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Recent Advances in Our Mechanistic Understanding of S_NV Reactions

CLAUDE F. BERNASCONI*,† AND ZVI RAPPOPORT‡

†Department of Chemistry and Biochemistry, University of California, Santa Cruz, California 95064, ‡Institute of Chemistry, The Hebrew University, Jerusalem 91904, Israel

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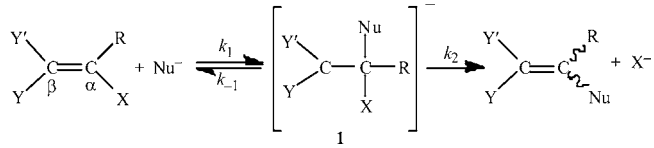
CONSPECTUS



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Nucleophilic vinylic substitution (S_NV), in which a leaving group such as halogen is replaced by a carbon, oxygen, nitrogen, sulfur, or other nucleophile, is an important synthetic tool. It generates compounds with a carbon- or heteroatom-substituted carbon−carbon double bond, such as vinyl ethers, enamines, a variety of heterocyclic systems, and intermediates to pharmaceutically important compounds. The S_NV reaction has many mechanistic variants, which depend on the substituents, nucleophile, leaving group, and solvent, among other factors. Among these mechanisms, the "addition−elimination" S_NV route is the most important to synthetic chemists.

S_NV reactions are involved in several biological processes, notably (i) in the inactivation of proteases, (ii) in intermediates of herbicide metabolism, and (iii) in the formation of mutagenic intermediates by reaction of glutathione with the environmental pollutant trichloroethylene. A variant involving a tetrahedral intermediate was found in the enzymatic transfer of an enolpyruvyl group of phosphoenolpyruvate.

The main S_NV mechanism was previously analyzed in terms of a variable transition state with perpendicular nucleophilic attack. Electron-withdrawing groups Y and Y′ in the β position adjacent to the C_α reaction site increase the nucleophilic attack rate; the retention of stereochemistry was mostly ascribed to formation of carbanionic intermediate **1**, in which internal rotation is slower than nucleofuge expulsion (k_2). As predicted, poor nucleofuges and high activation led to partial or complete stereoconvergence, and an intramolecular element effect in polyhaloethylenes gave competition ratios, $k_F/k_{Br} < 1$. Evidence for a zwitterionic intermediate comes from amine-catalyzed substitutions with amines.

The mechanistic spectrum investigated is wide in terms of rate constants, electron-withdrawing groups, nucleophiles, leaving groups, and solvents. However, the two extremes, that is, the very slightly activated systems where in-plane invertive substitution is feasible and conversely the highly activated systems carrying poor nucleofuges where the intermediate may be observable and kinetics examined, remained almost unexplored for a long time. In this Account, we describe the progress during the last two decades in these areas.

Computations on low-reactivity systems showed that the in-plane invertive single-step nucleophilic σ attack can have a lower barrier than the π-perpendicular retentive attack. A $k_{Br}/k_{Cl} > 1$ could be deduced for the $H_2C{=}CHX$ (X = Cl, Br) system. Several inverted substitution−cyclizations or inverted ring openings were observed. Alkenyl iodonium salts with superb nucleofuges, showed in-plane substitutions by various nucleophiles.

In parallel, we demonstrated that several highly activated systems carrying poor nucleofuges enabled a direct detection of the intermediate **1** when attacked by strong nucleophiles. Poor correlation between the equilibrium constants K_1^{RS} for RS^- attack and $pK_a(CH_2YY')$ indicates large nucleofuge steric effects (SPr > SMe > OMe≫H). Rate and equilibrium constants for RS^- attack as a function of YY′ also correlate poorly owing to differences in intrinsic barriers caused by different resonance effects of YY′. The expulsion of either the nucleofuge (k_2) or the nucleophile (k_{-1}) from **1** was analyzed with respect to several factors. Challenges still remain, including acquiring experimental data for unactivated systems and observing an intermediate carrying a good nucleofuge.

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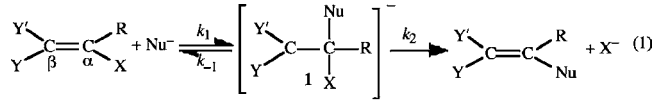
Introduction

In nucleophilic vinylic substitution (S_NV), the nucleophile, Nu^-, displaces the nucleofuge, X, by different mechanistic routes.[1] The most versatile among them is the multistep "addition−elimination", which generates a multitude of vinylic systems (vinyl ethers, thiols, organometallics, enamines) with defined stereochemistry, heterocycles (see below), and biologically and pharmaceutically active molecules such as antitumor derivatives.[2a−c] A mechanistic variant involving a tetrahedral intermediate is the enzymatic enolpyruvyl transfer of phosphoenolpyruvate ($H_2C{=}C(CO_2^-)OPO_3^{2-}$) to 3′-OH of UDPGlcNAc.[2d] It is also environmentally important. The halogens of the pollutant polyhaloethylenes are displaced by RO^- and ArS^-.[1a] Trichloroethylene (TCE) is converted to mutagenic intermediates by substitution with glutathione and the TCE−MeS^- reaction was computed as a model to this reaction.[2e] Likewise, the xenobiotic metabolism of the herbicide triallate involves trichloroacrolein as verified by its capture by glutathione.[2f]

The reaction proceeds when Y and Y′ are activating electron-withdrawing groups (EWGs) capable of negative charge delocalization by resonance and X is a poor (OR, SR, CN), good (Br, Cl, SO_3R), or excellent (OTf, PhI^+) nucleofuge. We discussed earlier[1c] the question general of substitution at other sp^2 carbons in S_NAr, C(X)=N or C(X)=O, whether it is a single or multistep process, that is, (a) if species **1** is a single transition state (e.g., TS **1a**) with concerted C−Nu bond formation and C−X bond cleavage or (b) a discrete carbanionic intermediate as in eq 1. Two contradictory relevant observations are the predominant retention of reactant configuration, and the "element effect" for X: $k_F \gg k_{Br} \geq k_{Cl}$. The expectation when **1**



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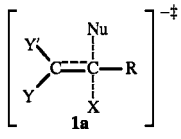
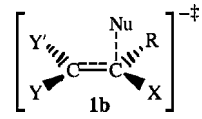


is a carbanion and intramolecular rotation precedes nucleofuge expulsion is stereoconvergence (formation of *E*/*Z* product(s) from *E*- or *Z*-precursor). When nucleofuge expulsion precedes the rotation, stereoselective formation of different regioisomeric products from *E*- and *Z*-reactants is predicted.

Since the C−X bond strength is C−F > C−Cl > C−Br, $k_F/k_{Br} \ll 1$ and $k_{Br}/k_{Cl} > 1$ are expected for route a. For route b with rate-determining (rd) C−Nu bond formation, k_F/k_{Cl} and $k_F/k_{Br} \gg 1$ and $k_{Br}/k_{Cl} \geq 1$ ratios were predicted and observed. The discrepancy between the two probes was reconciled by suggesting a variable S_NV TS where mechanistic details depend on the intermediate lifetime.[1c] Highly activated systems with powerful C_β-EWGs and a moderate or poor nucleofuge, for example, RO^- or F^-, give a sufficiently long-lived carbanion where faster internal rotation than nucleofuge expulsion results in partial or complete stereoconvergence. When X = Br or Cl, a shorter-lived carbanion gives a lower extent of stereoconvergence than when X = F; k_1 becomes rd with $k_F \gg k_{Br}$ or k_{Cl}.

At lower activation, the shorter intermediate lifetime will give a cleaner *retention*. With a perpendicular nucleophilic attack giving TS **1b**, rotation in the first formed carbanionic conformer and nucleofuge expulsion may become concerted, displaying a high k_{Br}/k_{Cl} ratio. Longer-lived carbanions carry-



ing poorer nucleofuges than Cl or Br will give stereoconvergence even in less activated systems and the in-plane attack with better nucleofuges via **1a** may be favored over **1b**, displaying *inversion* of configuration and $k_{Br}/k_{Cl} \gg 1$.

