

synthesis, resolution, and chemical studies. The sulfur atom aids X-ray studies while this same atom, acting as it were as an insulator, greatly simplifies the interpretation of spectral data. The absolute configuration of a heterohelicene is reported.

My collaborators who are named in the references deserve the major credit for the work from my laboratory that is described in this paper. Special thanks are due to Dr. Richard M. Kellogg and Dr. Marinus B. Groen whose loyal and dedicated work and major original contributions can hardly be overestimated.

Reactions of Nucleophiles with Ethylenic Substrates

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Intensive work on the mechanisms of nucleophilic substitution at saturated carbon began in the 1930's and at aromatic carbon in the early 1950's. However, it was not until the late fifties and early sixties that thorough scrutiny of nucleophilic substitution at vinylic carbon got under way.¹

There are well-recognized similarities between aryl halides and vinyl halides. It might therefore be supposed that nucleophilic substitution at vinylic centers would be merely a further chapter of aromatic nucleophilic substitution.

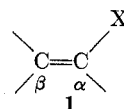
There are similarities, to be sure, but reactions of ethylenic substrates are mechanistically more diverse. Vinyl halides undergo β elimination to acetylenes with greater ease than aromatic compounds form arynes. The competition between substitution and elimination is, indeed, one of the most intriguing features of the reactions of vinylic compounds with nucleophiles. The cis-trans isomerism of substituted ethylenes offers substrates of known configuration for the study of β -elimination mechanisms and also poses obvious questions as to whether configuration is retained or inverted during substitution.

Moreover, a vinylic substrate necessarily carries an α substituent with respect to the leaving group. The α substituent may exert steric and electronic effects on the reaction rate and may itself be attacked by the nucleophile, thus opening new reaction pathways.

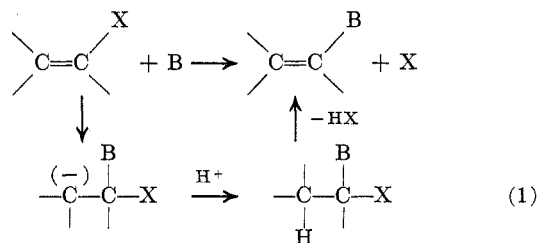
Finally, ethylenic substrates of suitable structure may undergo S_N1 -like reactions even at room temperature.² However, this mechanism does not interfere

to any significant extent when strong bases are present.

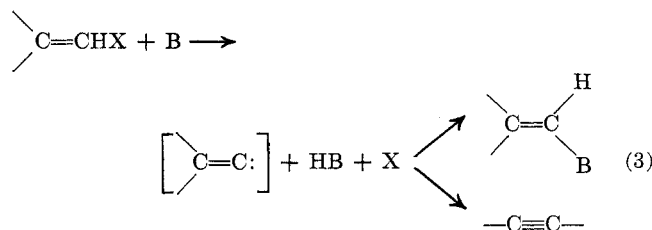
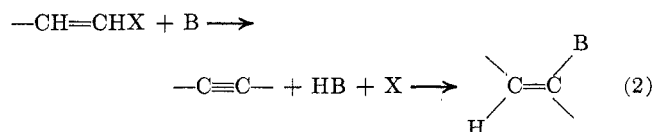
In summary, vinylic substrates (1) may react with a nucleophile B by: (1) attack at the α carbon³ to



give either substitution (direct substitution) or addition products (eq 1); the latter may undergo subsequent elimination of HX to give a product of formal substitution (addition-elimination, eq 1); (2) attack



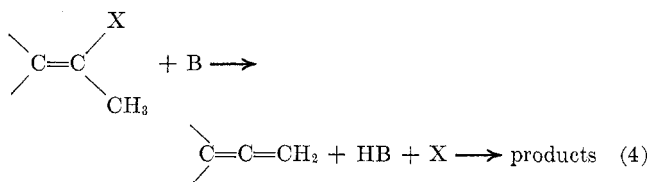
at hydrogen to trigger one of three independent elimination paths involving a β hydrogen (β elimination, eq 2) or the α hydrogen (α elimination, eq 3), or a β' hydrogen (β' elimination, eq 4).



(1) (a) D. E. Jones and C. A. Vernon, *Nature*, **176**, 791 (1955); (b) W. E. Truce and M. M. Boudakian, *J. Amer. Chem. Soc.*, **78**, 2748 (1956), and subsequent papers; (c) S. I. Miller and P. K. Yonan, *ibid.*, **79**, 5931 (1957); (d) F. Montanari, *Gazz. Chim. Ital.*, **86**, 406 (1956), and subsequent papers of the series; (e) G. Modena, *Ric. Sci.*, **28**, 341 (1958).

(2) G. Modena, U. Tonellato, and F. Naso, *Chem. Commun.*, 1363 (1968); G. Modena and U. Tonellato, *ibid.*, 1676 (1968); W. M. Jones and D. D. Maness, *J. Amer. Chem. Soc.*, **91**, 4314 (1969).

(3) Throughout this Account α indicates the carbon to which the leaving group X is linked and β the next one; cis and trans isomers are named on the basis of the relative position of X and the activating group Y.



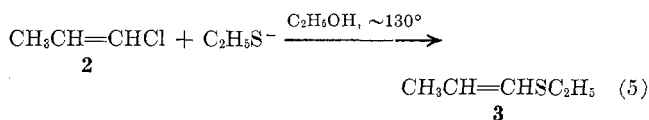
The elimination reactions are often followed by addition of HB to the initially formed acetylene or allene, or by other reactions. The acetylene derivative formed by β elimination in eq 2 may easily undergo base-catalyzed addition when it is substituted by electron-attracting groups. The allene derivative (eq 4) may also undergo base-catalyzed addition or rearrangement to an acetylene derivative when a β hydrogen is present. Finally, the α elimination may yield either products of formal substitution or acetylene derivatives by migration of one of the groups linked to the β carbon.

Other reaction paths are also possible. All these factors add variety to the study of nucleophilic reactions on ethylenic substrates.

