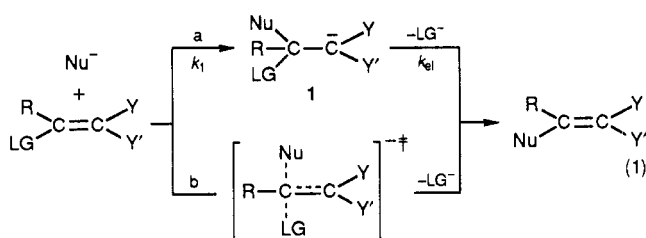# The Rapid Steps in Nucleophilic Vinylic "Addition–Elimination" Substitution. Recent Developments[1,2]

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In an earlier Account we addressed the question of a single-step vs multistep mechanism in nucleophilic vinylic substitution.[3] This is formulated in eq 1, where Nu^-, LG, and Y and Y' are the nucleophile, the leaving group (nucleofuge), and the electron-withdrawing activating substituents, respectively. The so-called "ad-


dition–elimination" route[2] commences by nucleophilic attack on C_β, and the question is whether it gives a discrete carbanion 1 which then expels the LG^- (multistep route a) or, on the other hand, it is coupled with nucleofuge expulsion (concerted single-step route b). We suggested that "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."[3] In other words, route b may be enforced if the lifetime of the intermediate is shorter than that of a bond vibration. On the basis of k_{Br}/k_{Cl} and k_{Cl}/k_F element effects, the stereochemistry, and MO calculations we concluded that almost all the results are consistent with route a.[3]

The main problem is that for "good" nucleofuges, i.e., LG = Cl, Br, and OSO_2R, the intermediate's lifetime is so short that experimental evidence for the involvement of the carbanion 1 is scarce. Although there are new results concerning the single-step vs multistep mechanisms,[4] our purpose here is to review only the recent experimental evidence for the involvement of 1 in vinylic substitution of activated systems. These include probes related to the rapid second step(s) of route a, i.e., internal rotation in 1 and expulsion of LG from 1 which occur after the rate-determining k_1. Such probes are the stereochemistry, nulceophilic isomerization, the intramolecular element effect, and the observation of the intermediate in favorable systems.

Stereochemistry. When we began our work, almost all the known nucleophilic substitutions of good nucleofuges proceeded with retention of configuration.[2]

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This seemed consistent with route b since carbanions with sufficient lifetimes even for one internal rotation should give a complete or a partial stereoconvergence. Only when MO calculations showed an appreciable hyperconjugative barrier for the rotation[5] did retention via the multistep route become a feasible process.[3] The barrier results from the overall stabilizing interaction of the C–X with the $C^-(2p)$ orbitals, which is at a maximum for 2a and is not present in 2b. The barrier is higher when X = Cl, Br, or OSO_2R than for other substituents, and hence in conformer 1a it favors 60° internal rotation (leading to retention) over 120° rotation (leading to inversion).[5]
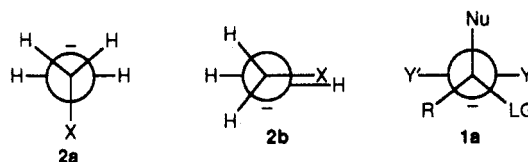
In our stereochemical approach the hyperconjugative barrier is reduced by studying systems which are highly activated by strongly resonative electron-withdrawing Y and Y'. Delocalization of the negative charge in 1a on Y and Y' reduces both the rotational barrier and k_{el}, thus increasing the probability of stereoconvergence. Formation of the same E-RNu/Z-RNu mixture or a single product from both E-RX and Z-RX is defined as complete stereoconvergence whereas it is a partial stereoconvergence when E-RX and Z-RX give different E-RNu/Z-RNu ratios.

It is essential to study the stereochemistry of both isomers, and hence the stereochemical tool is tedious. Both E-RX and Z-RX and both E-RNu and Z-RNu should be prepared, separated, assigned, and studied, and the E-RX ⇌ Z-RX and E-RNu ⇌ Z-RNu equilibria should be determined.

We have substituted 14 electrophilic alkenes differing in two aryl groups, in six combinations of Y and Y' and in six LG, by p-toluenethiolate ion ($TolS^-$), mostly also

(1) Presented at the 7th European Symposium on Organic Chemistry (ESOC 7), Namur, Belgium, July 15–19, 1991; Abstract, p 26.

(2) For general references of nucleophilic vinylic substitution, see: Rappoport, Z. Adv. Phys. Org. Chem. 1969, 7, 1; Recl. Trav. Chim. Pays-Bas 1985, 104, 309. Reference 3; Modena, G. Acc. Chem. Res. 1971, 4, 73. Miller, S. I. Tetrahedron 1977, 33, 1211. Shainyan, B. A. Usp. Khim. 1986, 35, 942.

(3) Rappoport, Z. Acc. Chem. Res. 1981, 14, 7.

(4) (a) Cohen, D.; Bar, R.; Shaik, S. S. J. Am. Chem. Soc. 1986, 108, 231. (b) Ochiai, M.; Oshima, K.; Masaki, Y. Ibid. 1991, 113, 7059. (c) Hoz, S.; Basch, H.; Wolk, J. L.; Rappoport, Z.; Goldberg, M. J. Org. Chem. 1991, 56, 5424.

(5) (a) Apeloig, Y.; Rappoport, Z. J. Am. Chem. Soc. 1979, 101, 5095. (b) Apeloig, Y.; Karni, M.; Rappoport, Z. Ibid. 1983, 105, 2784. (c) Karni, M.; Apeloig, Y. Unpublished results. (d) Rappoport, Z.; Avramovitch, B.; Karni, M.; Apeloig, Y. Isr. J. Chem. 1989, 29, 269.

