Figure 8. Concerted mechanism of the oxidation of acrolein to acrylic acid on a cobalt complex.

the insertion of oxygen into the C–H bond of the aldehyde group.

Conclusion

Results presented in this account show that the quantum-chemical description of intermediate complexes formed in the course of the catalytic reactions may supply valuable information concerning catalysis.

We have found modification of the reactivity of different bonds of the reacting molecule as the result of its interaction with the active center of the catalyst. This may contribute to an important degree to the understanding of the mechanism of the catalytic reaction and to identification of factors influencing its selectivity.

At present, exact discussion of the interaction of an adsorbed molecule with the group of atoms of the solid forming the active center is not yet possible, and many approximations must be introduced. The model chosen and the quantum-chemical method used depends on the particular problem to be solved. Advantages and limitations of various quantum chemical methods usually used to solve catalytic problems are summarized in Table III.

It may be hoped that with the development of quantum chemistry on one hand, and with further improvement in the knowledge of the mechanism of elementary acts in catalysis on the other hand, it will become possible to give a full description of the interactions between the reacting molecules and the catalyst as a basis for the development of the theory of catalysis.
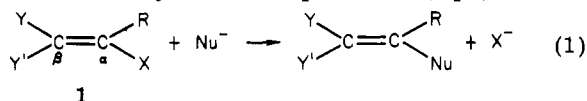
Nucleophilic Vinylic Substitution. A Single- or a Multi-Step Process?

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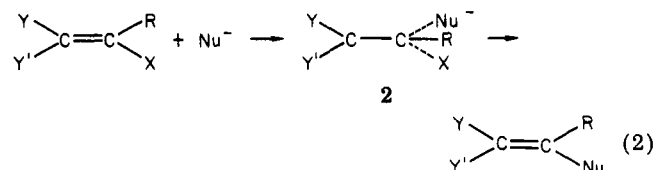
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A vinylic system substituted by the leaving group X and the β-substituents Y and Y′ (**1**) is an ambident electrophile, and many mechanistic routes are available for substitution by the nucleophile Nu⁻ (eq 1).[1] Two

$$\underset{\underset{\beta}{Y'}}{\overset{Y}{>}}C=C\underset{\underset{\alpha}{X}}{\overset{R}{<}} + Nu^- \longrightarrow \underset{Y'}{\overset{Y}{>}}C=C\underset{Nu}{\overset{R}{<}} + X^- \quad (1)$$

1

routes, one involving nucleophilic attack on C_α,[1-3] the other cleavage of the C–X bond to form a vinyl cation,[4] are the formal analogues of familiar aliphatic substitution mechanisms. Others involve α,α, α,β, and α,β' elimination–addition routes via a carbene, an alkyne, or an allene, respectively,[1] radical routes via atom[5a] or electron transfer,[5b] initial prototropy or two S_N2' routes,[1] electrophilic addition–elimination,[5c] and initial attack on X.[5d] Most of these routes have been previously reviewed.[1-4]

The purpose of this Account is to discuss a question common to substitutions at many unsaturated centers. Is the bimolecular substitution which involves nucleo-

philic attack on C_α a single- or a multi-step process? The terms "addition–elimination" for the multi-step route,[1] "synchronous addition–elimination"[6] for the concerted process, and "direct substitution"[2] have been used. I will use the descriptive terms "single-step process" when **2** (eq 2) is only a transition state and

$$\underset{Y'}{\overset{Y}{>}}C=C\underset{X}{\overset{R}{<}} + Nu^- \longrightarrow \underset{Y'}{\overset{Y}{>}}C-C\underset{X}{\overset{Nu}{<}}\overset{-}{R} \longrightarrow$$

2

$$\underset{Y'}{\overset{Y}{>}}C=C\underset{Nu}{\overset{R}{<}} \quad (2)$$

"multi-step process" when **2** is an intermediate. Since some facts are apparently contradictory, opinions on this question have been divided in recent years.[1-3,6,7] I will first present the evidence adduced in support of

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Table I
Some Substitution Reactions Giving >98% Retention for Both E and Z Isomers

reaction	ref	reaction	ref
$PhCH=CHBr + Ph_2P^-$ (or Ph_2As^-)	8	$2,4-(O_2N)_2C_6H_3CH=CHBr + TolS^-$	11
$p-O_2NC_6H_4CH=CHBr + PhS^-$	11	$m-O_2NC_6H_4SOCH=CHBr + p-O_2NC_6H_4S^-$	14
$ClCH=CHCN + EtS^-$	12	$ArSO_2CH=CHCl + N_3^-$ (or MeO^-)	15
$ClCH=CHCO_2Et + \underset{CH_2-CH_2}{\overset{NH}{\diagup\diagdown}}$	13	$p-O_2NC_6H_4COCH=CHCl + p-O_2NC_6H_4SO_2^-$	16

Scheme I
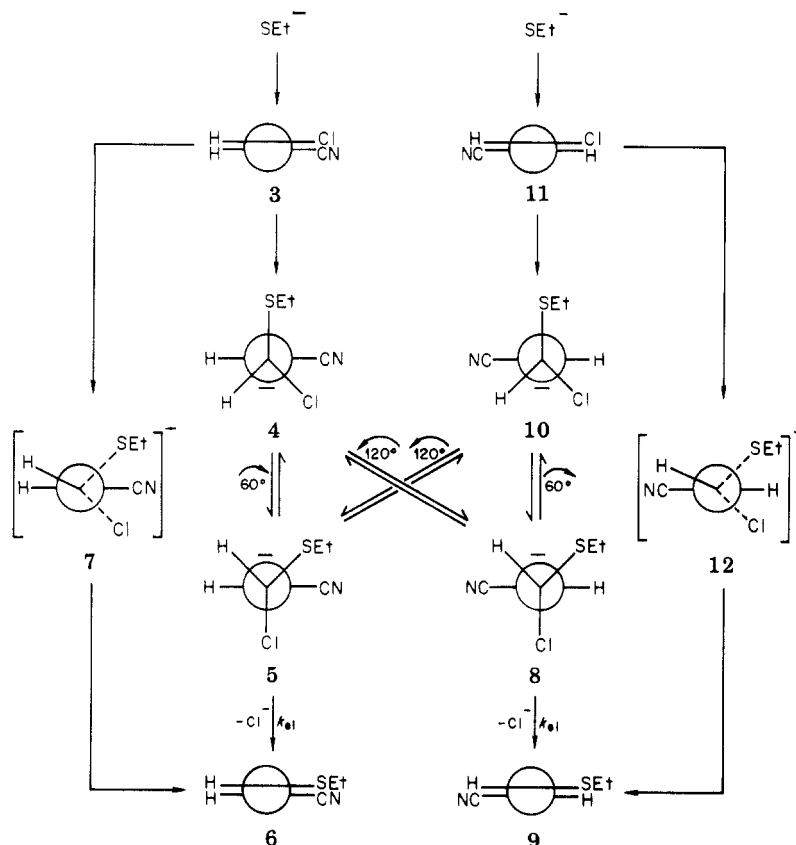
each view and then present my approach to the problem.