Most investigated systems with X = Cl or Br were mildly activated by a single β-EWG (CO, CN, RSO_2, etc.), which gave retention and $k_{Br}/k_{Cl} \approx 1$, but even for the highly activated $NCC(X){=}C(CN)_2$, k_{Br}/k_{Cl} is 2.4−3.8.[3] In the last 20 years, additional mechanistic understanding was gained by studying systems at both extremes of the reactivity scale. The stereochemistry of weakly activated systems with good nucleofuges was studied mostly by computation, and studies by fast kinetic methods of highly activated systems with poor nucleofuges enabled measurements of the rate constants k_1, k_{-1}, and k_2. These recent advances are discussed below.

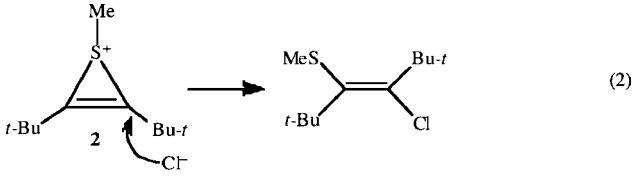
Weakly Activated Systems with Good Nucleofuges

In-plane or Perpendicular Attack. Observed inversion was rare up to 1992.[1d] Theoretical work suggested a stepwise mechanism,[1c] and computations preferred a perpendicular concerted[1g,4a] π attack with retention over in-plane σ^* attack with inversion.[4] $C_\beta^-/C_\alpha - \sigma^*$ orbital hyperconjugation rationalized the nucleophilic chlorine displacement from $H_2C{=}C(F)Cl$.[4d] However, later advanced computations favored the σ^* route ($S_NV\sigma$). A gas-phase G2(+) computation for $X^- + H_2C{=}CHX$, X = Cl or Br, detected an initial weak complex between the reactants followed by a preferred inversion, over the perpen-

dicular $S_NV\pi$ route,[5] with TSs 32.4 and 42.8 kcal/mol, respectively, above the complex, X = Cl.

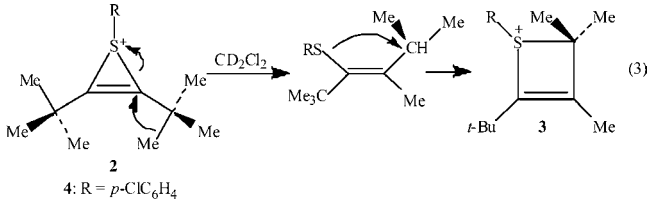
Extended computations for the $H_2C{=}CHCl + Cl^-$, Br^-, OH^-, or SH^- reactions[6] detected similar complexes. Cl^- and Br^- react preferentially via $S_NV\sigma$ with inversion and OH^- and SH^- preferred an $S_NV\pi$ route with retention. The gas-phase $\Delta\Delta G^{\ddagger}(\sigma-\pi)$ values for Cl^- (−4.8), Br^- (−7.4), and SH^- (+2.1) kcal/mol gave $\Delta G^{\ddagger} = 23$ ($S_NV\sigma$) and 39.4 kcal/mol ($S_NV\pi$) for the $Br^- + H_2C{=}CHCl$ reaction, that is, for $H_2C{=}CHX + Cl^-$, $\Delta\Delta G^{\ddagger}$ (X = Br − X=Cl) = 6.8 ($S_NV\sigma$) and 4.2 kcal/mol ($S_NV\pi$). The gas-phase barriers are lower than those in MeCN. The $S_NV\sigma$ route was confirmed for $Cl^- + H_2C{=}CRCl$, R = H, but when R = F the preferred route is $S_NV\pi$.[4d,7]

An early example of substitution with inversion is the ring opening of the thiirenium ion **2** (eq 2).[8]



(2)

The rearrangement of **2** and **4** to the thietium ion **3** (eq 3) was attributed to an initial concerted anionic migration of a methide ion from the *t*-Bu group to the double bond, with back cleavage of the $=C-S^+$ bond.[9a] The authors attempted to rationalize the S_NV stereochemistry from the energies of the

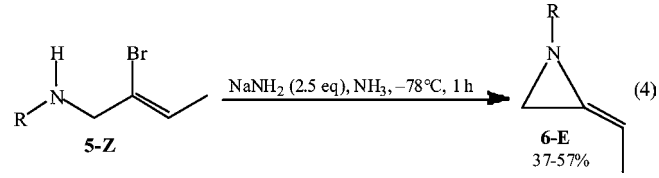


(3)

LUMO vinylic orbitals with π or σ symmetry attacked by the nucleophile,[9b] hypothesizing that they lead, respectively, to retention or inversion. Nucleophilic attack on the π orbital is dominated by the two-electron stabilizing interaction. For the thiirenium, iodirenium, arylidenium, and methyl vinyl iodonium ions and *cis*-BrC(F)=C(F)Br, the LUMO is of σ symmetry, and inversion was observed. $H_2C{=}CHCl$ with a lower π LUMO is attacked perpendicularly.

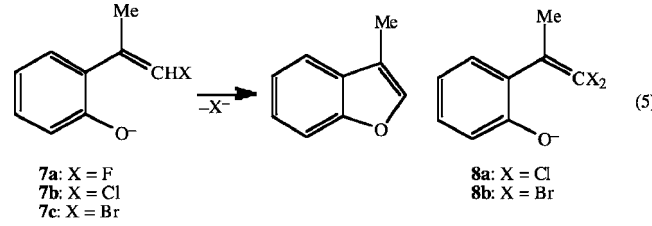
2-Ethyleneaziridine **6**-*E* is selectively formed with inversion by intramolecular bromide displacement by the nitrogen of **5**-*Z*, R = $PhCH_2$, (*S*)-CHMePh/$NaNH_2$ in liquid NH_3 (eq 4).[10] Likewise **5**-*E* gives 77−99% of **6**-*Z*.

A preferred $S_NV\sigma$ route was computed for the intramolecular cyclization of **7b** with NaH in DMF (eq 5).[11] For *E*-**7b** and *E*-**7a** $\Delta G^{\ddagger} = 14.4$ and 25.8 kcal/mol, respectively. In the gas phase, the $S_NV\pi$ route prevails.[11,12] In the nonplanar β,β-di-Cl



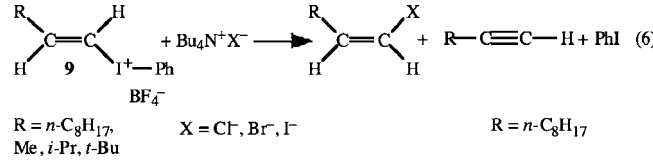
(4)

analog **8a**,[12] steric hindrance and electronic repulsion force a perpendicular oxyanion approach to the double bond, giving the $S_NV\pi$ route. The cyclization reactivities are *E*-**7b** ≫ *Z*-**7b**, *E*-**7c** > *Z*-**7c**, and *E*-**7b** > *E*-**7a**.[11]



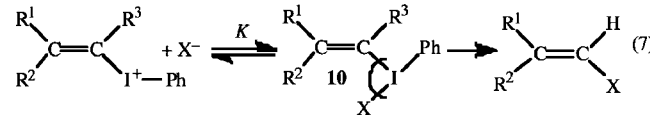
(5)

Higher probability for a single-step route is expected in unactivated systems[1c] carrying superb nucleofuges such as iodonio.[13] Ochiai, Okuyama et al. reacted vinyl iodonium tetrafluoroborates **9** with nucleophiles, obtaining elimination and substitution products,[1g] with stereochemistry ranging from retention to inversion (e.g., eq 6).[14] Iodonium halides are in equilibrium with the λ^3-haloiodane **10** (eq 7). For *E*-1-dece-



(6)

nyl(phenyl)iodonium tetrafluoroborate with $Bu_4N^+X^-$, X = Cl, Br, I, K = 5600−7600 M^{-1} in several solvents. The products are mixtures of inverted to retained substituted 1-haloalkene (97−100:0−3% in the *Z*/*E* mixture in several solvents), and



(7)

1-alkyne.[15,16] The retained product was ascribed to the $S_NV\pi$ route or to ligand coupling in **10**.