Table I. Stereochemistry of the Substitution of Activated Halo-Substituted Olefins with TolS⁻

substrate	geometry	solvent	E-RNu/Z-RNu	ref
PhC(I)=C(Ph)NO₂ (3)	E	EtOH	100/0	6
	Z		100/0	
PhC(Cl)=C(Ph)CHO (4)	E	DMF	100/0	7a
	Z		100/0	
p-O₂NC₆H₄C(Cl)=C(CHO)CO₂Me (5)	E	DMSO-d₆	52/48	7b
	Z		46/54	
p-O₂NC₆H₄C(Cl)=C(CN)CO₂Me (6)	E	CD₃CN	34/66	8
	Z		11/89	
p-MeC₆H₄C(Br)=C(CO₂Me)CO₂Bu-t (7)	E	DMSO-d₆	100/0	7b
	Z		0/100	

Table II. Kinetically Controlled E-RNu/Z-RNu Ratios from 10 or 11 with Nu⁻Na⁺

substrate	nucleophile	solvent	[E-Nu]/[Z-Nu]
10	PhO⁻	95/5 CD₃CN–DMSO-d₆	90/10
	p-TolO⁻	95/5 CD₃CN–DMSO-d₆	97/3[a]
	p-AnO⁻	95/5 CD₃CN–DMSO-d₆	89/11
	p-ClC₆H₄S⁻	95/5 CD₃CN–DMSO-d₆	90/10
	p-TolS⁻	95/5 CD₃CN–DMSO-d₆	90/10
		(CD₃)₂CO	96/4
	N₃⁻	95/5 CD₃CN–DMSO-d₆	95/5[b]
11	p-BrC₆H₄O⁻	CD₃CN	92/8
	PhO⁻	CD₃CN	93/7
	p-TolO⁻	CD₃CN	91/9
		DMSO-d₆	87/13
	p-MeOC₆H₄O⁻	CD₃CN	96/4
		DMSO-d₆	96/4
	p-ClC₆H₄O⁻	95/5 CD₃CN–DMSO-d₆	91/9
	p-TolS⁻	95/5 CD₃CN–DMSO-d₆	88/12

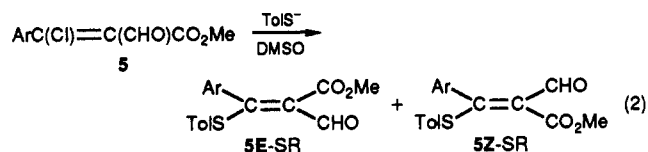[a] p-TolO⁻Li⁺, 86/14; p-TolO⁻K⁺, 90/10. [b] As a K⁺ salt.

by p-cresolate (TolO⁻) ion, and sometimes with other nucleophiles. Table I summarizes the kinetically controlled isomeric product compositions for reaction of TolS⁻ with five electrophilic vinyl halides (3–7), which appear in the table in the order of decreasing electrophilicity.

For **3** or **4** both E-RX and Z-RX give a single geometrically pure substitution product, i.e., complete stereoconvergence.[6,7a] The structure of the product from **3** is tentatively assigned as E on steric grounds, which may be erroneous since substitution of (E)- and (Z)-RC(NO₂)=C(NO₂)R with amines and NCS⁻ yielded only (Z)-RC(Nu)=C(NO₂)R, Nu = R₂N, NCS,[9] although previously an E configuration was tentatively assigned on steric grounds.[6a] In contrast, the product from **4** with TolS⁻ has the E configuration on the basis of X-ray crystallography; other products were assigned by NMR. The complete stereoconvergene is consistent with the high negative charge dispersal by single NO₂ and CHO groups that is enhanced by the presence of the phenyl group.
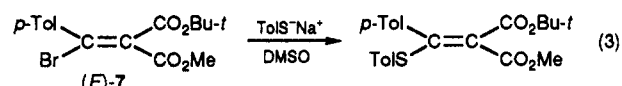
Compound **5**, which is formally more activated than **4**, since $\sigma_{CO_2Me} > \sigma_{Ph}$, reacts with TolS⁻ in DMSO in <2 min, to give completely both **5E-SR** and **5Z-SR** (eq 2). At [ArS⁻]/[RCl] = 1.1–1.2 the **5E-SR/5Z-SR** ratios are 46/54 from both isomers after 38–48 min. However, when the ratio is monitored immediately after completion of the reaction, a nulceophilic **5E-SR** ⇌ **5Z-SR** isomerization is observed. At [ArS⁻]/[RCl] = 0.5, the

(6) (a) Rappoport, Z.; Topol, A. *J. Am. Chem. Soc.* **1980,** *102,* 406; (b) *J. Org. Chem.* **1989,** *54,* 5967.
(7) (a) Rappoport, Z.; Gazit, A. *J. Org. Chem.* **1985,** *50,* 3184; (b) **1986,** *51,* 4112.
(8) Rappoport, Z.; Avramovitch, B. *J. Org. Chem.* **1982,** *47,* 1397.
(9) Park, K. P.; Ha, H.-J. *Bull. Chem. Soc. Jpn.* **1990,** *63,* 3006.

isomerization is slower and the **5E-SR/5Z-SR** ratios are 56/44 after 13 min from (E)-**5** and 36/64 after 10 min from (Z)-**5**. Extrapolation to zero reaction gives 52/48 and 45/55 ratios, respectively, i.e., a very slight preferred retention for each isomer.[7b]

$$ArC(Cl)=C(CHO)CO_2Me \xrightarrow[DMSO]{TolS^-}$$
5

$$\underset{\textbf{5E-SR}}{\overset{Ar}{\underset{TolS}{>}}C=C\overset{CO_2Me}{\underset{CHO}{<}}} + \underset{\textbf{5Z-SR}}{\overset{Ar}{\underset{TolS}{>}}C=C\overset{CHO}{\underset{CO_2Me}{<}}} \quad (2)$$

Since $\sigma_{CN} < \sigma_{CHO}$, a lower activation is expected for compound **6** than for **5**. Indeeed, (E)-**6** and (Z)-**6** formed both isomeric thioethers in appreciably different ratios. The extents of stereoconvergence based on the ratios in Table I and on the [E-RSTol]/[Z-RSTol] equilibrium ratio of 15/85 are 74 ± 1% starting from either stereoisomer.[8]

Each isomer of the least activated system, **7**, gives exclusively the retained product, as demonstrated in eq 3 for (E)-**7**.[7b]

$$\underset{(E)\text{-}\textbf{7}}{\overset{p\text{-Tol}}{\underset{Br}{>}}C=C\overset{CO_2Bu\text{-}t}{\underset{CO_2Me}{<}}} \xrightarrow[DMSO]{TolS^-Na^+} \overset{p\text{-Tol}}{\underset{TolS}{>}}C=C\overset{CO_2Bu\text{-}t}{\underset{CO_2Me}{<}} \quad (3)$$