Arguments for a Single-Step Process. A central and frequently cited argument for the single-step route is the stereochemistry.[1-3,6-16] Nearly complete retention of configuration was observed in the substitution of many vinyl chlorides and bromides. These range from unactivated β-bromostyrenes[8-10] to activated β-chlorovinyl ketones[16] and nitriles,[17] regardless of the initial

configuration of the nucleophile. (Electron-withdrawing β substituents are "activating"; they accelerate substitution.) Several examples of >98% retention are given in Table I. In terms of the multi-step mechanism, such results are discussed with attention to the conformations shown in Scheme I, illustrated for ethylthiodechlorination of β-chloroacrylonitriles 3 and 11 via planar carbanion intermediates. A similar analysis is possible for tetrahedral carbanion intermediates.[3]

In the multi-step route, perpendicular attack on the Z isomer 3 gives carbanion 4 which by 60° clockwise rotation gives conformer 5 which leads to retained product 6 by Cl^- expulsion (k_{el}). A 120° anticlockwise rotation gives 8, which will give inverted product 9. A 180° rotation to 10 or a rotation faster than leaving group expulsion will give stereoconvergence, i.e., formation of an identical mixture of E and Z products (6 and 9) from both isomeric precursors. Hence, two severe prerequisites for retention via the multi-step route are a rotational barrier (i.e., $k_{rot}(60°) \gg k_{rot}(120°)$) and leaving group expulsion faster than internal rotation ($k_{el} \gg k_{rot}(120°)$). The alternative single-step mechanism

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Table II
Some Element Effects in Vinylic Substitution

substrate	Nu⁻/solvent	k_{Br}/k_{Cl}	Nu⁻/solvent	k_{Br}/k_{Cl}	Nu⁻/solvent	k_F/k_{Cl}	ref
(E)-HCX=CHCOC₆H₄OMe-p	MeO⁻/MeOH	0.64	PhS⁻/MeOH	2.05			19
(Z)-HCX=C(Me)COPh					C₅H₁₀NH/EtOH	204	20
(E)-HCX=C(Me)SO₂C₆H₄NO₂-p	MeO⁻/MeOH	0.93	PhS⁻/MeOH	2.6			21
(Z)-MeCX=CHCO₂Et	EtO⁻/EtOH	17.4ᵃ	EtS⁻/EtOH	1.59	EtS⁻/EtOH	10.5	6
(E)-MeCX=CHCN	t-BuS⁻/EtOH	5.05ᵃ	EtS⁻/EtOH	6.7	EtS⁻/EtOH	12.8	22
(E)-HCX=C(Ph)C₆H₄NO₂-p	Cl⁻/DMFᵇ	5.09	TolS⁻/DMFᵇ	0.58			23
(E)-HCX=CHC₆H₄NO₂-p	MeO⁻/MeOH	0.64	PhS⁻/MeOH	2.10	MeO⁻/MeOH	288	11a, 24
					PhS⁻/MeOH	11	
(Z)-HCX=C(Ph)C₆H₄OMe-p	EtO⁻/EtOH	1.4			TolS⁻/DMFᵇ	4.2	25

ᵃ Probably an addition–elimination reaction. ᵇ DMF = dimethylformamide; Tol = 4-methylphenyl.

Scheme II
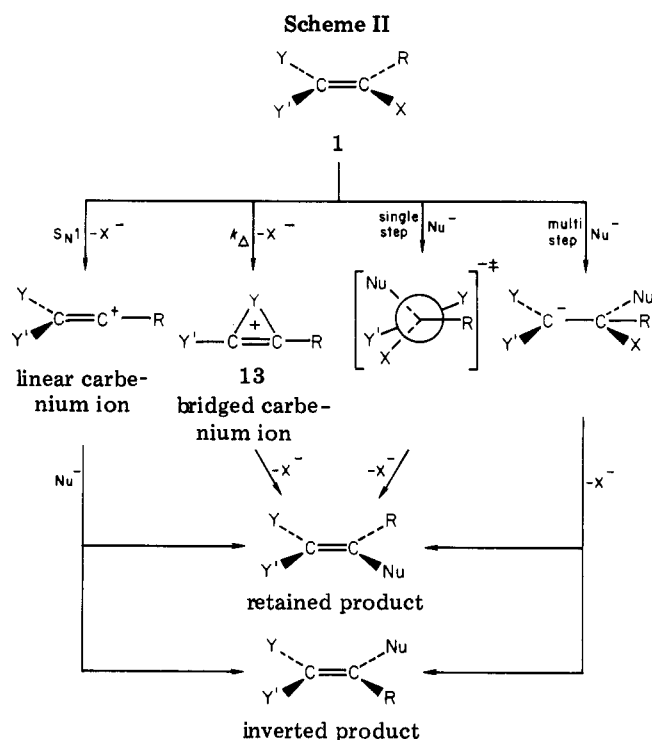
seems more attractive since it would give retained products (6 from 3, 9 from 11) via transition states 7 and 12 when attack, rotation, and expulsion were concerted, and it is free of the above constraints.

MO calculations suggest that retention is the stereochemical outcome for the single-step process.[7b,18] Finally, the reactivity order RF < RCl < RBr expected for such a process was recently observed for substitution in several slightly activated systems.[9,10]

Arguments for a Multi-Step Process. Several arguments support a multi-step substitution. First, there are analogies with the SₙAr reaction and the observation of carbanionic adducts of nucleophiles such as OH⁻, MeO⁻ and CN⁻ to activated olefins. However, the observation of carbanions does not ensure their intermediacy when a leaving group is present. Vinylic substitutions manifest several types of behavior that support the SₙAr mechanism of aromatic nucleophilic substitution, but they also benefit from the stereochemical probe which is not available for substitution at aromatic sites.

In vinylic substitution,[19–25] as in SₙAr, the "element effects", i.e., the relative reactivities of vinyl bromides, chlorides, and fluorides, are typically $k_{Br}/k_{Cl} \sim 1$ and $k_F/k_{Cl} \gg 1$ (Table II). These are consistent with a rate-determining nucleophilic attack without C–X bond cleavage, but with acceleration by electron withdrawal by the highly electronegative fluorine atom. The difference between the ratios for soft (RS⁻) and hard nucleophiles (RO⁻) is as expected.

Third, stereospecificity in the substitution reactions of vinyl chlorides is not complete. Thus, (E)-MeC(I)-=C(Me)CO₂Et gives 87% of the E thioether and 13% of the Z thioether on reaction with PhS⁻,[26] and a lower specificity is shown in eq 3.[27] For systems substituted
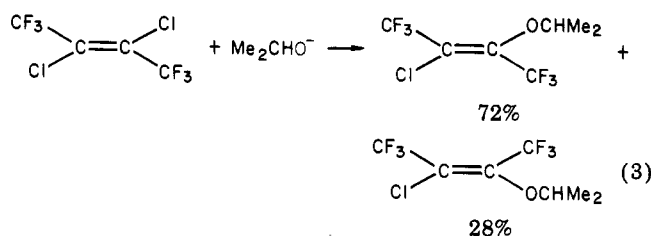
by sluggish leaving groups, the stereochemistry is partial or complete stereoconvergence. These results argue for the intermediacy of carbanions where $k_{rot} \geq k_{el}$.

Reconciliation of Contradictions: A Variable Transition State for Nucleophilic Vinylic Substitution. I now present a hypothesis, which was previously mentioned but not discussed in detail,[10] that the transition state in nucleophilic vinylic substitution is variable. Its position and the occurrence and the nature of possible intermediates depend on the nucleophile, on the solvent, and on structural features of the substrate, especially Y, Y', and X. Scheme II presents four extreme transition states and intermediates and the stereochemical consequences. On one extreme is the Sₙ1 route via a linear vinyl cation. Rate-determining unassisted C–X bond cleavage and

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bond formation to Nu⁻ take place in the plane of the substituents. This will predominate for electron-donating R, Y, and Y′ and will show element effects $k_{Br}/k_{Cl} \gg 1$ and $k_F/k_{Cl} \ll 1$. Stereoconvergence is predicted if the intermediate is a free vinyl cation and excess inversion when it is an ion pair. This route has been reviewed.[4] Neither it nor the observed changeover from it to the bimolecular route on changing the nucleophile[28] will now be discussed.

