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Reactions Involving Bimolecular Nucleophilic Substitution at a Vinyl Centre

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The present state of research into reactions involving bimolecular nucleophilic substitution at a vinyl centre is examined. Attention is concentrated on stereochemical questions and also on the influence of various details of the molecular structure of the reacting compound on the kinetics and mechanism of the reactions.
The bibliography includes 167 references.

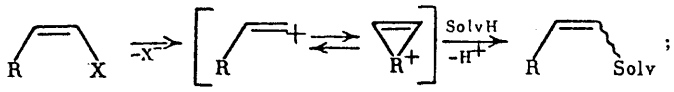
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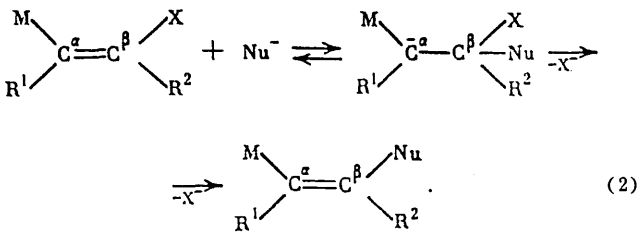
I. INTRODUCTION

The systematic study of nucleophilic vinyl substitution reactions was initiated by Italian chemists (Modena and others) approximately 25 years ago; this field of organic chemistry is much more recent than the fields which have already become classical, such as those involving the investigation of nucleophilic substitution in saturated compounds, nucleophilic aromatic substitution, or substitution at a carbonyl carbon atom. In order to characterise in broad outline the characteristics of nucleophilic vinyl substitution reactions, it is useful to compare them with the related types of reactions investigated previously, which have been enumerated above, as well as other.

Like the S_N1 and S_N2 reactions of alkyl halides, nucleophilic vinyl substitution can proceed via unimolecular (1) and bimolecular (2) mechanisms:

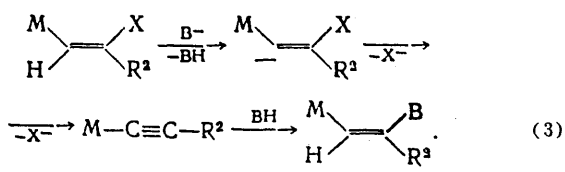


(1)



(2)

Reactions of the first type [reaction (1)] constitute an extensive and fairly completely investigated class of reactions and will not be considered in this review. In Scheme (2) and henceforth Nu represents the nucleophile, C^α the carbon atom linked to the activating electron-accepting group M, C^β the carbon atom linked to the leaving group, and R^1 and R^2 are the substituents in the α- and β-positions respectively, which can also be the activating or leaving groups. When $R^1 = H$, the substitution can take place under the influence of strong bases via the *ElcB* elimination with subsequent addition in accordance with Scheme (3):



(3)

For brevity, reactions of types (2) and (3) will be henceforth designated as S_NVin reactions.

We shall compare the bimolecular nucleophilic substitution reactions with participation of substrates of different classes. The large class of nucleophilic substitution reactions of the S_N2 type at an sp^3-carbon atom has been most thoroughly investigated in all respects. However, their comparison with nucleophilic vinyl substitution reactions reveals more differences than common features. In fact, in S_N2 reactions the processes in which a bond with a nucleophile is formed and that with the leaving group is ruptured are to a large extent synchronised. The possibility that the bond formation process is appreciably faster than the bond dissociation is ruled out by the impossibility of the expansion of the electron shell of carbon in excess of the octet. On the other hand, in S_NVin reactions of type (2) the formation of a bond with the nucleophile is as a rule rate-determining: this process predominates significantly and frequently wholly over the process in which the bond with the leaving group is broken, which leads to a stable anionic intermediate. As a result, a marked effect of the leaving group on the rate of substitution is observed in S_N2 reactions, whereas in S_NVin reactions this effect is absent.

Another fundamental difference follows from the examination of the interaction of the nucleophile with the electrophilic substrate from the standpoint of the theory of frontier orbitals. The highest occupied molecular orbital of the nucleophile (HOMO) interacts with the lowest unoccupied molecular orbital of the substrate (LUMO); in S_N2 reactions the substrate LUMO is the σ* orbital of the bond between the carbon atom and the leaving group. The bond formation and dissociation reactions take place along the same axis; this is the reason for the stereochemical result—the Walden inversion. In S_NVin reactions the substrate LUMO is a π* orbital localised in the plane perpendicular to that of the molecule in which the bond with the leaving group is located. The bond formation and dissociation processes are separated

both in time and as regards symmetry and the stereochemical result is determined by the relative contributions and the relative ease of the rotation and inversion processes in the intermediate carbanion—as a rule the configuration is retained.

In terms of the frontier molecular orbitals of the substrate interacting with the HOMO of the nucleophile, the S_NVin reactions resemble the nucleophile substitution reactions of aromatic (S_NAr) and carbonyl (S_NAc) compounds. However, variations in the stereochemical result of the reaction are impossible in either S_NAr or S_NAc reactions and this constitutes one of the powerful instruments for the investigation of the mechanism. Nevertheless, comparison of the reactivities for the reactions of the above classes is frequently useful.

The S_NVin reactions have much in common with nucleophilic addition to electron-deficient olefins (the Michael reaction); the first stage, namely the addition of a nucleophile to the double bond with formation of a carbanion, is the same in these reactions. When necessary, data for Ad_N reactions are therefore resorted to in the present review. S_NVin reactions are frequently complicated by elimination processes with formation of acetylenic or allenic products and sometimes they proceed simply via the E–Ad_N mechanism (3). Questions concerning the elimination reaction will therefore be dealt with in so far as it is necessary.

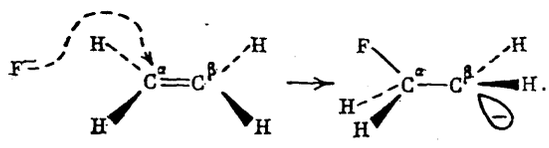
The review does not include purely synthetic studies because this would unjustifiably increase its scope. Attention is concentrated on investigations in the last 10–15 years, since the entire literature on this problem published up to 1968 has been surveyed in Rappoport's review[1] (see also special reviews[2,3]).

II. QUANTUM-CHEMICAL STUDY

The first calculations on the addition of anions to the C=C bond, modelling the first stage of S_NVin reactions, were carried out by Bazilevskii and Tikhomirov[4] and by Kelsey and Bergman.[5] The addition of CH_3^- to ethylene[4] has been investigated in terms of the "almost π-electron approximation" without the optimisation of the geometry but with allowance for the change in the degree of hybridisation of the reaction centre. Under the conditions of attack in the plane of the π-bond at nearly the tetrahedral angle, CH_3^- undergoes exothermic addition without an activation barrier. Bazilevskii and Tikhomirov[4] concluded that their approximation is inapplicable to calculations on ionic reactions (although calculations on the addition of radicals agree satisfactorily with experiment[6]).

The problem of the elucidation of the relative ease of the nucleophilic substitution at the sp^3- and sp^2-carbon atoms has been raised.[5] Calculations were made by the extended Hückel method (EHM) with partial optimisation of the geometry for the substitution of hydrogen in ethane and ethylene by the hydride ion. The aim was to compare the heights of the activation barriers, but no barriers were found in either reaction and the authors had to resort to an extremely artificial procedure involving the analysis of a "transition" step. In addition, the attack by H^- on a carbon atom, directed in the plane of the ethylene molecule at right angles to the C=C bond, was considered. Since it is clear from the form of the interacting frontier orbitals that nucleophilic attack takes place preferentially in the plane of the π-bond (in the direction of the π* orbital), this calculation cannot serve as an acceptable model of the S_NVin reaction. Analysis of the mutual orientation of the reactants in the attack by the nucleophile on the π-system[7,8] has indicated that attack by the nucleophile on the π-system[7,8] takes place preferentially in the direction of the bond formed, i.e. at a Nu–C=C angle of approximately 70°. For nucleophiles containing unoccupied 3*d* orbitals, this angle is somewhat greater apparently as a result of 3*d* back bonding: $\pi_{C=C} \rightarrow 3d_{Nu}$.[8]

A non-empirical calculation for the addition of F^- to ethylene[9] has shown that the formation of the *anti*-conformer of the fluoroethyl anion [the orientation of the F atom in relation to the lone electron pair (LEP) of the carbanion was considered] is more favourable than the formation of the *syn*-conformer (ΔE = 19, 22, and 21 kJ mole^{-1} in terms of the STO-3GF, 4-31GF, and 6-31GF basis sets respectively). This has been explained by the stabilising interaction of the LEP with the σ* orbital of the C–F bond. Calculation of the optimum path leading to the mutual approach of the reactants yielded the following addition scheme:



(4)

When the C^α–F distance is changed from 4 to 2.5 Å, the C–C–F angle diminishes to 115.5°, while the further decrease of the distance from 2.5 to 1.4 Å entails a slight increase of the angle to 118.7°, which leads to the *anti*-conformer. There is no activation barrier in reaction (4), which is exothermic in terms of the STO-3GF basis set: ΔE = −557 kJ mol^{-1}. However, in terms of the 4-31GF and 6031GF basis sets, reaction (4) is endothermic with ΔE = 60 and 67 kJ mol^{-1}.[9]

Calculations have been made for reaction (4) by a number of investigators in terms of various approximations. Apart from the study of Bach et al.[9], the instability of the $FCH_2 - CH_2^-$ anion in relation to decomposition has been demonstrated at the 3-21 + GF [10] and 4-31 + GF [11] levels (i.e. with additional Gaussian functions at the C and F atoms). On the other hand, calculation at the 3-21 GF level and in terms of the most refined 6-31 GF* basis set (with polarisation Gaussian functions for the *d* orbitals of heavy atoms) yields a real minimum on the potential energy surface for the β-fluoroethyl anion, the F atom and the lone electron pair being in the *anti*-conformation.[12]

A calculation has been made[13,14] for the interaction of H^-, HS^-, and F^- with ethylene by the CNDO/BW method with total optimisation of the geometry. Attack by the H^- or F^- ion directed at right angles to the molecular plane of ethylene entails the exothermic formation of the $C_2H_5^-$ or $CH_2FCH_2^-$ anion, while attack at low angles relative to the molecular plane over a distance of approximately 2.5 Å entails the abstraction of a proton with formation of the vinyl anion $C_2H_3^-$ and the H_2 or HF molecule. These data agree well with the parallel course of the elimination process in S_NVin reactions which is frequently observed and has been confirmed by experimental data for reactions of anions with fluoroethylenes by the method of ion–cyclotron resonance.[15]

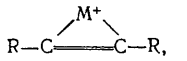
All these calculations refer to the gas phase and lead to barrier-free reactions. The attempt to take into account the influence of the medium even in the simplest version of the solvation model makes it possible to obtain reasonable activation barriers in the CNDO/BW and MINDO/3 methods.[16]

The above calculations were performed for simple ethylenes, while nucleophilic vinyl substitution and addition reactions are characteristic primarily of conjugated molecules with electron-accepting groups. An example of such a calculation is provided by the calculation in terms of the 4-31 GF basis sets of the local minima on the potential energy surface for

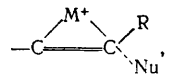
the $CH_2=CH-CHO+Nu^-$ system, where $Nu^- = F^-$ and CH_3O^-.[17] In both cases the absolute energy minima correspond to the products of the addition of the anion to the β-carbon atom of the acroleine molecule; the potentially possible competing deprotonation processes are energetically unfavourable. An experimental study of the above reactions in the gas phase by the method of ion–cyclotron resonance confirmed the results of the calculations.[17]

Analysis of the potential energy surface for the $F^- + FHC=CH-CN$ system within the framework of the CNDO/2 and MINDO/3 methods has shown that both reaction pathways, i.e. the addition of the nucleophile and the deprotonation of the substrate, are possible.[18]

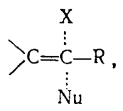
A number of theoretical studies have been devoted to the analysis of the stereochemistry of the nucleophilic vinyl substitution. As a rule, these reactions proceed with retention of configuration of the molecule of the initial substrate (*Z* or *E*). A partial inversion of configuration is sometimes observed[1] and in addition cases of stereoconvergence, i.e. of the formation of the same mixture of isomers of the reaction product regardless of the configuration of the initial substrate, have been described.[19–21] In particular, stereoconvergence is observed for vinyl halides with very strong electron-accepting groups in the α-position or for weakly nucleophilic leaving groups, i.e. in the case of long-lived carbanions. Finally, there exist two types of reactions which proceed, according to the author,[22] with total inversion of configuration when the nucleophile attacks in the molecular plane. These involve the formation of onium cations having the "cyclopropenyl" structure



where M = Ar, S, Br, or I, and the opening of these rings following the attack by an external nucleophile.[22] The transition state in these reactions should have the structure



analogous to the planar structure



which was already considered in an early study by Gold[23] (see also Kelsey and Bergman[5]). In this connection Rappoport[22] concluded that nucleophilic vinyl substitution cannot be regarded as a process proceeding stereospecifically with retention of configuration. The stereochemical specificity should depend on the charge of the leaving group, the capacity for the formation of small rings, and also on the nature of the α- and β-substituents.

Stohrer concluded that configuration is retained in S_NVin reactions and considered a correlation diagram including the orbitals of the reactants involved in the reaction (Fig.1). In the $R^1R^2\bar{C}^\alpha-C^\beta XYNu$ anion, formed after the attack by the nucleophile, the *p* orbital of the C^α atom tends to achieve maximum stabilisation by overlapping with the antibonding orbitals $\sigma^*_{C^\beta-X}$, $\sigma^*_{C^\beta-Y}$, and $\sigma^*_{C^\beta-Nu}$.[24] As can be seen from Fig.1, under these conditions the overlap of the p_{C^α} orbital with the $\sigma^*_{C^\beta-Nu}$ orbital is more favourable to the left of the point O and the overlap of the p_{C^α} orbital with the $\sigma^*_{C^\beta-X}$ orbital is more favourable to the right of this point.