Consequently, our hypothesis was borne out: highly electrophilic haloalkenes react with TolS⁻ to form carbanions which are sufficiently long-lived to undergo >60° rotation before nucleofuge expulsion. The Curtin–Hammett principle predicts complete stereoconvergence if the internal rotation rate (k_{rot}) appreciably exceeds the nucleofuge expulsion rate (k_{el}). This applies for systems **3** and **4** and probably for **5**. With **6**, $k_{rot} \approx k_{el}$, whereas for **7**, $k_{rot}(60°) \gg k_{rot}(120°)$; $k_{rot}(180°) < k_{el}$ (cf. eq 4).
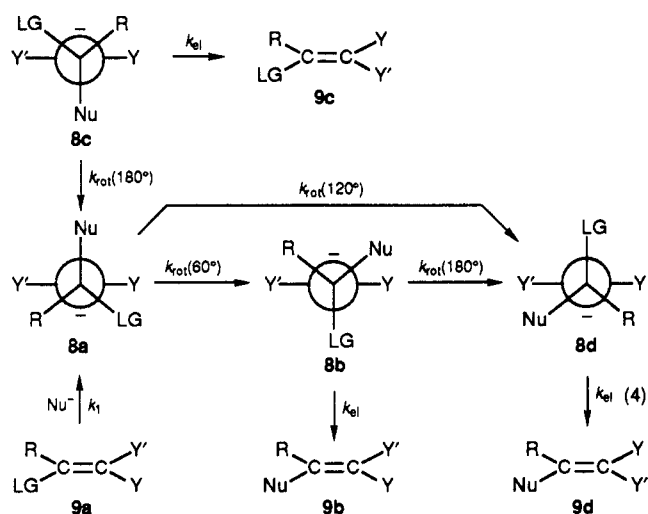
Questions of interest in connection with eq 4 include the following: (a) What is the effect of the nulceophile on the relative $k_{rot}(60°)$, $k_{rot}(120°)$, $k_{rot}(180°)$, and k_{el} rates? (b) What is the effect of the nucleofuge, the solvent, or the counterion of Nu⁻ on these parameters? (c) Could we distinguish between "inversion" products arising by a "counterclockwise" 120° (**9a → 8a → 8d → 9d**) rotation and a 240° "clockwise" rotation (**9a → 8a → 8b → 8d → 9d**)?

In discussing the effect of the nucleophile we should remember that thiolates are good single-electron (SE) donors and the low-LUMO alkenes are good SE acceptors. Consequently, substitution may proceed by a sequence of initial SET → radical/anion radical recombination giving 1 → LG expulsion. Internal rotation in the radical ion may then lead to stereoconvergence even if 1 completely expels the nucleofuge after 60° rotation. Assuming that a reversible ET from both isomeric radical anions will give precursor isomerization, we searched for (*E*)-3 after substitution of (*Z*)-3 with 0.5 equiv of TolS⁻ but found none.[6] This and the partial stereoconvergence observed with weaker SE donor oxygen nucleophiles argue against this route.

The extent of stereoconvergence is predicted to be nucleophile-independent if the rotational barrier is only hyperconjugative.[5a] However, steric effects are nucleophile-dependent since in the 60° rotation leading to retention the nucleophile is not involved in an eclipsing interaction, whereas it eclipses Y' or Y in the 120° or 240° rotation leading to inversion.

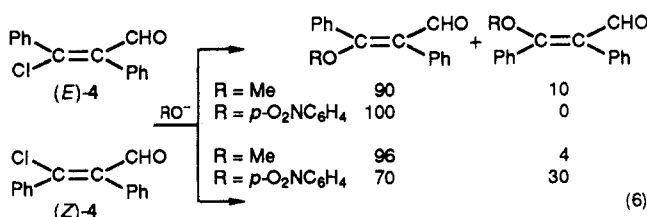The stereochemistry of substitution of systems 3–7 with oxygen and sometimes with nitrogen nucleophiles was also investigated. The slow reaction of (*E*)-3 with MeO⁻ in 6/100 MeOH–MeCN gives after 140 h at room temperature 56% of 3/7 E-ROMe/Z-ROMe products and 4% of a disubstitution product (eq 5a).[7a] The

$$\underset{(E)-3}{\overset{Ph}{\underset{I}{\diagup}}C=C\overset{NO_2}{\underset{Ph}{\diagdown}}} \quad \xrightarrow[\text{MeOH–MeCN}]{\text{MeO}^-}$$

$$\underset{\text{E-ROMe}}{\overset{Ph}{\underset{MeO}{\diagup}}C=C\overset{NO_2}{\underset{Ph}{\diagdown}}} + \underset{\text{Z-ROMe}}{\overset{Ph}{\underset{MeO}{\diagup}}C=C\overset{Ph}{\underset{NO_2}{\diagdown}}} + \underset{4\%}{\overset{Ph}{\underset{MeO}{\diagup}}C=C\overset{OMe}{\underset{Ph}{\diagdown}}} \quad (5a)$$

$$\underset{\substack{\text{N}\diagdown_O\diagup\text{N}\\ \diagdown O \diagdown O}}{Ph-C——C-Ph} \xleftarrow[-N_2]{N_3^-} \underset{(Z)-3}{\overset{(E)-3}{\text{or}}} \xrightarrow[X = O, CH_2]{\overset{X}{\underset{}{\diagup}}NH} \underset{\text{RNH}}{\overset{Ph}{\underset{RNH}{\diagup}}C=C\overset{Ph}{\underset{NO_2}{\diagdown}}} \quad (5b)$$
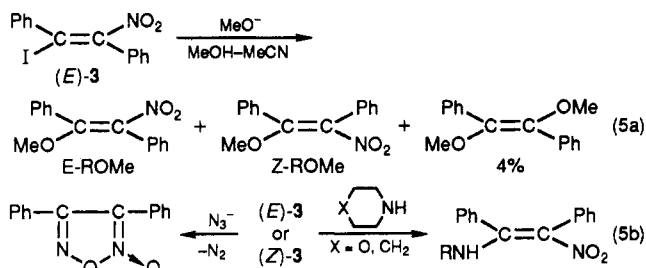
formation of the latter, presumably by a further substitution on E/Z-ROMe, is surprising since the MeO-substituted carbon is more electrophilic. In contrast, both (*E*)-3 and (*Z*)-3 give with N₃⁻ the same furoxan, formed after loss of N₂, and the same isomer, presumably the intramolecularly hydrogen bonded *Z* isomer from morpholine and piperidine (eq 5b).[6] However, the apparent stereoconvergence with these nucleophiles may take place after formation of a different kinetically controlled ratio either during the multistep reaction leading to the furoxan or by an intramolecular rotation around the C_α–C_β bond in the push–pull product enamines.
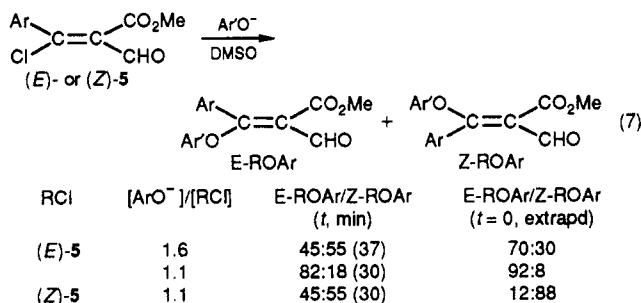
Other systems also give lower extents of stereoconvergence with oxygen nulceophiles. MeO⁻ and *p*-O₂NC₆H₄O⁻ give mainly the *E* product with (*E*)-4 and (*Z*)-4, but the *E/Z* product ratios from both isomers with MeO⁻ are much closer to one another than with the phenoxide (eq 6).[7a]
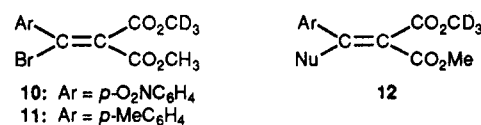
$$\underset{(E)-4}{\overset{Ph}{\underset{Cl}{\diagup}}C=C\overset{CHO}{\underset{Ph}{\diagdown}}} \longrightarrow \underset{RO}{\overset{Ph}{\underset{RO}{\diagup}}C=C\overset{CHO}{\underset{Ph}{\diagdown}}} + \underset{Ph}{\overset{RO}{\underset{Ph}{\diagup}}C=C\overset{CHO}{\underset{Ph}{\diagdown}}}$$

