Mechanistic Classification of Abnormal Allylic Substitution (SN2′) Reactions

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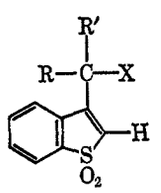
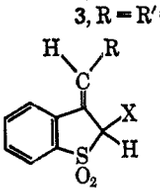
The secondary and tertiary chlorides, 3-(α-haloethyl)- and 3-(α-chloro-α-methylethyl)benzo[*b*]thiophene 1,1-dioxides (**2** and **3**), which are much more reactive than α-methylallyl chloride in SN2′ reactions with secondary amines in benzene, fail to give reactions with a number of other nucleophiles claimed to be effective for SN2′ reactions (thiourea, bromide ion, alkoxide ions, tertiary amines). The applicability of the SN2′ mechanistic label to a number of abnormal substitutions of allylic halides is reviewed in the light of these results and it is concluded that very few unambiguous assignments of this label can be made. Changing the solvent from benzene to methanol was found to *decrease* markedly the rate of the SN2′ reaction of piperidine with bromide **2** or **3**. This information, together with the small Br–Cl leaving-group effect for **2**, is used in discussing mechanisms for SN2′ reactions.

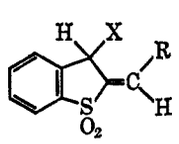
Evidence is now on hand to indicate that the seven halides **1**–**7** (one primary, one tertiary, and five secondary) react with piperidine in benzene by abnormal allylic substitution mechanisms.[1-3]



1, R = R′ = H; X = Cl
2, R = H, R′ = Me; X = Br, Cl
3, R = R′ = Me; X = Cl



4, R = H; X = Br, Cl, I
5, R = Me; X = Br



6, R = H; X = Br
7, R = Me; X = Br

Four of these halides (**4**–**7**) were produced as transient intermediates; further evidence for the mechanistic classification of these reactions is therefore difficult to obtain. A further study of the behavior of **2** and **3** has now been made, however, using additional nucleophiles and solvents. As a result of this study we have reached the conclusion that, although the SN2′ mechanistic classification has been suggested for numerous abnormal allylic substitutions, and many of these have been accepted as bonafide by workers prominent in the field,[4] relatively few completely unambiguous examples have been described.

In order to evaluate and compare potential nucleophiles for further investigation, the kinetic data for all previous studies wherein abnormal substitution products were obtained in a second-order process, presumably by an SN2′ mechanism, were collected. The rate constants, expressed in common units (M^{-1} sec^{-1}) and, where possible, at comparable temperatures (at or near 50°) are compared in Table I[5-17] with data obtained on the rates of halide release for compounds **1**–**4**.

Examination of Table I reveals that SN2′ reactions have been claimed for only a rather select group of nucleophiles. Six types are represented: (a) secondary amines, (b) tertiary amines, (c) ethyl sodiomalonate, (d) sodium ethoxide, (e) sodium thiophenoxide, and (f) lithium bromide. Thiourea may be added to this list since it has been reported to give abnormal substitution with α,α-dimethylallyl chloride with a second-order rate constant about ten times less than the SN2 rate constant for γ,γ-dimethylallyl chloride.[18] Most of these nucleophiles have been used in only one or two allylic systems. Judging from the results with α-methylallyl halide systems and ignoring solvent effects, ethyl sodiomalonate, secondary and tertiary amines, and lithium bromide all react at rates of a comparable order of magnitude; sodium thiophenoxide is several powers of ten more reactive (based on the α,α-dimethylallyl system), and sodium ethoxide is several orders of magnitude less reactive (based on the α-*t*-butylallyl system). Secondary chloride **2** in the 3-α-haloalkylbenzo[*b*]-thiophene 1,1-dioxide series is about 500 times as reactive toward piperidine as is α-methylallyl chloride toward dimethylamine, and tertiary chloride **3** is ten times as reactive. In view of the high reactivity of **2** and **3** toward secondary amines it was anticipated that these halides would react readily with the other nucleophiles on the list. Surprisingly enough, this was not the case.

Results

Excess thiourea failed to react to any appreciable extent with either **2** or **3** in alcohol even after extended reflux. With the secondary chloride (**2**) the reaction was

(1) F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Org. Chem.*, **33**, 3226 (1968).

(2) F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *ibid.*, **33**, 3233 (1968).

(3) F. G. Bordwell and D. A. Schexnayder, *ibid.*, **33**, 3236 (1968). See F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Amer. Chem. Soc.*, **89**, 7144 (1967), for a preliminary account of the present work.

(4) (a) R. H. DeWolfe and W. G. Young, *Chem. Rev.*, **56**, 769 (1956); (b) P. B. D. de la Mare, "Molecular Rearrangements, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 2, pp 62–68.

(5) R. D. Kepner, S. Winstein, and W. G. Young, *J. Amer. Chem. Soc.*, **71**, 115 (1949).

(6) W. G. Young, I. D. Webb, and H. L. Goering, *ibid.*, **73**, 1076 (1951).

(7) (a) D. C. Dittmer and A. F. Marcantonio, *Chem. Ind.* (London), 1237 (1960); (b) D. C. Dittmer and A. F. Marcantonio, *J. Amer. Chem. Soc.*, **86**, 5621 (1964).

(8) W. G. Young and I. J. Wilk, *ibid.*, **79**, 4793 (1957).

(9) W. G. Young, R. A. Clement, and C. H. Shih, *ibid.*, **77**, 3061 (1955).

(10) P. B. D. de la Mare, E. D. Hughes, P. C. Merriman, L. Pichet, and C. A. Vernon, *J. Chem. Soc.*, 2563 (1958).