The elimination of the leaving group X requires that the axes of the $C^\beta-X$ bond and the p_{C^α} orbital lie in the same plane. According to the diagram in Fig.1, a kind of enhancement of the effect is observed—the smaller the angle between the p_{C^α} orbital and the $C^\alpha C^\beta X$ plane, the greater the degree of loosening of the $C^\beta-X$ bond owing to the donation of electrons from p_{C^α} to $\sigma^*_{C^\beta-X}$ and the greater the degree of loosening of the bond the greater the degree of further rotation, which ultimately leads to the substitution product with retention of configuration (Fig.2).

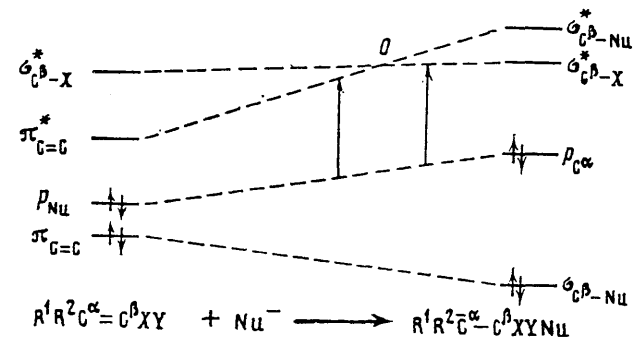


Figure 1. Correlation diagram for the stage involving the addition of the nucleophile Nu^- to the olefin $R^1R^2C^\alpha=C^\beta XY$.

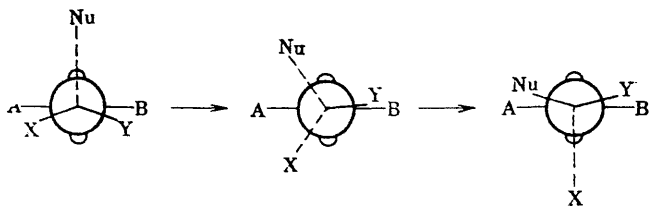
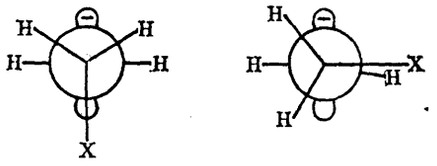


Figure 2. Retention of configuration in the synchronous mechanism of the substitution reaction.

An idea with a similar significance has been put forward by Texier et al.[25], who considered the elementary step in the substitution process as attack by the nucleophile at right angles to the molecular plane of ethylene "above" the leaving group within the framework of a synchronous substitution mechanism. This entails the "lateral" binding of the nucleophile to the β-carbon atom.

In the above study[24,25] the retention of configuration in S_NVin reactions was readily accounted for within the framework of a single-stage synchronous substitution mechanism. However, the question of whether nucleophilic vinyl substitution is a single-stage or a multistage process was recently examined in detail by Rappoport,[26] who concluded that so far there have been no reliable examples of S_NVin reactions proceeding via a single-stage synchronous substitution mechanism; on the other hand, the vast majority of the experimental data indicate a two-stage mechanism of

the S_NVin reactions. For a two-stage mechanism, the main question is why the clockwise rotation by 60° in the carbanion formed initially (Fig. 3), which leads to the retention of configuration, is preferable to the anticlockwise rotation by 120°, which leads to the inversion of configuration. On a qualitative level, the preferred rotation of the first type has been demonstrated by Texier et al.[25] As regards calculations of the rotation barriers, there have been two studies devoted to non-empirical calculations for substituted ethyl anions in two conformations (A) and (B):[27,28]



(A) (B)

The calculations were performed in terms of the STO-3GF [27] and 4-31GF [28] basis sets. Overall, the conformation (A) is more favourable than (B) (except in the case where $X = BH_2$) and the energy difference $\Delta E = E^{(A)} - E^{(B)}$ increases with increasing electronegativity of X. This can be explained by the hyperconjugation interaction, which represents the sum of the stabilising interaction of the $p_{C\alpha}$ orbital with $\sigma^*_{C\beta-X}$ and the destabilising $p_{C\alpha}{-}\sigma_{C\beta-X}$ interaction. The greater the electronegativity of X, the greater the contribution of the stabilising interaction, which is a maximum, as regards the overlap of orbitals, for the conformation (A). It has been noted that the introduction of electron-accepting groups at the carbanionic centre diminishes ΔE; thus, $\Delta E = 23$ kJ mol^{-1} for $CH_2F{-}C(CN)_2$, while $\Delta E = 42$ kJ mol^{-1} has been obtained for $CH_2F{-}CH_2$.[27]

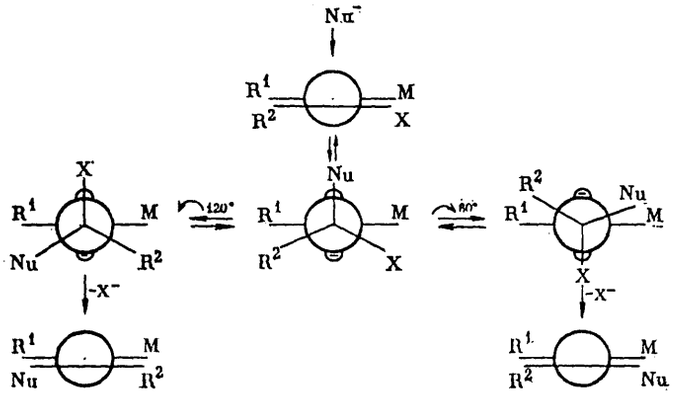


Figure 3. A general scheme for stereochemical transformations in the two-step carbanionic mechanism of the substitution reaction.

The application of the idea of the important role of hyperconjugation, put forward by Apeloid and Rappoport,[27] to the general scheme (Fig. 3) leads to the following conclusions: (1) if the energy of the interaction of $p_{C\alpha}$ with $\sigma^*_{C\beta-X}$ is greater than that of the interaction with $\sigma^*_{C\beta-Y}$, then the retention of configuration should be the stereochemical result; (2) when the above quantities are approximately equal, stereoconvergence should be observed; (3) if the energy of the interaction of $p_{C\alpha}$ with $\sigma^*_{C\beta-X}$ is smaller than that of the interaction with $\sigma^*_{C\beta-Y}$, then inversion should take place; (4) the stereochemical outcome is independent of the nature of the nucleophile, because the degree of hyperconjugation of $p_{C\alpha}$ with $\sigma^*_{C\beta-Nu}$ changes by the same amount on rotation by the same angle in either direction; (5) the same ratio of products with retention and inversion of the configuration should be obtained from the *Z*- and *E*-isomers of the substrate. Hence, the retention of the configuration in S_NVin reactions can be explained by the fact that as a rule Y is a hydrogen atom of an alkyl or allyl group and X is a halogen or another group containing a heteroatom and the capacity of the $\sigma^*_{C\beta-X}$ orbital for hyperconjugation is greater than that of the $\sigma^*_{C\beta-Y}$ orbital. There exist examples confirming the validity of this approach.[26,27]

In the above analysis the conclusion that the stereochemistry of the reaction is independent of the nature of the nucleophile appears doubtful especially since experimental data (see Section III) indicate the opposite state of affairs. Indeed, a more detailed analysis[29] has revealed a dependence of the stereochemistry of the S_NVin substitution on the nucleophile and in particular on the energy of the HOMO of the nucleophile. It has been shown that in the case of S_NVin reactions it is essential to take into account the four-electron interaction of the nucleophile HOMO with the substrate HOMO in addition to the two-electron interaction of the nucleophile HOMO with the substrate LUMO usually considered. Evidently the two-electron interaction is stabilising, but the four-electron interaction is destabilising and the latter is more pronounced the lower the energy of the nucleophile HOMO, the destabilising contribution predominating for neutral nucleophiles (for example, NH_3). Calculations for the reactions of a large series of vinyl halides with a large set of nucleophiles in terms of the 4-31GF basis set has shown[29] that, with increase of the energy of the nucleophile HOMO, the process becomes more exothermic and there is a shift towards an earlier transition state.† This approach agrees with Hammond's postulate and makes it possible to analyse the joint influence of the nucleophile and the leaving group on the stereochemical result of the S_NVin reaction.

The importance of the mixing of the unoccupied substrate orbitals of the σ* and π* types, which is responsible for the presence or absence of a tetrahedral intermediate in nucleophilic reactions involving the sp^2-carbon atom, has been pointed out in the literature,[30] but the authors' analysis is limited to S_NAc and S_NAr reactions.

The most complete theoretical analysis of the stereochemistry and reactivity in S_NVin reactions has been carried out by Cohen et al.[12] Bearing in mind the inconsistency

†It is necessary to explain what Bach and Wolber[29] referred to as the "transition state". Having chosen the Nu...C=C distance as the reaction coordinate, they observed the decrease of the height of the energy barrier to rotation about the C–C bond as the nucleophile approaches and the point at which this barrier becomes zero is called the transition state. It is assumed that at this point there is a transition from the process involving the addition of the nucleophile to one involving the expulsion of the leaving group.[29]

between many experimental data with the theory of frontier molecular orbitals and/or the Bell–Evans–Polanyi principle, the authors[12] used the method of correlation diagrams for states in order to set up a general picture describing the stereochemistry and the influence of the nucleophile and of the activating and leaving groups in S_NVin reactions. The heats of reaction, the activation barriers to reactions, and the barriers to inversion in carbanions were calculated, in terms of the double-ζ basis set using the geometry obtained in terms of the 4-31GF basis set, for eight reactions. The overall correlation diagram for states, including all the reaction stages, is presented in Fig. 4. The large difference between the energies of the π-CT and σ-CT levels [corresponding to charge transfer from the nucleophile to the π* and σ*(C–X) orbitals respectively] predetermines a two-stage mechanism with separation of the stages involving the attack by the nucleophile and the abstraction of the leaving group. The mutual approach of the π-CT and σ-CT levels increases the probability of a synchronous process. In essence, this conclusion is analogous to an intuitive idea: the greater the nucleophilicity of the leaving group, the shorter the lifespan of the intermediate carbanion, and hence the closer is the process to being synchronous. The authors[12] were able to describe from a single standpoint the changes in the structure of the transition state, the activation barriers, and certain other reaction parameters in good agreement with experimental data.

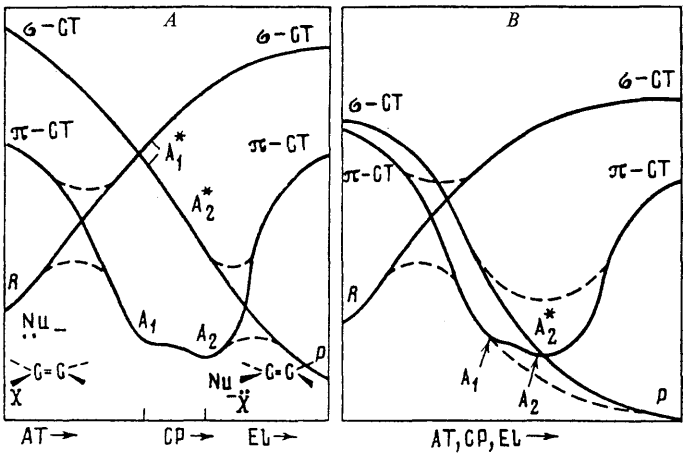
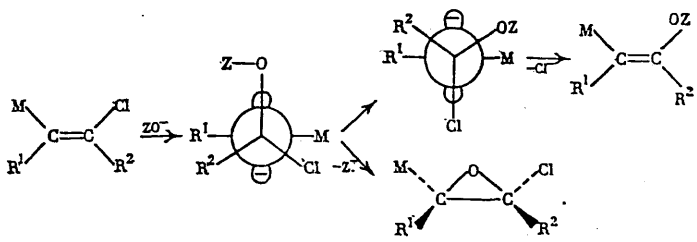


Figure 4. Correlation phase diagrams for S_NVin reactions: *A*) two-step mechanism with separation of the steps involving attack by the nucleophile and the abstraction of the leaving group; *B*) one-step synchronous mechanism; AT—step involving attack by the nucleophile; CP—step involving the conversion of the conformer A_1 (with a coplanar disposition of the LEP of the carbanionic centre and the bond with the nucleophile) into the conformer A_2 (with a coplanar disposition of the LEP of the carbanionic centre and the bond with the leaving group); El—step involving the abstraction of the leaving group; π-CT—level corresponding to charge transfer from the nucleophile to the $\pi^*_{C=C}$ orbital; σ-CT—level corresponding to charge transfer from the nucleophile to the σ^*_{C-X} orbital; A_1^* and A_2^*—excited configurations of the carbanions A_1 and A_2 respectively.

The competitive course of the S_NVin substitution process and the formation reaction of the epoxide when a chloroalkene is acted upon by the ZO^- nucleophile, where Z is the potential leaving group, has also been discussed:[31]



The subsequent reactions of the carbanion formed in the first stage depend on the relative nucleophilicity of Cl and Z and on treatment with, for example, hypochlorite (Z = Cl), an epoxide is obtained. The rotation barriers have been calculated[31] for a large series of anions of the type $ZQCH_2$–CYY', where Y and/or Y' = H or activating groups (NO_2 and CN), while Q = O, CH_2, or S and Z = Cl, F, H, OH, OCH_3, OCHO, SiH_3, or SH_2^+ (the calculation was carried out in terms of the STO-3GF, 3-21GF, 4-31GF, and 6-31GF basis sets).