R = Me	90	10
R = *p*-O₂NC₆H₄	100	0

$$\underset{(Z)-4}{\overset{Cl}{\underset{Ph}{\diagup}}C=C\overset{CHO}{\underset{Ph}{\diagdown}}} \qquad \text{RO}^-$$

R = Me	96	4
R = *p*-O₂NC₆H₄	70	30

$$(6)$$

Table III. Stereochemistry and Percent Stereoconvergence (SC) in the Substitution of (*E*)-13 and (*Z*)-13 by Nu⁻Na⁺ in CD₃CN

substrate	X	Nu = TolO⁻		Nu = TolS⁻	
		E-RNu/Z-RNu	% SC	E-RNu/Z-RNu	% SC
(*E*)-13	Cl	68/32	100	36/64	75
	Br	70/30	100	37/63	79
	OMs	83/17	61	63/37	42
	OTs	88/12	43	59/41	48
	OTf	90/10	36	45/55	65
(*Z*)-13	Cl	21/79	29	89/11	73
	Br	26/74	36	95/5	33
	OMs	27/73	38	95/5	33

The difference between kinetically controlled and thermodynamically controlled product ratios is demonstrated in the reaction of 5 with *p*-O₂NC₆H₄O⁻ (Ar'O⁻) in DMSO (eq 7). The apparent stereoconvergence observed after 30–37 min arises from a rapid (presumably Ar'O⁻-assisted) E-ROAr ⇌ Z-ROAr isomerization. The extrapolated kinetically controlled ratio indicates a preferred retention (85% and 78%, respectively, for (*E*)-5 and (*Z*)-5 based on the E-ROAr/Z-ROAr equilibrium).[7b] TolO⁻ also gives partial stereoconvergence with compound 6 (cf. Table III).

$$\underset{(E)\text{- or }(Z)\text{-5}}{\overset{Ar}{\underset{Cl}{\diagup}}C=C\overset{CO_2Me}{\underset{CHO}{\diagdown}}} \xrightarrow[\text{DMSO}]{\text{Ar'O}^-}$$

$$\underset{\text{E-ROAr}}{\overset{Ar}{\underset{Ar'O}{\diagup}}C=C\overset{CO_2Me}{\underset{CHO}{\diagdown}}} + \underset{\text{Z-ROAr}}{\overset{Ar'O}{\underset{Ar}{\diagup}}C=C\overset{CO_2Me}{\underset{CHO}{\diagdown}}} \quad (7)$$

RCl	[Ar'O⁻]/[RCl]	E-ROAr/Z-ROAr (*t*, min)	E-ROAr/Z-ROAr (*t* = 0, extrapd)
(*E*)-5	1.6	45:55 (37)	70:30
	1.1	82:18 (30)	92:8
(*Z*)-5	1.1	45:55 (30)	12:88

Can a system be found near the stereoconvergence/retention border for which the effect of a nucleophile can be easily evaluated? From the results for 6 and 7 in Table I, a system with sterically less demanding ester groups than in 7 may be near the stereoconvergence side of the border. We therefore prepared stereospecifically the two methyl trideuteriomethyl (*E*)-(aryl-bromomethylene)malonates 10 and 11 having chemically identical but NMR-distinguishable activating COOR groups in the isotopomeric products (*E*)-12 and (*Z*)-12.[10] The system has many practical advantages,

$$\underset{\substack{\text{10: Ar = } p\text{-O}_2NC_6H_4 \\ \text{11: Ar = } p\text{-MeC}_6H_4}}{\overset{Ar}{\underset{Br}{\diagup}}C=C\overset{CO_2CD_3}{\underset{CO_2CH_3}{\diagdown}}} \qquad \underset{12}{\overset{Ar}{\underset{Nu}{\diagup}}C=C\overset{CO_2CD_3}{\underset{CO_2Me}{\diagdown}}}$$

especially that it suffices to study only the *E* precursors 10 or 11 so that precursor separation is avoided. Also, at equilibrium (E-RNu)/(Z-RNu) = 1 and the stereochemistry of E-RNu and Z-RNu is easily assigned by δ(CO₂Me).

The kinetically controlled E-RNu/Z-RNu ratios for substitution of 10 and 11 with several nucleophiles are given in Table II. Both 10 and 11 are on the stereoconvergence side very near the border. The retained product is formed in >87% but <100% yield in all 15 Nu⁻/solvent combinations. Most importantly, changes

(10) Rappoport, Z.; Gazit, A. *J. Am. Chem. Soc.* 1987, *109*, 6698.

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in the α-aryl substituent (p-O$_2$NC$_6$H$_4$, p-Tol), the nucleophile (ArO$^-$, ArS$^-$, N$_3^-$), the solvent (DMSO, CD$_3$-CN), or the counterion (Li$^+$, Na$^+$, K$^+$) have no significant effect on the extent of stereoconvergence.