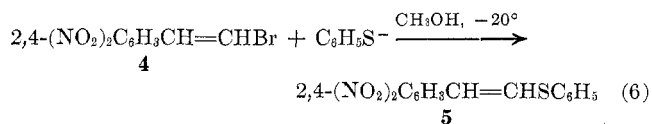
Comprehensive reviews⁴ on this subject are available; while reference to them will be made in this Account, primary attention will be given to some of the special problems involved with direct substitution and β elimination and to factors controlling competition between them.

Direct Substitution

Direct substitution arises from attack of the nucleophile at the α carbon (eq 1) and presents striking similarities with aromatic nucleophilic substitution. Simple ethylenic derivatives are extremely unreactive by this mechanism (for an example⁵ see eq 5). The low



reactivity may be explained by considering that the nucleophile attacks the α carbon from a direction perpendicular to the molecular plane and that, along this path, the approach of the reagent is severely hindered by the π -electron cloud. Electron-withdrawing groups (activating groups, Y) on the β carbon greatly enhance the rate of substitution (for an example⁶ see eq 6). The



effect is similar to that of ortho- and para-activating groups in aromatic nucleophilic substitution. However, the activating groups do not have quantitatively the same effect in aromatic and vinylic substitution. Whereas aromatic substitutions are satisfactorily

Table I
Effect of β Substituents on Rates of Reaction (Substitution) of *cis*-Vinyl Chloride (YCH=CHCl) with Benzenethiolate Ion in Methanol at 25°

	Y		
	<i>p</i> -NO ₂ C ₆ H ₄ ^d	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ ^{8a}	<i>p</i> -CH ₃ OC ₆ H ₄ CO ^e
<i>k</i> ^a	2.1 × 10 ⁻⁴	8.3 × 10 ⁻¹	3.0
σ^b	0.26	0.72 ^c	0.502 ^c
σ^-^b		1.049 ^c	0.87 ^c

^a The rate constants (*k*) in this and following tables are always in M⁻¹ sec⁻¹. ^b From J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, Chapter 4. ^c Values for CH₃SO₂ and CH₃CO, respectively. ^d G. Marchese, F. Naso, and G. Modena, *J. Chem. Soc. B*, 958 (1968). ^e D. Landini, F. Montanari, G. Modena, and F. Naso, *ibid.*, 243 (1969).

correlated⁷ by the Hammett equation, the rates of vinylic substitutions do not always follow the sequence predicted by either σ or σ^- (see Table I). This is not surprising since the activating group acts by both inductive and conjugative effects and the latter are influenced by the particular structure of the system. On the other hand, when the effects of substituents not directly bonded to the β -ethylenic carbon are considered, good Hammett correlations are observed with positive values of ρ . The magnitude of ρ changes with the length and the nature of the chain interposed between the substituent and the reacting center [*e.g.*, $\rho = 1.2$ – 1.8 for ZC₆H₄SO₂CH=CHHal + B (various nucleophiles) at 25° in methanol⁸ and 4.8 for (ZC₆H₄)₂C=CHCl + *p*-CH₃C₆H₄S⁻ in dimethylformamide⁹ (DMF) at 24°].

The available results as well as the analogy with aromatic nucleophilic substitutions lead^{1,4,5,8,10} to formulation of the general mechanism of reaction sketched in Scheme I. This is based on the following main hypotheses: (i) the nucleophile attacks C_α perpendicular to the molecular plane and the leaving group X also departs perpendicularly from it; (ii) the bond-forming process is largely advanced at the transition state whereas the C–X bond is only a little, or not at all, stretched; (iii) C_β keeps its planar configuration (or it rapidly inverts) throughout the reaction. For the sake of clarity Scheme I represents the mechanism of reaction as a sequence of elementary steps, the first of which is usually rate determining.

In agreement with and in support of this mechanism, the effect of the leaving group (*element effect*) on the rate of reaction is small: the sequence F > Cl ~ Br is usually observed (Table II). This same sequence is characteristic of aromatic nucleophilic substitution.¹¹ Also, the effects of nucleophiles on reaction rate and the variation of reactivity ratios for pairs of nucleophiles

(7) C. L. Liotta and D. F. Pinholster, *Chem. Commun.*, 1245 (1969).

(8) (a) G. Modena, P. E. Todesco, and S. Tonti, *Gazz. Chim. Ital.*, **89**, 878 (1959); (b) L. Maioli and G. Modena, *ibid.*, **89**, 854 (1959); (c) G. Modena and P. E. Todesco, *ibid.*, **89**, 866 (1959).

(9) P. Beltrame, P. L. Beltrame, and L. Bellotti, *J. Chem. Soc. B*, 932 (1969).

(10) S. I. Miller, *Advan. Phys. Org. Chem.*, **6**, 85 (1968).

(11) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Amer. Chem. Soc.*, **79**, 385 (1957); J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).

(4) (a) Z. Rappoport, *Advan. Phys. Org. Chem.*, **7**, 1 (1969); (b) S. Patai and Z. Rappoport in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, London, 1964, p 469; (c) B. P. De La Mare, *Progr. Stereochem.*, **2**, 165 (1958).

(5) D. E. Jones, R. O. Morris, C. A. Vernon, and R. F. M. White, *J. Chem. Soc.*, 2349 (1960).

(6) G. Marchese, G. Modena, and F. Naso, *Tetrahedron*, **24**, 663 (1968).