Both *E*- and *Z*-β-chloro, -bromo, and -iodo iodonium salts gave retained vicinal *Z*-vinyl dihalides with Cl^- or Br^-, presumably via intramolecular coupling in **10**.[17]

Inverted substitution products from the *E*-decenyl salt with Bu_2S, Bu_2Se, $(RO)_2P(=O)SeK$, $MeSO_3^-Bu_4N^+$, BF_4^- (to give fluorides) and the initial products from DMF were presumably formed via the $S_NV\sigma$ route.[18]

Element Effects

The *intermolecular* "element effect" discussed above predicts $k_{Br}/k_{Cl} \geq 1$ and k_{Br}/k_F and $k_{Cl}/k_F \ll 1$ for rd nucleophilic attack. The *intramolecular* element effect (the relative expulsion rates of two different geminal halides on C_α) is obtained from the product ratio. Only for rd nucleophilic attack, $k_{Br}/k_F \ll 1$, whereas $k_{Br}/k_F \gg 1$ means that the product-determining step involves C−X bond cleavage.

Intramolecular element effects were studied with tetrahaloethylenes. 1,2-dibromo-1,2-difluoroethylenes with 1 equiv of NaOMe in MeOH gave the substitution product BrC(F)=C(OMe)F, and excess $EtOCH_2CH_2O^-$ gave $k_{Br}/k_F \approx 19$. $TolS^-$ in DMSO gave one and two tolylthiodebrominations with apparent inversion. It is unknown whether these processes are kinetically controlled. For $Br_2C{=}C(F)Br$ with MeO^- and $EtOCH_2CH_2O^-$, $k_{Br}/k_F \geq 100$ and ca. 20, respectively.[19]

BrC(Cl)=C(Cl)Br gave with MeO^-, MeS^-, or $PhCH_2S^-$ in MeCN k_{Br}/k_{Cl} ratios of ≥100, ≥43 and ≥107, respectively. $Cl_2C{=}C(Br)Cl$ gave with MeO^- a small amount of *E*- and *Z*-BrC(Cl)=C(Cl)OMe, and $PhCH_2S^-$ gave k_{Br}/k_{Cl} of 3 in MeCN. The $k_{C(Br)Cl=C(Br)Cl}/k_{Cl_2C=CCl_2}$ ratios are 9.1 ± 1.7 with MeO^- and 11.2 ± 2.7 with $PhCH_2S^-$.[20] The high intramolecular and intermolecular element effects may indicate a single-step substitution.[20]

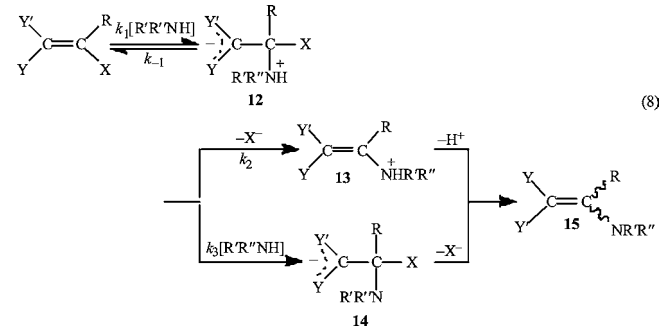
The two-step substitutions of both 9-(bromochloromethylene)fluorene (**11a**) and $(p\text{-}O_2NC_6H_4)_2C{=}C(Cl)Br$ (**11b**) by $p\text{-}MeC_6H_4Z^-$ (Z = O,S)[21] gave initial k_{Br}/k_{Cl} ratios of 2.1−2.8, which are nearly solvent-, nucleophile- and EWG-independent. The intermolecular $k(\alpha,\alpha\text{-}Cl_2)/k(\alpha,\alpha\text{-}Br_2)$ ratios are 1.2 for **11a** and 1.6 for **11b**. Neglecting the nonleaving halogen effect and nucleofuge/C_β^- hyperconjugation suggest for an intramolecular k_{Br}/k_{Cl} of ca. 1 an early TS for C−X bond cleavage.

For most compounds carrying one β-EWG and excellent to poor nucleofuges, the increased reactivity with better EWGs, $k_{Br}/k_{Cl} \approx 1$, and retention of configuration were ascribed to the $S_NV\pi$ route.

The Multistep Route

Stereochemistry. Stereoconvergence was found for systems carrying a β-EWG and poor nucleofuges such as F.[22] With the *two* strongly activating EWGs CN and CO_2Me, CHO and CO_2Me, or $CO_2Bu\text{-}t$ or CO_2Me and CO_2CD_3, the longer carbanion lifetime reduces C_β/C−X hyperconjugation and the internal rotation barrier, leading to partial or complete stereoconvergence with $p\text{-}RC_6H_4Z^-$ (Z = O, S) nucleophiles.[23]

Amine Catalysis. A probe for an S_NV intermediate is amine catalysis. For mildly activated systems, amine substitution is a second-order process, but highly activated systems carrying poor nucleofuges sometimes display both first- and second-order terms in the amine. This is explained by eq 8: R′R″NH attacks C_α reversibly, forming zwitterion **12**. Direct nucleofuge expulsion (k_2) gives **13**, which deprotonates to **15**. Alternatively, the nucleofuge expulsion is preceded by deprotonation of **12** by another amine molecule (k_3), giving a second-order term in the amine. Carbanion **14** then rapidly expels X^-.



The observed second-order rate constant $k_{obs} = k_1$ when $k_2 + k_3[\text{amine}] \gg k_{-1}$ or k_1k_2/k_{-1} when $k_{-1} \gg k_2 \gg k_3[\text{amine}]$. When $k_{-1} \gg k_2 + k_3[\text{amine}]$, $k_{obs} = (k_1/k_{-1})(k_2 + k_3[\text{amine}])$, and a linear k_{obs} vs [amine] plot gives the intercept k_1k_2/k_{-1} for the noncatalytic route, the slope k_1k_3/k_{-1} for the catalytic route, and k_3/k_2 from their ratio. The dependence of k_3/k_2 on YY′, nucleofuge, amine, and solvent was determined for the poor nucleofuges X = F, OEt, CF_3CH_2O, CN,[24] NO_2,[25] and MeS.[26,27] Regardless of the details of amine catalysis,[24a] the second-order term in the amine indicates the presence of an intermediate.

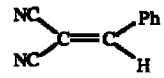
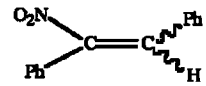
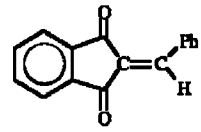
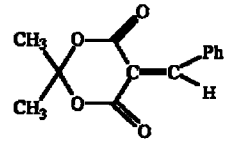
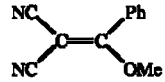
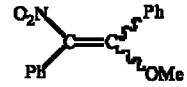
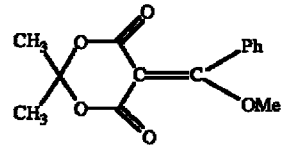
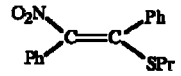
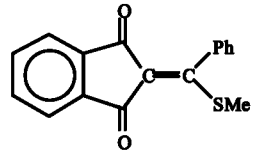
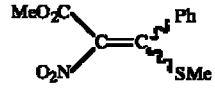
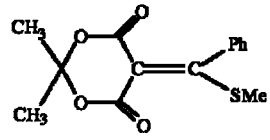
Directly Observable Intermediates

Our detailed understanding of S_NV reactions in activated systems greatly expanded by investigating cases where **1** (eq 1) is directly observable. Besides providing the most direct evidence for the multistep mechanism, this allowed the determination of k_1, k_{-1}, and k_2 in eq 1 and examination of how these steps depend on nucleophile, nucleofuge, activating groups, and solvent.