A reasonable prediction[3] is that a change from a good to a poor nucleofuge will increase the lifetime of carbanion 1 and hence will lead to a higher extent of stereoconvergence. This was observed on changing the nucleofuge from Br or Cl to F in moderately activated systems.[2,3] Little was known on this effect in the stereoconvergence region. Hence, methyl (E)- and (Z)-α-cyano-β-X-p-nitrocinnamates p-O$_2$NC$_6$H$_4$C(X)=C-(CN)CO$_2$Me ((E)-13 and (Z)-13, X = Cl, Br, OTs, OMs, OTf) were substituted with p-TolS$^-$ and p-TolO$^-$ having Li$^+$, K$^+$, and Na$^+$ counterions.[11]

All the kinetically controlled ratios (given for the Na$^+$ salts in Table III) indicate a partial stereoconvergence. The percentages of stereoconvergence were calculated by using the E-OTol/Z-OTol and E-STol/Z-STol equilibrium ratios. With TolS$^-$, the E-RNu/Z-RNu ratios changed only slightly and irregularly when the counterion was changed from Li$^+$ to Na$^+$ to K$^+$. With TolO$^-$ the K$^+$ salt gave mostly somewhat higher percentages of retention.

Table III shows that the extent of retention for (E)-13 increases with the increased nucleofugality. The apparently opposite trend for (Z)-13 may result from the small absolute changes due to the predominance of E-RNu at equilibrium. Also, higher retention was observed for (Z)-13.

Consequently, either $k_{\rm rot} \approx k_{\rm el}$ or $k_{\rm rot}(60°) \approx k_{\rm rot}(120°)$ so that the expected effect of X on both $k_{\rm el}$ and $k_{\rm rot}$ should be evaluated. In S$_N$1 or E1 reactions $k_{\rm Br}/k_{\rm Cl}$ = 10–10^3, $k_{\rm OTs}/k_{\rm Br}$ = 10^2–10^3, and $k_{\rm OTf}/k_{\rm OTs}$ = 10^4–10^5,[11] and hence the ease of C–X bond cleavage follows the order OTf $\gg$ OTs $\approx$ OMs > Br > Cl. Although the differences in $k_{\rm el}$ values for 1 are expected to be lower, the observed differences in the percentage of stereoconvergence are so small that they are unlikely to result from an exclusive C–X bond cleavage in the product-determining step.

$k_{\rm rot}$ is affected both by hyperconjugation and by steric effects. The calculated hyperconjugative stabilization values[5b–d] give the qualitative order OTf > Br > Cl $\geqslant$ OMs $\approx$ OTs for the hyperconjugation contribution for preferential 60° over 120° rotation. The eclipsing steric interactions in carbanion 14 formed from (E)-13 are Ar/CO$_2$Me for 60° clockwise rotation and X/CN; Nu/CO$_2$Me for 120° counterclockwise rotation. For 15, derived from (Z)-13, they are Ar/CN and X/CO$_2$Me; Nu/CN for the corresponding rotations. The relative steric interaction in the 60° rotation and the more severe one is the 120° rotation determine the steric component of the barrier. Sterically, CN < CO$_2$Me > OAr < SAr,

but the relative sizes of Ar and OSO$_2$R at the reaction site are unknown. The [E-RX]/[Z-RX] equilibrium constants; X = Cl (68:32), Br (83:17), OMs (54:46), OTs

(61:39), TolO (72:28), TolS (15:85),[11] indicate that the E isomer having an apparent larger Ar/CO$_2$Me interaction is more stable. If the same applies also in 14 and 15, then retention for (Z)-13 is preferred by both steric and hyperconjugative effects, whereas for (E)-13, retention by 60° rotation is preferred by hyperconjugation, but the 120° rotation is favored sterically. (E)-13 is therefore predicted to give less retention, as was indeed observed with ArS$^-$.[11]

We conclude that $k_{\rm el} > k_{\rm rot}$ so that the $k_{\rm rot}(60°)/k_{\rm rot}$-(120°) ratio determines the product ratios. *Thus, in a substitution involving a C–X bond cleavage, a change in the nucleofuge does not give information on the extent of the C–X bond cleavage in the product-determining elimination step.*

Nucleophilic Isomerization. Substitution proceeds when LG$^-$ is expelled after 60° or 120° rotations. Expulsion of the Nu$^-$ after 180° rotation leads to isomerized precursor olefin. Nucleophilic isomerizations by RO$^-$ or amines in the absence of a nucleofuge,[12a,b] or in the presence of poor nucleofuges, are known.[12c] The "postisomerizations" of the kinetically controlled to the thermodynamically controlled products during or after the reactions are other examples. Nucleophilic isomerization of an electrophilic vinyl bromide or chloride during its substitution should serve as very strong evidence for the intermediacy of β-halocarbanion. A few examples were found recently.

Slow Cl$^-$- or Br$^-$-catalyzed isomerizations were observed for 4, 6, and 7, and that of 6 was thoroughly investigated. (E)-6 and (Z)-6 were reacted with labeled chloride ion (Cl^{-*}), and the rates of both the (E)-6 $\rightleftharpoons$ (Z)-6 isomerization (with $k_{\rm isom}$) and the labeled chloride incorporation ($k_{\rm ex}$) were followed (e.g., eq 8). With [5] = 0.002 M and [Et$_4$NCl*] = 0.03 M in MeCN at 23 °C, $10^4 k_{\rm ex}$ = 11.8 s^{-1} ((E)-6) and 58.4 s^{-1} ((Z)-6), $10^5 k_{\rm isom}$ = 220 s^{-1} ((E)-6) and 4.8 ((Z)-6), and $k_{\rm ex}/k_{\rm isom}$ = 54 ((E)-6) and 122 ((Z)-6).[13]

(8)
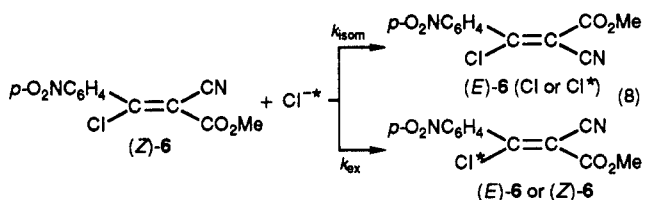
These results lead to four important conclusions. First, the exchange is much faster than previously encountered. The half-life for the exchange of (E)-6 under the above conditions is 2 min. In contrast, $k_{\rm ex}$ $\approx$ $k_{\rm isom}$ is ca. 5 × 10^{-5} M^{-1} s^{-1} at 170 °C in DMF for (Z)-AnC(Ph)=CHCl + Cl^{-*}.[14] Second, the reactivity difference of 6 with Cl$^-$ and piperidine, $k_{\rm Cl}/k_{\rm Pip}$(MeCN) = 2.7, is much higher than those with less activated systems. Third, since $k_{\rm ex}/k_{\rm isom}$ = 54–122, the exchange proceeds with 98–99% retention, much higher than with TolO$^-$ or TolS$^-$ (Table I). Fourth, both exchange and isomerization of (Z)-6 are faster than with (E)-6.[13]

The high $k_{\rm ex}/k_{\rm isom}$ ratio suggests that exchange is the proper measure of Cl$^-$ nucleophilicity. Since the

(11) Avramovitch, B.; Rappoport, Z. *J. Am. Chem. Soc.* 1988, *110*, 911. Note that 6 = 13, X = Cl.