(11) B. D. England, *ibid.*, 1615 (1955).

(12) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 3555 (1953).

(13) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 3331 (1952).

(14) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 3325 (1952).

(15) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 3628 (1952).

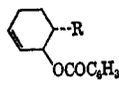
(16) (a) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4609 (1956); (b) G. Stork and F. H. Clarke, *ibid.*, **78**, 4619 (1956).

(17) D. A. Schexnayder, Ph.D. Dissertation, Northwestern University, June 1968.

(18) Unpublished work cited in ref 4a, p 779.

TABLE I

KINETIC DATA FOR BIMOLECULAR ABNORMAL ALLYLIC (SN2′) SUBSTITUTIONS

Ref	Halide	Nucleophile	Solvent	Temp, °C	k_2, M^{-1} sec^{-1}	E_a, kcal/mol	ΔS^*, eu
5	CH_2=CHCH(Et)Cl	$NaCH(CO_2Et)_2$	EtOH	50	2.2×10^{-5}		
6	CH_2=CHCH(Me)Cl	Et_2NH	C_6H_6	62.7	6.4×10^{-6}		
7	CH_2=CHCH(Me)Cl	Et_2NH	C_6H_6	60	5.8×10^{-6}	15	−39
7	CH_2=CHCH(Me)Cl	Et_2ND	C_6H_6	60	5.8×10^{-6}		
7	CH_2=CHCH(Me)Cl	PhNHMe	C_7H_{16}	80	(3.9×10^{-3})[a]		
8	CH_2=CHCH(Me)Cl	Me_2NH	C_6H_6	49.6	1.5×10^{-5}	18	−26
9	CH_2=CHCH(Me)Cl	Me_3N	Me_2C=O	49.7	1.1×10^{-5}	14.5	−38
10	CH_2=CHCH(*t*-Bu)Cl	NaOEt	EtOH	50	1.0×10^{-7}	26	−12
11	CH_2=CHCH(Me)Br	LiBr*	Me_2C=O	50	1.7×10^{-4}	19	−19
11	MeCH=$CHCH_2$Br	LiBr*	Me_2C=O	50	5.8×10^{-5}	~19	−21
12	CH_2=$CHC(Me)_2Cl$[b]	NaSPh	EtOH	50	1.9×10^{-2}		
13	CH_2=$CHCHCl_2$	NaSPh	EtOH	50	6.8×10^{-4}		
14	CH_2=$CHCHCl_2$	NaOEt	EtOH	100	2.4×10^{-4}		
15	CH_2=$C(Me)CCl_3$	NaOEt	EtOH	64.8	1.3×10^{-5}		
15	CH_2=$C(Me)CCl_3$	NaSPh	EtOH	50	1.4×10^{-3}		
16a		$C_5H_{10}NH$	$Me_2C_6H_4$	129.5	1.7×10^{-7} (R = Me)		
16a		$C_5H_{10}NH$	$Me_2C_6H_4$	129.5	3.9×10^{-7} (R = *i*-Pr)		
16a		$C_5H_{10}NH$	$Me_2C_6H_4$	129.5	9.7×10^{-7} (R = *t*-Bu)		
16a		$NaCH(CO_2Et)_2$	BuOH	104.7	2.2×10^{-5} (R = *i*-Pr)		
16a		$NaCH(CO_2Et)_2$	BuOH	104.7	3.6×10^{-5} (R = *t*-Bu)		
16b	α-Chlorococide	$C_5H_{10}NH$	C_6H_6	50	4.7×10^{-5}	14	−37
17	**1**, R = R′ = H	$C_5H_{10}NH$	C_6H_6	50	1.3×10^{-2}		
1	**2**, R = H; R′ = Me	$C_5H_{10}NH$	C_6H_6	50	2.1×10^{-3} (X = Cl)	10	−42
3	**2**, R = H, R′ = Me	$C_5H_{10}NH$	C_6H_6	50	3.4×10^{-2} (X = Br)	8	−43
3	**2**, R = H, R′ = Me	$C_5H_{10}NH$	MeOH	50	1.5×10^{-3} (X = Br)	15	−26
1	**3**, R = R′ = Me	$C_5H_{10}NH$	C_6H_6	50	1.6×10^{-4}	11	−43
1	**3**, R = R′ = Me	$C_5H_{10}NH$	MeOH	50	1.8×10^{-5}	17	−32
1	**3**, R = R′ = Me	$C_5H_{10}NH$	Me_2C=O	50	2.2×10^{-4}		
1	**3**, R = R′ = Me	$C_5H_{10}NH$	DMF	50	6.5×10^{-4}		
1	**3**, R = R′ = Me	Bu_2NH	C_6H_6	50	3.4×10^{-5}		
2	**4**, X = Br	$C_5H_{10}NH$	MeOH	50	$(>2 \times 10^{-1})$[c]		

[a] The rate expression also contains a second-order term in PhNHMe. [b] CH_2=CHCH(Me)Cl reacts with PhSNa by an SN2 process; the maximum SN2′ rate has been estimated to be 1.9×10^{-3} M^{-1} sec^{-1}.[12] [c] Estimated. The rates were corrected for per cent SN2′ component where pertinent.

tried for periods ranging from 2 to 48 hr in refluxing methanol, ethanol, and ethylene glycol monomethyl ether. From 70 to 90% starting material was recovered from these runs.[19] With the tertiary chloride (**3**) starting material was recovered after 3-hr reflux in ethanol or acetonitrile. The failure of thiourea to effect SN2′ reactions with halides **2** or **3** is striking in view of their reactivity toward piperidine (Table I), and the small difference between thiourea and piperidine as nucleophiles in SN2 reactions of the parent allyl halides (Table II).