Scheme I

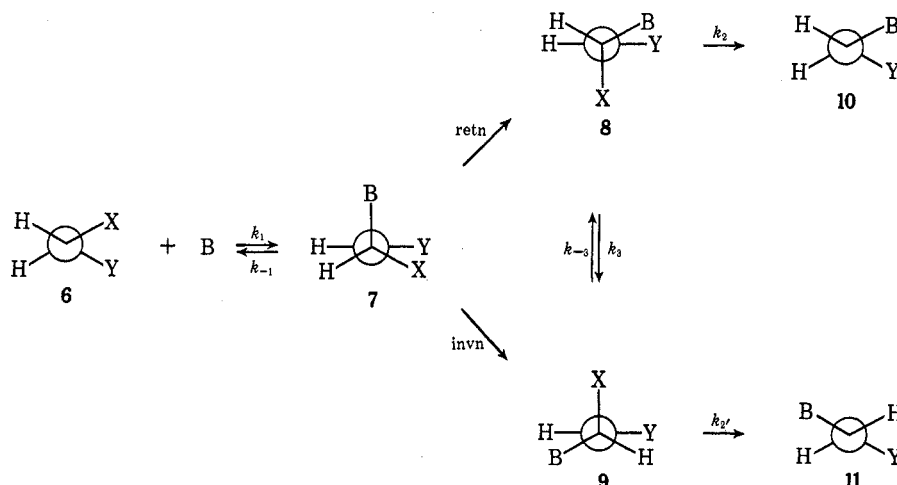


Table II

Effects of Base and Leaving Group on Rates of Reaction (Substitution) of β -Halo-*p*-nitrostyrenes with Benzenethiolate and Methoxide Ion in Methanol at 25 $^{\circ}$ ^a

Hal	C ₆ H ₅ S ⁻		CH ₃ O ⁻	
	$k_{trans} \times 10^4$	$k_{cis} \times 10^4$	$k_{trans} \times 10^4$	$k_{cis} \times 10^4$
Br	22	6.9	0.016	<i>b</i>
Cl	10.5	2.05	0.025	<i>c</i>
F	111	22.3	7.21	1.68

^a G. Marchese, F. Naso, and G. Modena, *J. Chem. Soc. B*, 290 (1969). ^b Complete elimination. ^c Mostly elimination.

as the leaving group is altered¹² follow similar patterns in aromatic and vinylic substitutions (Table II).

The *cis* or *trans* configuration of the ethylenic substrate has a minor effect on the rate of substitution, consistent with the geometry of attack of the nucleophile (Table III). The higher reactivity of *trans* over *cis* isomers, sometimes observed, may be rationalized⁶ on the basis of a more efficient conjugation between the activating group Y and the double bond. Relatively large k_{trans}/k_{cis} ratios are in fact observed when greater steric hindrance to coplanarity, and hence decreased conjugation, in *cis* than in *trans* isomers can be safely postulated as in the case of 2,4-dinitrostyrene (see Table III).

The reaction mechanism proposed above allows for different stereochemical courses: *retention of configuration* (configuration of the products the same as that of the reagents), *equilibration or racemization* (configuration of the products determined by the thermodynamic equilibria of the products or of their precursors, but independent of the configuration of the reagents), and *inversion of configuration*.

Experimentally it is found that substitution at vinylic carbon is, in most cases, highly stereoselective with a degree of retention of configuration often greater than 95%. Sometimes total or partial racemization has been observed, but never true inversion⁴ (for examples see eq 7^{13a} and eq 8^{13b}).

(12) A. Ricci, P. E. Todesco, and P. Vivarelli, *Tetrahedron Lett.*, 3703 (1964); *Gazz. Chim. Ital.*, **95**, 101 (1965); L. Di Nunno and P. E. Todesco, *Tetrahedron Lett.*, 2899 (1967).

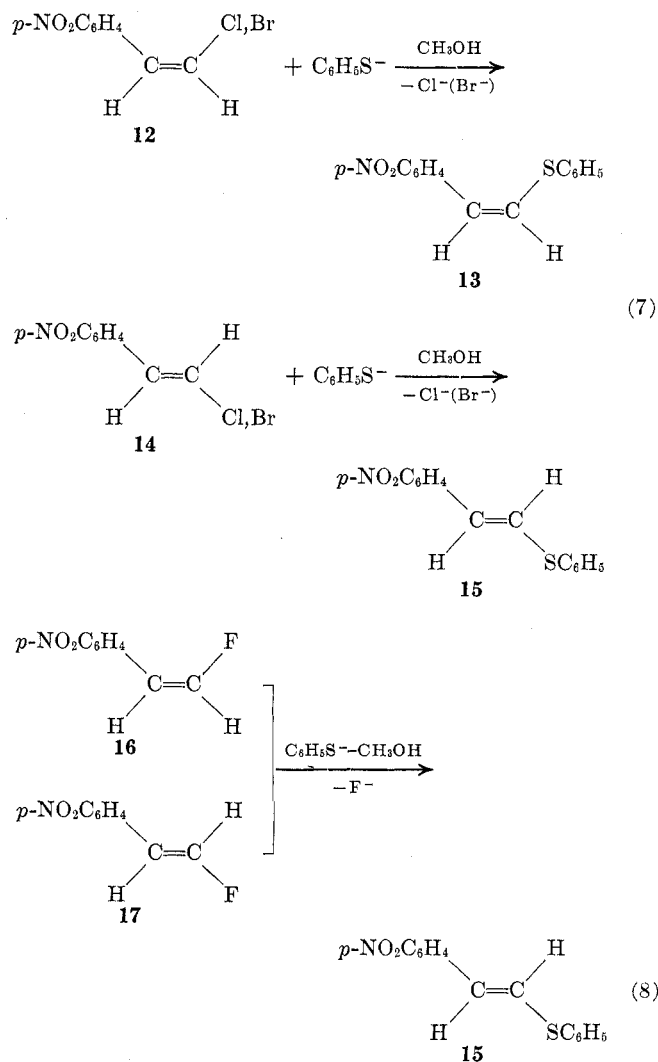
(13) (a) See Table I, footnote *d*; (b) see Table II, footnote *a*.

Table III

Reactivity Ratios of Some *cis*- and *trans*-Chloroethylenes (YCH=CHCl) with Benzenethiolate Ion in Methanol at 25 $^{\circ}$

	Y			
	<i>p</i> -CH ₃ -C ₆ H ₄ SO ₂ ^b	<i>p</i> -NO ₂ -C ₆ H ₄ ^c	<i>p</i> -CH ₃ -C ₆ H ₄ CO ^b	2,4-(NO ₂) ₂ -C ₆ H ₃ ^c
k_{trans}/k_{cis}	0.5	5	15	35

^a See Table I, footnote *d*. ^b See Table I, footnote *e*. ^c Bromo derivative; see ref 6.