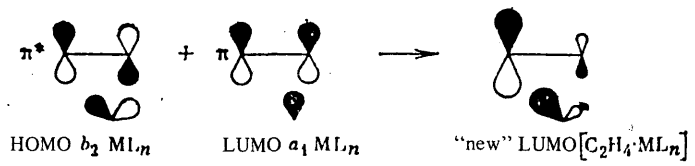


Figure 5. The mixing of the orbitals on passing from the symmetrical π-complex to the σ-complex.

An increase of the reactivity of the double bond in relation to nucleophiles can be induced not only by the introduction of an electron-accepting group but also by complex formation with transition metals. The causes of such activation are not evident and cannot be accounted for solely by the electrostatic effect, since this phenomenon is observed for both cationic and neutral complex forming agents and for anions and neutral molecules as the nucleophile.[32] At first sight complex formation should in general deactivate ethylene, since the interaction of the LUMO of ethylene with the molecular orbitals of the complex-forming agent ML_n increases the energy of the π* orbital and weakens its interaction with nucleophiles. If the population of the $H^- \ldots C_2H_4$ bond corresponding to the "reasonable" distance of 2 Å is chosen as the reactivity index in the calculation for the interaction of H^- with ethylene activated by complex formation with ML_n, then in all cases the population is smaller than in the absence of the complex forming agent. However, when ML_n "slides" along the C=C bond from its centre to one of the carbon atoms (Fig. 5), the index increases and for a σ-complex exceeds that for free ethylene. This results in the mixing of the orbitals and the new LUMO of the complex $[C_2H_4.ML_n]$ is less reactive in relation to the nucleophile than $\pi^*_{CH_2=CH_2}$. The $\pi^*_{C=C}$ orbital naturally predominates in this new LUMO,

but the contribution of $\pi_{C=C}$ is also important, since the $(H^- \ldots \pi^*)$ interaction component of the overall $H^- \ldots C_2H_4$ bond population cannot exceed the analogous value for free ethylene whatever the ML_n shift.

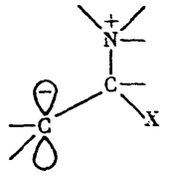
III. STEREOCHEMISTRY OF THE REACTIONS

The principal electronic interactions determining the stereochemical outcome of nucleophilic vinyl substitution reactions were discussed above. We shall now consider the principal classes of compounds and specific reactions leading to the retention, stereoconvergence, or inversion of the configuration. Since the olefinic carbon atom is achiral, the above terms will be used in relation to the geometrical sequence of the groups compared with the initial compound: the retention of configuration corresponds to the disposition of the nucleophile in the same position relative to the activating group where the leaving group had been located; inversion implies the presence of the nucleophile in the opposite position; stereoconvergence implies the formation of the same mixture of products (or of one product) regardless of the structure of the initial substrate. The term "racemisation" used previously is not entirely exact because the formation of one (most stable) of the two isomers of the product,[1] which is identical with retention of the configuration of one of the isomers and the inversion of that of the other, was frequently regarded as racemisation.

We shall consider initially reactions proceeding in accordance with the direct substitution mechanism (2) via an intermediate carbon atom or zwitter-ion because the stereochemical outcome of reactions involving the elimination–addition mechanism (3) is regulated by the rules governing the addition of nucleophiles to an activated triple bond.[33]

The vast majority of the almost 80 reactions examined in a review[1] take place with retention of configuration. For reactions with amines, the formation of the thermodynamically stable *E*-isomer (with the *trans*-disposition of the activating group and the R_2N residue) is as a rule observed; an exception is ethyleneimine, which reacts with retention of configuration. The causes of the preferential retention of configuration in reactions with anions as nucleophiles were examined above (Section II). There are two alternative explanations (which may also supplement one another) for the formation of the *E*-isomers of enamines in reactions with amines. The first is that a product with retention of configuration is formed initially and then isomerises rapidly to the thermodynamically more stable *E*-enamine. The ease of such postisomerisation is ensured by the strong conjugation of the LEP of the nitrogen atom with the C=C double bond. Thus, it has been shown by NMR that there is free rotation about the C=C double bond in the enamines $(CH_3)_2N{-}CH = C[C(O)R_2]$ ($R = CH_3$ or OCH_3).[34]

The other explanation is based on the zwitter-ionic character of the intermediate complex:



A barrier, due to electrostatic forces, preventing rotation and the attainment of the conformation with a coplanar disposition of the LEP in the carbanionic centre and the bond with the leaving group (the group X is split off in this conformation) arises in the above structure, i.e. the lifespan of the intermediate increases. The possibility of the formation of the thermodynamically most stable conformer of the intermediate, from which the enamine is formed, is thereby achieved.

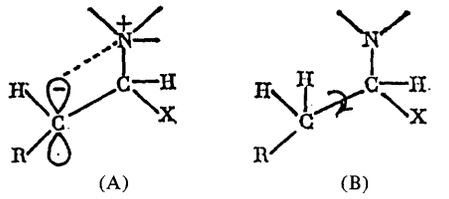
If the first explanation is valid, there should be no differences in the stereochemistry of the substitution reactions with R_2NH or R_2N^- (in the form of sodium amide) as the nucleophile. Unfortunately, reactions with amines and with their anions have not been compared experimentally; the situation is probably complicated by the fact that the amide anions, which are very strong bases, are capable of eliminating the HX group and can thus react via a different mechanism. On the other hand, if the "zwitter-ionic" hypothesis is valid, there should be a fundamental difference between the reactivities of amines and their anions. The retention of the configuration in reactions with ethyleneimine, where effective conjugation of the LEP of the nitrogen atom with the double bond is impossible owing to the pronounced steric strain, supports the view that substitution with retention of configuration takes place also in reactions with other amines and is then followed, as a result of the postisomerisation, by the formation of the thermodynamically more stable *E*-isomer of the substitution product.

The change in the course of the reaction on moving down Group V of the Periodic System, i.e. on passing from amines to phosphines and arsines, has not been studied in detail. It has only been shown that trimethyl phosphite affords the *E*-isomer of the substitution product in reaction with 1,2-di(toluene-*p*-sulphonyl)ethylene.[35] On the other hand, the anion Ph_2R^- reacts with 1,2-dichloroethylene and β-bromostyrenes with retention of configuration;[36–38] the salts of the arsine anion Ph_2As^- also react with retention of configuration.[39] Mention should be made of a study[40] devoted to the stereochemistry of the substitution of the bromine atom in α-bromoacrylic acids or their esters by cuprates, i.e. by the anion $(CH_3)_2Cu^-$; here too retention of configuration was noted in all cases.

Interesting results have been obtained in studies[41,42] of the nucleophilic substitution of bromine in 2-*cis*-β-bromovinyl-5-nitrothiophen. The stereochemistry of the compound was established by ^1H NMR from the coupling constant $^3J_{H-H}$. It has been established for a large set of nucleophiles that the substitution proceeds with retention of configuration for tertiary amines, with partial inversion for ArO^-, ArS^-, and N_3^-, and with total inversion for secondary amines and sulphinate anions. Overall, the series obtained is as follows:

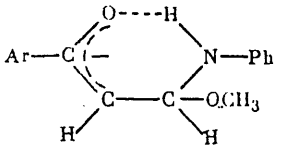
Nucleophile	R_3N	pyridine	ArO^-	N_3^-	ArS^-	$ArSO_2^-$	R_2NH
Degree of inversion, %	0	0	25	33	50	100	100

The sharp difference in the behaviour of tertiary and secondary amines indicates the important role of the proton, which has also been noted by Rappoport.[1] The strong electrostatic interaction between the positively charged nucleophilic residue and the carbanionic centre in the zwitter-ion probably prevents the clockwise rotation of group (A) by 120° which would lead to inversion. For secondary amines, there is a possibility of the protonation of the neighbouring carbanionic centre (B) and rotation to give the thermodynamically stable conformer is facilitated:



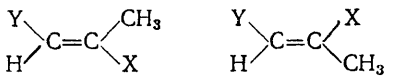
(A) (B) (5)

The importance of the formation of the hydrogen bond in the intermediate zwitter-ion and its influence on the stereochemical result of the reaction are indicated by the results in a study by Chu et al.[43]: the reaction of primary amines ($PhNH_2$) with *E*-3-methoxy-4'-acrylophenones proceeds with inversion of configuration, while the reaction of secondary amines ($PhNHCH_3$) takes place with retention of configuration. The hydrogen-bonded conformation



is the most favourable for the reaction with aniline with the carbanion formed on deprotonation of the zwitter-ion, and the elimination of the methoxy-group from it gives rise to the *Z*-isomer of the substitution product. In the case of *N*-methylaniline there is no hydrogen bond and the sterically less strained *E*-isomer is formed.[43]

A series of studies by French investigators[44-55] has been devoted to nucleophilic vinyl substitution in the esters and nitriles of halogenocrotonic and halogenoacrylic acids. In the reactions of the *Z*- and *E*-isomers of β-halogenocrotonic esters and nitriles (X = Cl or Br; Y = $COOC_2H_5$ or CN), i.e.



with $C_2H_5S^-$ and PhS^- the configuration is retained to an extent greater than 95%.[44] However, in the presence of an excess of the nucleophile Y = CN, the *Z*-isomer of the substitution product is formed either exclusively or preferentially regardless of the configuration of the initial substrate. The author[44] explained this by the isomerisation of the product formed initially in the alkaline medium. The study of the reactions of the same compounds with various amines also revealed a number of characteristic features.[45,46] Only one thermodynamically stable *Z*-isomer of the substitution product is formed in reactions with secondary amines for both Y=CN and Y = $COOC_2H_5$. The nitriles (Y = CN) react with primary amines to form also the *Z*-isomers of the substitution product, while the esters (Y = $COOC_2H_5$) produce almost exclusively (to the extent of 91–98%) the *E*-isomers regardless of the configuration of the substrate. Ethyleneimine reacts with retention of configuration in all cases.

Comparison of these results with the data obtained by the same workers for the reactions involving the addition of various amines to the acetylenic substrates $CH_3-C\equiv C-Y$ (Y = CN or $COOC_2H_5$) [47] permits reliable conclusions about the mechanism of the substitution process. It has been found that both the substitution of the halogen by an amine in crotonic acid derivatives and the addition of amines to the corresponding acetylenic esters and nitriles yield the same product or mixture of products, which led the authors to the conclusion that substitution involves the elimination–addition mechanism (3) via the acetylenic intermediate. The latter is apparently formed under the influence of the strong base $R'O^-$, whose presence in the reaction medium is due to the following equilibrium:

$$RNH_2 + R'OH \rightleftarrows \overset{+}{R}NH_3 + R'O^-.$$

The stereochemistry of the reaction along the initial section of the conversion curve (degree of reaction approximately 5%) has also been investigated.[45] It was found that the product formed under the conditions of kinetic control is thermodynamically stable only in the reaction with ethyleneimine. On the other hand, in the reactions with the remaining amines under the conditions of kinetic control products with retention of configuration were obtained and then isomerised to the thermodynamically stable isomers.[45,46] These results have been confirmed by a special study of the isomerisation of the enamines obtained.[47]

The joint effect of the nature of the leaving and activating groups and of the character of the nucleophile on the mechanism and stereochemistry of the vinyl substitution reactions has been investigated in relation to fluorene- and arene-substituted esters and nitriles of crotonic acid in reactions with O^-, N^-, and *S*-nucleophiles.[48,49] The fluoro-derivatives react with $C_2H_5O^-$ to form preferentially the *E*-isomer of the product from both the *E*- and *Z*-isomers of the substrate. The iodo-derivatives give rise to elimination products in their reactions with $C_2H_5O^-$—either acetylenes or allenes. Both iodo- and fluoro-derivatives react stereoselectively with "soft" anions (PhS^-, $C_2H_5S^-$), forming vinyl substitution products with retention of the configuration. The above compounds react with amines to form mixtures of isomers, the thermodynamically more stable *E*-isomers predominating; *Z*-β-iodocrotononitrile gives rise to an acetylenic derivative. The reaction with ethyleneimine proceeds as a rule with retention of configuration.

The behaviour of the same substrate in reactions with nucleophiles containing a branched hydrocarbon residue, namely $t\text{-}C_4H_9O^-$ and $t\text{-}C_4H_9S^-$, is of interest.[50] Reactions with the highly basic $t\text{-}C_4H_9O^-$ yield exclusively hydrogen halide elimination products, while in the reactions with $t\text{-}C_4H_9S^-$ the composition of the products depends markedly on the nature of the leaving group (the halogen atom) and on the structure of the substrate. On passing from F to Cl and Br and further to I, the content of the elimination and rearrangement products ($CH_2=CX-CH_2Y$) increases, the reaction of the fluoro-derivatives with $t\text{-}C_4H_9S^-$ leads exclusively to substitution products predominately with retention of the configuration, while the Z-isomers of the iodo- and bromo-derivatives afford 90–95% of the acetylenes $CH_3-C\equiv C-Y$ and only 5–10% of the substitution products. The latter (except in the case where X = F) are also formed via the elimination–addition mechanism (3), which has been confirmed by isotope exchange data.