(12) (a) Rappoport, Z. In *Nucleophilicity*; Adv. Chem. Ser. 1987, *215*, 399. (b) Kroeger, D. J.; Stewart, R. *J. Chem. Soc. B* 1970, 217. (c) Chalchat, J. C.; Théron, F.; Vessière, R. *Bull. Soc. Chim. Fr.* 1973, 2501.
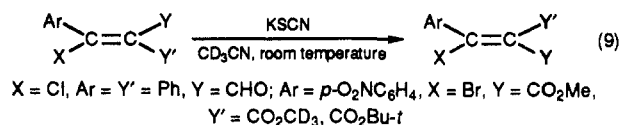
(13) Lodder, G.; van Dorp, J. W. J.; Avramovitch, B.; Rappoport, Z. *J. Org. Chem.* 1989, *54*, 2574.

(14) Beltrame, P.; Bellobono, I. R.; Fere, A. *J. Chem. Soc. B* 1966, 1165.

exchange is degenerate, the ratios $k_{ex}((Z)\text{-}6)/k_{ex}((E)\text{-}6)$ = 5 and $k_{isom}((Z)\text{-}6)/k_{isom}((E)\text{-}6)$ = 2.2 are ascribed to different steric interactions in the transition states. In the initially formed carbanion conformations derived from (Z)-6 and (E)-6, the steric interactions in the 60° rotation are Ar/CN and the more demanding Ar/CO$_2$-Me, respectively. In the 120° counterclockwise rotation, Cl/CO$_2$Me and Cl/CN interactions are encountered in both cases. The (E)-6/(Z)-6 ratio at equilibrium is 2:1, almost identical with the (Z)-6/(E)-6 reactivity ratio.[13]
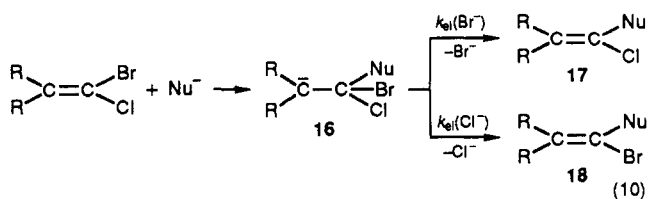
An interesting consequence is that the clockwise 180° and counterclockwise 120° rotations which lead to isomerization can *in principle* be distinguished. According to eq 4, for Nu = Cl* and LG = Cl, the former $(9a \rightarrow 8a \rightarrow 8d \rightarrow 9d)$ should give an unlabeled isomer and the latter $(9a \rightarrow 8a \rightarrow 8c \rightarrow 9c)$ should give a labeled isomer. Unfortunately, this was not investigated due to the low extent of isomerization of 6.

NCS⁻-catalyzed isomerizations were found in 1978[15] to accompany the substitution of (E)- and (Z)-MeC-(Cl)=C(Me)CHO. We found recently that also with KSCN at CD$_3$CN, (E)-4 isomerizes 28% to (Z)-4 after 300 h[5d] and 10 isomerizes after 100 h to a 55/45 mixture of 10/Z-isomer of 10,[15] both without substitution. (E)-7 gave mainly isomerization but also some substitution[5d] (eq 9).

$$\begin{array}{c} \underset{X}{\overset{Ar}{>}}C=C\underset{Y'}{\overset{Y}{<}} \xrightarrow[\text{CD}_3\text{CN, room temperature}]{\text{KSCN}} \underset{X}{\overset{Ar}{>}}C=C\underset{Y}{\overset{Y'}{<}} \end{array} \quad (9)$$

X = Cl, Ar = Y' = Ph, Y = CHO; Ar = *p*-O$_2$NC$_6$H$_4$, X = Br, Y = CO$_2$Me, Y' = CO$_2$CD$_3$, CO$_2$Bu-*t*

The isomerization is surprising since it is interpreted as involving formation of ArC(X)(CNS)C⁻YY′ carbanions, which undergo internal rotation and expel the poorer NCS⁻ nucleofuge[16] in preference to expulsion of the better nucleofuges Br⁻ or Cl⁻. The calculated hyperconjugative stabilizations of Cl and CNS (3-21G, kcal mol⁻¹: ClCH$_2$C⁻H$_2$, 45.7; NCSCH$_2$C⁻H$_2$, 39.2; ClCH$_2$C⁻(CN)$_2$, 16.3; NCSCH$_2$C⁻(CN)$_2$, 12.7) indicate that hyperconjugative control of k_{rot} does not account for the isomerization since that of Cl is higher. At present we lack an explanation, and mechanistic alternatives for the isomerization, e.g., one involving an initial SET, should be considered.

The Intramolecular Element Effect. A competition experiment was devised in order to estimate if the transition state for k_{el} is early or late. When both Cl and Br are substituents at the same carbon of an electrophilic olefin, they can be displaced competitively (eq 10), giving an intramolecular element effect where

$$\underset{R}{\overset{R}{>}}C=C\underset{Cl}{\overset{Br}{<}} + Nu^- \longrightarrow \underset{R}{\overset{R}{>}}\overset{\vert}{C}-\overset{\vert}{C}\underset{Cl}{\overset{Nu}{\underset{Br}{<}}} \begin{array}{c} \xrightarrow[-Br^-]{k_{el}(Br^-)} \underset{R}{\overset{R}{>}}C=C\underset{Cl}{\overset{Nu}{<}} \quad \mathbf{17} \\ \\ \xrightarrow[-Cl^-]{k_{el}(Cl^-)} \underset{R}{\overset{R}{>}}C=C\underset{Br}{\overset{Nu}{<}} \quad \mathbf{18} \end{array}$$

$$\mathbf{16} \qquad\qquad\qquad (10)$$

the product ratio is identical to the ratio of the

(15) Korobov, M. S.; Nivorozhkin, L. E.; Minkin, V. I.; Levkovich, M. M.; Testoedova, S. I. *Zh. Org. Khim.* **1978**, *14*, 788; *J. Org. Chem. USSR (Engl. Transl.)* **1978**, *14*, 728.

(16) (a) Thorstenson, T.; Songstad, J. *Acta Chem. Scand.* **1978**, *32A*, 133. (b) Maartmann-Moe, K.; Sanderud, K. A.; Songstad, J. *Ibid.* **1982**, *36B*, 211.