For detecting intermediates in two-step reactions, two conditions have to be met. (1) The equilibrium of the first step must be favorable (eq 9). This requirement is met for reactions of strong nucleophiles with highly activated substrates. (2) The *rate* of intermediate formation must

$$k_1[Nu^-] \geq 1 \qquad (9)$$

TABLE 1. Rate and Equilibrium Constants for S_NV Reactions with $HOCH_2CH_2S^-$ in 50% DMSO−50% Water at 20 °C[28]

Substrate		$pK_a^{CH_2YY'}$	k_1^{RS} M^{-1} s^{-1}	K_1^{RS} M^{-1}	k_2^{RS} s^{-1}	$\log k_o^{RS}$	$\log k_o^{PT}$
	**(20-H)**	10.21	4.40×10^6	5.18×10^4		ca. 5.7	ca. 7.0
	**(16-H)**	7.90	5.18×10^4	8.16×10^6		3.4	–0.25
	**(18-H)**	6.35	4.47×10^6	1.16×10^9		4.8	3.13
	**(17-H)**	4.70	1.44×10^7	5.38×10^{10}		5.2	3.90
	**(20-OMe)**	10.21	2.80×10^5	1.62×10^2	0.133	ca. 5.1	ca. 70
	**(16-OMe)**	7.90	3.85×10^2	7.59×10^3	9.60×10^{-6}	2.2	–0.25
	**(17-OMe)**	4.70	4.4×10^4	2.57×10^4	2.16×10^{-4}	3.7	3.90
	**(20-SPr)**	7.90	4.70	10.4	4.50×10^{-2}	0.29	–0.25
	**(18-SMe)**	6.35	5.62×10^2	2.25×10^2	0.245	2.5	3.13
	**(19-SMe)**	5.95	2.48×10^2	$\geq 5 \times 10^4$	5.80×10^{-5}	≤1.1	2.44
	**(17-SMe)**	4.70	9.22×10^2	3.32×10^2	0.115	2.5	3.90

exceed that of its conversion to products (eq 10). This requirement is met with strong nucleophiles, strong activating groups, and sluggish nucleofuges.

$$k_1[Nu^-] \geq k_2 \qquad (10)$$

Systems that meet both requirements mainly include reactions of thiolate and alkoxide ions with **16-X**−**20-X**.[28] In contrast, for reasons discussed below, none of the OH^- reactions allowed detection of intermediates, and only a few reactions with amine nucleophiles led to intermediate accumulation.[29,30]

Reactions with Thiolate Ions. The reactions of **16-X**−**20-X** with thiolate ions provide the most insights into structure−reactivity relationships. Table 1 summarizes k_1^{RS}, K_1^{RS}, and k_2^{RS} values for representative reactions with $HOCH_2CH_2S^-$. Included are $pK_a^{CH_2YY'}$ values of CH_2YY', log k_o^{RS} for the *intrinsic*

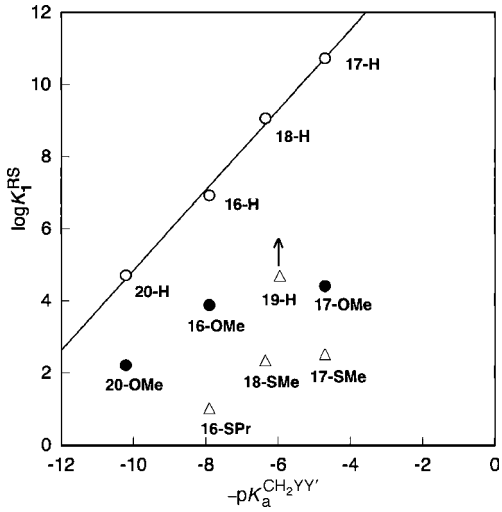


FIGURE 1. Plots of log K_1^{RS} (RS = $HOCH_2CH_2S^-$) versus $-pK_a^{CH_2YY'}$: (○) X = H; (●) X = OMe; (△) X = SMe.

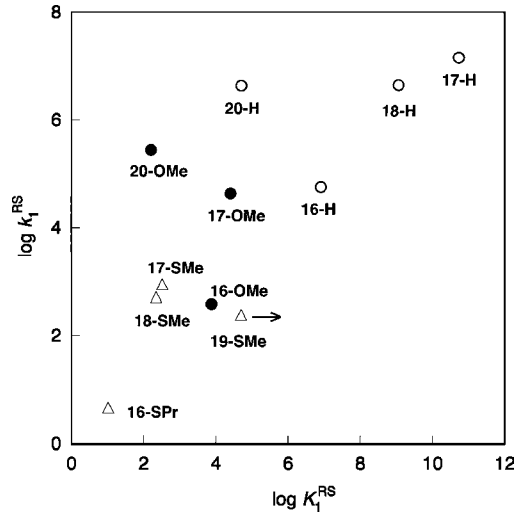


FIGURE 2. Plots of log k_1^{RS} versus log K_1^{RS} (RS^- = $HOCH_2CH_2S^-$) generated by varying YY′: (○) X = H; (●) X = OMe; (△) X = SMe.

rate constants[31] for RS^- addition, and log k_o^{PT} values for the *intrinsic* rate constant of proton transfer from CH_2YY' to secondary alicyclic amines.

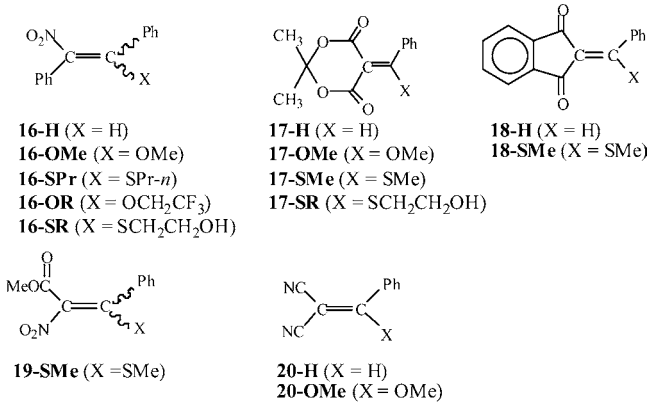


Figure 1 shows an excellent correlation of log K_1^{RS} with $-pK_a^{CH_2YY'}$ for X = H (○) (slope = 1.11), indicating charge stabilization by YY′ in the adduct is similar to that in $CHYY'^-$. For X = OMe and SMe the correlation is poor (● and Δ) due to steric crowding in the adduct, which is strongest for YY′ = MA,[32] intermediate for YY′ = ID,[32] (NO_2, CO_2Me) and (Ph, NO_2), and smallest for YY′ = $(CN)_2$. The small steric effect for the latter explains why here K_1^{RS} is large enough for intermediate detectability despite the weaker polar effect of $(CN)_2$. The nucleofuge steric effects follow the expected order SPr > SMe > OMe ≫ H.

Figure 2 shows that the correlations between log k_1^{RS} and log K_1^{RS} are poor, implying that k_o^{RS} differs substantially from substrate to substrate, with k_o^{RS} high for YY′ = $(CN)_2$, intermediate for YY′ = MA[32] and ID,[32] and low for YY′ = (NO_2, CO_2Me) and (NO_2, Ph). Approximate log k_o^{RS} values determined by varying RS^- basicity[31] are reported in Table 1.

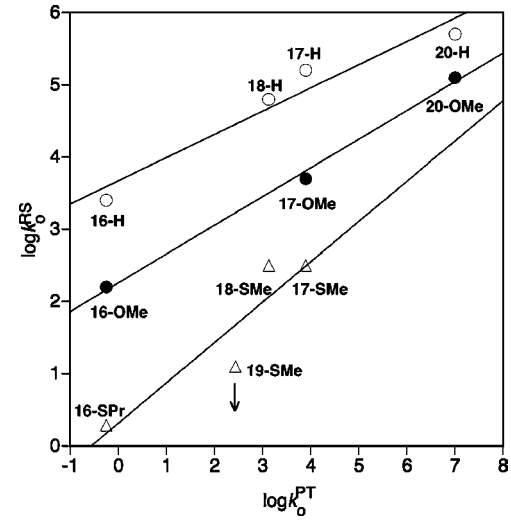


FIGURE 3. Plots of log k_o^{RS}(RS^- = $HOCH_2CH_2S^-$) versus log k_o^{PT}: (○) X = H; (●) X = OMe; (△) X = SMe.