The influence of the α-methyl group was investigated in relation to the *E*- and *Z*-isomers of the compounds $CH_3CX=C(CH_3)COOC_2H_5$ (X = Cl, Br, or I).[51-53] The allene $CH_2=C=C(CH_3)-COOC_2H_5$ is formed in the reactions with alkoxides as in the case of β-halogeno crotonates, while a large amount of the normal substitution product $CH_3-C(Nu)=C(CH_3)-Y$ is formed in the reactions with *S*-nucleophiles, in contrast to the non-methylated substrate, which gives rise to substitution products with rearrangement, i.e. $CH_2=C(Na)-CH_2Y$. In this case substitution also proceeds in accordance with the elimination–addition mechanism.[53] The reactions of β-halogenoacrylic esters[54] and β-halogenoacrylonitriles[55] with $C_2H_5O^-$ and $C_2H_5S^-$ also take place preferentially with either the complete retention of the configuration, although isomerisation sometimes occurs in the reaction with the more basic ethoxide anion, or with addition of a second ethanol molecule and the formation of a saturated adduct.

However, the involvement of a larger series of nucleophiles (including the carboxylate, nitrite, and thiocyanate anions) in the reaction with β-chloroacrylonitrile shows that the reaction proceeds non-stereoselectively. The more stable *E*-isomer of the substitution product is formed as a rule in reactions not only with secondary amines but also with the anions quoted above.[56] Reactions with the anions lead to identical or almost identical mixtures of products,

regardless of the configuration of the initial β-chloroacrylonitrile, i.e. stereoconvergence is observed. In addition, one should note that under certain conditions the *Z*- and *E*-β-chloroacrylonitriles are capable of interconversion and this is also true of the products of the substitution of the chlorine in these substances by the RO, RS, and other groups.[57] The substitution reactions under the influence of RO^- and RS^- proceed, as shown also by Biougne et al.[55], with preferential retention of configuration, but under more severe conditions both products and initial reactants isomerise.[57] The energy differences $\Delta G = \Delta G_Z - \Delta G_E$ have been determined for XCH=CHCN, where X = Cl, CN, CH_3O, n-C_4H_9O, iso-C_3H_7O, C_4H_9S, t-C_4H_9S, and CH_3COO. The *Z*-isomer is more stable with the exception of the cases where X = CH_3O and C_4H_9O. The differences ΔE have also been calculated semiempirically by the CNDO/2 method, but the calculated values agree poorly with the experimental data.[57]

The substitution of the fluorine in 2-pentafluoropropenyltetrahydrofuran by alkoxide anions[58] leads to a mixture of the *Z*- and *E*-isomers with the ratio $Z/E = 2.0-5.8$, which differs from that for the initial substrate ($Z/E = 1.9$):

$$R'-CF=CF-CF_3 + RO^- \rightarrow R'-C(OR)=CF-CF_3 + F^-.$$

The author interprets these data from the standpoint of the relative stabilities of the conformers of the carbanion leading to the *Z*- and *E*-isomers of the product, but notes that the *Z*-isomer of the substrate is more reactive and the results obtained for low conversions do not therefore prove the relative stabilities of the conformers.

In the study of the substitution of fluorine in β-fluorovinyl sulphones it has been shown[59] that, on interaction with CH_3O^- and PhS^- in methanol, *E*-$PhSO_2CH=CHF$ gives rise to substitution products with retention of configuration, while the *Z*-isomer produces mixtures with the compositions *Z* : *E* = 1 : 1.5 and 3 : 1 for the reactions with CH_3O^- and PhS^- respectively. Since the adduct $PhSO_2CH_2CHFSPh$ and the acetylenic sulphone $PhSO_2C\equiv CH$ are stable under the reaction conditions, the non-stereospecificity of the reaction of the *Z*-isomer is apparently associated with the longer lifetime of the carbanion, which permits the establishment of the conformational equilibrium before the elimination of the leaving group.

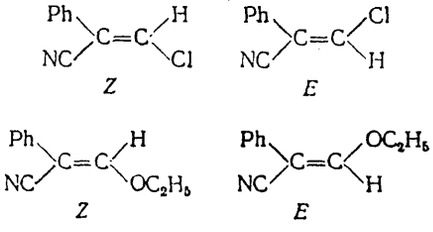
It has been shown[60] that the configuration is retained in the reactions of the *Z*- and *E*-isomers of the nitrile $(CH_3O)_2$.CHCBr=CHCN with piperidine, while the reaction with ammonia leads in all cases to the more stable *Z*-enamine. The data obtained have been compared with the stereochemical result of the reactions involving addition to the corresponding acetylenes.

The majority of the reactions described above have been investigated in proton-donating solvents, although the rule of the preferential retention of the configuration holds also in solvents of the type of dimethylformamide (DMF).[61-64]

Interesting data have been obtained in the study of the reactions of the isomeric β-bromovinyl sulphones $ArSO_2CH=CHBr$ with a series of neutral *N*-, *P*- and *S*-nucleophiles.[65-70] It has been shown that the reactions of these compounds with tertiary amines, containing at least one methyl group, involve substitution with retention of configuration. The reactions of more bulky amines (triethylamine or tri-n-butylamine) lead to the formation of the thermodynamically more stable *E*-isomer of the substitution product. On further branching (in the case of tribenzylamine), the reaction does not take place. The data obtained can be interpreted satisfactorily from the standpoint of steric interactions in the intermediate zwitter-ion.[67] The reactions of β-bromovinyl sulphones with tervalent phosphorus acid amides proceed in a more complex manner.[68,69] Both *N*- and *P*-substitution products are formed, the sulphonyl group also being substituted in a number of instances after the substitution of the bromine atom. The stereochemistry on the whole corresponds to the formation of the less sterically strained *E*-isomers, but it has been established by special investigations (EPR and ^{31}P CINP) that these reactions proceed via a one-electron transfer mechanism[70] and cannot therefore be interpreted unambiguously within the framework of the direct vinyl substitution mechanism (2) with participation of an intermediate zwitter-ion. It has been shown in relation to dimethyl sulphide that *S*-nucleophiles react with β-bromovinyl sulphones only under severe conditions, forming methylthiosulphonylmethylenes with retention of configuration and via the following mechanism:[65,66]

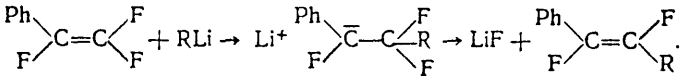
$$ArSO_2CH=CHBr \xrightarrow[100°,50h]{(CH_3)_2S} ArSO_2CH=CH\overset{+}{S}(CH_3)_2\ Br^- \xrightarrow{(CH_3)_2S} \rightarrow ArSO_2CH=CHSCH_3 + (CH_3)_3\overset{+}{S}Br^-.$$

In the presence of more than two substituents at the double bond (in the case of two protons the configuration can be readily determined from the spin–spin coupling constant $^3J_{H-H}$), the question of the unambiguous assignment of the configurations of the substrates and products when the stereochemistry of S_NVin reactions is considered proves to be of fundamental importance. This is well illustrated in relation to a study[71] where the substitution of chlorine in the *Z*- and *E*-isomers of 3-chloro-2-phenylpropenonitrile under the influence of various nucleophiles (ArS^-, $C_2H_5O^-$, N_3^-, PhO^-, piperidine, and morpholine) was investigated:



The authors[71] concluded that the substitution proceeds with retention of configuration of the nucleophile anions, while in the case of amines only one isomer is formed (regardless of the configuration of the substrate), to which the structure of the *E*-isomer was attributed. However, subsequently these data were disproved by other investigators,[72] who claimed that Rappoport and Topol[71] incorrectly assigned the structures of the products of the substitution of chlorine by the ethoxy-group, because comparison of the ^1H NMR spectra of the *Z*- and *E*-isomers with spectra calculated in accordance with an additive scheme leads to the opposite assignment. Subsequently it was concluded[72] that reactions with amines involve the initial formation of products with retention of configuration, one of which then rearranges to the more stable product. In contrast to the conclusions reached by Rappoport and Topol,[71] the structure of the *Z*-isomer was attributed to the latter. In the controversy which followed[73] Rappoport agreed with some of the evidence concerning the structure of the substitution product and at the same time pointed out that many discrepancies are associated with the different experimental conditions used by himself[71] and by Le Guillanton and Cariou[72] (concentration, reactant ratio, temperature, etc.) and also dealt critically with the suitability of individual methods for the determination of the structure of compounds, including the stereochemical result of the substitution reaction as one of the criteria of the structure of the initial compound.

Until recently, little was known about the S_NVin reactions with participation of *C*-nucleophiles, i.e. carbanions.[1] Only in recent years have studies been published in which the nucleophilic reactivities of a large series of carbanions were investigated quantitatively in relation to the substitution of fluorine in αββ-trifluorostyrene.[74-76] The reaction takes place stereoselectively with substitution of one fluorine atom:

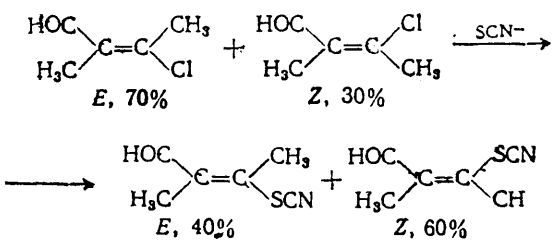


The *trans*-disposition of the fluorine atoms in the substitution product follows unambiguously from the values of $^3J_{F-F}$ in the ^{19}F NMR spectra (approximately 130 Hz). The substitution of bromine in the *cis*- and *trans*-isomers of β-bromostyrene in its reactions with n-C_4H_9Li and n-C_4H_9MgBr also proceeds stereospecifically with retention of the configuration.[77]

The reactions of β-halogenovinyl ketones with the soft nucleophile (PhS^-) take place with retention of configuration in the initial stage, but the *E*-isomer of the reaction product isomerises at the end of the process to the *Z*-isomer.[78] The causes of this isomerisation are not altogether clear, because *E*-isomers are as a rule more stable. Thus *Z*- and *E*-β-fluoro-*p*-nitrostyrenes react with the same nucleophile (PhS^-) to form the *E*-isomer of the substitution product,[79] although in the initial stage under the conditions of kinetic control the *Z*-isomer reacts with retention of the configuration. These compounds react analogously also with CH_3O^-, forming *E*-$O_2NC_6H_4SO_2CH=CHOCH_3$.[79] The observed stereochemical differences from the β-chloro- and β-bromo-derivatives have been explained[79] by the longer lifespan of the carbanion in which the leaving group is less nucleophilic (F^-).

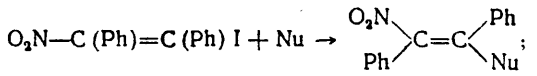
It was noted above (Section II) that, when certain conditions are maintained, stereoconvergence, i.e. the formation of the same mixture of products regardless of the structure of the substrate, can take place but not as a result of post-isomerisation (as happens frequently in reactions with amines or as happened in the study quoted above[78]) but is a consequence of the independent formation of the *Z*- and *E*-isomers from the corresponding conformers of the intermediate carbanion.[80] The number of such examples is small. For "poor" leaving groups (F, OR), this was demonstrated by the studies quoted above,[19,20] while for "satisfactory" leaving groups (Cl, I) stereoconvergence was observed in a series of other investigations.[21,81,82]

The stereoconvergence in substitution reactions with "good" leaving groups is one of the indications of the multistage nature of the S_NVin substitution process[26] and it is therefore useful to examine these cases in greater detail. Korobov et al.[81] (whose study was the first where stereoconvergence was noted for a "good" leaving group despite Rappoport's claims[82]) investigated the following reaction:



A mixture of products of the same composition is also obtained from the individual isomers and it was shown specially that the *Z*- and *E*-isomers are not interconverted under the reaction conditions.[83]

A highly reactive system with a "good" leaving group yields only one product# in reactions with a whole series of nucleophiles:[21]

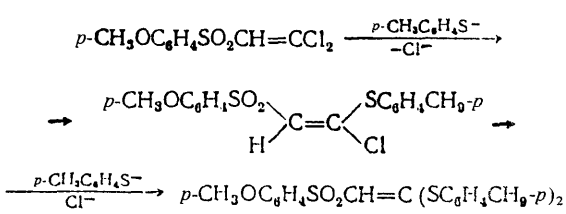


Nu = SCN^-, *p*-$C_6H_4S^-$, N_3^-, piperidine, or morpholine.

In the somewhat less reactive *Z*- and *E*-$CH_3OCOC(CN)=C(Cl)C_6H_4NO_2$ [82] and *Z*- and *E*-HOC–C(Ph)=C(Ph)Cl [84] systems, the interaction with *p*-$CH_3C_6H_4S^-$, CH_3O^-, *p*-$CH_3C_6H_4O^-$, and Cl^- proceeds with either complete or partial stereoconvergence. The aim of the authors of the above studies[82,84] was essentially to find the frontier region between moderately activated substrates, reacting with retention of configuration, and more activated substrates giving rise to complete stereoconvergence.[21] The structure of the isomers put forward in the above communications[82,84] arouses no doubts (in contrast to those in Refs. 71–73), because X-ray diffraction analysis was carried out on individual isomers.