A more detailed analysis of the mechanism proposed may explain these results. Retention and inversion at the α carbon depend on the balance between 60° clockwise and 120° counterclockwise rotations (see Scheme I). The former rotation appears to be easier than the latter; this may be explained on the basis of less motion as well as less eclipsing (H/H instead of the combination of X/Y and B/H). A similar scheme may be drawn for a trans substrate; in this case the eclipsing for the 60° clockwise rotation leading to retention is H/Y, and for the 120° counterclockwise rotation leading to inversion X/H and B/Y.¹⁴

Nevertheless, even if the energy barriers for clockwise and counterclockwise rotations are different, they cannot be very high, and the rotation about the C-C bond must be fairly fast. It follows that the reaction may be stereoselective only if C-X bond breaking is quite a fast process. Were this not the case, the system would reach conformational equilibrium before completion of the reaction and the stereochemistry would be controlled by the relative population of conformers **8** and **9** (and their enantiomers, not indicated).

Finally, the carbanions **8** and **9** may be long-lived enough to abstract a proton from the solvent. The adduct may be the final product (Michael addition and related reactions), or it may undergo elimination (addition-elimination, eq 1). The stereochemistry in these cases will no longer depend on the configuration of the reagents but rather on that of the adduct formed.

A direct consequence of the above is that the reaction path largely depends on the leaving group. A typical example is the reaction of *p*-nitrohalostyrenes with benzenethiolate in methanol. Both geometrical isomers of bromine and chlorine derivatives give substitution with complete retention of configuration (eq 7), whereas *trans*- as well as *cis*-fluoronitrostyrene yield *trans*-1-*p*-nitrophenyl-2-phenylthioethene (eq 8), which means complete loss of stereoselectivity.¹³ Preliminary results indicate that the same trend is followed by a series of bromo-, chloro-, and fluoroarylsulfonylethyl- enes.¹⁵

β Elimination

The most important and frequently observed elimination reaction is the so-called β elimination, which may occur whenever a hydrogen is present at the β -ethylenic carbon (eq 2). As opposed to substitution, it occurs readily even on nonactivated substrates. Indeed, simple haloethylenes undergo β elimination at rates comparable to, and sometimes faster than, those of haloalkanes.¹⁶ This behavior may be related to the

greater electronegativity of sp^2 carbon than of sp^3 carbon, which makes removal of the proton easier. Furthermore, as the C-H bond is in the nodal plane of the π -electron cloud, it cannot efficiently interfere with the approach of the nucleophile. The facility of elimination from vinyl systems has no counterpart in reactions of aromatic compounds. It reflects the fact that the formation of a stable triple bond in elimination from vinyl derivatives partially balances the breaking of C-H and C-X bonds, whereas no comparable gain in energy occurs in the formation of an aryne intermediate.

Substitution of an electron-withdrawing group at the β carbon increases the rates of β elimination as it increases the acidity of the β hydrogen.

The configuration of the substrate has, generally, a large effect on the reaction rate, anti elimination (H and X trans to each other) being faster than syn elimination. For example, the ratio of anti to syn elimination ($k_{E\text{ anti}}/k_{E\text{ syn}}$) is about 5×10^5 in the case of 1,2-dibromoethene reacting with methoxide ion at 60° ¹⁷ and about 3×10^3 for *p*-nitro- β -bromostyrene¹⁸ with *tert*-butoxide ion in *tert*-butyl alcohol at 30° . However, there are cases where the anti/syn reactivity ratios are much smaller. Elimination rates from chloromaleic and chlorofumaric acids¹⁹ or from *cis*- and *trans*-chlorocrotonitriles²⁰ are almost equal, the $k_{E\text{ anti}}/k_{E\text{ syn}}$ ratios being 12 and 2, respectively. Some data suggest that the reactivity ratios might decrease with increasing strength of the base and with increasing solvent basicity. For example, the $k_{E\text{ anti}}/k_{E\text{ syn}}$ ratio is 200 for the elimination from 1,2-diphenylchloroethenes by NaOH in 92.6% aqueous ethanol, but it is only 6 for the same reaction in the *tert*-butoxide-*tert*-butyl alcohol base-solvent system.²¹ No simple explanation of these facts can be given yet, since the mechanism of syn elimination is rather obscure. On the contrary the β anti elimination has been studied in some detail.

β Anti Elimination. The study of the β anti elimination indicates that acetylene-forming eliminations follow mechanisms very similar to those formulated for ethylene-forming eliminations. The same formalism may therefore be used for three principal mechanisms (eq 9-11). Intermediate mechanisms between E1 and E2 limits may be termed, after Bunnett,²² *paenecarbonium* mechanisms and between E2 and E1cB *paenecarbonium*.

The *paenecarbonium* range is practically unexplored. However, a few reports on elimination reactions from vinyl derivatives, probably occurring by *paenecarbonium* E2 mechanisms, have been published.²³ All

(14) Replacing of H's with larger groups could in principle alter the balance. The results available⁴ indicate that this is not the case. Probably a major role is played by the more polar nature of groups eclipsed in the route leading to inversion. Another factor in favor of retention of configuration could arise if the bond-making and bond-breaking processes are to some degree concerted with partial conservation of double bond character in the C-C bond.

(15) F. Naso, personal communication.

(16) Some reactivity ratios have been reported by S. I. Miller [*J. Org. Chem.*, **26**, 2619 (1961)]: e.g., 2-chloropropane/2-chloropropene = 20 at 109° ; β -bromoethylbenzene/ β -bromostyrene = 10^{-2} - 10^{-3} at 55° .

(17) S. I. Miller and R. M. Noyes, *J. Amer. Chem. Soc.*, **74**, 629 (1952).