On the other side of the mechanistic spectrum are bimolecular routes which predominate for electron-withdrawing substituents Y and Y′. Nucleophilic attack involves the π^* orbital and is perpendicular to the plane of the double bond. In the extreme case, long-lived carbanions are formed and the stereochemistry is stereoconvergence. Since the extents of bond formation and cleavage should change continuously, concerted in-plane nucleophilic attack from the rear leading to inversion and perpendicular attack leading to retention are also feasible. Whereas the latter route is common (Table I), inversion has never been observed for simple systems, and calculations show that in-plane attack of hydride ion on ethylene is energetically much more costly than perpendicular attack.[29] Nevertheless this route is realized in neighboring group participation which involves two in-plane inversions during the solvolysis of (*E*)-3-phenyl-2-butenyl triflate[30] or of compounds 14 (eq 4).[31] The ring-opening reactions of the

14

(4)
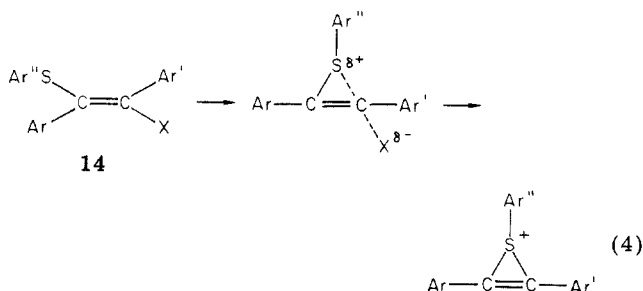
related bridged ions **13** such as the thiirenium ion **13a**[32] proceed with inversion (eq 5) and probably involve an


13a
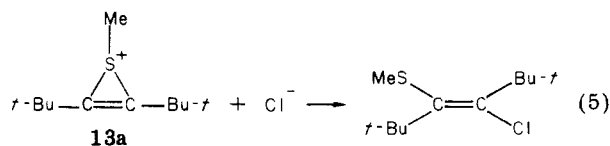
in-plane attack via a planar tetracoordinate carbon in the transition state.[33]

In the region of perpendicular nucleophilic attack, both the single- and the multi-step routes are feasible. When Y, Y′ are very strongly electron withdrawing, the extensive charge delocalization will reduce the rate constant for the expulsion of X (k_{el}). For poor leaving groups, C–X bond cleavage may lag behind C–Nu bond formation; one then has a multi-step substitution. When the electron-withdrawing abilities of Y and Y′ decrease or the leaving ability of X increases, k_{el} will

increase simultaneously with the decrease of k_1 until they merge to a single-step process. The problem is to identify experimentally the range of operation of each route as a function of X, Y, and Y′.

Our approach involves six steps: (a) division of the systems according to the stability of the derived carbanions; (b) estimation of k_{el} from related processes; (c) search for the multi-step route for poor leaving groups, e.g., fluorine, with which it is most likely to operate; (d) search for the multi-step route for systems substituted by good leaving groups, e.g., Cl, albeit the carbanions are expected to be very short lived; (e) calculations on the feasibility of retention by both routes; and (f) search for a single-step process.

Classification of Systems According to Carbanion Stability. Our systems may be divided on the basis of the extent of resonative charge dispersal by Y and Y′. The better they accommodate negative charge, the longer the lifetimes of the carbanions and the lower the k_{el} values. The stabilities of the carbanion adducts of OH⁻ (eq 6) are shown by the equilibrium constants, K_L,
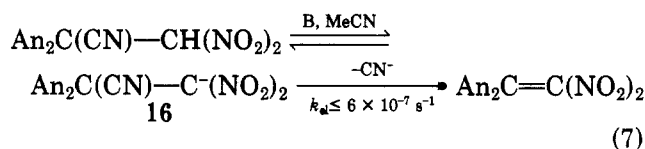
$$RR'C{=}CYY' + OH^- \underset{99\% \text{ MeOH}}{\overset{K_L}{\rightleftharpoons}} RR'C(OH){-}C^-YY'$$
15
(6)
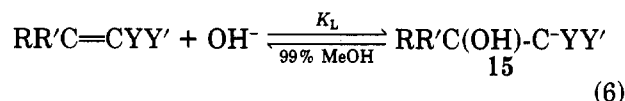
determined by Schuster et al.[34] However, these are available only when Y = Y′ = CN, COR′, CO₂R″ or CONHR″. Other measures are the log k values for nucleophilic attack of amines on compounds CH₂=C-HY[35] which are correlated with the pK_a's of the corresponding acids CH₃Y. Since the pK_a's of carbon acids (CH₃Y, CH₂YY′) reflect the stability of the derived carbanions, we use them to define five regions of activation: (i) very strongly activated systems, where pK_a(CH₂YY′) < 10; (ii) strongly activated systems, with pK_a(CH₂YY′) = 10–20; (iii) moderately activated systems, with pK_a(CH₃Y) = 20–31; (iv) slightly activated systems, with pK_a(CH₂YY′) = 30–41; (v) very slightly activated systems, with pK_a(CH₃Y) > 40.

My hypothesis is that for good leaving groups (e.g., Cl, Br, OTs) the multi-step route operates for very strongly activated systems, and the single-step one for very slightly activated systems.

Methods for Evaluating k_{el}. The k_{el} value in the substitution is usually unattainable since C–X bond cleavage occurs after the rate-determining step. However, three methods were recently used to evaluate it in similar processes.

First, several strong carbon acids carrying poor leaving groups are converted completely by a base B to their conjugate bases. The E1cB elimination of X from the carbanions was directly measured in few cases.[39] Thus, it could be estimated in reactions 7[36a] and 8[36b]

$$An_2C(CN){-}CH(NO_2)_2 \overset{B, \text{ MeCN}}{\rightleftharpoons}$$

$$An_2C(CN){-}C^-(NO_2)_2 \xrightarrow[k_{el} \leq 6 \times 10^{-7} \text{ s}^{-1}]{-CN^-} An_2C{=}C(NO_2)_2$$
16
(7)

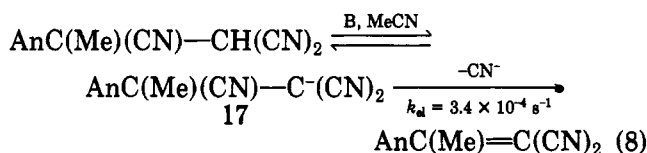(28) Z. Rappoport and A. Gal, *J. Org. Chem.*, **37**, 1174 (1972).

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$$AnC(Me)(CN)-CH(CN)_2 \xrightleftharpoons{B, MeCN}$$

$$AnC(Me)(CN)-C^-(CN)_2 \xrightarrow[k_{el} = 3.4 \times 10^{-4} \, s^{-1}]{-CN^-}$$

$$AnC(Me){=}C(CN)_2 \quad (8)$$
$$\mathbf{17}$$

that the expulsion of CN^- from the β,β-dicyano activated carbanion **17** is ≥ 560 times faster than from the longer lived β,β-dinitrocarbanion **16**.