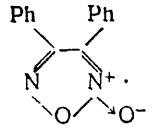
The use of an aprotic dipolar solvent [hexamethylphosphoramide (HMP)] makes it possible to carry out smoothly S_NVin substitution reactions in usually inert unsubstituted chloroalkenes,[62,85] vinyl sulphides, and vinyl selenides.[63,64] It has been shown that, in conformity with the general rule, they react with thiolate and selenolate anions with retention of configuration. It may be that in this case the above result is a consequence of a synchronous substitution process, because this process is most likely to operate precisely in weakly activated or non-activated substrates with "good" leaving groups.[26] The study of the "effect of the element" (see Section IV) can provide an answer to this question, because the magnitude of the "effect of the element" is the most apt criterion for the choice between the synchronous and multistage processes.[20]

Systems with two geminal leaving groups substituted in succession have been investigated and it has been shown that, in the reaction

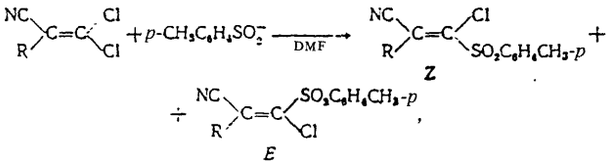


the intermediate 2-chloro-1-*p*-methoxybenzenesulphonyl-2-*p*-tolylthioethylene has the structure of the *E*-isomer.[86] Bearing in mind the general rule governing the retention of configuration in S_NVin reactions, one may conclude that the chlorine atom in the *trans*-position relative to the

#In the case where Nu = N_3^- the product is



α-hydrogen atom is very mobile. This conclusion agrees with the relative reactivities of the *Z*- and *E*-isomers of vinyl halides in S_NVin reactions; overall, the *Z*-isomers are more reactive.[1] In the presence of substituents in the α-position the stereospecificity breaks down:[87]



The *Z* : *E* ratios are 100 : 0, 90 : 10, and 70 : 30 for R = C_6H_5, CH_3, and t-C_4H_9 respectively.[87] The preferential formation of the *Z*-isomer may be associated with the increased energy of the conformer of the carbanion leading to the *E*-isomer owing to the repulsion of the like dipoles (S–O and C–N); the appreciable amount of the *E*-isomer in the case of R = t-C_4H_9 is evidently to be explained by the smaller steric strain in the carbanion in the interaction of the $(CH_3)_3C$ and Cl groups than in the interaction of the $(CH_3C)_3C$ and p-$CH_3C_4H_4SO_2$ groups.

Despite the fact that the attack by the nucleophile in the plane of the molecule is as a rule less favourable in S_NVin reactions owing to both electronic and steric factors, it can apparently occur in certain special cases (see Section II). Thus the retention of both the configuration of the double bond and the chirality of the substituent in a sterically strained system containing a chiral constituent is believed[88] to be explained best within the framework of the hypothesis that the nucleophile attacks in the molecular plane, since attack in the plane of the π-bond should lead to partial or total loss of chirality.

IV. QUANTITATIVE DESCRIPTION OF REACTIVITY

1. The Influence of the Nature of the Activated Group

Since the occurrence of S_NVin reactions via the mechanism (2) involves the formation of an intermediate carbanion, the increase of the electron-accepting strength of the substituent in the β-position relative to the leaving group evidently accelerates the reaction. In general, this rule is observed but it has not been possible to construct a universal reactivity series for such groups. This is due in the first place to the fact that the quantitative data for the reactivity of systems with different activating groups include data for interaction with various nucleophiles. Thus, assuming that the relative activating capacities of the groups depend only slightly on the nature of the nucleophile, Rappoport[1] proposed the following series:

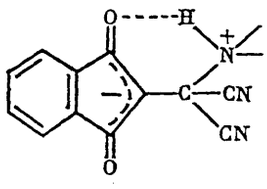
$$2,4\text{-}(NO_2)_2C_6H_3 > PhCO > C_2H_5CO > PhSO_2 > CN > COOC_2H_5 > > PhSO > p\text{-}NO_2C_6H_4 > PhS \gg Cl.$$

However, more detailed analysis using the data of other studies[54,55] yields another series for the reactions of RO^-:

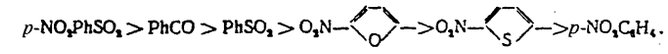
$$CN > SO_2 > CO > SO > 2.4\text{-}(NO_2)_2C_6H_3 > COOR > p\text{-}NO_2C_6H_4.$$

Approximately the same kind of series holds also for the soft nucleophile PhS^-, although the reactions can proceed via different mechanisms [mechanism (2) for PhS^- and mechanism (3) for RO^-]. The relative reactivity may depend on the structure of the substrate. Thus the *E*-isomer of β-bromo-2,4-dinitrostyrene reacts with PhS^- faster than the *E*-isomer of β-bromovinyl sulphone while the opposite relation holds for the *Z*-isomers.[1]

The reactivity series has been derived in a review[89] from data for the direction of nucleophilic attack on the double bond activated by different groups in CHX = CHY: NO_2 > COR > COOR > $PO(OR)_2$. On the grounds of these considerations, the data of Rappoport and Ladkani[90] for addition to $(RCO)_2C=C(CN)_2$ yield the relation RCO > CN, which is confirmed by calculations by the extended Hückel method,[91] but it does not agree with many experimental data. Evidently the nucleophilic attack in αα-diacyl-ββ-dicyanoethylenes on the carbon atom linked to the cyano-groups, although the latter delocalise the negative charge more effectively than the carbonyl groups, can be explained by the fact that the result is not determined solely by the stability of the final carbanion, and in the given instance not even to a major extent, but is determined by the electrophilicity of the carbon atom in the initial state. Furthermore, in the systems investigated by Rappoport and Ladkani[90] the attack of the nucleophile on the carbon atom of the dicyanomethylene group promotes the formation of an intramolecular hydrogen bond and the aromatic character of the anion formed:



Mainly on the basis of the results of their own studies of reactions involving amines,[92–99] Popov et al.[99] proposed the following sequence of groups in terms of their activating strength:



The activating capacity of the nitrogen-group is estimated by comparing the activity data for α-chloro-β-nitrostyrene *E*-$PhCCl=CHNO_2$ and 1,1-dicyano-2-chloro-2-(*p*-dimethylaminophenyl)ethylene $(CH_3)_2NC_6H_4CCl=C(CN)_2$.[100] The authors estimated the ratio $k(PhCCl=CHNO_2)/k[PhCCl=C(CN)_2]$ as 0.22 in terms of the value of ρ for the substituents in the aryl group, which is 1.5, i.e. the electron-accepting properties of one nitro-group are only 4–5 times weaker than those of two cyano-groups. In the case of complete additivity (which naturally does not obtain but such an assumption is acceptable for qualitative conclusion in the given instance[101,102]), the ratio $k(NO_2)/k(CN) = 0.22k(PhCCl=CHCN)/k(PhCCl=CH_2)$ and, since the introduction of the cyano-group in the β-position accelerates the reaction by several orders of magnitude, it is evident that $k(NO_2) > k(CN)$.

Since the first stage of the S_NVin reactions, namely addition to the sp^2-carbon atom, is analogous to the first stage in addition to the Ad_N type to electrophiles, a study[103] where the reactivity series has been formulated for Ad_N reactions is of special interest:

$$NO_2 > PhCO > CH_3CO > (C_4H_9)_3P^+ > RSO_2 > (CH_3)_2NSO_2 > > COOCH_3 > CN > \text{4-pyridyl} > PO(OR)_2 > CONHR.$$

In the above series the $COOCH_3$ and CN groups can change places depending on the nucleophile. The following series

follows from the authors' own data:[103]

$$PhCO > PhSO_3 > CHO > CH_3CO > PhCOO > p\text{-}CH_3C_6H_4SO_2 > > CH_3COO > CN > CONH_2 > PO(OR)_2 > p\text{-}O_2NC_6H_4$$

After combining all the available data, it is possible to establish the following expanded reactivity series for electron-accepting groups:

$$NO_2 > PhCO > PhSO_3 > CHO > CH_3CO > (C_4H_9)_3P^+ > PhCOO > > p\text{-}CH_3C_6H_4SO_2 > CN > (CH_3)_2NSO_2 > COOCH_3 > PhSO > > 4\text{-pyridyl} > PO(OCH_2CH_2Cl)_2 > CONH_2 > PO(OC_2H_5)_2 > > CONHR > p\text{-}O_2NC_6H_4 > PhS > Cl.$$

It is of interest that extrapolation of the temperature variations for the few available kinetic data at 200 °C yields a different sequence:

$$PhSO_3 > CH_3CO > PhCO > CHO > PhCOO > p\text{-}CH_3C_6H_4SO_2 > > CN > CH_3COO > CONH_2 > PO(OC_2H_5)_2,$$

i.e. certain members of the series have changed places.

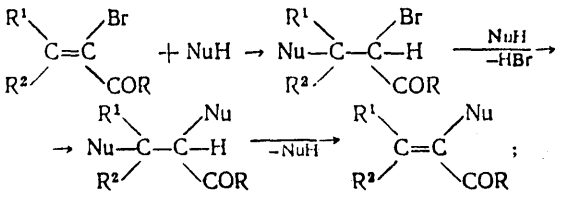
According to Fischer and Jentzch,[104] the dimethyliminomethylene group $(CH_3)_2\overset{+}{N}=CH-$ is a powerful activating group, greatly superior to the carbonyl group, especially in reactions with mild nucleophiles.

The above analysis suggests that the available insufficiently long relative reactivity series for substrates makes it possible to describe satisfactorily the reactivity within the framework of the direct substitution mechanism (2), but their predictive power is fairly weak owing to their dependence on the nature of the nucleophile, the solvent, temperature, etc.

The influence of the second activating group in the β-position with respect to the leaving group is extremely difficult to estimate from the existing investigations, because there are no reactivity data for mono- and di-activated compounds with the same nucleophiles under identical conditions. It is known only that, whereas substrates with a single activating group CN or COOR react solely with aliphatic amines,[49,71] the analogous substrates with two such groups react smoothly with the much less basic anilines.[101] Apparently the electronic influence of two activating groups is to a first approximation additive, provided that the conjugation of each with the double bond does not break down (analogously to the non-uniform variation of the acidities of the substituted methanes with different numbers of CN and NO_2 groups[105]). It is noteworthy that the activating capacity of the group X does not always vary in parallel with the pK_a for the corresponding acid CH_3X, but a correlation with the rate of ionisation of these acids is sometimes observed.[106]

If the activating group and the nucleophile in the intermediate carbanion are attached to the same carbon atom, then its influence is much weaker, since the effective stabilisation of the carbanion via the conjugation mechanism is impossible, and furthermore, additional steric hindrance arises in the transition state. These two effects can overlap the activating influence of the group. Thus the introduction of the chlorine atom in the α-position in Z-β-chlorovinyl phenyl sulphone accelerates the reaction with CH_3O^- by a factor of 1.3 and with PhS^- by a factor of 1.4,[1] while the introduction of a chlorine atom in the β-position retards the reaction with CH_3O^- by a factor of 1.5 [107] and with PhS^- by a factor of 4.4.[108]

On the other hand, if the activating group is separated from the double bond by the methylene bridge, as in $CH_2=CHal-CH_2CN$, $CH_2=CHal-CH_2COOC_2H_5$,[109] $CH_2=CCl-CH_2SO_2Ph$,[110] or $CH_2=CBr-CH_2PO(OC_2H_5)_2$,[111] then the reaction proceeds via the formation of the allyl anion and then the intermediate allene and not only with hard *O*-nucleophiles but also with soft *S*-nucleophiles.[109] If the electron-accepting group is linked directly to the double bond, as in $R^1R^2C=CBr-COR$,[112] then it polarises the C=C bond in such a way that the Michael addition of the nucleophile takes place initially and then the halogen in the saturated adduct is readily substituted via a mechanism of the S_N2 type as in α-halogenoketones. Finally the elimination of the conjugate acid of the nucleophile affords the substitution product:[112]



NuH=PhOH, PhSH. (6)

The last stage of reaction (6) can yield two different products depending on which of the nucleophile residues is split off. The above example corresponds to regiospecific substitution with retention of the configuration, but there exist examples of the formation of both possible products[113] and of the inversion of regioselectivity.[114]

Finally, the methyl groups in the α- and β-positions in the molecule reduce its reactivity, the effect in the β-position reflecting the electron-donating and steric influence of the CH_3 group, while the introduction of the substituent in the α-position rules out in addition the occurrence of reaction via the elimination–addition mechanism (3). In certain cases this can reduce the rate by 4–5 orders of magnitude.[115]

2. The Influence of the Nucleophile

It has been noted in a review[1] that the nucleophilicity sequence in S_NVin reactions differs from that for S_N2 reactions involving an sp^2-carbon atom, but is close to the nucleophilicity series for S_NAr reactions. The corresponding nucleophilicity series are given below:

$PhCH_2S^- > p\text{-}CH_3C_6H_4S^- >$ piperidine $> PhS^- > CH_3O^- >$ n-$(C_4H_9)_2NH >$ cyclohexylamine $> N_3^- > I^-, Br^-, Cl^-$ (Refs.1, 116) and

$ArS^- > C_2H_5O^-$ > piperidine $> PhO^-$ > morpholine $> N_3^-$ (Ref.71)

for S_NVin reactions,

$$CN^- > HS^- > I^- > SCN^- > \text{aniline} > HO^- > N_3^- > Br^- > PhO^- > Cl^- > F^- \quad \text{(Ref.117)}$$

for S_N2 reactions, and

$$PhS^- > CH_3O^- > PhO^- > HO^- > SCN^- > \text{piperidine} > \text{aniline} > I^- > Br^- > Cl^- \quad \text{(Refs.118-120)}$$

for S_NAr reactions.

It is noteworthy that the above series can vary for different substrates (particularly in conformity with Pearson's "symbiosis" effect), and in addition have been obtained for proton-donating solvents. Thus the inversion of the series for S_NAr reactions has been demonstrated in aprotic dipolar solvents:[121,122] $F^- \gg SCN^- > Cl^- > Br^- > I^-$. Even for a single solvent, the relative nucleophilicities can vary fairly widely for slight changes in the substrate structure. Thus piperidine reacts with 1-benzoyl-2-chloro-1-phenylethylene in DMF faster by an order of magnitude than

sodium azide, with 1-benzoyl-2-chloro-1-methylethylene the two nucleophiles react almost identically, while with 1-acetyl-2-chlorocyclopentene the azide ion reacts twelve times faster than piperidine.[123] An analogous behaviour has been observed in ethanol.