(18) G. Marchese, G. Modena, F. Naso, and N. Tangari, *Boll. Sci. Fac. Chim. Ind. Bologna*, **26**, 209 (1968); *J. Chem. Soc. B*, 1196 (1970).

(19) S. J. Cristol and A. Begoon, *J. Amer. Chem. Soc.*, **74**, 5025 (1952).

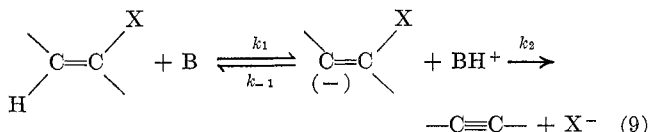
(20) F. Théron, Ph.D. Thesis, University of Clermont-Ferrand, Clermont-Ferrand, France, 1967.

(21) S. J. Cristol and C. A. Whittemore, *J. Org. Chem.*, **34**, 705 (1969).

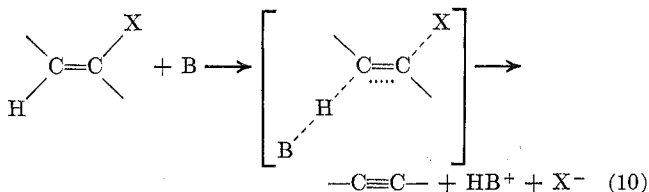
(22) J. F. Bunnett, *Surv. Progr. Chem.*, **5**, 53 (1969).

(23) M. Hanaack, *Accounts Chem. Res.*, **3**, 209 (1970).

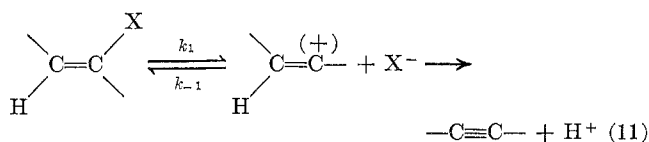
E1cB, or two-step elimination (eq 9)



E2, or concerted elimination (eq 10)



E1, or carbonium ion mechanism (eq 11)



the other studies deal with eliminations in the presence of strong bases, and a common feature is that C–H bond breaking is more advanced in the transition state than C–X bond breaking.

At least two cases of elimination occurring by way of an E1cB mechanism have been reported: elimination from *cis*-arylsulfonylchloro- and -bromoethylenes²⁴ and from 1,2-dihaloethylenes.²⁵ By using a labeled system it was observed that in both cases hydrogen–deuterium exchange at the β carbon is faster than elimination, the unreacted substrate having completely, or almost completely, exchanged at every stage of the reaction. Reaction rates depend strongly on the leaving group. Bromo derivatives usually react much more rapidly than the corresponding chloro compounds (see Table IV).

The reactivity of *trans* derivatives differs significantly from that of the *cis* isomers. *Trans* isomers undergo either elimination at a much slower rate²⁵ or substitution, since *syn* elimination is often too slow to compete with substitution.²⁴ This dependence of reactivity on the configuration of the substrate implies that vinyl carbanions are configurationally stable. This has been independently established by measuring separately the rates of hydrogen–deuterium exchange and of inversion in some activated ethylene derivatives not undergoing elimination.²⁶ Also, theoretical calculations suggest that the energy barrier for inversion at an sp^2 carbon may be fairly high.²⁷

Concerted mechanisms of the *paenecarbanion* kind have been identified in elimination from bromo- and

chlorostyrenes,¹³ chloro- and bromovinyl ketones,²⁸ bromocrotonate esters,²⁸ and bromocrotononitriles.²⁹ The concerted character of the eliminations cited is shown by the absence of substantial hydrogen–deuterium exchange at the β carbon in properly labeled systems (exchange from 0 to 15% at about 50% reaction) and by kinetic isotope effects which are small but significant ($k_{\text{H}}/k_{\text{D}} = 1.5\text{--}4.5$). More information on the properties of the transition states for concerted eliminations leading to acetylenes may be obtained by an analysis of the data available, particularly those concerning reactions of halostyrenes with alkoxide ions.^{6,13,18}

The two sets of results for reactions in methanol and *tert*-butyl alcohol with the lyate ion of the solvent as base (Table IV) show how the rates and the isotope effects are affected by structural variation: the rates are greater with the better leaving group ($\text{Br} > \text{Cl}$) and with nitro activation. The isotope effect decreases with decreasing leaving ability of the halogen and with increasing ability of the aryl group to stabilize the incipient carbanion. The effect of nitro substitution on rates is greater for chloro than for bromo derivatives.

The observed trends could have been anticipated on the basis of the variable transition-state theory for elimination leading to ethylenes,^{22,30} and it has been suggested^{13,18} that the same theory is also valid in the case of acetylene-forming elimination. The transition state is shifted toward the E1cB limit by dispersal of the charge at the β carbon (nitro activation in our case) and by increasing difficulty of C–X bond breaking. The anticipated shifts are manifested by the changes in isotope, element, and nitro activation effects.

However, when changes in base strength and solvent^{15,18} are considered (see Tables IV and V), some other factor must be invoked to rationalize the results. Indeed a stronger base (*tert*- $\text{C}_4\text{H}_9\text{O}^-$ or CH_3O^- in DMSO in our case) should cause a shift toward the E1cB limit. The same shift should be caused by poorer solvating media for the leaving group (*tert*- $\text{C}_4\text{H}_9\text{OH}$ and DMSO in our case). However these changes are accompanied by increased isotope effects. As far as the magnitude of the isotope effect may be taken as an indication of the degree of proton transfer to the base, these results indicate that the C–H bond is *less* broken in the transition state, a shift just in the opposite direction. On the contrary, other evidence (the greater effect of nitro substitution and the smaller leaving group effect) suggests that with the more basic nucleophiles the reactions have transition states less balanced as far as C–H and C–X bond breaking are concerned.

It seems, therefore, that the changes in the transition state anticipated by the theory are observed along

(24) (a) S. Ghersetti, G. Modena, P. E. Todesco, and P. Vivarelli, *Gazz. Chim. Ital.*, **91**, 620 (1961); (b) L. Di Nunno, G. Modena, and G. Scorrano, *J. Chem. Soc. B*, 1186 (1966).

