom undergoing substitution, thus preventing attack by the nucleophilic reagent; attack can thus take place only 'from the frontside', leading to retention of configuration. Thus base hydrolysis of the 1,2-chlorohydrin (34) is found to yield the 1,2-diol (35) with the same configuration (retention):



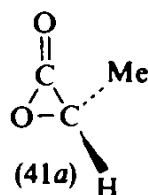
Initial attack by base on (34) yields the alkoxide anion (36), *internal* attack by this  $\text{RO}^\ominus$  then yields the epoxide (37) with inversion of configuration at  $\text{C}^*$  (these cyclic intermediates can actually be isolated in many cases); this carbon atom<sup>†</sup>, in turn, undergoes ordinary  $\text{S}_\text{N}2$  attack by  $\ominus\text{OH}$ , with a second inversion of configuration at  $\text{C}^*$ . Finally, this second alkoxide anion (38) abstracts a proton from the solvent to yield the product 1,2-diol (35) with the same configuration as the starting material (34). This *apparent* retention of configuration has, however, been brought about by two successive inversions.

Another example of oxygen as a neighbouring group occurs in the hydrolysis of the 2-bromopropanoate anion (39) at low  $[\ominus\text{OH}]$ , which is also found to proceed with retention of configuration (40). The rate is found to be independent of  $[\ominus\text{OH}]$ , and the reaction is believed to proceed:



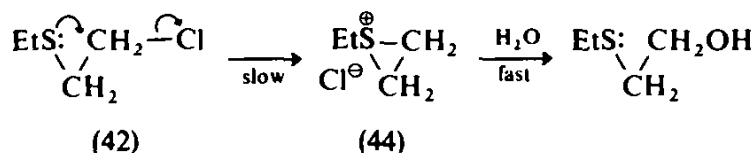
Whether the intermediate (41) is a zwitterion as shown or a highly

<sup>†</sup> Preferential attack takes place on this, rather than the other, carbon of the three-membered ring as it will be the more positive of the two, carrying as it does only one electron-donating alkyl group.

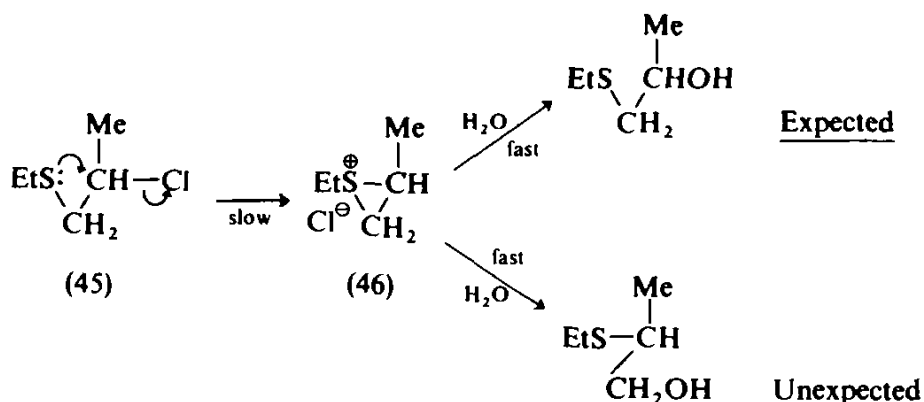
labile  $\alpha$ -lactone (41a)

has not been clearly established. As the concentration of nucleophile,  $[\text{OH}^-]$ , is increased an increasing proportion of normal  $\text{S}_{\text{N}}2$  'attack from the back', with inversion of configuration, is observed.