The dependence of log k_o^{RS} is mainly governed by resonance effects of YY′. Resonance lowers k_o^{RS} just as it lowers k_o^{PT} because at the transition states (TS) charge delocalization lags behind bond formation in the nucleophilic addition reactions (**21**) or behind proton transfer in the deprotonation of CH_2YY' (**22**), respectively.[33] This reduction is a manifestation of the principle of nonperfect synchronization (PNS) according to which any product stabilizing factor whose development at the TS lags behind bond changes lowers k_o.[33]

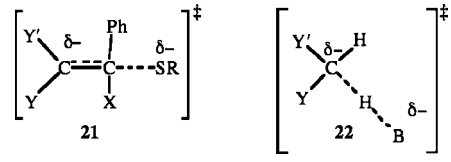
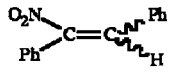
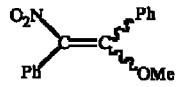
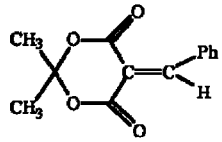
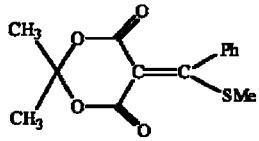
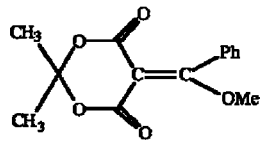


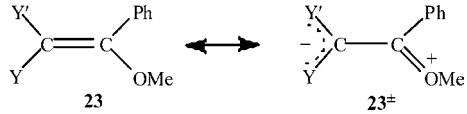
Figure 3 shows that for a given X, there is a linear correlation between log k_o^{RS} and log k_o^{PT}. However, the slopes (0.32

TABLE 2. Rate and Equilibrium Constants for S_NV Reactions with $CF_3CH_2O^-$ and OH^- in 50% DMSO−50% Water at 20 °C[28]

Substrate		k_1^{RO} $M^{-1}\,s^{-1}$	K_1^{RO} M^{-1}	k_1^{OH} $M^{-1}\,s^{-1}$	K_1^{OH} M^{-1}	$\log\frac{k_1^{RS}}{k_1^{OH}}$	$\log\frac{k_1^{RS}}{k_1^{RO}}$	$\log\frac{K_1^{RS}}{K_1^{RO}}$	$\log\frac{K_1^{RS}}{K_1^{OH}}$
	**(16-H)**			0.219	2.34×10^6	5.37			0.54
	**(16-OMe)**[35]	0.73	1.45×10^4	0.691	ca. 2.6×10^7	2.75	2.73	−0.28	ca. −3.5
	**(17-H)**[36]	2.09×10^4	6.43×10^6	1.80×10^3	1.17×10^{10}	3.90	2.84	3.92	0.67
	**(17-SMe)**[36]	1.41	2.86×10^1	0.634	ca. 5.1×10^4	3.16	2.81	1.07	ca. −2.2
	**(17-OMe)**[36]	1.08×10^3	6.81×10^4	5.41×10^2	ca. 1.2×10^8	1.61	1.91	−0.42	ca. −3.7

for X = H, 0.40 for X = OMe, and 0.56 for X = SMe (X = *n*-PrS for **16-SR**)) indicate reduced sensitivity to resonance. This implies a smaller TS imbalance than that for proton transfer; it is attributed to the sp^2-hybridization of the pro-carbanionic carbon, which facilitates π-overlap with the YY′ groups at the TS, reducing the k_o-lowering PNS effect.

The influence of X on k_o for a given YY′ is H ≫ OMe ≫ SMe. Two factors play a role: (1) π-donor resonance (e.g., **23**$^{\pm}$) of the OMe and SMe group: its loss at the TS is ahead of bond formation, reducing k_o^{RS}.[34] Due to its greater π-donor strength, the effect is stronger for OMe than for SMe. (2) The k_o^{RS}-reducing PNS effect arising from steric repulsion: it is stronger for the larger SMe. The fact that log k_o^{RS} is always lower for X = SMe than for X = OMe suggests dominance of the steric factor.



23 **23**$^{\pm}$

Reactions with Alkoxide and Hydroxide Ions. The studies involving RO^- and HO^- are limited to reactions with **16-OMe**, **17-H**, **17-OMe**, and **17-SMe**[35,36] and show important contrasts with the RS^- reactions. Relevant data are summarized in Table 2 for $CF_3CH_2O^-$ and HO^-. For the HO^- reactions, the intermediate was not detectable except for X = H; hence, K_1^{OH} and k_2^{OH} were not experimentally accessible and the reported K_1^{OH} values are estimates.

Of special interest are the rate and equilibrium constant *ratios*. The positive log(k_1^{RS}/k_1^{RO}) values are consistent with the generally observed higher nucleophilicity of RS^- compared with RO^- of equal pK_a.[37,38] Since the pK_a of $HOCH_2CH_2S^-$ (10.56) is lower than that of $CF_3CH_2O^-$ (14.0), the ratios understate the superior reactivity of RS^-.

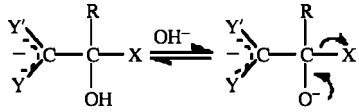
For K_1^{RS}/K_1^{RO}, the situation is more complex; these ratios indicate that the generally much higher carbon basicity of thiolate ions[38] manifests itself only toward **17-H** (log K_1^{RS}/K_1^{RO} = 3.92). For **17-SMe**, K_1^{RS} is only about 10-fold higher than K_1^{RO}, while for **16-OMe** and **17-OMe** K_1^{RS} is slightly lower than K_1^{RO}, although after corrections for the pK_a difference, K_1^{RS} would be modestly larger than K_1^{RO} even for these latter cases.

Two factors depress K_1^{RS}/K_1^{RO} in the reactions of **16-OMe**, **17-OMe**, and **17-SMe**: (1) steric crowding in the intermediate with RS^-, which increases with increasing size of X, is responsible for the reduction in K_1^{RS}/K_1^{RO} for **17-SMe** relative to **17-H**; (2) enhancement of K_1^{RO} with **16-OMe** and **17-OMe** due to stabilization of the intermediate by the anomeric effect from the two geminal oxygen atoms.[39,40] Detailed analysis of this effect has been reported.[41]

The data with HO^- lead to similar conclusions. K_1^{RS}/K_1^{OH} follows the trend of K_1^{RS}/K_1^{OH} except that they are 2000-fold lower than the corresponding K_1^{RS}/K_1^{RO}, reflecting the 2000-fold higher K_1^{RO} due to the higher basicity of HO^-. Interestingly, k_1^{RS}/k_1^{OH} does not show a similar reduction because k_1^{OH}

is quite similar to k_1^{RO}, that is, the higher basicity of HO^- does not enhance its nucleophilicity. This represents another PNS effect resulting from exceptionally strong solvation of HO^- and the fact that its partial desolvation is ahead of bond formation.[33,42]

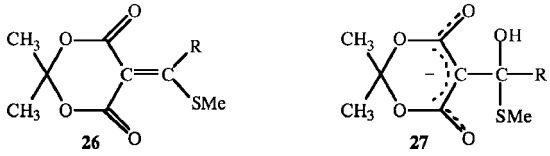
For the reactions with HO^-, no intermediates have been detectable because their formation is always slower than their conversion to products due to additional pathways for the latter.[28,35] One such pathway involves the conjugate base of the intermediate (**25**); the charge on oxygen provides extra



24 **25**

"push" for nucleofuge expulsion. Another is intramolecular acid catalysis of leaving group departure by the OH proton in **24**.

The study of formation of **27** by reaction of **26** with HO^-[43] confirmed the importance of TS steric crowding but also pro-



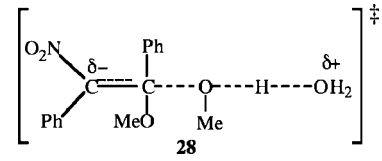
26 **27**

vided insights into reactant steric effects as seen in the rate constant trend: H > Me > Et > *s*-Bu < *t*-Bu. *Ab initio* calculations[43] suggest the reversal for *t*-Bu reflects *reactant* destabilization from sterically induced twisting and elongation of the C=C double bond by *t*-Bu.

Breakdown of Intermediates. Table 3 summarizes data for the breakdown of intermediates into products (k_2) or back to reactants (k_{-1}).[44,45] These rate constants depend on the nature of X, its basicity, its π-donor, inductive and steric effects when acting as the group left behind, and potential anomeric effects.

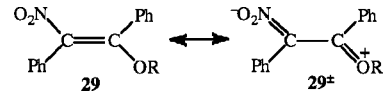
(1) For alkoxy nucleofuges, the rate decreases sharply with increasing basicity of RO^-: $k_{-1}(CF_3CH_2O)/k_{-1}(MeO) = 2500$ (entries 2a/1a), equivalent to $\beta_{lg} \approx -1.06$; $k_2(CF_3CH_2O)/k_2(MeO) = 1460$ (entries 5/4), equivalent to $\beta_{lg} \approx -0.99$. This implies a TS with extensive C−O bond cleavage. In contrast, for H_3O^+ catalysis, MeO^- departure is faster than $CF_3CH_2O^-$ departure (k_{-1}^H, entries 1b/2b);[44] partial protonation of the more basic nucleofuge (**28**) is energetically so much more favorable that this more than offsets its inherently weaker nucleofugality.