Recalling that SN2 reactions are ordinarily greatly favored over SN2′ reactions, it is interesting to note that the rate of SN2 reaction of allyl chloride with piperidine in benzene (Table II) is an order of magnitude *slower* than the rate of SN2′ reaction of **2** with piperidine under comparable conditions (Table I), and that the SN2′ rate for **3** with piperidine in methanol is not much slower than the SN2 rate of allyl chloride with piperidine in methanol. In contrast, the SN2 rate for thiourea and allyl chloride in methanol must be many orders of magnitude *faster* than the SN2′ reactions of **2** or **3** with this nucleophile. It is apparent that piperidine is a highly favored nucleophile for the SN2′ reaction.

Reaction of **2** with sodium bromide in refluxing acetone for 48 hr gave a good yield of the corresponding secondary bromide (SN2 product).[19] On the other hand, tertiary chloride **3** was recovered unchanged from a comparable reaction run for 65 hr. A solution of **3** in anhydrous acetone was allowed to stand for 31 days with lithium bromide. The nmr spectrum of the recovered organic material resembled that of the starting material closely; there was no indication of the presence of an abnormal substitution or rearranged product. Microanalysis of the crude organic product for carbon and hydrogen gave close agreement with the calculated values for **3** indicating that no more than 1% bromide

TABLE II

COMPARISON OF PIPERIDINE, N-METHYLPIPERIDINE, AND THIOUREA AS NUCLEOPHILES IN SN2 REACTIONS

Halide	Nucleophile	Solvent	Temp, °C	k_2, M^{-1} sec^{-1}
$CH_3CH_2CH_2Br$[a]	$C_5H_{10}NH$	MeOH	25	1.9×10^{-5}
$CH_3CH_2CH_2Br$[a]	S=$C(NH_2)_2$	MeOH	25	1.7×10^{-5}
$CH_3CH_2CH_2Br$[a]	$C_5H_{10}NH$	MeOH	50	1.9×10^{-4}
$CH_3CH_2CH_2Br$[a]	S=$C(NH_2)_2$	MeOH	50	1.7×10^{-4}
H_2C=$CHCH_2Br$[a]	$C_5H_{10}NH$	MeOH	25	3.4×10^{-3}
H_2C=$CHCH_2Br$[a]	S=$C(NH_2)_2$	MeOH	25	2.3×10^{-3}
H_2C=$CHCH_2Br$[a]	$C_5H_{10}NH$	MeOH	50	2.4×10^{-2}
H_2C=$CHCH_2Br$[a]	S=$C(NH_2)_2$	MeOH	50	1.4×10^{-2}
H_2C=$CHCH_2Br$[a]	$C_5H_{10}NH$	C_6H_6	50	8.9×10^{-3}
H_2C=$CHCH_2Br$[b]	$C_5H_{10}NCH_3$	C_6H_6	50	6.6×10^{-4}
H_2C=$CHCH_2Cl$[b]	$C_5H_{10}NH$	C_6H_6	50	8.9×10^{-5}
H_2C=$CHCH_2Cl$[b]	$C_5H_{10}NH$	MeOH	50	5.3×10^{-3}
H_2C=$CHCH_2Cl$[b]	$C_5H_{10}NCH_3$	MeOH	50	1.1×10^{-4}

[a] Conductometric rates measured by P. E. Sokol.[19] [b] Titrimetric rates; only one or two runs were made in most instances.

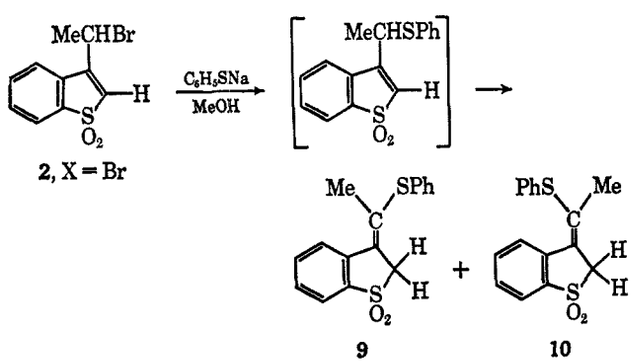
(19) P. E. Sokol, Ph.D. Dissertation, Northwestern University, Aug 1959.

could have been formed. It is evident from these results that **2** is much more prone to undergo SN2 than SN2′ displacement with bromide ion, and that **3** is essentially inert toward bromide ion.

When **3** was heated with sodium methoxide in methanol, chloride ion was slowly released. The products of this reaction have not been identified as yet, but the nmr spectrum of the crude material did not reveal absorption in the vinyl hydrogen region. The methyl enol ether corresponding in structure of the enamine formed from **3** and piperidine under these conditions[3] is evidently not present. In another investigation **4** has been found to react at least 10^2 times faster with piperidine than with methoxide ion in an SN2′ reaction.[3]