Another possibility for a sharp change in the nucleophilicity sequence is associated with the occurrence of the reaction via different mechanisms [mechanisms (2) and (3)]. This is shown particularly clearly for the PhS^-/CH_3O^- pair. PhS^- is usually more reactive than CH_3O^- in reactions via the direct substitution mechanism, for example in reactions with the *Z*- and *E*-isomers of $PhSO_2CH=CHCl$.[1] The reaction with the *Z*-isomer of the bromo-derivative, from which HBr is very readily split off, involves the reversal of this ratio: $k(CH_3O^-) > k(PhS^-)$. For the *E*-isomer of the bromo-derivative, the $E\text{-}Ad_N$ mechanism is less probable and the ratio $k(PhS^-) > k(CH_3O^-)$ is valid. The introduction of the methyl group in the α-position relative to the sulphonyl group rules out the possibility of the elimination of HBr, so that we also have $k(PhS^-) > k(CH_3O^-)$ for $p\text{-}O_2NC_6H_4NO_2.C(CH_3)=CHBr$.[1]

However, despite the lack of a universal scale, the difference between the nucleophilicity series is too great to be attributed to the effects of the medium, non-additivity, etc. The causes of the difference may be more far-reaching and the main cause is apparently the difference in the character and energies of the frontier orbitals. The lowest unoccupied molecular orbital (LUMO) of the substrate in the S_NVin reactions is a π* orbital and its energy is much lower than that of the σ* orbital (the LUMO of the substrate in S_N2 reactions). When the highest occupied molecular orbital (HOMO) of the nucleophile interacts with the σ* orbital of the electrophile-substrate, the nucleophilic reactivity is described quantitatively by the Swain–Scott equation.[117] On the other hand, when the LUMO of the electrophile is an orbital of the π* type, for example in carbanions, the Swain–Scott equation does not hold and Ritchie[124] proposed a new N_+ nucleophilicity scale in relation to the reactions of nucleophiles with the carbonium ion of the Malachite Green dye. The applicability of this scale to the reactions of nucleophiles with different π-systems, namely carbonyl-containing,[125] aromatic,[126] and electrophilic olefins,[127] was demonstrated subsequently. Consequently the nucleophilic reactivity of the anions in the S_NVin reactions of activated olefins with a low-lying π* orbital should also be described by Ritchie's equation; indeed the rate of reaction of nucleophile anions with substituted 9-methylenefluorenes $R^1R^2C=CXY$ (R^1, R^2 = fluorenyl; X, Y = H, CN, or NO_2) increases in the sequence $CN^- < OH^- < N_3^-$, which is inconsistent with the Swain–Scott scale and is characteristic of Ritchie's scale.[106]

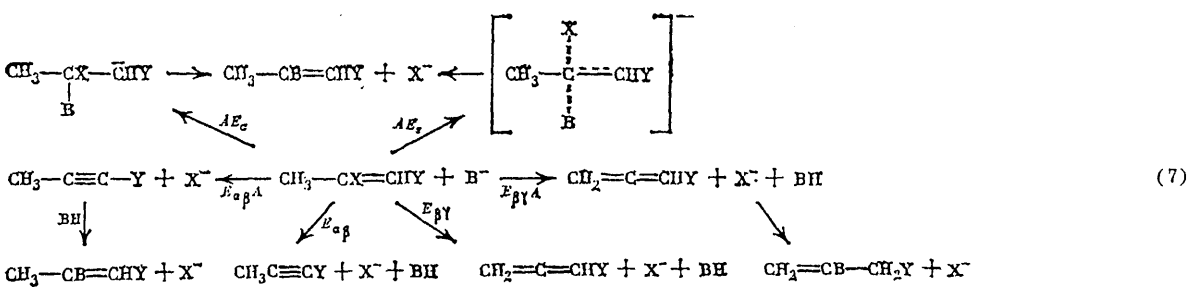
The influence of the nature of the nucleophile on the mechanism of the S_NVin reactions is described satisfactorily in terms of the principle of hard and soft acids and bases. The two electrophilic centres in the substrate molecule, the proton in the α-position and the β-carbon atom§, tend to react respectively with hard and soft nucleophiles. The criteria used to assign the reaction to a particular mechanism are the isotope exchange when the reaction is carried out in deuteriated solvents, the kinetic isotope effect, and the sign of the activation entropy for the reaction. The occurrence of isotope exchange is an essential but not a sufficient criterion of the occurrence of the reaction via the $E\text{-}Ad_N$ mechanism; on the other hand, the positive value of $\Delta S^{\neq}$ indicates reliably the operation of the $E\text{-}Ad_N$ mechanism. The mechanisms (2) and (3) sometimes operate in parallel and the sign of $\Delta S^{\neq}$ then indicates the predominance of one or other mechanism. Only a few examples of the occurrence of the S_NVin reaction with $\Delta S^{\neq} > 0$ have been noted in Rappoport's review;[1] they all take place with participation of CH_3O^- or $C_2H_5O^-$ and only for the *Z*-isomers, i.e. for the *trans*-orientation of the α-hydrogen atom and of the leaving group in the β-position.

In the presence of the methyl group in the β-position, there is a possibility of βγ-elimination with formation of an allene:[44]

$$CH_3\text{—}CX{=}CH\text{—}Y\text{—}\begin{cases}\xrightarrow{RO^-\,(Y=COOR)} CH_2{=}C{=}CH\text{—}Y \xrightarrow{ROH} CH_3\text{—}C(OR){=}CH\text{—}COOR;\\ \xrightarrow[RS^-,\,(X=Br,\,Y=CN)]{} CH_3\text{—}C{\equiv}C\text{—}CN.\end{cases}$$

As can be seen from the above scheme the elimination can also take place under the influence of the soft nucleophiles RS^-.[44] β-Halogenoacrylate esters $C_2H_5OCO\text{—}CH=CHX$ react with RO^- to form a substitution product and the acetylenic ester $C_2H_5OCO\text{—}C\equiv CH$, the content of the acetylene increasing in the sequence X = Cl, Br, and I.[54] The corresponding β-halogenoacrylonitriles also react with RO^- via the $E\text{-}Ad_N$ mechanism, which is indicated by the positive values of $\Delta S^{\neq}$ for the *Z*-isomers, the low negative values of $\Delta S^{\neq}$ for the *E*-isomers, and the high (up to 10^3) values of the ratio k_Z/k_E.[55]

The study of the interaction of β-halogenocrotonates and β-halogenocrotononitriles with various *O*-, *N*-, and *S*-nucleophiles enabled Chalchat and co-workers[49,50,53] to formulate the following general reaction scheme:[50]



(7)

§ The involvement of a halogen atom in the α-position at the electrophilic centre is considered below (Section IV).

The $E_{\alpha\beta}$, $E_{\beta\gamma}$, $E_{\alpha\beta}A$, and $E_{\beta\gamma}A$ mechanisms in Scheme (7) are readily distinguishable even in terms of the structure of the products involved. As regards the mechanisms AE_C (via an intermediate carbanion) and AE_S [synchronous mechanism via the transition state illustrated in Scheme (7)], the authors[50] draw a distinction between them using the analysis of the stereochemistry of the substitution process. If the reaction is stereospecific with retention of configuration, a synchronous process is implied, for which the retention of configuration is the only natural result (see Sections II and III above) but, when a mixture of isomers is produced, the reaction is believed to proceed via a stable intermediate carbanion, whereupon the stereochemical outcome is determined by the relative contributions of the processes involving inversion at the carbanionic centre, rotation in the anion, and the elimination of the leaving group.

On this basis, it was concluded that β-fluorocrotononitriles and β-fluorocrotonates react with almost all *O*-, *N*-, and *S*-nucleophiles via the AE_C mechanism, elimination of the $E_{\alpha\beta}$ or $E_{\beta\gamma}$ type occurring only for the highly basic and bulky t-$C_4H_9O^-$. Bromides behave analogously, although in this case the reaction does not stop at the elimination stage and proceeds via the $E_{\alpha\beta}A$ mechanism for the *Z*-isomers and via the $E_{\beta\gamma}A$ mechanism for the *E*-isomers.[50] Iodides usually react via the $E_{\alpha\beta}$ or $E_{\beta\gamma}$ mechanism ($E_{\beta\gamma}$ elimination with formation of allenes is characteristic of the *E*-isomers), but reactions with soft nucleophiles (PhS^-, ethyleneimine) involve substitution via the AE_S mechanism. For α-methylated substrates $CH_3CX=C(CH_3)Y$, $E_{\alpha\beta}$ elimination is impossible and there is a smooth shift from the $E_{\beta\gamma}$ mechanism to the *AE* mechanism on passing from hard (RO^-) to soft (RS^-) nucleophiles.[53] It is noteworthy that the probability of the occurrence of a synchronous process has been shown[26] to be low and so far there have been no reliable examples. The AE_S and AE_C mechanisms presented in Scheme 7 should therefore be treated as carbanionic mechanisms with short and long lifetimes of the carbanion respectively.

3. The Influence of the Leaving Group (the "Element Effect")

The influence of the leaving group is one of the most interesting and informative effects in the study of the mechanisms of $S_NV$in reactions. Most of the processes associated with this effect were examined in detail previously[1] and in the present Section we shall therefore describe briefly the main principles and will present later data which were not included in Rappoport's review.[1]

The influence of the leaving group is frequently called the "element effect", because the majority of the studies have been carried out for halogen-substituted substrates, usually for the Cl/Br pair. The causes of the fundamental importance of the "element effect" consists in the fact that the vinyl substitution process (2) is a two-stage reaction and the influence of the nature of the leaving group on these stages is markedly different. In fact, if the rate of reaction is determined by the first stage, i.e. by the addition of the nucleophile to the β-carbon atom with formation of a carbanion, then it will increase with increasing electronegativity of the halogen atom: $k(I) \leq k(Br) \leq k(Cl) \leq k(F)$. On the other hand, if the abstraction of the leaving group from the carbanion (the second stage) is rate-determining, then the opposite relation should obtain in conformity with the bond strength: $k(F) < k(Cl) < k(Br) < k(I)$. The latter sequence should hold also for a synchronous process with the simultaneous dissociation and formation of bond, as in S_N2 reactions at an sp^3-hybridised carbon atom.

Many data for the Cl/Br pair were examined in Rappoport's review[1] and only two instances were quoted for F/Cl. The results of later investigations make it possible to analyse the entire series of halogens from F to I. Thus it has been shown for the compounds $CH_3-CX=CH-Y$ (Y = COOR or CN; X = F, Cl, Br, or I) that the rate of reaction with $C_2H_5S^-$ varies in the following manner: $k(Cl) < k(F)$, $k(Br) \cong k(I)$ (Y = CN) and $k(Cl) < k(F)$, $k(Br) \leq k(I)$ (Y = COOR). The data for the *E*-isomers were used, because in this case the distortions introduced by the contribution of the elimination process are minimal.[49] For the reactions of the same compounds with t-$C_4H_9S^-$, the sequence is somewhat different: $k(F) < k(Cl) < k(Br) < k(I)$, which reflects the contribution of the elimination process.[50] Unfortunately the kinetic data for the reaction with PhS^-, which is uncomplicated by the contribution of the E-Ad_N mechanism according to the results of Chalchat,[49] are lacking.

Comparison of the data for the interaction of CH_3O^- and PhS^- with β-fluoro-*p*-nitrostyrene with the corresponding data for the β-chloro- and β-bromo derivatives showed[79] that the ratio $k(F)/k(Cl, Br)$ depends on the nature of the nucleophile and amounts to only about 3 for the soft anion CH_2S^-. An analogy has been drawn[79] with S_NAr reactions,[128] where this phenomenon has been attributed to Pearson's "symbiosis effect", i.e. to the tendency by substrates containing heavy polarisable leaving groups to bind in the transition state to more polarisable nucleophiles. This has been confirmed by data[129] indicating a decrease of the ratio $k(F)/k(Cl)$ in the series RO^-, R_3N, RS^-, i.e. with increase of the "softness" of the nucleophile, for the reactions of $Ar_2C=CHX$ (X = F or Cl) in DMF. Hence it was concluded that London dispersion forces play a significant role in determing the "effect of the element".

Another aspect of the "element effect" is examined in relation to the reaction of 1,1-dicyano-2-halogeno-2-(*p*-dimethylaminophenyl)ethylenes with anilines in acetonitrile[130] and alcohols.[131] Very low ratios $k(F)/k(Cl)$ (from 0.71 to 3.05) were observed in all the media in contrast to the normally high (approximately 10^2) values of this parameter. This has been explained by the fact that $k_{exp} = (k_1/k_{-1})k_2$, where k_1 is the rate constant for the formation of the zwitter-ion, k_{-1} the rate constant for its decomposition into the initial compounds, and k_2 the rate constant for the abstraction of the leaving group from the zwitter-ion. The "element effect" is high ($\gg 1$) for k_1, amounts to approximately 1 for k_{-1}, and is very small ($\ll 1$) only for k_2, because k_2 refers to the C–Hal bond dissociation stage (probably, by analogy with reactions of the S_N1 type, the "element effect" for k_2 amounts to 10^{-2}–10^{-6}).