(2) For alkylthio nucleofuges, dependence on basicity is also strong. Thus, the 5.5-fold reduction in k_{-1} for *n*-PrS^- versus $HOCH_2CH_2S^-$ (entries 6/7) and the 5.4-fold reduction in k_2 for the same change in X (entries 7/8) translates into β_{lg} values of −0.84 and −0.83, respectively.



28

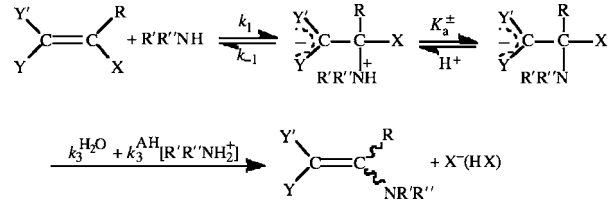
(3) The "push" by MeO is stronger than by CF_3CH_2O as seen in the 6-fold higher k_{-1} in entry 2a vs 3. The larger k_2 value for entry 1a vs 2a shows the same phenomenon. The push arises from the developing resonance effect that stabilizes **29** (**29**$^{\pm}$).



29 **29**$^{\pm}$

(4) Regarding relative nucleofugalities of RS^- and RO^-, $k_2(HOCH_2CH_2S)/k_2(CF_3CH_2O) = 18$ (entries 5/6) and $k_{-1}(HOCH_2CH_2S)/k_{-1}(CF_3CH_2O) = 106$ (entries 9/10) and 5.7 (entries 11/12, respectively). However, adjusting the rate constants for the pK_a difference between $CF_3CH_2O^-$ (14.0) and $HOCH_2CH_2S^-$ (10.56) by assuming $\beta_{lg} = -1.0$ leads to corrected $HOCH_2CH_2S^-/CF_3CH_2O^-$ ratios of 6.54×10^{-3}, 3.85×10^{-2}, and 2.07×10^{-2}, respectively, indicating that RO^- are inherently better nucleofuges than RS^-.

Reactions with Amines. Due to the acidic nature of **12**, the mechanism (eq 11) involves acid−base equilibria prior to R'R''NH_2^+-catalyzed (k_3^{AH}) or water-catalyzed ($k_3^{H_2O}$) nucleofuge departure. Intermediate detectability requires eqs 12 and 13.[46]



(11)

$$\frac{K_1 K_a^{\pm}[\text{R'R''NH}]}{a_{H^+}} > 1 \qquad (12)$$

$$k_1[\text{R'R''NH}] > k_3^{H_2O} + k_3^{AH}[\text{R'R''NH}_2^+] \qquad (13)$$

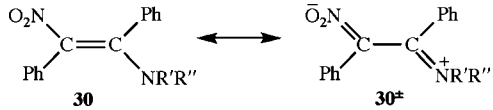
Conventional wisdom predicts chances of detecting intermediates should be best for highly nucleophilic amines. However, it is the reactions of **16-OMe** with the *weakly basic* methoxyamine (pK_a = 4.70) and *N*-methylmethoxyamine (pK_a = 4.67) that allowed detection of intermediates[29] rather than the reaction with piperidine or *n*-butylamine.[47,48] The reason for this paradox is that $k_3^{H_2O}$ depends more strongly on amine basicity ($\beta_{push} \approx 0.71$)[29] due to developing product resonance (**30**$^{\pm}$) than

TABLE 3. Rate Constants for the Breakdown of S_NV Intermediates in 50% DMSO−50% Water at 20 °C[a,b]

no.	reactants		intermediate		products
1a	MeO^- + **16-OMe**	$k_{-1}=2\times10^{-8}$	**16-$(OMe)_2^-$**	$k_2=2\times10^{-8}$	**16-OMe** + MeO^-
1b	MeOH + **16-OMe**	$k^H_{-1}=3.73\times10^2$	**16-$(OMe)_2^-$**	$k^H_2=3.73\times10^2$	**16-OMe** + MeOH
2a	RO^- + **16-OMe**	$k_{-1}=5.0\times10^{-5}$	**16-(OMe,OR)$^-$**	$k_2<\times10^{-8}$	**16-OR** + MeO^-
2b	ROH + **16-OMe**	$k^H_{-1}=51.4$	**16-(OMe,OR)$^-$**	$k^H_2=5.4$	**16-OR** + MeOH
3	RO^- + **16-OR**	$k_{-1}=8.2\times10^{-6}$	**16-$(OR)_2^-$**	$k_2=8.2\times10^{-6}$	**16-OR** + RO^-
4	RS^- + **16-OMe**	$k_{-1}=5.1\times10^{-2}$	**16-(OMe,SR)$^-$**	$k_2=9.6\times10^{-6}$	**16-SR** + MeO^-
5	RS^- + **16-OR**	$k_{-1}=0.10$	**16-(OR,SR)$^-$**	$k_2=1.4\times10^{-2}$	**16-SR** + RO^-
6	RS^- + **16-SR**	$k_{-1}=0.25$	**16-$(SR)_2^-$**	$k_2=0.25$	**16-SR** + RS^-
7	PrS^- + **16-SR**	$k_{-1}=0.045$	**16-(SR,SPr)$^-$**	$k_2=0.35$	**16-SPr** + RS^-
8	PrS^- + **16-SPr**	$k_{-1}=0.065$	**16-$(SPr)_2^-$**	$k_2=0.065$	**16-SPr** + PrS^-
9	RO^- + **17-OMe**	$k_{-1}=1.6\times10^{-2}$	**17-(OMe,OR)$^-$**		
10	RS^- + **17-OMe**	$k_{-1}=1.7$	**17-(OMe,SR)$^-$**	$k_2=2.2\times10^{-4}$	**17-SR** + MeO^-
11	RO^- + **17-SMe**	$k_{-1}=4.9\times10^{-2}$	**17-(SMe,OR)$^-$**	$k_2\leq2.3\times10^{-2}$	**17-OR** + MeS^-
12	RS^- + **17-SMe**	$k_{-1}=2.8$	**17-(SMe,SR)$^-$**	$k_2=0.11$	**17-SR** + MeS^-

[a] k_{-1} and k_2 in s^{-1}, k^H_{-1} and k^H_2 in $M^{-1}\ s^{-1}$. [b] RO = CF_3CH_2O; RS = $HOCH_2CH_2S$; PrS = $CH_3CH_2CH_2S$.

k_1 ($\beta_{nuc} = 0.25$).[29] Only for the reactions of piperidine and morpholine with **19-SMe** were intermediates detectable.



In the reaction of **17-SMe** with piperazine, 1-(2-hydroxyethyl)piperazine, and morpholine,[27] the deprotonation of the first intermediate is not a rapid equilibrium but is rate-limiting at low [R_2NH] and low [KOH] because of very high k_{-1} values. In contrast, the reactions of **17-SMe** with piperidine and primary aliphatic amines,[48] as well as the reaction of α-isobutyl-α-(methylthio)methylene Meldrum's acid with primary amines[49] are "normal" in that the proton transfer is rapid.

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BIOGRAPHICAL INFORMATION

Claude F. Bernasconi was born in Zürich, Switzerland, in 1939. He received his undergraduate degree and Ph.D. (with the late Heinrich Zollinger) from the Swiss Federal Institute of Technology (ETH). Following a postdoctoral year with Manfred Eigen at the Max-Planck Institute for Physical Chemistry in Göttingen, Germany, he joined the faculty at the University of California, Santa Cruz, in 1967 where he is now Distinguished Professor of Chemistry. His research is focused on the kinetics and mechanisms of organic reactions with emphasis on structure−reactivity questions in nucleophilic addition/substitution reactions, Fischer carbene complexes, and proton transfers including *ab initio* calculations. He is the author of *Relaxation Kinetics.*

Zvi Rappoport was born in Jerusalem in 1936, received M.Sc. and Ph.D. degrees (Chemistry, 1959, 1962), and B.A. (History and South East Asia studies, 2006) at the Hebrew University, conducted postdoctoral research at UCLA with the late Saul Winstein, has been a Professor of Organic Chemistry at the Hebrew University from 1974, and is presently an emeritus professor. His research interests include nucleophilic vinylic reactions, vinyl cations, stable simple enols, vinyl propellers, Chemophilately (all subjects of previous Accounts), reactivity and selectivity, and enols of carboxylic acid derivatives. He is the editor of "The Chemistry of Functional Groups" series.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: bernasconi@chemistry.ucsc.edu.