(25) S. I. Miller and W. G. Lee, *J. Amer. Chem. Soc.*, **81**, 6313 (1959).

(26) D. H. Hunter and D. J. Cram, *ibid.*, **86**, 5478 (1964); D. Y. Curtin and J. W. Crump, *ibid.*, **80**, 1922 (1958); A. N. Nesmeyanov and A. E. Borisov, *Tetrahedron*, **1**, 158 (1957).

(27) G. W. Koepl, D. S. Sagatys, G. S. Krishnamurthy, and S. I. Miller, *J. Amer. Chem. Soc.*, **89**, 3396 (1967).

(28) See Table I, footnote *e*.

(29) F. Théron, *Bull. Soc. Chim. Fr.*, 278 (1969); see also ref 20.

(30) C. K. Ingold, *Proc. Chem. Soc.*, 225 (1962); J. F. Bunnett, *Angew. Chem., Int. Ed. Engl.*, **1**, 225 (1962); D. V. Banthorpe in "Studies on Chemical Structure and Reactivity," J. H. Ridd, Ed., Methuen, London, 1966, Chapter 3.

Table IV
Structural and Isotope Effects in Reactions of Various Halostyrenes with CH_3O^- in CH_3OH and with *tert*- $\text{C}_4\text{H}_9\text{O}^-$ in *tert*- $\text{C}_4\text{H}_9\text{OH}$ at 30° ¹⁸

	Rates (<i>k</i>)		Isotope effects (<i>k_H/k_D</i>)	
	$\text{CH}_3\text{OH}-\text{CH}_3\text{O}^-$	$\text{C}_4\text{H}_9\text{OH}-\text{C}_4\text{H}_9\text{O}^-$	$\text{CH}_3\text{OH}-\text{CH}_3\text{O}^-$	$\text{C}_4\text{H}_9\text{OH}-\text{C}_4\text{H}_9\text{O}^-$
<i>cis</i> - $\text{C}_6\text{H}_5\text{CH}=\text{CHBr}$	7.2×10^{-6}	2.3×10^{-2}	2.9 ^a	4.6
<i>cis-p</i> - $\text{NO}_2\text{C}_6\text{H}_4\text{CH}=\text{CHBr}$	1.4×10^{-8}	8.3	2.2 ^b	4.3
<i>cis</i> - $\text{C}_6\text{H}_5\text{CH}=\text{CHCl}$	2.3×10^{-8}	1.9×10^{-4}	2.2 ^c	3.2
<i>cis-p</i> - $\text{NO}_2\text{C}_6\text{H}_4\text{CH}=\text{CHCl}$	7.5×10^{-8}	2.2×10^{-1}	1.6 ^b	3.5

^a Calculated at 50° . ^b Calculated at 45° . ^c Calculated at 78.2° .

Table V
Effect of Dimethyl Sulfoxide (DMSO) on Rates and on Isotope Effects (*k_H/k_D*) of Anti β Elimination of *cis-p*- $\text{NO}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}-\text{Hal}$ with Methoxide Ion in Methanol at 20° ¹⁵

Solvent		Hal = Cl		Hal = Br	
CH_3OH , %	DMSO, %	<i>k</i> $\times 10^4$	<i>k_H/k_D</i>	<i>k</i> $\times 10^4$	<i>k_H/k_D</i>
100		0.014 ^a	1.6 ^b	3.5	2.2
75	25			120	2.8
50	50	32	2.1	4500	3.0
25	75	4100	2.4		

^a Extrapolated from data at higher temperatures. ^b At 100° .

with a displacement of the transition state toward a more "reactantlike" configuration due to the general effect of the stronger base.^{31,32}

The above evidence indicates that the β *anti* elimination may occur by a continuous spectrum of mechanisms in which the geometry of the transition state is continuously varied by the nature of the substrate, the nucleophile, the solvent, etc. This framework also accommodates the recently proposed (E1cB)_{ip} mechanism.³³ This requires a fast abstraction of the β proton by the base with the subsequent formation of a tight ion pair (within which the acid-base equilibrium is established) between the carbanion and the conjugate acid of the nucleophile, followed by the rate-limiting breaking of a C-X bond.

The (E1cB)_{ip} mechanism could also offer³³ a rationale for some eliminations which occur with very low isotope effects and small or no H-D exchange at the β carbon. On the other hand this may represent the merging point of *paenecarbanion* and E1cB mechanisms and adds further support to the hypothesis of the existence of a continuum of mechanisms from E1cB to E2 (and perhaps E1).

The relations between the strength and the nature of the activating group and the location of the mechanism along the reaction coordinate are not simple. Even though, as discussed above, within a homogeneous series of compounds an increased activation corresponds to a shift toward the E1cB limit, these observations

(31) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(32) For a discussion on this point for the olefin-forming elimination see: A. F. Cockerill, *J. Chem. Soc. B*, 964 (1967); A. F. Cockerill and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **89**, 4985 (1967); W. H. Saunders, Jr., and D. H. Edison, *ibid.*, **82**, 138 (1960); C. G. Swain and E. R. Thornton, *ibid.*, **84**, 817 (1962); L. J. Steffa and E. R. Thornton, *ibid.*, **89**, 6149 (1967); G. M. Fraser and H. M. R. Hoffmann, *J. Chem. Soc. B*, 265 (1967).