Second, in reversible E1cB reactions (eq 9), the observed

$$B + RR'CX-CH_2Y \xrightleftharpoons[k_{-1}]{k_1} BH^+ +$$

$$RR'CX-C^-HY \xrightarrow{k_{el}} RR'C{=}CHY + X^- \quad (9)$$
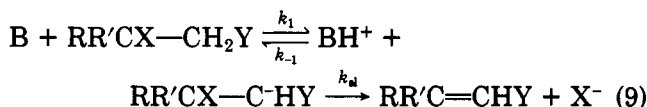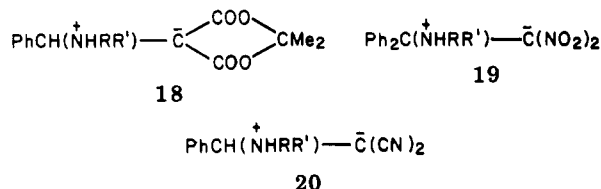
served rate constant is given by $k_{obsd} = (k_1/k_{-1})k_{el}$. The k_{el} values were estimated by Stirling and co-workers,[37] when Y = CN, COPh, or SO_2R, by assuming that k_{-1} is diffusion controlled and its value is $10^{11} \, M^{-1} \, s^{-1}$. Several log k_{el} values when Y = SO_2Ph for X are Me_2N^+Ph (9.2), MeS^+Tol (9.8), OPh (8.9), SPh (8.7), OMe (6.1), CMe_2NO_2 (2.6), CN (<0.5). The values are insensitive to the nature of Y over a change in five $pK_a(CH_3Y)$ values, indicating an early transition state for the k_{el} process. The log k_{el} value for NR_3^+ in EtOH is 10 ± 0.8 when Y = CN or SO_2Ph. Consequently, only if Cl^- is a much better leaving group from carbanions than NR_3^+ will k_{el} for the substitutions of moderately activated systems be higher than kT/h and the single step route will be realized.

Third, Bernasconi,[38a] Schuster,[38b] and co-workers measured k_1 and k_{el} values for reaction 10 by rapid

$$RR'NH +$$

$$PhCR''{=}CYY' \xrightleftharpoons[k_{el}]{k_1} PhCR''(N^+HRR')-C^-YY' \quad (10)$$
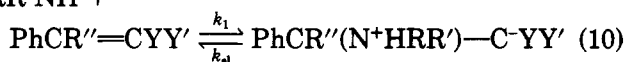
reaction techniques. The k_{el} values (in s^{-1}) when RR'NH = morpholine for **18**, **19**, and **20** are 2(H_2O, 25

$$PhCH(\overset{+}{N}HRR')-\overset{C}{\underset{COO}{\overset{COO}{<}}}CMe_2 \qquad Ph_2C(\overset{+}{N}HRR')-\bar{C}(NO_2)_2$$

$$\mathbf{18} \qquad\qquad\qquad \mathbf{19}$$

$$PhCH(\overset{+}{N}HRR')-\bar{C}(CN)_2$$

$$\mathbf{20}$$

°C):2400(1:1 Me_2SO-H_2O, 20 °C):2.6 × 10^5(1:1 Me_2SO-H_2O, 20 °C), respectively.[38a] The **20**/**19** reactivity ratio for RR'NH$^+$ resembles the **17**/**16** ratio for the poor CN leaving group, indicating a more productlike transition state for the strongly activated systems than for the singly activated ones. From k_{el} for **20** and Stirling's log k_{el} values,[37] it may be deduced that k_{el} of Cl^- may be relatively low and measurable for strongly activated systems.
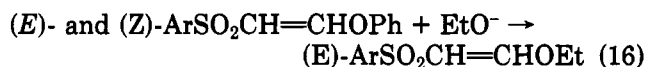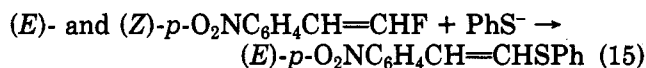
Evidence for the Multi-Step Route for Poor Leaving Groups. Several phenomena indicate a multi-step route for systems carrying poor leaving groups such as F, CN, or OR. First, the corresponding carbanions derived from highly activated systems can be sometimes isolated, e.g., **21** from reaction 11.[39]

$$(MeO)_2C{=}C(CN)_2 + MeO^-Na^+ \xrightarrow{MeOH}$$

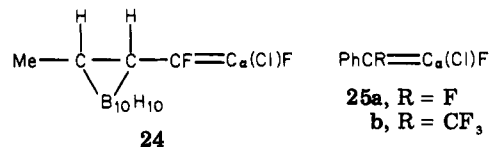$$(MeO)_3C-C(CN)_2^-Na^+ \quad (11)$$
$$\mathbf{21}$$
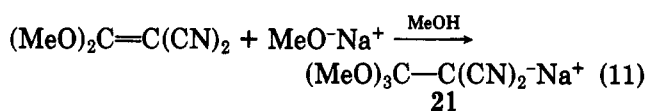
Second, such carbanions can be captured by a proton before leaving-group expulsion. Thus, substitution with excess alkoxide ion is frequently accompanied by a further process, namely, addition of the alkoxide ion to the initially formed vinyl ether (eq 12).[24,40] Likewise,

$$RC(Cl){=}CHY + R'O^- \rightarrow$$

$$RC(OR'){=}CHY \quad \begin{cases} \xrightarrow{OR'^-} RC(OR')_2-CH_2Y \\ \xrightarrow{OR''^-} RC(OR')(OR'')-CH_2Y \end{cases} \quad (12)$$

$$(E){-} \text{ or } (Z){-}PhSO_2CH{=}CHF + PhS^- \rightarrow$$
$$\mathbf{22}$$

$$(E){-} + (Z){-}PhSO_2CH{=}CHSPh + PhSO_2CH_2CH(F)SPh \quad (13)$$

$$\mathbf{23}$$
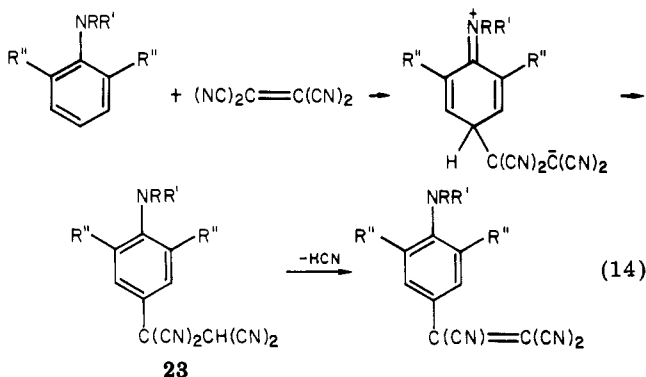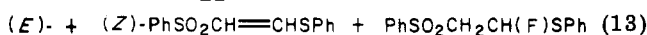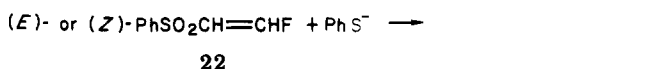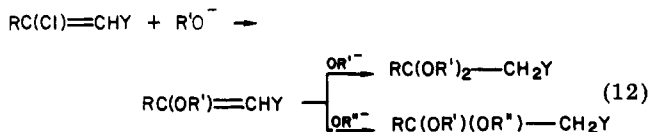
thiophenoxydefluorination of **22** is accompanied by adduct formation (eq 13).[41] The displacement of the cyano group of tetracyanoethylene by aromatic amines such as N,N-dimethylaniline also proceeds via the intermediate zwitterion or via adduct **23** (eq 14).[42,43] Third, complete stereoconvergence was observed in several substitutions of F and OR (eq 15[24] and 16[40b])

$$(E){-} \text{ and } (Z){-}p{-}O_2NC_6H_4CH{=}CHF + PhS^- \rightarrow$$
$$(E){-}p{-}O_2NC_6H_4CH{=}CHSPh \quad (15)$$

$$(E){-} \text{ and } (Z){-}ArSO_2CH{=}CHOPh + EtO^- \rightarrow$$
$$(E){-}ArSO_2CH{=}CHOEt \quad (16)$$

and partial stereoconvergence with preferred formation of the retained isomer was the outcome of reaction 13[41] or the substitution of $(E){-}$ and $(Z){-}MeCF{=}CHCO_2Et$ by PhS$^-$ ion.[6] However, retention was observed in the substitution of the α fluorine of slightly activated $(E){-}$ and $(Z){-}$vinyl fluorides such as **24** by PhS$^-$,[44] of **25a** by

$$\mathbf{24}$$

$$PhCR{=}C_\alpha(Cl)F$$
$$\mathbf{25a}, R = F$$
$$\mathbf{b}, R = CF_3$$

(37) P. J. Thomas and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1130 (1978); D. R. Marshall, P. J. Thomas, and C. J. M. Stirling, *ibid.*, 1898 (1977).