A calculation based on the rate constant in Table I shows that at 50° the reaction of **2** with piperidine in benzene is essentially complete in 40 min using 1 *M* concentrations of reagents. From a run made with **2** and 10 equiv of 2 *M* triethylamine in refluxing benzene for as long as 48 hr 60% or more of starting material was recovered. The reaction of the tertiary chloride **3** with piperidine in benzene is essentially complete in 15 hr at 50°. In preparative runs with excess piperidine in benzene high yields of enamine product were obtained in a 4-hr reflux period. Under comparable conditions with triethylamine a nearly quantitative recovery of starting material was obtained. A similar result was obtained using N-methylpiperidine in methanol (7 hr reflux). A solution of **3** and excess N-methylpiperidine in benzene was kept at 50° and aliquots were titrated periodically for chloride ion. None was detectable even after 23 days. A further 35 days at room temperature still failed to produce chloride ion. Even granting 2% completion for the reaction the *maximum* second-order rate constant would be 2×10^{-7} M^{-1} sec^{-1}, which is 10^3 slower than the rate observed with **3** and piperidine. These results indicate that piperidine is remarkably more effective than N-methylpiperidine in SN2′ reactions. On the other hand, in SN2 reactions the difference is relatively small (Table II).[20]

Secondary bromide **2** reacts with piperidine in methanol to give about equal amounts of SN2 and SN2′ products.[3] On the other hand, the product from bromide **2** and thiophenoxide ion in methanol appears to consist entirely of a mixture of products formed by SN2 displacement and subsequent tautomerism (**9** and **10**). These results once again demonstrate the unusual effectiveness of secondary amines in promoting SN2′ reactions as compared to other nucleophiles.



(20) Diethylamine reacts about twice as rapidly with the methyl iodide in methanol as do the tertiary amines, triethylamine and N,N-dimethylcyclohexylamine: R. G. Pearson, H. R. Sobel, and J. Songstad, *J. Amer. Chem. Soc.*, **90**, 319 (1968).

Tertiary chloride **3** reacts readily with sodium thiophenoxide in ethanol, but resolution of the mixture of products obtained has not been accomplished as yet. The one successful SN2′ reaction with thiophenoxide ion thus far achieved in our systems is that with **4**.[2]

Our experience with **1**, **2**, and **3** confirms that of previous workers (Table I) in singling out secondary amines as the nucleophiles of choice for SN2′ reactions and singling out benzene as the solvent of choice. With α-methylallyl chloride all nucleophiles other than secondary amines, with the possible exception of trimethylamine in acetone (see below), prefer the SN2 to the SN2′ route. The choice of benzene as a solvent for secondary amines is important here because in changing from alcohol to benzene the SN2 reaction is *retarded* (by 16-fold for allyl chloride, see Table II), whereas the results with **2** (bromide) and **3** indicate that SN2′ reactions are *accelerated* by this solvent change (by about 9- to 22-fold, see Table I). The rate for **3** with piperidine is increased only slightly in changing from benzene to acetone, but is increased about fourfold in changing from benzene to dimethylformamide (Table I).[21,22]

The relatively low activation energies and high negative activation entropies recorded in Table I for the SN2′ reactions with amines in benzene are in line with the results obtained in SN2 reactions of amines with alkyl halides in benzene, nitrobenzene, and the like.[23,24] Brown and Eldred[23b] found that in the reaction of triethylamine in nitrobenzene the activation energies increased from 9.7 to 12.5 to 16.0 kcal/mol in the series MeI, EtI, *i*-PrI, whereas the activation entropies remained essentially constant (−34.7, −35.6, and −33.7).[23d] Cox observed that, for the reaction of aniline with phenacyl bromide, E_a increased from 8.1 in benzene to 11.1 in acetone to 12.4 in methanol while ΔS^* increased from − 56 to −39 to −33; at 37.8° the rates were 9.84×10^{-4}, 2.69×10^{-2}, and 7.48×10^{-2} M^{-1} min^{-1}, respectively.[23] The effect on the activation parameters of changing the solvent from benzene to methanol for the SN2′ reactions of **2** and **3** with piperidine is similar. With **2** (X = Br), E_a increases from 8 to 15 in going from benzene to methanol (ΔS^* increases from −43 to −26); for **3** the change in E_a is from 11 to 17 (ΔS^* increases from −43 to −32). The difference between SN2 and SN2′ reactions is that in the latter the increase in activation energy in changing from benzene to methanol overshadows the increase in activation entropy and the rate decreases, whereas the reverse is true in the SN2 reactions.

Discussion

The inertness of **2** and **3** toward thiourea, lithium bromide, and tertiary amines contrasts sharply with earlier results which suggests that these nucleophiles have about the same reactivity in SN2′ reactions as do secondary amines (Table I). It would seem that either **2** and **3** are not as good models for assessing the SN2′

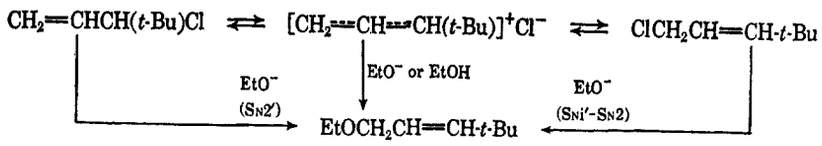
(21) The rates of SN2 reactions involving *anionic* nucleophiles are greatly accelerated by dimethylformamide (DMF) and related aprotic dipolar solvents, but the rates with neutral nucleophiles are not much affected.[22]

(22) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).

(23) (a) K. J. Laidler and C. N. Hinshelwood, *J. Chem. Soc.*, 853 (1938); (b) H. C. Brown and N. R. Eldred, *J. Amer. Chem. Soc.*, **71**, 455 (1949); (c) H. C. Brown and A. Cahn, *ibid.*, **77**, 1715 (1955); (d) summarized by A. W. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., New York, N. Y., 1963, p 22.

(24) H. E. Cox, *J. Chem. Soc.*, **119**, 142 (1921).

SCHEME I



reactivity of nucleophiles as their behavior toward piperidine would indicate, or the SN2′ mechanistic label has not been applied correctly in the previous instances. As will be brought out in the following discussion, there is reason to believe that the latter may be the correct interpretation.