Neighbouring group effects have also been observed with atoms other than oxygen, e.g. sulphur and nitrogen, and in situations where, though no stereochemical point is at issue, unexpectedly rapid rates suggest a change in reaction pathway. Thus  $\text{EtSCH}_2\text{CH}_2\text{Cl}$  (42) is found to undergo hydrolysis  $10^4$  times faster than  $\text{EtOCH}_2\text{CH}_2\text{Cl}$  (43) under comparable conditions, and this has been interpreted as involving S: acting as a neighbouring group:



By contrast, O: in (43) is sufficiently electronegative not to donate an electron pair (unlike  $\text{O}^-$  in  $\text{RO}^-$  and  $\text{RCO}_2^-$  above), and hydrolysis of  $\text{EtOCH}_2\text{CH}_2\text{Cl}$  thus proceeds *via* ordinary  $\text{S}_{\text{N}}2$  attack by an external nucleophile—which is likely to be very much slower than the *internal* nucleophilic attack in (42)  $\rightarrow$  (44). That a cyclic sulphonium salt such as (44) is involved is demonstrated by the hydrolysis of the analogue (45), which yields two alcohols (the unexpected one in greater yield) indicating the participation of the unsymmetrical intermediate (46):



N: can act as a neighbouring group in similar circumstances, e.g. the hydrolysis of  $\text{Me}_2\text{NCH}_2\text{CH}_2\text{Cl}$ , but the rate is markedly slower,

under comparable conditions, than that for (42) above, because of the greater stability of the cyclic immonium ion intermediate corresponding to (44). Such cyclic species are formed during the hydrolysis of mustard gas,  $S(CH_2CH_2Cl)_2$  and the related nitrogen mustards, such as  $MeN(CH_2CH_2Cl)_2$ : the cyclic immonium salts derived from the latter are also powerful neurotoxins. The  $\pi$  orbital system of the benzene ring can also act as a neighbouring group (*cf.* pp. 105, 376).

## 4.5 EFFECT OF ENTERING AND LEAVING GROUPS

### 4.5.1 The entering group

Changing the nucleophilic reagent employed, i.e. the *entering group*, will not directly alter the rate of an  $S_N1$  displacement reaction for this reagent does not take part in the rate-limiting step of the overall reaction. In an  $S_N2$  displacement, however, the more strongly nucleophilic the reagent the more the reaction will be promoted. The *nucleophilicity* of a reagent might perhaps be expected to correlate with its basicity, as both involve the availability of electron pairs and the ease with which they are donated. The parallel is by no means exact, however, in that basicity involves electron pair donation to hydrogen, whereas nucleophilicity involves electron pair donation to another atom, very often carbon; basicity involves an equilibrium (thermodynamic), i.e.  $\Delta G^\ominus$ , situation, whereas nucleophilicity usually involves a kinetic, i.e.  $\Delta G^\ddagger$ , one; basicity is likely to be little affected by steric influences, whereas nucleophilicity may be markedly affected.

This distinction follows to some extent the recently introduced one between *hard* and *soft bases*: a hard base is one in which the donor atom is of high electronegativity, low polarisability, and is hard to oxidise, i.e.  ${}^\ominus OH$ ,  ${}^\ominus OR$ ,  $R_3N:$ ; while a soft base is one in which the donor atom is of low electronegativity, high polarisability, and is easy to oxidise, e.g.  $RS^\ominus$ ,  $I^\ominus$ ,  $SCN^\ominus$ ; for a given degree of basicity, softness promotes nucleophilicity. Basicity data are often the more readily available, however, and can be used as a guide to nucleophilicity provided like is being compared with like. Thus if the attacking atom is the same (*cf.* electronegativity above), then the two run reasonably in parallel, and we find the stronger the base the more powerful the nucleophile:



A shift in mechanistic type can also occur with change of nucleophile, thus a displacement that is  $S_N1$  with, for example,  $H_2O:$ ,  $HCO_3^\ominus$ ,  $MeCO_2^\ominus$ , etc., may become  $S_N2$  with  ${}^\ominus OH$  or  $EtO^\ominus$ .

Nucleophilicity is found to be very much affected by the *size* of the attacking atom in the nucleophile, at least for comparisons within