(38) (a) C. F. Bernasconi, and D. J. Carré, *J. Am. Chem. Soc.*, **101**, 2698 (1979); C. F. Bernasconi, J. P. Fox, and S. Fornarini, *ibid.*, **102**, 2810 (1980); C. F. Bernasconi and S. Fornarini, *ibid.*, **102**, 5329 (1980); (b) B. Schreiber, H. Martinek, P. Wolschann, and P. Schuster, *ibid.*, **101**, 4708 (1979).

(39) O. W. Webster, M. Brown, and R. E. Benson, *J. Org. Chem.*, **30**, 3223 (1965).

(40) (a) J. Biougne, F. Theron, and R. Vessiere, *Bull. Soc. Chim. Fr.*, 2882 (1972); (b) M. J. van der Sluijs and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1268 (1974).

(41) G. Marchese and F. Naso, *Chim. Ind. (Milano)*, **53**, 760 (1971).

(42) Z. Rappoport, *J. Chem. Soc.*, 4498 (1963); Z. Rappoport and A. Horowitz, *ibid.*, 1348 (1964).

(43) P. J. Farrell, J. Newton, and R. F. M. White, *J. Chem. Soc. B*, 637 (1967); Z. Rappoport and E. Shohamy, *ibid.*, 77 (1969); P. J. Farrell and R. K. Wojtowski, *J. Chem. Soc. C*, 1390 (1970).

EtO$^-$,[45] and of **25b** by MeO$^-$.[46] Fourth, the high k_F/k_{Cl} ratios in cases listed in Table II are consistent with the multi-step route. Fifth, the reaction of ethyl (Z)-β-fluorocrotonate **26-Z** with EtO$^-$ gives both the substitution product and **26-E**.[6] A long-lived carbanion, **27**, where $k_{rot}(180°) > k_{el}$, is a likely intermediate (eq 17).
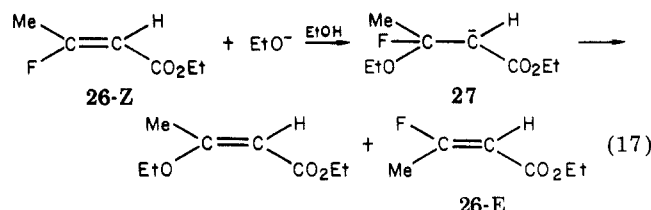
Finally, a tool which was used for S$_N$Ar reactions[47] has been very rewarding when applied to vinylic substitutions.[48-52] This is the observation of amine catalysis in substitutions involving amine reagents. In the carbanion formed by attack of an anionic nucleophile, the nucleophile-derived moiety usually enhances leaving group expulsion by mesomeric electron donation (cf. **28**). However, attack by amines gives a zwitterion in
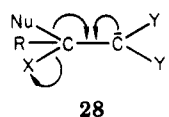
which the amine-derived ammonio group is unable to assist in that way. Indeed, due to its electron-attracting character it retards expulsion of the leaving group. Moreover, the ammonio group is nucleofugal, and easily exits to regenerate reactants. The consequences are demonstrated in eq 18 for the extensively studied 2,2-
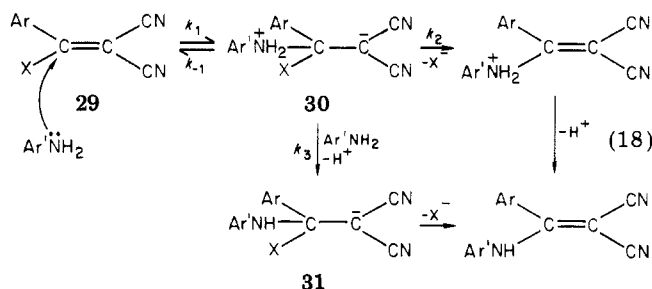

dicyano-1-[p-(dimethylamino)phenyl]-1-X system **29**.[48-50,52] When zwitterion **30** is formed in a preequilibrium, the substitution product may be obtained by two competing routes. Uncatalyzed leaving group expulsion ($k_2 = k_{el}$) may compete with a second-order

deprotonation of the ammonio group of **30** by another amine molecule (k_3) to form **31**, which then rapidly expels the leaving group. The k_2 and the k_3 steps may be more complicated (e.g., k_3 is probably a specific base–general acid catalyzed step),[50] but this aspect does not concern us here.

The observed second-order rate constant k_{obsd} is given by eq 19, and four kinetic situations are possible. (a)

$$k_{obsd} = \frac{k_1(k_2 + k_3[amine])}{k_{-1} + k_2 + k_3[amine]} \quad (19)$$

If $k_{-1} << (k_2 + k_3[amine])$, nucleophilic attack is rate determining and the reaction shows second-order kinetics with $k_{obsd} = k_1$. (b) If uncatalyzed leaving group expulsion (step 2) is rate limiting, i.e., $k_{-1} >> k_2 >> k_3[amine]$, the reaction is second order with $k_{obsd} = k_1k_2/k_{-1}$ and $\Delta H^* = \Delta H° + \Delta H_2^*$. There is evidence that $\Delta H°$ is negative,[41b,53] and since ΔH_2^* is probably low, low and even negative ΔH^* values are predicted, and were indeed observed. (c) When $k_{-1} >> (k_2 + k_3[amine])$, a linear k_{obsd} vs. [amine] relationship is expected, with a slope to intercept ratio of k_3/k_2. The reactions of **29**, X = F, with anilines[48a] or of compound **32**, in which CN is the leaving group with amines in
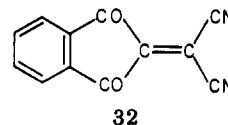
MeCN[51] are extreme examples of this situation since they are of an overall third order, i.e., only the catalyzed route operates. Change to a protic solvent reduces the k_3/k_2 values; the reaction of **29**, X = F, with anilines in i-PrOH is kinetically mixed first and second order in the amine.[48b] Linear k_{obsd} vs. [amine] plots were also observed for other slow leaving groups, e.g., for **29**, X = OEt, CF$_3$CH$_2$O, PhO, and CN;[50] in the reactions of these four substrates with piperidine, the k_3/k_2 values were 119, 514, 2815, and 1672, respectively, indicating the predominance of the catalyzed route. (d) When $k_{-1} \sim (k_2 + k_3[amine])$, a curved k_{obsd} vs. [amine] relationship and a linear $1/k_{obsd}$ vs. $1/[amine]$ plot are expected. An example is the reaction of **29**, X = OEt, with morpholine in EtOH.[50a] These kinetic manifestations, together with the above evidence, argue strongly that the multi-step route prevails for substitution of slow leaving groups in highly, moderately, and slightly activated systems.