The variety of reaction courses available to allylic halides makes mechanistic labeling of their reactions unusually hazardous. It has been suggested that the SN2′ label can be applied with reasonable certainty only after it has been established (1) that the reaction shows a first-order dependence on nucleophile concentration and on allylic halide concentration (to rule out the SN1 mechanism) and (2) that the abnormal product does not arise either from prior (rapid) rearrangement of the allylic halide (followed by SN2 displacement) or subsequent rearrangement of an SN2 (normal) product.[4a] The most difficult condition to meet is to rule out prior rearrangement of the allylic halide, since such rearrangements (SNi′ reactions) are known to occur very readily.[25] One test that has been applied is to recover the allylic halide from an incomplete reaction (of secondary halide) and examine it for rearranged (primary) halide. If this is shown to be absent, it is presumed not to be an intermediate in the reaction. Even this test may not be wholly convincing unless it can be demonstrated that an appreciable quantity of the primary halide is to be expected at equilibrium (the usual case) and that the primary halide has not been removed selectively by reaction with the nucleophile. The latter is a distinct possibility if an equimolar quantity of nucleophile is used since primary allylic chlorides undergo SN2 displacements at rates about 100 times that of the isomeric secondary chlorides.[23d] Unfortunately, the test, in any form, has been applied to only a few of the reactions listed in Table I.[6,9,16]

In the reaction of α-*t*-butylallyl chloride with sodium ethoxide prior rearrangement to the primary chloride followed by a rate-controlling SN2 reaction appears to offer an alternative to the SN2′ mechanism suggested.[10] Still another possibility is that there is rapid formation of an ion pair which is attacked by the nucleophile selectively at the primary carbon atom.[26] Support for this view can be derived from the observations that ethanolysis of this halide gives only the abnormal product and that the concentration of ethoxide ion must be about 2 *N* in order to make the reaction predominantly second order. The mechanistic possibilities may be summarized as shown in Scheme I.

As has been pointed out,[4a] the SNi′–SN2 route remains as a reasonable alternative to the SN2′ route for the exchange reactions of α- and γ-methylallyl bromides with radioactive lithium bromide in acetone solution.[11] The inertness of **3** toward lithium bromide in acetone makes the SNi′–SN2 alternative appear more likely.

From a consideration of the probable structure of the transition state for SN2′ reactions it has been concluded that alkyl substitution at the α- and γ-carbon atom will have an accelerating effect.[4a] However, α-alkyl substitution strongly favors SN1 and SNi′ mechanisms, and γ-allyl substitution is known to favor the SN2 mechanism. Because the SN2′ mechanism requires the nucleophile to attack an electron-rich carbon atom, it is already at a disadvantage with respect to SN1, SNi′, and SN2 mechanisms; it would be surprising, then, to find the SN2′ mechanism ever winning out in simple allylic systems, if this is indeed a proper view of the transition state and a proper assessment of the effect of alkyl substitution. This was, in effect, the conclusion arrived at by the English school after failing to realize the SN2′ mechanism with sodium ethoxide and α-methylallyl chloride and in other systems.[27] Later this view was altered when systems were devised which contained structural features presumably prejudicing them in favor of the SN2′ mechanism.[10–15] According to the present analysis, however, the SNi′–SN2 route (either involving rearrangement to a primary halide or formation of the abnormal product from an ion-pair intermediate) remains as a reasonable alternative for all of these systems. For the α-*t*-butylallyl chloride[10] and α-methylallyl bromide[11] systems the SNi′–SN2 route appears more likely than the SN2′ route. The presence of two or three chlorine atoms at C_α should favor the SN2′ pathway,[13–15] but even here some reservations must be held as to the mechanistic label.

If the SN2′ process is to succeed it will be necessary for the nucleophile to overcome the energy barrier it encounters in approaching the π bond. That this barrier is sizable is evident from the difficulty experienced by even the most powerful bases, including isopropyllithium,[28] solvated electrons,[29] or dimsyl ion ($DMSO^-$)[30] in adding to unconjugated C=C bonds. Even when the C=C bond is conjugated to the strongly electron-withdrawing nitro group the rate of addition of a basic nucleophile, such as methoxide ion, to the C=C bond is only moderate.[31] In view of the reluctance of even powerful bases to add to ordinary C=C bonds, nonbasic nucleophiles such as thiourea and bromide ion would be expected to experience great difficulty in initiating SN2′ reactions. The inertness of **2** and **3** toward these reagents is understandable on this basis. Negatively charged nucleophiles, such as alkoxide ions, would

(25) W. G. Young, S. Winstein, and H. L. Goering, *J. Amer. Chem. Soc.*, **73**, 1958 (1951). See ref 4 for additional examples.

(26) The possibility of ion-pair intermediates for SN2′ reactions is given credence by the recent demonstration of an ion pair in an SN2 reaction; see R. A. Sneen and J. W. Larson, *ibid.*, **88**, 2593 (1966).

(27) A. G. Catchpole, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 8 (1948).

(28) (a) J. E. Mulvaney and Z. G. Gardlund, *J. Org. Chem.*, **30**, 917 (1965); (b) J. A. Landgrebe and J. D. Shoemaker, *J. Amer. Chem. Soc.*, **89**, 4465 (1967).

(29) R. A. Benkeser, *J. Org. Chem.*, **38**, 1094 (1963), and references cited therein.

(30) C. Walling and L. Bollyky, *ibid.*, **29**, 2698 (1964).