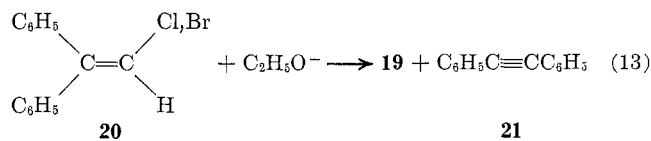
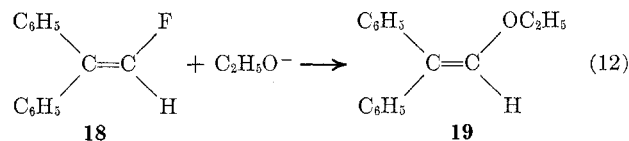
(33) W. K. Kwok, W. G. Lee, and S. I. Miller, *J. Amer. Chem. Soc.*, **91**, 468 (1969).

cannot be generalized. Indeed there are strong indications that other factors are more important than activation in determining the position of the transition state along the reaction coordinate. There are fast and slow concerted eliminations as well as fast and slow E1cB eliminations. So far, elimination by the E1cB mechanism seems to be promoted most effectively by activating groups of the third or higher periods (SO_2 , halogens),^{24,25} whereas concerted elimination seems to be favored when the activating group is a carbon derivative.^{13,28,29}

Competition between Substitution and Elimination Reactions

Many data on the competition between β elimination and substitution are available, and the factors which effect the balance between the two reaction paths are of considerable interest. This is, of course, only one type of competition between mechanisms. Almost all the other conceivable competitions between two or more of the reaction paths listed above may be observed in the reactions of vinylic substrates with bases.

One well-known case of competition between substitution and α elimination is represented by the reactions of 1,1-diphenyl-2-haloethenes with ethoxide ion:^{34,35} the fluoro derivative³⁵ reacts by substitution (eq 12) whereas the chloro and bromo derivatives react by substitution or by α elimination with rearrangement (eq 13) in different proportion depending



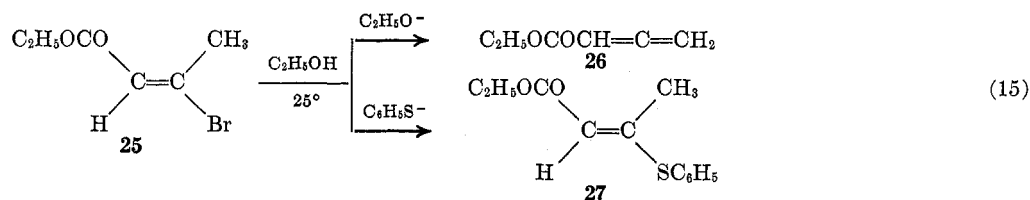
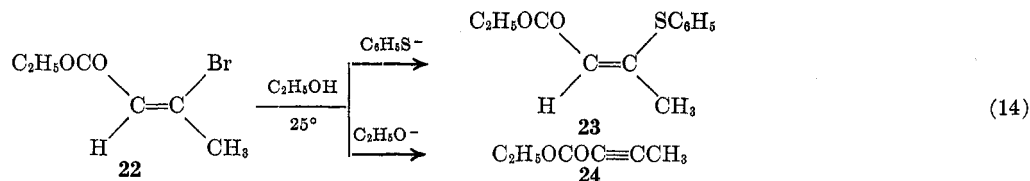
on the leaving group and substituents in the phenyl rings.³⁴

An example of the much less studied competition between substitution, β elimination, and β' elimination

(34) P. Beltrame and S. Carrá, *Gazz. Chim. Ital.*, **89**, 2027 (1959); **91**, 889 (1961); P. Beltrame and G. Favini, *ibid.*, **93**, 757 (1963); P. Beltrame and G. Cortili, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Natur., Rend.*, **39**, 284, 475 (1965); P. Beltrame and D. Pitea, *Chim. Ind. (Milan)*, **49**, 56 (1967).

(35) E. F. Silversmith and D. Smith, *J. Org. Chem.*, **23**, 427 (1958).

Scheme II



(see eq 4) is presented by the reaction of ethyl bromocrotonates,²⁹ which is summarized in Scheme II.

The variety of mechanisms available and the possibility that the same final product may be formed by different mechanisms call for particular caution in studying vinylic reactions. The most powerful tests so far used to identify the reaction mechanism are: (i) experiments to detect H-D exchanges in the unreacted substrate as well as in the products by isotopic labeling of substrate or solvent; (ii) measures of kinetic isotope effects; (iii) analysis of the reacting system by physical methods from the very early stages of the reaction to detect transient intermediates or better to identify the kinetically controlled product of the reaction; and (iv) analysis of the activation parameters. The last test proved to be very useful in detecting changes of mechanism within a related series of reactions, particularly when the change in mechanism is not accompanied by a dramatic change in reaction rate.

Activation parameters are often quite different for different mechanisms. For example, β anti elimination, which frequently competes with direct substitution, has an entropy of activation either positive or slightly negative, whereas substitution has definitely negative entropies. In these cases the change of mechanism is shown by change in the activation parameters (Table VI).

Competition between β Elimination and Substitution.

The factors which affect the competition between the two reaction paths are those that could have been anticipated by an analysis of the factors which influence the isolated reactions. The electrophilic center is different (H and C), the breaking of the C-X bond is differently situated with respect to the energy maximum, and, finally, the two reactions have different stereochemical requirements. Hence, the competition is controlled by the nature of the nucleophile, by the leaving group, and by the configuration of the substrate. The competition is also affected by the level of activation since activation has qualitatively but not quantitatively the same effect on the two paths. Also, the solvent modifies the balance between substitution and elimination since it modifies the property of the nucleophile and, probably, the energetics of the C-X bond-breaking process.