The Multi-Step Route for Good Leaving Groups. Obviously, the search for the multi-step route for good leaving groups should start with highly activated systems. The fact that studies of base catalysis of reactions with amine nucleophiles have been so rewarding suggests their application to system **29**, X = Cl.

Amine Catalysis. When **29**, X = Cl, was substituted by aniline and ring-substituted anilines in MeCN[48a] or tetrahydrofuran,[52] k_{obsd} was observed to increase appreciably and linearly with the amine concentration, but the k_3/k_2 values were very low, less than 7, and some less than 1.[48a] Such modest accelerations have been encountered also in S$_N$Ar reactions in which amine nucleophile attack is surely rate determining. They may represent medium effects, but the fact that the

(44) L. I. Zakharkin and V. N. Lebedev, *Zh. Obshch. Khim.*, **42**, 558 (1972).

(45) J. Normant, R. Sauvetre, and J. Villiers, *Tetrahedron*, **31**, 891 (1975).

(46) D. J. Burton and H. C. Krutzsch, *J. Org. Chem.*, **36**, 2351 (1971).

(47) Cf. C. F. Bernasconi, *MTP, Int. Rev. Sci., Org. Chem., Ser. One*, **3**, 33 (1973).

(48) Z. Rappoport and R. Ta-Shma, *J. Chem. Soc. B*: (a) 871 (1971); (b) 1461 (1971).

(49) Z. Rappoport and N. Ronen, *J. Chem. Soc., Perkin Trans. 2*, 955 (1972).

(50) Z. Rappoport and P. Peled: (a) *J. Chem. Soc., Perkin Trans. 2*, 616 (1975); (b) *J. Am. Chem. Soc.*, **101**, 2682 (1979); (c) unpublished results.

(51) Z. Rappoport and D. Ladkani, *J. Chem. Soc., Perkin Trans. 2*, 1045 (1973).

(52) Z. Rappoport and A. Topol, *J. Chem. Soc., Perkin Trans. 2*, 863 (1975).

(53) Z. Rappoport and S. Gertler, *J. Chem. Soc.*, 1360 (1964).

Nucleophilic Vinylic Substitution

p-nitro analogue of **29**, which probably forms a longer lived zwitterion, gives k_3/k_2 values one order of magnitude higher than for **29**, X = Cl,[52] is consistent with genuine base catalysis according to eq 18.

In contrast, the reaction of **29**, X = Cl, with *p*-toluidine or *p*-anisidine in *i*-PrOH or in *t*-BuOH shows no amine catalysis.[48b] However, the low ΔH^* values (e.g., 4.9 kcal mol^{-1} with *p*-anisidine in *i*-PrOH) suggest a rate-determining C–Cl bond cleavage (k_2). In MeCN solvent, amine catalysis is observed and the ratios of the catalytic third-order constant k_F/k_{Cl} are 35–125 for various anilines, reflecting the higher carbon basicities ($K = k_1/k_{-1}$) of **29**, X = F, and the higher acidity of the corresponding zwitterions. The ratios of the second-order constants for these amines are k_F/k_{Cl} = 1.05–3.05 in *i*-PrOH and *t*-BuOH[48b] and 1.25 for 2,6-diethylaniline in MeCN.[48a] Since each k value is the product of K and k_{el}, k_{el} is most probably higher for X = Cl than for X = F, in line with the prediction of a multi-step process.

There are other cases where low ΔH^* and high negative ΔS^* values for a second-order process reveal a highly polar transition state. Examples are the substitution of *p*-O$_2$NC$_6$H$_4$C(OTs)=C(CO$_2$Et)$_2$ by piperidine in MeCN where ΔH^* = 3.1 kcal mol^{-1}, ΔS^* = –54 eu,[54] and the reaction of the very strongly activated tricyanovinyl chloride **33** with the *p*-position of N,N-disubstituted anilines, R = Me, Et, Pr, Bu (eq 20) where

(20)
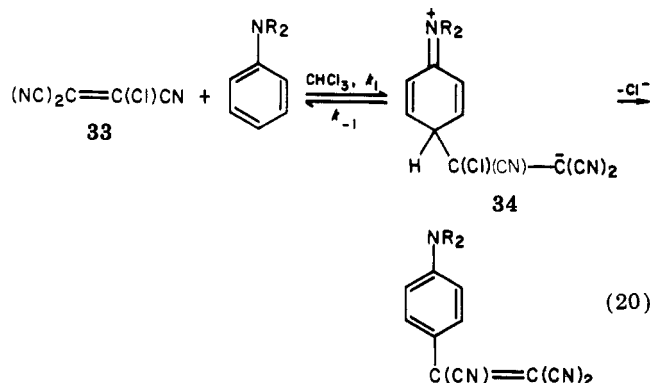
ΔH^* = 0.8–2.0 kcal mol^{-1} and ΔS^* = –52 to –56 eu.[55] Preequilibrium formation of the zwitterion **34**, followed by a rate-determining C–Cl bond cleavage slower than the C–C bond cleavage (k_{-1}), may be indicated.

In the substitution of **33** by dihydropyran (eq 21) the

(21)
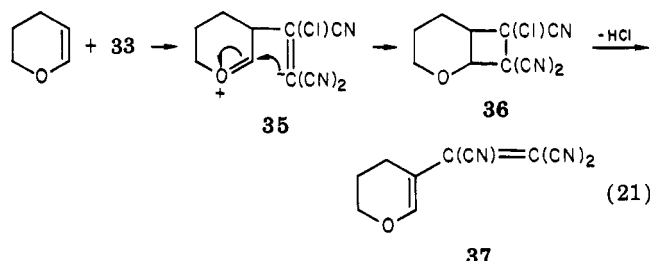
cycloadduct **36** is obtained in nonpolar solvents, and loss of HCl with ring opening to **37** is affected by mild heating or by dissolution in polar solvents.[56] Since the analogous reaction with *p*-methoxystyrene is highly

accelerated in polar solvents,[56] the intermediacy of the zwitterion **35** is likely. That the ring closure **35** → **36** is faster than Cl$^-$ expulsion suggests an appreciable lifetime of the chloro zwitterion **35**.

Leaving Group Effect. Another indication for a multi-step route comes from the leaving group effect on the substitution of the dicarboethoxy-activated system **38** (eq 22).[52] Table III shows a large rate dif-

(22)
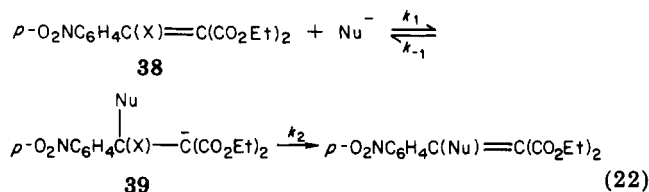
ference between the chloride and the sulfonate leaving groups for the reactions of amines with **38**. The differences in the electron-withdrawing power of Cl and OTs is small (σ^*(CH$_2$Cl) = 1.05; σ^*(CH$_2$OTs) = 1.31). Consequently, the ratios seem more consistent with a rate-determining C–X bond cleavage due to steric enhancement of k_{-1} by the four bulky vinylic substituents than with a rate-determining nucleophilic attack. In the less crowded HCX=C(CN)$_2$ system $k_2 > k_{-1}$, and k_1 is rate determining as judged by the k_{OMs}/k_{Cl} ratio of unity for the substitution by *p*-cyanoaniline.[54]

The results of Table III raise again the question of mechanistic information from the k_{Br}/k_{Cl} ratios. Since the ratios in vinylic S$_N$1[4] and elimination reactions[57] resemble their aliphatic counterparts, there is no appreciable contribution of a ground-state halogen–double bond interaction to the element effect. The k_{Br}/k_{Cl} ratios of 0.85–1.20 for the strongly activated systems[52,54] resemble those for the singly activated systems (Table II). Two exceptions which may reflect London dispersion effects are: (a) a k_{Br}/k_{Cl} ratio of 6.7 for the reaction of (*E*)-MeCX=CHCN with EtS$^-$[6] which may include a contribution from an elimination–addition route; (b) k_{Br}/k_{Cl} ratios of 4.2–9.9 for the reaction of Cl$^-$ with (*E*)- and (*Z*)-HCX=C(Ph)C$_6$H$_4$NO$_2$-*p* and with (*p*-O$_2$NC$_6$H$_4$)$_2$C=CHX in DMF[23b] which may be authentic examples of a single-step route. The similar ratios of Tables II and III for most systems are more consistent with the multi-step route than with a concerted route having an early transition state.