Table IV. Product Distribution and $k_{el}(Br)/k_{el}(Cl)$ Ratios

alkene	Nu⁻	solvent	% reactn	[RCl]/[RBr]	k_{Br}/k_{Cl}
19	TolO⁻	CD$_3$CN	9–29	71/29	2.4
		DMSO-d_6	32–56	74/26	2.9
	TolS⁻	CD$_3$CN	6–83	68/32	2.1
		9/1 DMSO-d_6–CD$_3$OD	16	74/26	2.9
20	TolO⁻	CD$_3$CN	4–21	68/32	2.1
		DMSO-d_6	42–52	68/32	2.1
	TolS⁻	CD$_3$CN	9–80	70/30	2.3

elimination rate constants, $k_{el}(Br^-)/k_{el}(Cl^-) = [17]/[18]$, if the ground state, i.e., carbanion 16, is *assumed* to be the same. However, the non-displaced halogen differs in the two transition states for elimination, and this could affect the $k_{el}(Br^-)/k_{el}(Cl^-)$ ratios.

The intramolecular element effect was investigated in the substitution of (bromochloromethylene)fluorene (19) and 1-bromo-1-chloro-2,2-bis(p-nitrophenyl)ethylene (20) with the soft TolS⁻ and the harder TolO⁻.[17]

$(p\text{-O}_2\text{NC}_6\text{H}_4)_2\text{C}=\text{C(Br)Cl}$ $(p\text{-O}_2\text{NC}_6\text{H}_4)_2\overset{\_}{\text{C}}\text{CH}^{35}\text{Cl}^{37}\text{Cl}$

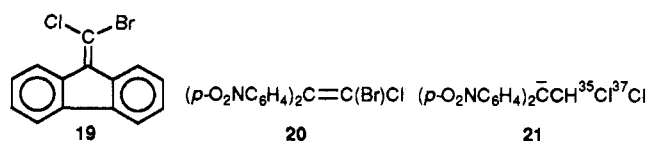**19**   **20**   **21**

Table IV shows that the k_{Br}/k_{Cl} values (2.1–2.9) are not very high, and most of them are regarded as identical within the combined experimental error in spite of the two substrates, two nucleophiles, and three solvents.

The intramolecular element effect is a k_{el} transition state probe if three prerequisites are fulfilled. (a) The process followed is addition–elimination, as is the case for 19 and 20.[17] (b) The ratio relates to the C–X bond cleavage and not to a hyperconjugative barrier. (c) The different interactions of the two halogens in the transition states leading to 17 and 18 are either similar or sufficiently small so that the k_{Br}/k_{Cl} ratio reflects the extent of C–X bond cleavage. We believe that this is the case since the anomeric effect due to Br–C–Cl is small as Br is a third-row element.[18]

If carbanion 22 is short-lived, Br⁻ or Cl⁻ will be expelled once the proper stereoelectronic conformation is achieved. When the rate-determining step is the rotation, the products are determined by the relative population of the two conformers, i.e., $k_{rot}/k_{rot'} = [17]/[18]$. If $k_{rot} \approx k_{rot'} \gg k_{el}$, the ground state for both eliminations is identical and only then does $k_{el}(Br)/k_{el}(Cl)$ measure the extent of C–X bond cleavage (eq 11).

$$(11)$$
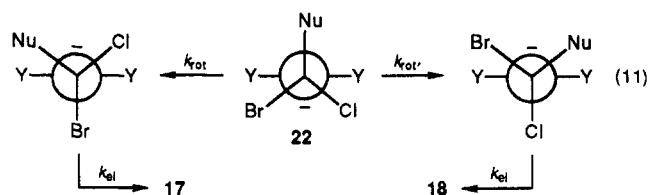
Since Y = Y′, the steric barrier in the k_{rot} step is lower than that for $k_{rot'}$. If hyperconjugative stabilization (HCA) by Br and Cl are similar, the hyperconjugative component of the barrier is low, whereas if HCA(Br)

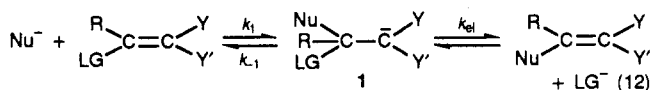(17) Avramovitch, B.; Weyerstahl, P.; Rappoport, Z. *J. Am. Chem. Soc.* **1987**, *109*, 6687.

(18) Schleyer, P. v. R.; Jemmis, E. D.; Spitznagel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6393.

> HCA(Cl), a k_{Br}/k_{Cl} ratio $\gg 1$ is expected. Although the HCA values for Br and Cl (39.2 at 3-21G*//3-21G* vs 38.1 at 3-21G*/3-21G*)[5c] are close to one another, ordering them in a "real" system having the Y and Y' groups and a solvent is at present impossible. However, the observed ratio indicates that HCA(Br) is not much higher than HCA(Cl). Since the rotational barriers are low, even if k_{rot} and $k_{rot'}$ are rate determining k_{el}(Br) and k_{el}(Cl) will be very high and the corresponding transition state will be early. In spite of criticism of k_{Br}/k_{Cl} ratios as measures of the extent of C–X bond cleavage,[19] we believe that the ratios for **19** and **20**, which are much lower than those for S_N1 reactions, are consistent with an early transition state with only a slight C–X bond extension in the transition states over that in **22**. The intramolecular chlorine isotope effect $k_{el}(^{35}Cl)/k_{el}(^{37}Cl) = 0.99995 \pm 0.00026$ found for carbanion **21** formed in an E1cB reaction[20] and its interpretation parallel our conclusion.

The overall picture agrees with the prediction. For singly activated systems (only Y is strongly electron-withdrawing) the transition state for the elimination is early regardless of the nature of the nucleofuge or of Y.[21] For highly activated systems (Y and Y' strongly electron-withdrawing) the transition state is early for expulsion of the very good Br⁻ and Cl⁻ nucleofuges, but it becomes less reactant-like for moderate and poor nucleofuges.