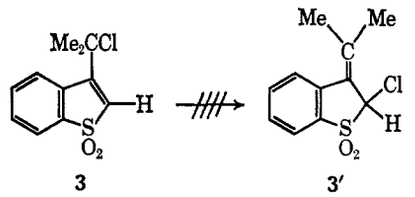
(31) The rate constant for addition of methoxide ion to *trans*-β-nitrostyrene to form the nitronate ion $C_6H_5CH(OMe)CH{=}NO_2^-$ is about 2 M^{-1} sec^{-1} at 25° (unpublished results of W. J. Boyle, Jr.).

be expected to be less effective than neutral, basic nucleophiles such as amines. There is qualitative evidence to support this view from the behavior of **2** and **3**, but the best example is with **4** where piperidine has been found to be over 100 times as reactive as methoxide ion in initiating an SN2′ reaction.[2] The best established examples of SN2′ reactions appear to be those involving secondary amines in benzene solution (Table I). The reason for this appears to be that the neutral nucleophile is best for effecting an approach to the C=C bond and that the nonpolar, aprotic solvent accelerates the SN2′ process and retards the SN2 process. Hydrogen bonding between the nucleophile and leaving halide ion, as is possible with secondary (or primary, but not tertiary) amines, also appears to provide an important driving force for the reaction.[5,6]

The particular success of systems **1–7** in promoting SN2′ reactions is no doubt associated with the presence of the electron-withdrawing sulfonyl grouping, which renders the C=C bond more susceptible to attack by the nucleophile.[32] The group not only reduces the electron density in the C=C bond, but also serves to delocalize the negative charge developing at the β position in the transition state.[3]

The presence of the sulfonyl group also serves to eliminate competition from SN1- or SNi′-type processes by greatly retarding the rate of formation of allylic carbonium ions. This is made clearly evident by the reluctance of tertiary allylic chloride **3** to undergo solvolysis. It can be crystallized without change from hot methanol; a solution of **3** in methanol was kept at 50° for 21 days and then at 25° for 35 days. During this time aliquots were removed periodically and titrated. No chloride ion was detected in any of these, which means that no more than 2% could have been released. The methanolysis rate for **3** must then be less than 10^{-8} sec^{-1} at 50°; for comparison, the ethanolysis rate for α,α-dimethylallyl chloride is 2×10^{-4} sec^{-1} at 44.6°.[33] In view of its low solvolysis rate there appears to be little danger that **3** will react by the SNi′–SN2 pathway discussed above, and this is even more true for the primary and secondary chlorides **1** and **2**. If an SNi′ reaction did occur, SN2 attack at the carbon atom α to the sulfone group would be extremely slow under these conditions.[34] The SNi′ product would be **4** (from **1**), **5** (from **2**), or **3′**, an analogous *exo*-dimethylmethylene compound (from **3**). These compounds would give SN2′ reactions, not SN2 reactions.[2] Thus the SNi′–SN2 route is excluded for the reaction of **1**, **2**, or **3** with nucleophiles.

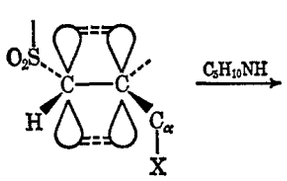
Although rearrangement of tertiary chloride **3** to the isomeric allylic chloride **3′** by a carbonium ion mechanism is highly unlikely, this could conceivably occur by a carbanion mechanism. No evidence for this isomerization was obtained in runs with **3** carried to partial completion. As discussed above, even if **3′** were to be formed it would not be expected to react by an SN2 process,[34] but, instead, it should undergo an SN2′ reaction



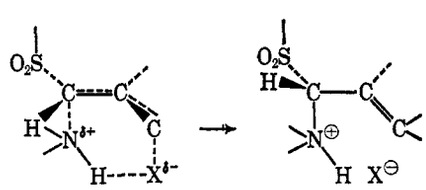
3 **3′**

in a manner analogous to **4** or **5**. Products of this type have not been observed from reactions of **3**.

It has been argued that specific hydrogen bonding between the entering and leaving groups is probably helpful, but not necessary, for the SN2′ reaction of amines.[5,6,9] In view of the remarkably greater effectiveness of secondary amines than tertiary amines or thiourea in bringing about SN2′ reactions with **2** and **3** the presence of the hydrogen atom appears to be indeed necessary. Aside from exerting a smaller steric effect than an alkyl group, hydrogen may be more effective in delocalizing the positive charge developing on the nitrogen atom, probably through hydrogen bonding.[5,6] No isotope effect is observed when an N-deuterio secondary amine reacts with α-methylallyl chloride,[7] but the isotope effect would be expected to be small and hydrogen bonding is not excluded by this evidence.



1, 2, or 3



dipolar transition state — SN2′ product

Hydrogen bonding, together with a lesser steric requirement, appears to offer the best explanation for the much greater rate of reaction of **3** with piperidine than with N-methylpiperidine. Since **3** is at least as reactive as α-methylallyl chloride toward secondary amines, it is surprising to find that **3** is inert to tertiary amines, whereas α-methylallyl chloride reacts nearly as rapidly with trimethylamine in acetone as it does with dimethylamine in benzene (Table I). It is also noteworthy in this connection that α-methylallyl chloride reacts very slowly with tertiary amines in benzene,[6] and that the SN2′ reaction between **3** and piperidine is accelerated only slightly in changing from benzene to acetone (Table I). One possible explanation is that the reaction of α-methylallyl chloride with trimethylamine in acetone proceeds by an SNi′–SN2 mechanism, which is not available to **3** (see above). A mechanism involving rapid rearrangement of α-methylallyl chloride to γ-methylallyl chloride has been ruled out,[9] but rapid formation of an ion pair which reacts with trimethylamine

$$CH_2{=}CH{-}CH(Me)Cl \underset{}{\overset{\text{acetone}}{\rightleftharpoons}} Me_3NCH_2CH{=}CHMe^+Cl^- \quad (70\%)$$

$$[CH_2{=}CH{=}CHMe]^+Cl^- \xrightarrow[(slow)]{Me_3N} CH_2{=}CHCH(Me)NMe_3^+Cl^- \quad (30\%)$$