The k_{OTs}/k_{Cl} ratios of Table III are much lower than the values for aliphatic substitutions or those (20–300) for vinylic S$_N$1 reactions.[4] Consequently, if they indeed reflect a rate-determining k_{el} step, the transition state for this step is early, in agreement with the insensitivity of k_{el} to the nature of Y for moderately activated systems.

Stereoconvergence. Final evidence for the multi-step route comes from our recent stereochemical studies.[58,59] The prediction of stereoconvergence when the rotational barrier in the carbanion is reduced owing to charge dispersal by Y and Y′ is realized in two cases. Compounds **40-E** and **40-Z**, which are strongly activated by a nitro group, gave each a single substitution product with each of five different nucleophiles (eq 23).[58] With piperidine and morpholine this reflects a configurational

(54) Z. Rappoport and A. Topol, *J. Chem. Soc., Perkin Trans. 2*, 1823 (1972).

(55) Z. Rappoport, P. Greenzaid, and A. Horowitz, *J. Chem. Soc.*, 1334 (1964).

(56) J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.*, 84, 2216 (1962).

(57) G. Marchese, F. Naso, N. Tangari, and G. Modena, *J. Chem. Soc. B*, 1196 (1970).

(58) Z. Rappoport and A. Topol, *J. Am. Chem. Soc.*, 102, 406 (1980).

(59) B. Avramovitch and Z. Rappoport, 47th Meeting of the Israel Chemical Society, Rehovot, Sept 29–30, 1980, Abstracts, p 196.

41a

40-E

40-Z

Nu⁻ = SCN⁻,
p-MeC₆H₄S⁻
piperidine,
morpholine

41b

N₃⁻

   (23)
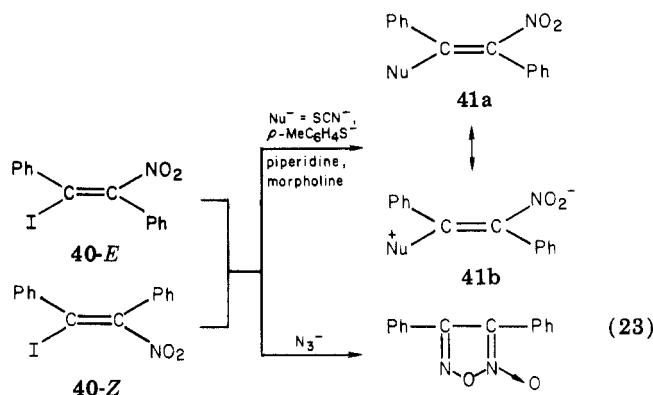
instability of the nitro-enamines (cf. 41a–41b); for the sulfur and the azido nucleophiles this is ascribed to a faster internal rotation compared with leaving group expulsion in the long-lived α-nitro carbanionic intermediate. Substitution of the slightly less activated isomers 42-E and 42-Z with p-MeC₆H₄S⁻ and MeO⁻ ions also gives nearly or complete stereoconvergence. Only 43-Z is obtained when Nu = p-MeC₆H₄S and mainly 43-E when Nu = OMe (eq 24).[59] The change from

42-Z   or   42-E

↓Nu⁻   (24)

43-E
Nu = OMe
(major product)

43-Z
Nu = p-MeC₆H₄S
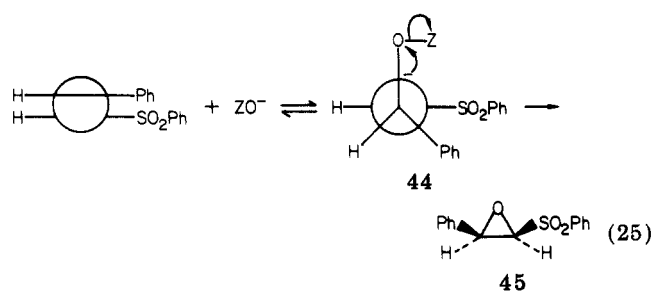Nu = OMe (minor product)
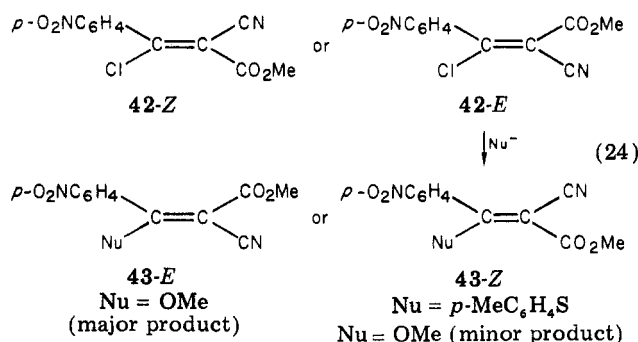
retention for moderately activated systems to stereoconvergence for strongly activated ones argues strongly for the multi-step route for the latter when other stereoconvergence routes are excluded.

Stereoconvergence for strongly activated systems may be of other genesis. Increased activation increases the ease of a one-electron transfer (e.g., from ArS⁻ to 40-Z) with a possible consequent isomerization of the starting material at the radical anion stage and stereoconvergence. The reduced barrier to internal rotation in the products which are push–pull ethylenes (cf. 41a ↔ 41b)[60] may give the appearance of stereoconvergence by postisomerization. Nucleophilic addition–elimination of the nucleophile to the activated product 41 may also give stereoconvergence.

Feasibility of Retention via Carbanions. An Analogy. For short-lived carbanions the basic question is why a 60° clockwise rotation of the initially formed conformer which leads to retention is preferred over the anticlockwise 120° rotation which gives inversion. A recent work[61] shows an analogous behavior. Epoxidation of electrophilic olefins by the nucleophile ZO⁻ proceeds by an initial nucleophilic attack, followed by intramolecular displacement of Z by attack of the carbanionic C_α on the oxygen. The epoxidation of (Z)-

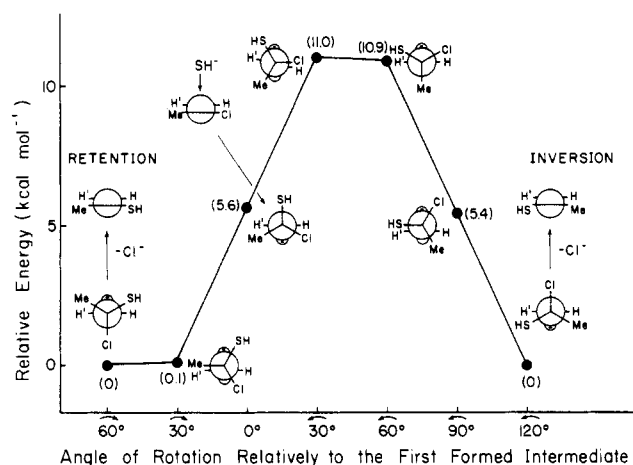(60) U. Sjostrand and J. Sandstrom, *Tetrahedron*, 34, 3305 (1978), and references therein.
(61) (a) R. Curci and F. Di Furia, *Tetrahedron Lett.*, 4085 (1974); (b) A. Robert and A. Foucaud, *Bull. Soc. Chim. Fr.*, 2531 (1969); (c) R. Curci, F. Di Furia, and M. Meneghin, *Gazz. Chim. Ital.*, 108, 123 (1978).