If the substitution proceeds via the carbanionic mechanism (2), then the "element effect" should not differ sharply for the *Z*- and *E*-isomers of the substrate. On the other hand, for reactions via the E-Ad_N (3) mechanism, the dependence on the nature of the leaving group is qualitatively different, because the *Z*-isomers split off HHal much more readily than the *E*-isomers. Indeed, for the esters $C_2H_5OCO-CH=CHX$ (X = Cl, Br, or I), the variation of the rate of reaction with $C_2H_5O^-$ in ethanol for the *Z*-isomers is in the sequence $k(Cl) \ll k(Br) \ll k(I)$, whereas for the *E*-isomers we have $k(I) < k(Cl) \lesssim k(Br)$.[54] For the reactions of the same esters with $C_2H_5S^-$, the "element effect" is much weaker and is in the range 1–2.[54] When the methyl group is introduced in the α-position, the E-Ad_N mechanism is ruled out and the "element effect" is close to unity [$k(Br)/k(Cl) = 1.3$].[53] β-Halogenoacrylonitriles $CN-CH=CHX$ (X = Cl or

Br) behave analogously: $k(Br)/k(Cl) = 10^3$ for the *Z*-isomers and 0.82 for the *E*-isomers.[55]

Since strong bases react with activated vinyl halides as a rule via the $E\text{-}Ad_N$ mechanism while "soft" bases react via the direct substitution mechanism (2), large values of $k(Br)/k(Cl)$ are to be expected for the reactions with RO^- and values close to unity for the reactions with RS^-. The experimental ratio $k(Br)/k(Cl)$ for ββ-dihalogenovinyl sulphones $ArSO_2CH = CX_2$ (X = Cl or Br) amounts to 10^2–10^3 for the reaction with CH_3O^- and to 1.7–3.3 for the reaction with ArS^-.[132]

Values of the "element effect" $k(Br)/k(Cl)$ close to unity (from 0.6 to 1.2), i.e. indicating that the C–Hal bond is not involved in the rate-limiting step, have been obtained for the reaction of $Ar_2C=CHX$ with ArS^- in DMF,[61] but, in the reaction involving the exchange of the halogen X for ^{36}Cl under the influence of $Li^{36}Cl$ in DMF, the quantity $k(Br)/k(Cl)$ is much higher (5.1–7.6) and the chloride anion is much less reactive than ArS^- (by 9–10 orders of magnitude).[133]

For 2-halogenovinyl ketones $ArCOCH=CHX$ (X = Cl or Br), the "element effect" has been studied for reactions with both anions[78] and with a wide range of amines.[134] In the case of PhS^-, the ratio $k(Br)/k(Cl)$ for the *Z*- and *E*-isomers is in the range 1.7–2.0, while in the reaction of the *Z*-isomer with CH_3O^- a greater "element effect" is observed (approximately 47); for the *E*-isomer, the effect is less than unity (0.64). The high value for the *Z*-isomer is associated with the contribution by the $E\text{-}Ad_N$ mechanism, which has been confirmed by the positive activation entropy ($\Delta S^{\neq} > 0$) [78] and the ratio $k(Br)/k(Cl) < 1$ for the *E*-isomer is evidently caused by the "symbiosis effect" mentioned above. In the reaction of $E\text{-}PhCOCH=CHX$ with amines,[134] the "element effect" is hardly manifested [$k(Br)/k(Cl) = 0.88$–1.23].

The decrease of the ratio $k(Br)/k(Cl)$ with increase of solvent polarity has been demonstrated for the reaction of $p\text{-}O_2NC_6H_4SO_2CH=CHBr$ with piperidine[97] (by comparison with data for the chloro-derivative[135,136]). Hence, it was concluded that in less polar solvents, where the "element effect" is a maximum, the transition state is more "product-like", i.e. it includes a more extended C–Hal bond.

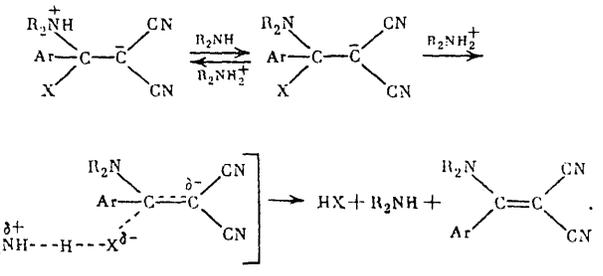
The influence of the leaving group on the substitution of species exhibiting nucleofugacity other than halogen atoms has been investigated.[101,137–139] The ratios $k(Br)/k(Cl)$ [reaction (8)], $k(OSO_2CH_3)/k(Cl)$ [reaction (9)], and $k(OSO_2C_6H_4Br\text{-}p)/k(OSO_2C_6H_4CH_3\text{-}p$ [reaction (10)] were measured:[101]

$$(CH_3OCO)_2C=CHX + ArNH_2 \rightarrow (CH_3OCO)_2C=CHNHAr + HX; \quad (8)$$
X=Cl, Br;

$$(NC)_2C=CHX + p\text{-}NCC_6H_4NH_2 \rightarrow (NC)_2C=CHNHC_6H_4CN\text{-}p + HX; \quad (9)$$
X=Cl, OSO_2CH_3;

$$(C_2H_5OCO)_2C=CXC_6H_4NO\text{-}p + HN\langle\rangle Z \rightarrow (C_2H_5OCO)_2C=C\langle N\langle\rangle Z \text{ (with } C_6H_4NO_2\text{-}p\text{)}; \quad (10)$$
X=$OSO_2C_6H_4CH_3\text{-}p$, $OSO_2C_6H_4Br\text{-}p$; Z=O, CH_2.

The observed ratios [$k(Br)/k(Cl) \cong 1$, $k(OSO_2CH_2)/k(Cl) = 1$, and $k(OSO_2C_6H_4Br\text{-}p)/k(OSO_2C_6H_4CH_3\text{-}p) = 1.63$–$1.90$] show that the rate-limiting step in the process is the formation of a bond with the nucleophile without the participation of the leaving group and the ratio $k(OSO_2C_6H_4Br\text{-}p)/k(OSO_2C_6H_4.CH_3\text{-}p) > 1$ is caused by the greater electronegativity of the β-carbon atom owing to the more electron-accepting character of the Br atom compared with the CH_3 group. By varying the strength of the activating group and by introducing a bulky substituent in the β-position, it is possible to alter the ratio of the rates of the individual elementary stages, so that k_{exp} will include the rate of dissociation of the bond with the leaving group. Indeed, the following ratios hold for the reaction of $(C_2H_5OCO)_2C=CXC_6H_4NO_2\text{-}p$ with various nucleophiles in different solvents: $k(OSO_2CH_3)/k(Cl) = 10$–60, $k(OSO_2C_6H_4CH_3\text{-}p)/k(Cl) = 10$–$30$, and $k(OSO_2C_6H_4Br\text{-}p)/k(OSO_2C_6H_4CH_3\text{-}p) = 1.56$ to 2.85, while $k(Br)/k(Cl) = 0.67$–1.32 has been obtained for the reaction of $ArANH_2$ with $(NC)_2C=CXC_6H_4NO_2\text{-}p$ and $E\text{-}CH_3OCOC(CN)=CHX$.[137] The dependence on the nature of the leaving group has been observed in the substitution groups with weak nucleofugacity (F, CN, C_2H_5O).[138] The fact that the above groups do indeed show "poor" nucleofugacity has been confirmed by the base catalytic effect—the zwitter-ion formed initially reacts with a second amine molecule, abstracting a proton and forming a carbanion, which reacts in its turn with a third amine molecule:



The following sequence in terms of nucleofugacity has been observed: $C_2H_5O(1) \ll CN(10^4) \ll F(10^7)$,[138] which is close to the sequence based on the variation of the pK_a: $C_2H_5OH(16) > HCN(9.3) > HF(3.45)$. In the course of the continuation of these studies, the substitution of the CF_3CH_2O group in 1,1-dicyano-2-(*p*-dimethylaminophenyl)-2-trifluoroethoxyethylene was investigated[139] and it was shown that the rate of substitution of the CF_3CH_2O group is higher by 2–3 orders of magnitude than the rate of substitution of the C_2H_5O group and the ratio $k(CF_3CH_2O)/k(C_2H_5O)$ for the amine-catalysed process is greater by an order of magnitude than for the uncatalysed process. This can be explained by taking into account data[130,131,140] for the dependence of the relative contributions of the catalytic and non-catalytic pathways on the nucleofugacity of the leaving group; evidently, the better the leaving group, the less need for the electrophilic cooperation by the solvent or the conjugate acid of the nucleophile.

One must note that the causes of the catalysis of S_NVin reactions by amines may be various. It was believed for a long time[130,131,137,138] that the zwitter-ion formed in the first stage is rapidly and reversibly deprotonated to a carbanion, which then splits off the leaving group and this last stage is in fact catalysed by the amine. However, it has been shown[141,142] (the same idea has been put forward by Rappoport and Peled[139]) that, under certain conditions, in particular in the presence of strong steric hindrance, the rate-limiting stage may be the deprotonation of the zwitter-ion. Thus, in contrast to the expected diffusion-controlled values of the rate constant (10^8–10^9 s^{-1}), values up to 10^3 s^{-1} were obtained, i.e. smaller by a factor of approximately 10^6.[141] In many cases this permits a critical revision of the causes of the catalysis of S_NVin reactions by amines with participation of "poor" leaving groups.[142]

In the only study where the leaving group was varied for a series of substituents (in the sense that it can be described by a single set of σ constants) the substitution of the ArO group in *E*-4-aryloxybut-3-en-2-zones by various *N*- and *S*-nucleophiles was investigated.[143] The reaction proceeds via the direct substitution mechanism and the rate

is determined by the stage involving the addition of the nucleophile to the double bond. The reaction rate increases with enhancement of the electron-accepting strength of the substituent in the benzene ring, as the nucleofugacity of the leaving group increases, but the Hammett constants ρ (the σ constants were calculated from data for the ionisation of the corresponding phenols) are very low: 0.11 for the reaction with aminoethanol and 0.14 for the reaction with *N*-acetylcysteine, which also confirms the low degree of dissociation of the ArO...C bond in the transition state.

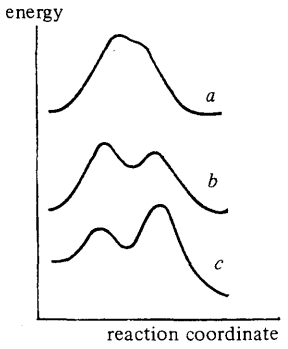


Figure 6. The energy profile for nucleophilic vinyl substitution reactions: *a*) one-step mechanism; *b*) two-step mechanism in which attack by the nucleophile is the rate-limiting stage; *c*) two-step mechanism in which the abstraction of the leaving group is the rate-limiting step.

The concept of a variable transition state in S_NVin reactions has been recently put forward and elaborated in detail.[26,144] It is suggested that the position of the transition state and also the presence and structure of the possible intermediates depend greatly on a series of external and internal factors, in the first place on the strength of the activating groups and on the nucleofugacity of the leaving group. We shall examine the overall variation of the "element effect" as a function of the stability of the carbanion. In the limiting case where the carbanion is extremely unstable, it can degenerate into a transition state, and the substitution can proceed as a synchronous process with a high "element effect" $k(Br)/k(Cl) > 1$ (Fig.6, curve *a*). With increase of the stability of the carbanion, so long as $k_{exp} = k_1$ the "element effect" should be approximately 1 (Fig.6, curve *b*). Finally, for very stable carbanions, where $k_{exp} = (k_1/k_{-1})k_2$, the "element effect" should again increase due to k_2 (Fig.6, curve c). In order to achieve the last situation, a study has been made[145] of the substitution of a halogen in the most activated system among those investigated kinetically hitherto, namely tricyanovinyl halides. However, the value of the "element effect" $k(Br)/k(Cl)$ found amounted to only 2.4, i.e. did not exceed the usual values. The authors explain the result[145] by the earlier transition state in the reaction involving the abstraction of the leaving group from the carbanion (see, for example, Thomas and Stirling[146]) and concluded that the "element effect" precludes the identification of the rate-determining state—the formation of the carbanion or the abstraction of the leaving group from the latter.

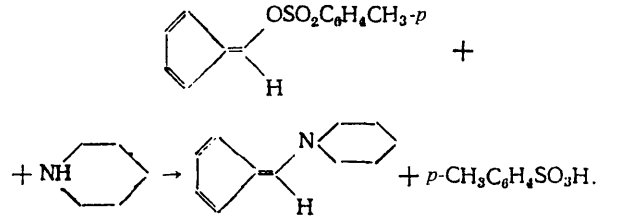
4. The Influence of the Solvent

The influence of the solvent on the rates and mechanism of S_NVin reactions has been investigated mainly for reactions with amines. A single study,[123] permitting a comparison of the rates of the reactions of certain β-halogenovinyl ketones with piperidine and the azide ion in ethanol and DMF, is quoted in Rappoport's review.[1] Only a slight acceleration (and sometimes even a retardation) of the reaction with piperidine in DMF compared with ethanol has been observed, the acceleration of the reaction with N_3^- being much greater (by a factor of 4–40). However, a dipolar aprotic solvent does not always accelerate the reaction—the rate of reaction of carbanions with αββ-trifluorostyrene in aprotic dipolar solvents increases as ethanol is added.[147] In this case the solvent influences mainly the solvation of the transition state in which a partial negative charge is transferred largely to fluorine atoms.

The influence of the solvent on S_NVin reactions involving amines has been studied systematically in a series of investigations.[92,95,97,135,136,148–150] Thus the change from polar solvents (*o*-dichlorobenzene, nitrobenzene) to non-polar solvents (n-alkanes) diminishes the rate of reaction of β-halogenovinyl ketones;[92] it is of interest that this retardation is much smaller (by a factor of 4–6) for primary and secondary amines than for tertiary amines (by a factor of 10^3). This indicates an insignificant increase of the polarity of the transition state compared with the initial state for amines containing a proton in the NH group and the sharp increase of its polarity in the absence of such a proton. The polarity of the zwitter-ion is probably reduced for primary and secondary amines owing to the formation of a hydrogen bond and ultimately the protonation of the carbanionic centre (5); hence the reason for the very sharp difference between the sensitivities to changes in solvent polarity. A monotonic increase in the rates of reaction of β-halogenovinyl sulphones[97,135] and β-bromo-*p*-nitrostyrene[148] with piperidine with increase of the dielectric constant ε has been observed for solvents whose interaction with the reactants is of the type of non-specific solvation. In addition the "element effect" diminishes steadily with increase of ε (see Section IV).