(32) The carbonyl group can serve a similar function; see N. H. Cromwell and R. P. Rebman, "*Tetrahedron Lett.*," No. 52, 4833 (1955); N. H. Cromwell and E. Ming Wu, *ibid.*, 1499 (1966); N. H. Cromwell and E. Doomes, *ibid.*, 4037 (1966). An anion-radical mechanism has not been rigorously excluded for such systems, but it appears unlikely that the kinetic data can be accommodated by a mechanism of this type.

(33) C. A. Vernon, *J. Chem. Soc.*, 4462 (1954).

(34) F. G. Bordwell and G. D. Cooper, *J. Amer. Chem. Soc.*, **73**, 5184 (1951); F. G. Bordwell and B. B. Jarvis, *J. Org. Chem.*, **33**, 1182 (1968).

to give normal and abnormal products remains as a possibility.[26]

One unattractive feature of this mechanism is that the ion pair must give only secondary chloride on internal return.

The reason for the reversal of solvent effects on the rates of SN2′ compared with SN2 reactions of secondary amines in changing from benzene to methanol is not immediately apparent. The increase in SN2 rate in going from benzene to methanol is explained qualitatively by the Hughes–Ingold solvation rule, the more polar solvent providing greater stabilization of the highly polar transition state.[35] A similar factor should operate in SN2′ reactions. Factors which might lead to a reversal of this effect for SN2′ reactions are (1) hydrogen bonding between the nucleophile and leaving halide ion,[5,6,9] (2) greater nucleophilicity of the secondary amine for the C=C bond in benzene than methanol due to lesser solvation of the donor electron pair, and (3) electrostatic attraction between the nucleophile and the substrate.

Intramolecular hydrogen bonding between the nucleophile and leaving halide ion would be expected to be stronger in benzene than in methanol because of the strong intermolecular hydrogen bonding in methanol.

The greatly enhanced reactivity of anionic nucleophiles in solvents which are poor at solvating anions (dipolar aprotic) suggests that the lesser solvation of secondary amines in benzene than in methanol may be important in enhancing their nucleophilicities in benzene.[22] This cannot be the controlling factor, however, unless the resulting change in nucleophilicity is manifested to a much greater extent in an attack on a C=C bond than in attack on an sp^3 carbon atom (in SN2 reactions this effect is apparently completely overshadowed by other factors—see Table II).

Electrostatic attraction between the nucleophile and the substrate might be invoked to explain the unusual reactivity of **1–3** and **6** and **7** in SN2′ reactions if it is assumed that this unusual reactivity can be compared with the higher reactivity of *o*-nitroaryl halides toward secondary amines, compared with their *para* isomers, in nucleophilic aromatic substitution reactions. The higher reactivity of the *ortho* isomers toward amines may be explained in terms of electrostatic attraction between the amine and the nitro group in the transition state; this attraction is probably enhanced by hydrogen bonding.[36,37] The sulfone grouping in **6** and **7** could conceivably play an electrostatic role akin to that of the nitro group in *o*-nitroaryl halides. A similar effect could be imagined in **1–3**, although here the sulfone group would be α rather than β to the carbon atom being attacked. That this is not the dominant factor is indicated, however, by the ability of **4** and **5** to undergo SN2′ reactions. In these systems attack of piperidine cannot be aided by the sulfone grouping since the latter is in a γ position. It is interesting to note in this respect that **4** actually appears to be more reactive in SN2′ reactions than **1–3**.[2]

(35) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp 345–349.

(36) M. F. Hawthorne [*J. Amer. Chem. Soc.*, **76**, 6358 (1954)] found no deuterium isotope effect for the displacement of the chlorine atom from *o*-nitrochlorobenzene using piperidine and N-deuteriopiperidine. Nevertheless, a strong case for hydrogen bonding has been made on the basis of the failure of *ortho* acceleration to materialize when a tertiary amine is used.[37] The *ortho* isomers are less reactive toward alkoxides than are the *para* isomers.

(37) S. D. Ross and M. Finkelstein, *ibid.*, **85**, 2603 (1963).

A reversal of solvent effects is observed for *o*- when compared with *p*-nitrochlorobenzenes, whereas the rate for the *para* isomer with piperidine is retarded by 12.5-fold in changing from ethanol to benzene; that for the *ortho* isomer is accelerated by 1.3-fold.[38] Again these effects are similar to those observed for SN2 *vs.* SN2′ reactions, although the reversal is more dramatic for the latter. Bunnett and Morath have suggested that electrostatic attraction between the nitro group and piperidine, which probably involves hydrogen bonding,[37] may act as "built-in solvation" allowing the reaction to proceed more rapidly in benzene than in ethanol. This factor conceivably could be important also in accounting for the reversal of solvent effects for SN2′ *vs.* SN2 reactions, but, for reasons given above, we prefer to visualize the hydrogen bonding as occurring between piperidine and the leaving halide ion rather than between piperidine and the sulfone group.[39]

Whatever the basis for this solvation effect it often seems to provide the decisive factor in allowing SN2′ reactions to compete successfully with SN2 reactions. Thus the unusual effectiveness of secondary amines in producing SN2′ reactions in allylic halides in benzene (or other aprotic solvents) appears often to arise as a result of (a) a decrease in the rate of the competing SN2 reaction (relative to other nucleophiles and other solvents) and (b) an increase in the rate of the SN2′ reaction (relative to other nucleophiles and other solvents).