1-(phenylsulfonyl)-2-phenylethylene (eq 25) gives 100%,

44

   (25)

45

≥95%, 10%, and 0% of the less stable retained epoxide 45, when Z = Cl, m-ClC₆H₄COO, t-BuO, and OH, respectively.[61a] Consequently, here also Cl⁻ expulsion is faster than internal rotation in the carbanion 44, Z = Cl, whereas the opposite is true for 44, Z = OR. Retention was also observed for the epoxidation of ArCH=C(CN)CO₂Et by ClO⁻ [61b] but the epoxidation of (E)-PhCH=C(Me)NO₂ by ClO⁻ showed a lower specificity.[61c] A barrier for the free rotation for carbanions derived from moderately and even some strongly activated systems is therefore indicated.

MO Calculations. A recent study established the reason for the preferred 60° rotation. A qualitative analysis by Texier[18] showed that the 60° rotation is preferred over the 120° rotation in both the single and the multi-step routes. The barriers for internal rotation in β-X-substituted ethyl anions were calculated by Apeloig[62] from the energy difference between the conformers 46a and 46b. The strong conformational

46a   46b
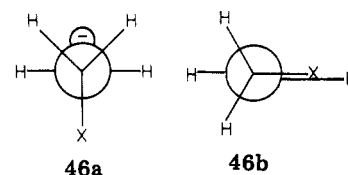
preference for 46a is ascribed to hyperconjugation. The hyperconjugation ability (HCA) of X is a sum of the destabilizing σ_{C-X}–C⁻(2p) interaction and a stabilizing σ^*_{C-X}–C⁻(2p) interaction and is maximal for 46a when the interacting orbitals are parallel and minimal for 46b when they are orthogonal. Some of the barriers are rather high, e.g., the values in kcal mol⁻¹ relative to H are Cl (16.7), F (10.1), MeO (12.6), SH (9.2), NH₂ (4.8), Me (2.1). The HCA(X) is reduced by charge delocalization at C_α and the barrier is 5.5 kcal mol⁻¹ for FC-H₂C(CN)₂⁻. When the relative energies of various conformers were applied to nucleophilic vinylic substitution of RC(X)=CYY′ it was found that a 60° clockwise rotation is preferred when HCA(X) >> HCA(R) regardless of the nucleophile. Inversion is anticipated when HCA(X) << HCA(R) and stereoconvergence when HCA(X) ~ HCA(R). Since HCA(Cl) is the highest value calculated, retention is the preferred stereochemical outcome via short-lived carbanions for all the cases investigated so far when $k_{el} > k_{rot}$. A reaction profile for the substitution of H₂C=C(Me)Cl by HS⁻ (Scheme III) predicts a preferred retention when H_β = D. In the multi-step route a barrier for expulsion

(62) Y. Apeloig and Z. Rappoport, *J. Am. Chem. Soc.*, 101, 5095 (1979).

Table III
Leaving Group Effects for Strongly Activated Systems[52,54]

| | | | rel k_{obsd} at 30 °C | | | | |
substrate	nucleophile	solvent	X = Cl	X = Br	X = OTs	X = OMs	X = OBs
$p\text{-}O_2NC_6H_4C(X)\text{=}C(CO_2Et)_2$	morpholine	EtOH	1		24.5	19.3	44.3
	piperidine	MeCN	1		15.5	17.6	26.9
	$p\text{-}ClC_6H_4S^-$	EtOH	1		1.41	1.6	4.2
$HCX\text{=}C(CN)_2$	$p\text{-}NCC_6H_4NH_2$	MeCN	1			1.0	
$HCX\text{=}C(CO_2Me)_2$	$p\text{-}MeC_6H_4NH_2$	MeCN	1	0.91			
	$p\text{-}BrC_6H_4NH_2$	MeCN	1	1.05			
$HCX\text{=}C(CN)CO_2Me$	$p\text{-}NCC_6H_4NH_2$	MeCN	1	1.20			
$p\text{-}O_2NC_6H_4CX\text{=}C(CN)_2$	$p\text{-}ClC_6H_4NH_2$	MeCN	1	1.16			

Scheme III

Angle of Rotation Relatively to the First Formed Intermediate

of Cl⁻ exists even from the two conformers with relative energy of O in Scheme III.

The Single-Step Process. The experimental evidence and the MO calculations suggest that the multi-step route prevails for an extended structural range of Y and Y'. At what degree of activation will the single-step mechanism start to take over? Most of the mechanistic tools discussed above are unsuitable to answer this question. For slightly activated systems retention is predicted for both routes. Moreover, catalysis will not be observed in reactions by the two-step mechanism since the monomolecular C–X bond cleavage will be faster than the bimolecular proton transfer. Indeed, catalysis is not observed for strongly and moderately activated systems when Y = NO₂, COR, and Y' = H.[62,63]

The best mechanistic tool is the element effect which should be appreciable for the single-step route. A priori, the substitution of the very slightly activated β-halostyrenes which require powerful nucleophiles may proceed via the single-step route. Indeed, considerable element effects were observed in two reactions. Naso

(63) (a) Z. Rappoport and S. Hoz, *J. Chem. Soc., Perkin Trans. 2*, 272 (1975); (b) J. H. Chu, B. S. R. Murty, and L. Fedor, *J. Am. Chem. Soc.*, **98**, 3632 (1976).

and co-workers found that the substitution by lithium dimethylcuprate gives retained products (eq 26) and a

$$PhCH\text{=}CH\text{—}CH\text{=}CH_2 \quad (26)$$
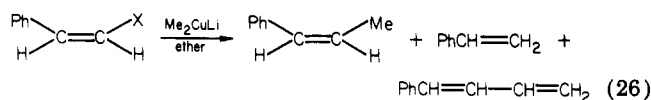
k_{Br}/k_{Cl} ratio of ca. 10^2 whereas the fluoro compound was unreactive.[10] However, the formation of styrene and butadienes, the reduction and coupling products, indicate that the substitution may proceed via attack on X which forms a configurationally stable vinyl anion, or via an organocopper intermediate.

Substitution of β-halostyrenes by bis(dimethylglyoximato)(pyridine)cobaltate(I) ion also proceeds with retention of configuration and gives no side products; the qualitative reactivity order is RI >> RBr >> RCl > RF.[9] This may be an authentic case of the single-step mechanism, but alternative routes involving an initial complex formation or an electron-transfer mechanism should be first ruled out.

Conclusions. For a perpendicular attack on C_α there is overwhelming evidence for a multi-step substitution of poor leaving groups. For good leaving groups, the evidence for this route is strong for strongly activated systems and highly suggestive for moderately activated ones. The variable-transition-state hypothesis predicts the operation of the single-step route for very slightly activated systems, but clear-cut experimental evidence for it is meager. Wide gaps exist in our qualitative picture. Thus, the exact structural region where stereoconvergence becomes retention is not defined. The question whether catalysis could be observed for singly activated systems is yet not answered. The magnitude of the k_{Br}/k_{Cl} ratios for very strongly activated systems, when k_{el} may become rate determining, is unknown. These and many related problems should be explored in the future.