REFERENCES

1 (a) Rappoport, Z. Nucleophilic vinylic substitution. *Adv. Phys. Org. Chem.* **1969**, *7*, 1–114. (b) Modena, G. Reactions of nucleophiles with ethylenic substrates. *Acc. Chem. Res.* **1971**, *4*, 73–80. (c) Rappoport, Z. Nucleophilic vinylic substitution. A single- or a multi-step process. *Acc. Chem. Res.* **1981**, *14*, 7–15. (d) Rappoport, Z. The rapid steps in nucleophilic vinylic "addition−elimination" substitution. Recent developments. *Acc. Chem. Res.* **1992**, *25*, 474–479. (e) Rappoport, Z. The rich mechanistic world of nucleophilic vinylic (S_NV) substitution. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 309–349. (f) Shainyan, B. A. Reactions involving bimolecular nucleophilic substitution at a vinylic centre. *Russ. Chem. Rev.* **1986**, *55*, 511–530. (g) Cohen, D.; Bar, R.; Shaik, S. S. Nucleophilic vinylic substitution. A theoretical study. *J. Am. Chem. Soc.* **1986**, *108*, 231–240. (h) Okuyama, T.; Lodder, G. Nucleophilic vinylic substitution and vinyl cations intermediates in the reactions of vinyl iodonium salts. *Adv. Phys. Org. Chem.* **2002**, *37*, 1–56.

2 (a) Fei, Z.; McDonald, F. E. Synthesis of the aglycones of altromycins and kidamycin from a common intermediate. *Org. Lett.* **2005**, *7*, 3617–3620. (b) Barr, P. J.; Jones, A. S.; Verhelst, G.; Walker, R. T. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1665–1670. (c) Krafts, G. A.; Katzenellenbogen, J. A. Synthesis of haloenol lactones. Mechanism based inactivation of serine proteases. *J. Am. Chem. Soc.* **1981**, *103*, 5459–5466. (d) Skarzynski, T.; Kim, D. H.; Lees, W. J.; Walsh, C. T.; Duncan, K. Stereochemical course of enzymatic enolpyruvyl transfer and catalytic conformation of the active site revealed by the crystal structure of the fluorinated analogue of the reaction tetrahedral intermediate bound to the active site of the C115A mutant of MurA. *Biochemistry* **1998**, *37*, 2572–2577. (e) Shim, J.-Y.; Boon, P. F.; Richard, A. M. Theoretical study of the S_NV reaction of trichloroethylene (TCE)

and CH_3S^- as a model for glutathione conjugation of TCE. *Chem. Res. Toxicol.* **1999**, *12*, 308–316. (f) Hackett, A. G.; Kotyk, J. J.; Fujiwara, H.; Logusch, E. W. Identification of a unique glutathione conjugate of trichloroacrolein using heteronuclear multiple quantum coherence ^{13}C NMR spectroscopy. *J. Am. Chem. Soc.* **1990**, *112*, 3669–3671.

3 Rappoport, Z.; Rav-Acha, C. The k_{Br}/k_{Cl} element effect for nucleophilic vinylic substitution of the highly reactive tricyanovinyl-X system by substituted anilines. *Tetrahedron Lett.* **1984**, *25*, 117–120.

4 (a) Bergman, R. G.; Kelsey, D. R. Application of the extended Huckel molecular orbital method to the properties of vinyl cations. Conformational energies of some 1-cyclopropylvinyl cations and a comparison of S_N1 displacement at saturated and vinylic carbon. *J. Am. Chem. Soc.* **1971**, *93*, 1953–1961. (b) Stohrer, W. D. Ein argument fur den konzertierten verlauf der nucleophilen vinylischen substitution mit konfigurationserhalt. *Tetrahedron Lett.* **1975**, 207–210. (c) Apeloig, Y.; Rappoport, Z. The importance of hyperconjugation in nucleophilic vinylic substitution. *J. Am. Chem. Soc.* **1979**, *101*, 5095–5098. (d) Bach, R. D.; Wolber, G. J. Nucleophilic substitution at vinylic carbon. The importance of the HOMO−HOMO interaction. *J. Am. Chem. Soc.* **1984**, *106*, 1401–1409.

5 Glukhovtsev, M. N.; Pross, A.; Radom, L. Is S_N2 substitution with inversion of configuration at vinylic carbon feasible? *J. Am. Chem. Soc.* **1994**, *116*, 5961–5962.

6 Kim, C. K.; Hyun, K. H.; Kim, C. K.; Lee, I. Nucleophilic substitution at unactivated vinylic carbon. Factors conducive to the energetic preference for the in-plane S_N2 pathway. *J. Am. Chem. Soc.* **2000**, *122*, 2294–2299.

7 Bach, R. D.; Baboul, A. G.; Schlegel, H. B. Inversion versus retention of configuration for nucleophilic substitution at vinylic carbon. *J. Am. Chem. Soc.* **2001**, *123*, 5787–5793.

8 See Rappoport, Z. Planar tetracoordinate carbon in a transition state. *Tetrahedron Lett.* **1978**, 1073–1076.

9 (a) Luccini, V.; Modena, G.; Pasquato, L. An authentic case of in-plane nucleophilic vinylic substitution. The anionotropic rearrangement of di-*tert*-butylthiirenium ions into thietium ions. *J. Am. Chem. Soc.* **1993**, *115*, 4527–4531. (b) Luccini, V.; Modena, G.; Pasquato, L. S_N2 and Ad_N-E mechanisms in bimolecular nucleophilic substitutions at vinyl carbon. The relevance of the LUMO symmetry of the electrophile. *J. Am. Chem. Soc.* **1995**, *117*, 2297–2300.

10 Shiers, J. J.; Shipman, M.; Hayes, J.; Slawin, A. M. Z. Rare example of nucleophilic substitution at vinylic carbon with inversion: Mechanism of methyleneaziridine formation by sodium amide induced ring closure revisited. *J. Am. Chem. Soc.* **2004**, *126*, 6868–6869.

11 Ando, K.; Kitamura, M.; Miura, K.; Narasaka, K. Theoretical and experimental study on the in-plane S_N2-type substitution reaction of haloalkenes with inversion of configuration at the sp^2 carbon. *Org. Lett.* **2004**, *6*, 2461–2463.

12 Ando, K. Theoretical study of the nucleophilic 5-endo-trigonal cyclization of 1,1-difluoro-1-alkenes. *J. Org. Chem.* **2004**, *69*, 4203–4209.

13 Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. Solvolysis of cyclohexenyliodonium salt. A new precursor for the vinyl cation: Remarkable nucleofugality of the phenyliodonio group and evidence for internal return from an intimate ion−molecule pair. *J. Am. Chem. Soc.* **1995**, *117*, 3360–3367. Since the nucleofuge may be the λ^3-phenyliodanyl group, it also have high nucleofugality.

14 Ochiai, M.; Oshima, K.; Masaki, Y. Inversion of configuration in nucleophilic vinylic substitution of (*E*)-β-alkylvinyliodonium tetrafluoroborates with halides. *J. Am. Chem. Soc.* **1991**, *113*, 7059–7061.

15 Okuyama, T.; Takino, T.; Sato, K.; Ochiai, M. In-plane vinylic S_N2 substitution and intramolecular β-elimination of β-alkylvinyl(chloro)- λ^3-iodane. *J. Am. Chem. Soc.* **1998**, *120*, 2275–2282.

16 Okuyama, T.; Takino, T.; Sato, K.; Oshima, K.; Imamura, S.; Yamataka, H.; Asano, T.; Ochiai, M. Vinylic S_N2 reaction of 1-decenyliodonium salt with halide ions. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 243–257.

17 Ochiai, M.; Oshima, K.; Masaki, Y. Synthesis of (Z)-1,2-dihalo-1-alkenes by the reaction of (Z)-(β-halovinyl)phenyliodonium salts with *n*-Bu_4NX or KX/CuX. Competition between nucleophilic vinylic substitutions and aromatic substitutions. *Chem. Lett.* **1994**, *87*, 1–874.