Actual Observation of the Intermediate. An important recent development is Bernasconi's observation of the intermediate.[22] The rates of formation of **1** and its conversion to product suggest that **1** is on the reaction coordinate for the substitution.
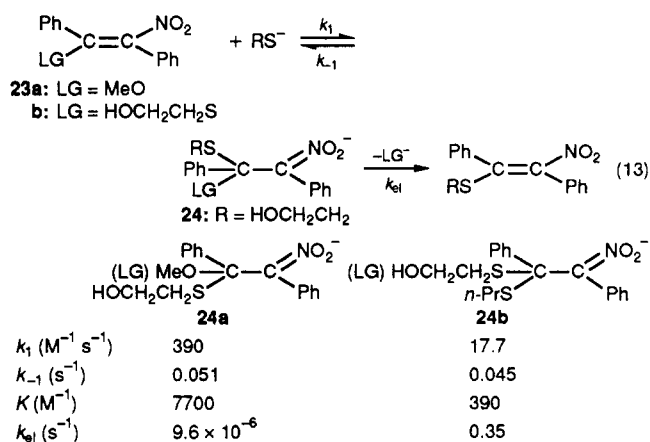
Three conditions must be met for the intermediate **1** in route a (eq 12) to be observable: (a) favorable

$$\text{Nu}^- + \overset{R}{\underset{LG}{>}}C=C\overset{Y}{\underset{Y'}{<}} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\underset{\mathbf{1}}{LG}}{\overset{Nu}{\underset{R}{>}}}C-\bar{C}\overset{Y}{\underset{Y'}{<}} \overset{k_{el}}{\rightleftharpoons} \overset{R}{\underset{Nu}{>}}C=C\overset{Y}{\underset{Y'}{<}} + \text{LG}^- \quad (12)$$

equilibrium in its formation, i.e., $k_1/k_{-1}[\text{Nu}^-] = K_1[\text{Nu}^-] > (\gg) 1$; (b) slower conversion of **1** to products than its formation, i.e., $k_1[\text{Nu}^-] > (\gg) k_{el}$ (when $[\text{Nu}^-]_0 \gg [\text{vinyl-X}]$); (c) low absolute magnitude of k_{el} to allow detection of **1**.

β-Methoxy-α-nitrostilbene (**23a**) fulfills these conditions for three reasons: (a) The activating Ph and NO₂ confer high stability to **1**, implying a high k_1 value and a relatively low k_{el}. (b) Nitronate ion forming/consuming reactions have low intrinsic rate constants. This depresses k_{el} compared with systems where **1** is of similar thermodynamic stability, but with high intrinsic rate constant. (c) MeO⁻ is a poor nucleofuge, i.e., k_{el} is small.

Intermediates **24**, LG = MeO, RS (but not I), were indeed spectrophotometrically observed in the substitutions displayed in eq 13 using several thio nucleophiles in 1/1 DMSO–H₂O. Rate data for two systems at 20 °C are shown below.

(19) Bird, R.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1221.

(20) Grout, A.; McLennan, D. J.; Spackman, I. H. *J. Chem. Soc., Chem. Commun.* **1976**, 775; *J. Chem. Soc., Perkin Trans. 2* **1977**, 1758.

(21) Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198.

(22) (a) Bernasconi, C. F.; Killion, R. B.; Fassberg, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1989**, *111*, 6862. (b) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Rappoport, Z. *Ibid.* **1990**, *112*, 3169; (c) *J. Org. Chem.* **1990**, *55*, 4568; (d) **1991**, *113*, 4937.

$$\overset{Ph}{\underset{LG}{>}}C=C\overset{NO_2}{\underset{Ph}{<}} + \text{RS}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}$$

23a: LG = MeO
  b: LG = HOCH₂CH₂S

$$\overset{RS}{\underset{\underset{Ph}{LG}}{>}}C-C\overset{NO_2^-}{\underset{Ph}{<}} \overset{-LG^-}{\underset{k_{el}}{\rightarrow}} \overset{Ph}{\underset{RS}{>}}C=C\overset{NO_2}{\underset{Ph}{<}} \quad (13)$$

24: R = HOCH₂CH₂

	$\overset{Ph}{\underset{HOCH_2CH_2S}{>}}$(LG) MeO$-C-C\overset{NO_2^-}{\underset{Ph}{<}}$ **24a**	$\overset{Ph}{\underset{n\text{-PrS}}{>}}$(LG) HOCH₂CH₂S$-C-C\overset{NO_2^-}{\underset{Ph}{<}}$ **24b**
k_1 (M⁻¹ s⁻¹)	390	17.7
k_{-1} (s⁻¹)	0.051	0.045
K (M⁻¹)	7700	390
k_{el} (s⁻¹)	9.6×10^{-6}	0.35

k_1(**24a**)/k_1(**24b**) = 22, and since k_{-1}(**24a**) ≈ k_{-1}(**24b**), the equilibrium for formation of **24a** is 20 times higher. Most remarkable are k_{el} values of ca. 10^{-5} and 0.35 s⁻¹ for **24a** and **24b**. Apparently, a minor structural change decreases drastically the lifetime and the probability for detecting the intermediate.[22a]

The k_{el} values of $2.5 \times 10^{-1} - 1.8 \times 10^{-8}$ s⁻¹ for several intermediates **24** are $10^{13}-10^{20}$-fold lower than the rate constant of molecular vibration at which the multistep route merges into the single-step route. Hence, it is reasonable that intermediate carbanions exist in many cases (but not necessarily always) even when substituted by good nucleofuges. Moreover, the expulsion rates of EtS⁻ and HOCH₂CH₂S⁻ when R = H and R = MeO from PhCR(LG)C⁻(Ph)NO₂ (**25**) are very similar, so that no anomeric EtS/MeO stabilizing effect on intermediate **1** is observed. Likewise, RS/RS anomeric stabilization, if at all present, is low since for **25** k_{el}(R = SCH₂CH₂OH)/k_2(R = H) = 3.6. In contrast, MeO/MeO stabilization seems to exist, judging by the k_{el} values of 1.8×10^{-8} s⁻¹ for **25**, R = LG = MeO, compared with 9.6×10^{-6} s⁻¹ for **25**, R = HOCH₂CH₂S, LG = MeO. Finally, intramolecular competition favors expulsion of MeO⁻ over HOCH₂CH₂S⁻ by 4300-fold.[22a]

The intermediate was not observed in a reaction analogous to eq 13 with amines.[22c] This is ascribed to a higher k_{el} value which reflects a product stability due to push–pull interaction.

Conclusion. The stereoconvergence and the nucleophilic isomerization in substitution of vinylic systems carrying good nucleofuges serve as evidence for the intermediacy of carbanionic intermediates capable of undergoing at least some internal rotation. Few intermediate carbanions carrying poor nucleofuges were indeed observed. Intramolecular 60° and 120° rotations which are governed by hyperconjugation and steric effects in the intermediates compete with one another and with the expulsion of the nucleofuge. The transition state for the expulsion of a good nucleofuge seems to be early. The rotation can be product-determining, and we propose the complete descriptive designation of this route as "the nucleophilic addition–rotation–elimination route".