In their analysis of the interaction between substrate structure and polarity of the medium, Litvinenko et al.[136] obtained a non-additive equation reflecting the decrease of the sensitivity to solvent polarity with increasing electrophilicity of the substrate.

A varied series of solvents, including non-polar, polar, aprotic, and dipolar aprotic solvents, has been investigated for the reaction of β-halogenovinylnitrofuran with piperidine.[95,149,150] Naturally it was not possible to isolate any one parameter characterising the influence of solvents of such different nature, but, bearing in mind the possibility of the formation of solvation complexes with different structures, the influence of the acidity in the case of alcohols, the polarisability, the formation of hydrogen bonds with the amine, etc., the authors[95] explained successfully all the observed changes. The influence of solvents on the rate of reaction of piperidine with 6-(toluene-*n*-sulphonyloxy)-fulvene has been accounted for analogously:[151]

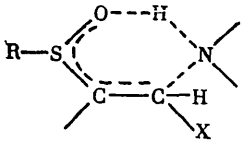


The acceleration of the reaction in the series of alcohols $CH_3OH < C_2H_5OH <$ iso-C_3H_7OH is associated with the decrease of the acidity of the alcohol and hence with the increase of the activity of the amine, while the acceleration of the reaction in acetonitrile compared with chloroform is due to the increase of solvent polarity. Comparison of the data of two investigations by Rappoport and Ta-Shma[130,131] shows that the replacement of acetonitrile as the solvent[130] by alcohols[131] in the reactions of 1,1-dicyano-2-(*p*-dimethylaminophenyl)-2-halogenoethylenes with anilines leads to a change in the reaction order with respect to amines. Whereas in acetonitrile the reaction is of second order with respect to the amines where Hal = F and of "almost" first order for Hal = Cl, in alcohols the reaction order with respect to the amine decreases and is more than unity but less than two for fluorine and is unity for chlorine. Since the amine participates in the stage involving the abstraction of the leaving group, evidently an increase in the acidity of the solvent, which competes with the amine at this stage, reduces the order of the reaction with respect to the amine (an analogous decrease of the order with respect to the amine with increasing "proton-donating capacity" of the medium had been known previously for S_NAr reactions[152]). On passing to "poor" leaving groups in the same substrate, the trend persists—the amine-catalysed process involving the abstraction of the leaving group predominates in acetonitrile and the non-catalysed process becomes the main reaction pathway in alcohols.[138]

As was to be expected, an increase in the polarity of the medium (the change from the composition $CCl_4 : CH_3CN = 1:1$ to $CCl_4 : CH_3CN = 1:3$) accelerates the reaction. The rate of reaction in various alcohols is determined by the relative acidities and is a maximum for the least acid alcohol.[138] The substitution of various leaving groups by amines in $(C_2H_5OCO)_2C=CXC_6H_4NO_2$ has been investigated in acetonitrile, THF, and ethanol. In most cases the rate of substitution increases in the sequence $C_2H_5OH <$ THF < CH_3CN. The changes are small and for the THF/CH_3CN pair can be explained by the changes in the polarity of the medium. The low rate of reaction in ethanol is due to the solvation of the ground state as a result of the formation of the hydrogen bond with amine, which is reflected also in the activation parameters of the reaction. $\Delta H^{\neq}$ increases owing to the necessity to dissociate the intermolecular hydrogen bond and $\Delta S^{\neq}$ becomes less negative, since such dissociation entails the "unfreezing" of some of the degrees of freedom.[137] The reactivity changes analogously in the series THF, CH_3CN, DMSO.[139] In all three media electrophilic assistance with the abstraction of the leaving group is lacking and the observed effects are associated with the change in the dielectric constant of the medium.

The accelerating effect of an aprotic dipolar solvent in the reactions of nucleophile-anions should be much stronger than for amines. Indeed, the substitution of the halogen atom in β-halogeno-*p*-nitrostyrenes by sodium methoxide in methanol is accelerated by a factor of 10^4–10^6 after the addition of 85% DMSO. The increase of the DMSO content then entails an increase of the contribution of the HX elimination step.[153]

The transition state in the reactions of activated vinyl halides with amines is either an open-chain zwitter-ion or, in the case of hydrogen bond acceptor groups (CO, SO etc.), a cyclic structure of the type



The transition state of the open-chain zwitter-ionic type is more polar than the initial reactant, while the formation of a hydrogen bond can diminish the polarity of the system. Hence one may expect that in polar media, where the open-chain zwitter-ionic structure is more favourable, the rate of reaction will increase with increase of ε, while in media of low polarity it will decrease. This has not been observed for β-halogenovinyl ketones[92] but for β-halogenovinyl sulphoxides the cyclic structure is more favourable in media with low and moderate polarity, because the SO group is a better hydrogen bond acceptor than the CO group.[154] As a consequence, the rate of the reaction

$$E\text{-}p\text{-}O_2NC_6H_4SO{-}CH{=}CHBr + C_5H_{10}NH \rightarrow E\text{-}p\text{-}O_2NC_6H_4SO{-}CH{=}CH{-}NC_5H_{10} + C_5H_{10}\overset{+}{N}H_2Br^-$$

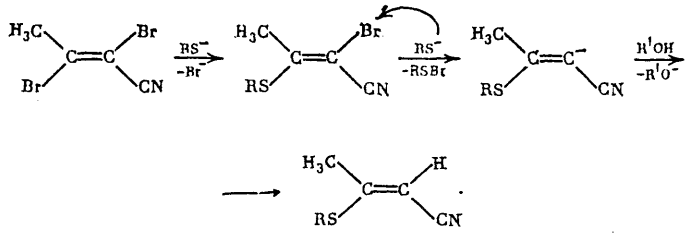
in aprotic solvents falls with increase of ε from 2 to 9 and then increases as ε increases further to 37.5.[154]

V. REDUCTION AND REARRANGEMENT PROCESSES IN NUCLEOPHILIC VINYL SUBSTITUTION REACTIONS

All the reactions examined above are initiated by the attack of the nucleophile either on the β-carbon atom [mechanism (2)] or on the α-hydrogen atom [mechanism (3)]. However, in the molecules of vinyl halides, which are the most typical substrates in S_NVin reactions, yet another centre potentially susceptible to attack by the nucleophile is present, namely the halogen atom. The ease of halogenophilic substitution increases with increasing electronegativity of the carbon atom linked to the halogen, i.e. in the sequence $C_{sp^3} < C_{sp^2} < C_{sp}$. Thus halogenophilic substitution in halogenoacetylenes is encountered fairly frequently,[155] while in the series of saturated compounds it is necessary that several electron-accepting groups should be present at the C–Hal bond.[156,157] Vinyl halides occupy an intermediate position and in the absence of an electron-accepting group in the α-position halogenophilic substitution usually does not occur. In the presence of two vicinal halogen atoms at the double bond, the halogen atom occupying the α-position which is geminal in relation to the activating group has a greater tendency to undergo halogenophilic attack. In the reaction of 3-halogeno-2-butenonitriles with thiolates the halogen atom is substituted,[44,49,53] while 2,3-dihalogeno-2-butenonitriles give rise to either disubstitution products or products of substitution with reduction depending on the nature of the halogen:[158]

$$CH_3CX{=}CXCN + RS^- \rightarrow \begin{cases} CH_2C(SR){=}C(SR)CN & (X{=}Cl); \\ CH_3C(SR){=}CHCN & (X{=}Br). \end{cases}$$

2,3-Dihalogenocrotonate esters $CH_3CX{=}CXCOOC_2H_5$ react analogously.[159] The reduction product is formed in the second reaction as a result of the halogenophilic attack on the bromine atom in the α-position:



When the halogen is substituted by the dimethylcuprate anion in β-halogenostyrenes[144] or in β-bromoacrylic acid derivatives,[40] reduction products are also formed, probably as a result of the halogenophilic attack by $(CH_3)_2Cu^-$. The monohalogenovinyl sulphones $PhSO_2CH=CHBr$ and $PhSO_2CH=CHI$ are formed as cyclic products in the reaction involving the substitution of bromine by iodine in the ββ-dibromovinyl sulphone $PhSO_2CH=CBr_2$ on treatment with sodium iodide.[160] The higher content of β-iodovinyl sulphone compared with β-bromovinyl sulphone is consistent with the relative ease of the halogenophilic attack on the iodine and bromine atoms.

Until recently, the available information about the rearrangements in the S_NVin reactions was restricted to double bond migration reactions in the presence of the CH_3 group in the β-position:[49,50,53]

$$Y-CR=CX-CH_3 + NuH \xrightarrow[-HX]{} Y-CR=C(Nu)-CH_3 + Y-CHR-C(Nu)=CH_2, \quad (11)$$

or in the presence of the methylene bridge between the activating group and the double bond (the reverse reaction):[52,109]

$$Y-CH_2-CX=CH_2 + NuH \xrightarrow[-HX]{} Y-CH_2-C(Nu)=CH_2 + Y-CH=C(Nu)-CH_3. \quad (12)$$

The mechanism of both rearrangements consists of the formation of the intermediate allene $Y-CR=C=CH_2$, common to reactions (11) and (12), which can subsequently give rise to both αβ- and βγ-adducts. The product $Y-CHR-C(Nu)=CH_2$ is formed under the conditions of kinetic control owing to the greater stability of the anion $Y-\bar{C}R-C(Nu)=CH_2$ compared with $Y-CR=C(Nu)-\bar{C}H_2$, while the product $Y-CR=C(Nu)CH_3$ is formed under the conditions of thermodynamic control (as a consequence of the conjugation of its double bond with the electron-accepting group).

A new type of rearrangement in nucleophilic vinyl substitution reactions has been discovered recently:[161,162]

$$PhSO_2CH=CX_2 \xrightarrow{\text{KF.18-crown-6}} PhSO_2(X)C=C(H)X; \quad (13)$$

X = Cl, Br.

In reaction (13) the rearrangement is not accompanied by substitution, but in other cases both processes take place:[132,162,163]

$$RSO_2CH=CCl_2 \xrightarrow[-Cl^-]{I^-} RSO_2CI=CHCl \begin{cases} \xrightarrow{\text{KF.18-crown-6}} RSO_2CI=CHF; \\ \xrightarrow{CH_3E,\ CH_3OH} RSO_2CI=CHOCH_3. \end{cases} \quad (14)$$

A rearrangement with substitution under the influence of amines takes place in compounds with similar structures:[164]

$$E\text{-}RSO_2CCl=CClSO_2R + R'NH_2 \longrightarrow (RSO_2)_2C=C(NHR')_2 + \overset{+}{R}NH_3Cl^-. \quad (15)$$

We may note that in 1977 in a review on 1,2-anisotropic rearrangements this type of rearrangement involving ethylenes was classified as "unknown but susceptible to observation" and the author expressed surprise that it had not yet been discovered.[165]

The mechanism of the rearrangement has not been fully elucidated; the first stage of reaction (13) is evidently the deprotonation of dihalogenovinyl sulphone, which is confirmed by the occurrence of the rearrangement under the influence of bases other than F^-.[162] The 1,2-migration of the halogen may take place in the vinyl anion formed, leading to the *Z*-isomers of the reaction products on subsequent protonation. In reactions (14) and (15) the vinyl anion can be formed as a result of the halogenophilic attack on the chlorine atom, although the authors[164] have not discussed the mechanism of the observed rearrangement. The prohibition of the 1,2-migration in anions by orbital symmetry is in this case probably proved owing to the contribution by a structure of the carbene type $RSO_2-\ddot{C}=\bar{C}X_2$, which creates an electron deficiency at a formally carbanionic centre—the α-carbon atom. We may note that the contribution of structures of the carbene type is a characteristic feature of vinyl anions and vinyl cations, in contrast to their saturated analogues; it had been considered earlier in the case of vinyl cations in order to account for their anomalous behaviour in rearrangements.[166]

The hypothesis of the 1,2-migration of the nucleophilic group in the anion was put forward[167] to explain the anomalous mode of the elimination reaction:

$$PhCH(OCH_3)-CH_2SO_2R \xrightarrow[-H^+]{} PhCH(OCH_3)-\bar{C}HSO_2R \rightleftarrows \rightleftarrows Ph\bar{C}H-CH(OCH_3)-SO_2R \xrightarrow[-RSO_2^-]{} PhCH=CHOCH_3.$$

The alternative mechanism—the elimination of HX and addition with inversion of the configuration—is unlikely in reaction (13), because the formation of 1,2-dihalogenovinyl sulphones by the addition of HX to the acetylenes $RSO_2C\equiv CX$ conflicts with the rules governing the regioselectivity in addition to activated acetylenes.[155]

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Thus the study of the nucleophilic vinyl substitution reactions, which had not been hitherto regarded as an independent class of reactions in any of the modern textbooks of the theoretical principles of organic chemistry (apart from the fundamental monograph by C.K.Ingold, who devoted several pages to them), nowadays constitutes an entirely independent field of study characterised by interesting reactions, specific features, and significant differences from related types of reactions. In assessing the prospects for the development of the research in this field, one may expect that the most interesting results will be obtained in the study of the influence of the leaving group (previously restricted as a rule to halogen atoms), the influence of the solvent (it has been hardly studied for reactions with nucleophile-anions), the competition course halogenophilic processes, and finally, new rearrangements accompanying the nucleophilic vinyl substitution reactions.

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