18 See refs 45, 51, 52, and 54 in ref 1h.

19 Shainyan, B. A.; Rappoport, Z. Vinylic substitution of 1,2-dibromo-1,2-difluoroethylene and tribromofluoroethylene. An intramolecular k_{Br}/k_F element effect and apparent inversion of configuration in S_NV reactions. *J. Org. Chem.* **1993**, *58*, 3421–3428.

20 Beit-Yannai, M.; Rappoport, Z.; Shainyan, B. A.; Danilevich, Y. S. Intramolecular geminal and vicinal element effects in substitution of simple bromo(chloro)alkenes by methoxide and thiolate ions. An example of a single-step substitution. *J. Org. Chem.* **1997**, *62*, 8049–8057.

21 Avramovitch, B.; Weyerstahl, P.; Rappoport, Z. Nucleophilic attacks on carbon-carbon double bonds. 34. Intramolecular element effect in competitive expulsion of two halide nucleofuges as a tool for investigating the rapid step of nucleophilic vinylic substitution. *J. Am. Chem. Soc.* **1987**, *109*, 6687–6697.

22 Marchese, G.; Naso, F.; Modena, G. Nucleophilic reactions in ethylenic derivatives. Part XII. Reactions of β-fluoro-4-nitrostyrenes with nucleophiles. *J. Chem. Soc. B* **1969**, 290–293.

23 For summary, see Tables 1 and 2 and refs 6−8 and 10 in ref 1d.

24 (a) Reference 48 in ref 1c. (b) References 49−51 in ref 1c.

25 Rappoport, Z.; Topol, A. Nucleophile and nucleofuge effects, catalysis and stereochemistry in vinylic substitution of electrophilic nitro-olefins. *J. Org. Chem.* **1989**, *54*, 5967–5977.

26 Beit-Yannai, M.; Chen, X.; Rappoport, Z. Amine catalysis in the vinylic substitution of α-methylthio-α-arylmethylene Meldrum's acids and its absence in the substitution of methyl β-iodo-α-nitrocinnamates by amines. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1534–1545.

27 Bernasconi, C. F.; Ali, M.; Nguyen, K.; Ruddat, V.; Rappoport, Z. Reactions of substituted (methylthio)benzylidene Meldrum's acids with secondary alicyclic amines in aqueous DMSO. Evidence for rate limiting proton transfer. *J. Org. Chem.* **2004**, *69*, 9248–9254.

28 Bernasconi, C. F.; Ketner, R. J.; Ragains, M. L.; Chen, X.; Rappoport, Z. Unraveling structure-reactivity relationships in S_NV reactions. Kinetics of the reactions of vinylic substrates with OH^- and thiolate ions. *J. Am. Chem. Soc.* **2001**, *123*, 2155–2164, and references cited therein. This paper summarizes much of the previous work.

29 Bernasconi, C. F.; Leyes, A. E.; Eventova, I.; Rappoport, Z. Kinetics of the reactions of β-methoxy-α-nitrostilbenes with methoxyamine and *N*-methylmethoxyamine. Direct observation of the intermediate in nucleophilic vinylic substitution. *J. Am. Chem. Soc.* **1995**, *117*, 1703–1711.

30 Bernasconi, C. F.; Brown, S. D.; Eventova, I.; Rappoport, Z. Spectroscopic and kinetic evidence for an accumulating intermediate in an S_NV reaction with amine nucleophiles. Reaction of methyl β-methylthio-α-nitrocinnamate with piperidine and morpholine. *J. Org. Chem.* **2007**, *72*, 3302–3310.

31 The intrinsic rate constant is the rate constant in the absence of thermodynamic driving force ($\Delta G^\circ = 0$) and is obtained from interpolation or extrapolation of log k_1 versus log K_1 to $K_1 = 1$.

32 MA = Meldrum's acid moiety; ID = 1,3-indandione moiety.

33 (a) Bernasconi, C. F. Intrinsic barriers of reactions and the principle of nonperfect synchronization. *Acc. Chem. Res.* **1987**, *20*, 301–308. (b) Bernasconi, C. F. The principle of nonperfect synchronization. *Adv. Phys. Org.* **1992**, *27*, 119–238.

34 Late development in one direction equals early loss in the reverse direction.[33].

35 Bernasconi, C. F.; Fassberg, J.; Killion, R. B.; Schuck, D. F.; Rappoport, Z. Kinetics of reactions of OH^- and water with α-nitro-β-X-stilbenes (X = Cl, I, SEt, OMe, SCH_2CH_2OH). Search for the intermediate in nucleophilic vinylic substitution. *J. Am. Chem. Soc.* **1991**, *113*, 4937–4946.

36 Bernasconi, C. F.; Ketner, R. J.; Chen, X.; Rappoport, Z. Detection of S_NV intermediates. Reactions of thiomethoxybenzylidene Meldrum's acid with RS^-, RO^- and OH^-. *Can. J. Chem.* **1999**, *77*, 584–594.

37 Pearson, R. G.; Songstad, J. Application of the principle of hard and soft acids and bases to organic chemistry. *J. Am. Chem. Soc.* **1967**, *89*, 1827–1836.

38 Sander, E. G.; Jencks, W. P. Equilibria for additions to the carbonyl group. *J. Am. Chem. Soc.* **1968**, *90*, 6154–6162.

39 Hine, J. Polar effects on rates and equilibria. Double bond-no bond resonance. *J. Am. Chem. Soc.* **1963**, *85*, 3239–3244.

40 Wiberg, K. B.; Squires, R. Determination of the enthalpies of hydrolysis of some polyoxygenated hydrocarbons. *J. Chem. Thermodynamics* **1979**, *11*, 773–786.

41 Karni, M.; Bernasconi, C. F.; Rappoport, Z. Role of negative hyperconjugation and anomeric effects in the stabilization of the intermediate in S_NV reactions. *J. Org. Chem.* **2008**, *73*, 2980–2994, and references cited therein.

42 Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, G.; Nakamura, C. Non-linear Brønsted correlations: The roles of resonance, solvation and changing transition state structure. *J. Am. Chem. Soc.* **1982**, *104*, 7045–7051.

43 Bernasconi, C. F.; Brown, S. D.; Ali, M.; Rappoport, Z.; Yamataka, H.; Salim, H. Hydrolysis of the α-alkyl-α-(methylthio)methylene Meldrum's acids. A kinetic and computational investigation of steric effects. *J. Org. Chem.* **2006**, *71*, 4795–4802.

44 Bernasconi, C. F.; Schuck, D. F.; Ketner, R. J.; Eventova, I.; Rappoport, Z. The $CF_3CH_2O^-$ adducts of α-nitro-β-(2,2,2-trifluoromethoxy)stilbene and β-methloxy-α-nitrostilbene, and the MeO^- adduct of β-methoxy-α-nitrostilbene. Competition between protonation and acid catalyzed alkoxide ion departure. *J. Am. Chem. Soc.* **1995**, *117*, 2719–2725.

45 Bernasconi, C. F.; Ketner, R. J.; Brown, S. D.; Chen, X.; Rappoport, Z. Acid-catalyzed breakdown of alkoxide and thiolate ion adducts of benzylidene Meldrum's acid, methoxybenzylidene Meldrum's acid and thiomethoxybenzylidene Meldrum's Acid. *J. Org. Chem.* **1999**, *64*, 8829–8839.

46 These simplified equations pertain to pH ≫ $pK_a^{\pm}$, which drives the equilibrium towards the anionic intermediate.[29,30]

47 Bernasconi, C. F.; Fassberg, J.; Killion, R. B.; Rappoport, Z. Kinetics of reactions of amines with α-nitro-β-substituted-stilbenes. Search for the intermediate in S_NV reactions. *J. Org. Chem.* **1990**, *55*, 4568–4575.

48 Bernasconi, C. F.; Biswas, S.; Rappoport, Z. Kinetics and mechanism of reactions of substituted (methylthio)benzylidene Meldrum's acids with primary amines. *J. Phys. Org. Chem.* **2006**, *19*, 647–653.

49 Biswas, S.; Ali, M.; Rappoport, Z.; Salim, H. Reactions of α-isobutyl-α-(methylthio) -methylene Meldrum's acid with primary amines. *Can. J. Chem.* **2006**, *84*, 1679–1685.