Effect of the Nucleophile. Two typical nucleophiles have been widely investigated, benzenethiolate and methoxide ions (as well as similar sulfur and oxygen nucleophiles). They have quite different behavior. The sulfur nucleophiles in almost every case attack carbon and hence react by direct substitution; the oxygen nucleophiles prefer to attack hydrogen, and this leads to elimination. However, the separation is not sharp. At least one case in which a sulfur nucleophile reacts *via* elimination has been reported ($\text{C}_2\text{H}_5\text{S}^- + \text{cis-}\beta\text{-bromocrotononitrile}$ in ethanol).²⁹ On the other hand, alkoxide ions are much less selective. Because the elimination reaction, unlike direct substitution, is sensitive to the configuration of the reagent and to the leaving group, reactions with alkoxide ions follow either one or the other mechanism depending on the configuration of the substrate and on the nature of the leaving group.^{4a}

Investigations on the behavior of other nucleophiles are scarce. From the data available it seems that azide,^{30,36} phosphide,^{37,38} arsenide,^{38,39} and halide ions^{1c,40} as well as primary and secondary amines^{36,41} react preferentially by direct substitution. Carbanions, on the other hand, react by elimination or substitution depending on the particular system investigated.^{4a,36,42}

In conclusion, strongly basic nucleophiles react, as far as possible, *via* attack at hydrogen (elimination), whereas less basic nucleophiles of high polarizability prefer to react *via* attack at carbon (substitution). The same kind of behavior is well established for reactions of alkyl halides.⁴³

(36) J. S. Meek and J. S. Fowler, *J. Org. Chem.*, **33**, 985 (1968).

(37) A. M. Aguiar and D. Daigle, *J. Amer. Chem. Soc.*, **86**, 2299 (1964); *J. Org. Chem.*, **30**, 2826, 3527 (1965).

(38) G. Marchese and F. Naso, *Boll. Sci. Fac. Chim. Ind. Bologna*, **26**, 283 (1968).

(39) A. M. Aguiar and T. G. Archibald, *J. Org. Chem.*, **32**, 2627 (1967).

(40) P. Beltrame, P. L. Beltrame, G. Carboni, and M. L. Cereda, *J. Chem. Soc. B*, 730 (1970).

(41) (a) S. Ghersetti, G. Lugli, G. Melloni, G. Modena, P. E. Todesco, and P. Vivarelli, *ibid.*, 2227 (1965); (b) W. E. Truce, J. E. Parr, and M. L. Gorbarty, *Chem. Ind. (London)*, 660 (1967); (c) J. C. Chalchat, F. Théron, and R. Vessière, *C. R. Acad. Sci., Ser. C*, **267**, 1864 (1968).

(42) G. Köbrich, *Angew. Chem., Int. Ed. Engl.*, **4**, 49 (1965).

(43) G. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1969, Chapter 7.

Table VI
Activation Parameters of the Reactions (Elimination and Substitution) of Haloethylenes with Methoxide Ion in Methanol

Substrate		Elimination		Substitution		Ref
		E_a , kcal/mole	ΔS^\ddagger_{25} , cal/deg mole	E_a , kcal/mole	ΔS^\ddagger_{25} , cal/deg mole	
$p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}=\text{CHBr}$	<i>cis</i>	25	8.8			6
	<i>trans</i>			25	-3	6
$p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{CH}=\text{CHCl}$	<i>cis</i>	24	26	17	-7	24b
	<i>trans</i>			17	-8	24b
$p\text{-CH}_3\text{OC}_6\text{H}_4\text{COCH}=\text{CHCl}$	<i>cis</i>	19	0.5 ^a			28
	<i>trans</i>			13.5	-18 ^a	28
$p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}=\text{CHF}$	<i>cis</i>			21	-7	13b
	<i>trans</i>			20	-8	13b

^a At 0°.

Effect of Configuration and Activation of the Substrate. At low levels of activation and with alkoxide ions or similar strongly basic nucleophiles, the β -elimination reactions, either syn or anti, are practically the only ones observed. However, sometimes α or β' eliminations intrude.

On activated substrates, substitution becomes competitive with β -elimination reactions. The difference in rates of syn and anti elimination determines the typical picture that substitution is faster than syn elimination but slower than anti elimination. Consequently, in many cases *trans* substrates⁴ react by substitution and not by elimination (which would be syn elimination), and *cis* substrates, where H and X are *trans* to each other, react *via* the more facile anti elimination. Of course, changes in the nature of the nucleophile as well as changes in the solvent or leaving group may shift the balance to give either elimination or substitution with both substrates.

Effect of the Leaving Group. The different sensitivity of elimination and substitution with the leaving group causes a crossover of the two mechanisms upon changing the nature of the leaving group. Typical examples are series of fluoro, chloro, and bromo derivatives (see Table VII). As said above the rate of elimination is much greater for bromo than for chloro derivatives. Although comparable data for fluoro compounds are not available, they should be much less reactive than either chloro or bromo analogs. On the contrary, the rate of substitution is almost independent of the leaving group, being with fluoro compounds somewhat faster than with chloro and bromo derivatives. Consequently, when the rate of elimination is faster than that of substitution with bromoethylenes, which is often the case, it may occur that the balance between the two reaction paths is greatly

Table VII
Effect of Leaving Group on the Competition between Elimination and Substitution in the Reactions of Haloethylenes with Methoxide Ion in Methanol

	Temp, °C	Elimination, %	Ref
<i>cis-p-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{CH}=\text{CHBr}</i>	0	100	24a
<i>cis-p-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{CH}=\text{CHCl}</i>	0	50	24a
<i>cis-p-NO}_2\text{C}_6\text{H}_4\text{CH}=\text{CHBr}</i>	45	100	6
<i>cis-p-NO}_2\text{C}_6\text{H}_4\text{CH}=\text{CHCl}</i>	45	90	13a
<i>cis-p-NO}_2\text{C}_6\text{H}_4\text{CH}=\text{CHF}</i>	45	0	13b

modified with chloro analogs, substitution being either predominant or significant. The inertia of fluoro derivatives toward elimination is such that quite often the substitution reaction is the only one observed. The poor leaving ability of fluoride ion is also confirmed by the loss of stereoselectivity on passing from bromo or chloro to fluoro derivatives.

The few examples of competition discussed in this Account are indicative of how close is the balance among different mechanisms of reactions occurring at an ethylenic center. Indeed minor variations of either structural factors, reagent, or reaction medium quite often cause a dramatic change in mechanism.

This great flexibility of ethylenic systems may prove useful in studying the properties of nucleophiles and leaving groups as well as solvent effects. Indeed the behavior of sulfur and oxygen nucleophiles is more differentiated in reactions at ethylenic than at aliphatic or aromatic centers.

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