It is possible to represent the SN2′ reactions of **1–7** with piperidine as proceeding through either a dipolar transition state (see above) or a dipolar intermediate. In methanol the formation of a dipolar intermediate by reaction of piperidine with **4** accounts better for the absence of a leaving-group effect.[3] If a dipolar intermediate is formed from **2** and piperidine in benzene it must be formed reversibly to account for the leaving group effect, *i.e.*, $k_{Br}:k_{Cl} = 16:1$ (E_a for bromide **2** is 2 kcal/mol less than that of chloride **2**; see Table I). This small leaving group effect can also be accommodated by assuming the formation of a dipolar ion transition state in which C–X bond breaking has not progressed very far.

The argument can be made that systems containing electron-withdrawing groups are not representative of SN2′ processes because they permit the formation of dipolar ion or carbanion intermediates or transition states. Our view is that systems of this type represent an important mechanistic class of SN2′ reactions. The other major mechanistic class appears to relate to reactions involving allylic halides with primary or secondary amines in benzene or like solvents.[6–8,16] Here either dipolar transition states or ion-pair intermediates may in involved. (Relatively few unambiguous examples of SN2′ reactions initiated by anionic nucleophiles appear to have been recorded.[5,16]) There is little evidence to indicate that bond making and bond breaking in SN2′ reactions is synchronous, although the limited evidence available with respect to the stereochemistry of the reaction is most readily interpreted in this way.[16] Finally, it seems clear that additional mechanistic studies are desirable, that some of the earlier SN2′ mechanistic classifications need to be reexamined, and that the SN2′

(38) J. F. Bunnett and R. J. Morath, *ibid.*, **77**, 5051 (1955).

(39) Note that built-in solvation is not essential to the success of the SN2′ reaction in our systems since **2** (bromide), **3**, and **4** give SN2′ reactions in methanol as well as in benzene.

mechanistic classification needs to be assigned with increased caution in the future.

Experimental Section[40]

Kinetic Data.—The preparation of halides **1**, **2**, and **3** has been described previously.[1-3] The rates reported in Tables I and II were determined titrimetrically by the method described earlier.[2]

Attempted Methanolysis of 3-(α-Chloro-α-methylethyl)benzo[b]thiophene 1,1-Dioxide (3).—A solution of 12.24 mg of **3** in 100 ml of absolute methanol was thermostated at 50° for 21 days and then kept at room temperature (*ca.* 25°) for 35 days. Samples were withdrawn periodically, treated with 10 ml of 0.25 *M* nitric acid, and titrated using a Sargent automatic constant-rate buret (Model C) with 1.5×10^{-3} *M* silver nitrate as the titrant. End points were determined graphically from the inflection points of the titration curves and compared with end points found for standard methanolic solutions, using the same pipet. None of the samples taken, including three taken after 56 days, gave measurable amounts of chloride ion. Check runs with known standards showed that as little as 2% chloride ion could have been detected readily. Assuming that the conditions were equivalent to about 30 days at 50° and that 2% of **3** has solvolyzed

$$k = \frac{-2.3 \log (0.98)}{2.7 \times 10^{6} \text{ sec}} = 7 \times 10^{-9} \text{ sec}^{-1}$$

Thus, the solvolysis rate is less than 1×10^{-8} sec^{-1} at 50°.

Attempted Reactions of 3 with Nucleophiles. A. With Triethylamine.—A solution of 300 mg of **3**, 10 ml of benzene, and 623 mg (0.6 *M*) of triethylamine was refluxed 4 hr. No solid formed. The solution was evaporated under an air jet, leaving 309 mg of white solid, mp 143.5–145.5°; the mixture melting point with authentic **3** was undepressed. The sample was dissolved in 20 ml of boiling triethylamine. After 15 min the solution was cooled in an ice bath and filtered. There was thus obtained 216 mg (72%) of long white needles, mp 140–142°; the mixture melting point with authentic **3** was undepressed.

B. With N-Methylpiperidine in Benzene.—A solution of 6.14 mg of **3** in 50 ml of 0.30 *M* N-methylpiperidine in benzene was thermostated at 50° for 23 days and then kept at room temperature for 35 days. Titration as described above showed that less than 2% of **3** had reacted; therefore

$$k_2 < \frac{-2.3 \log (0.98)}{0.30\ M \times 2 \times 10^{-6} \text{ sec}} \text{ or } 2 \times 10^{-7}\ M^{-1} \text{ sec}^{-1} \text{ at } 50°$$

C. With Lithium Bromide in Acetone.—A solution of 121 mg of **3** and 86.9 mg of anhydrous lithium bromide (1 mmol) in 12.5 ml of anhydrous acetone was kept at room temperature (*ca.* 25°) for 31 days. The solvent was distilled at reduced pressure and the residue was extracted with deuteriochloroform: nmr, δ 7.0–8.3 (aromatic, 4 H), 6.55 (singlet, 1 H), and 1.98 (singlet, 1 H) attributed to **3** and 2.7, 2.2, and 1.3. These latter peaks, due to impurities, were reduced in intensity when the solvent was evaporated and a new spectrum was taken. The solvent was evaporated and the sample was digested in 15 ml of water at room temperature for 2 days.

Anal. Calcd for $C_{11}H_{11}O_2ClS$: C, 54.43; H, 4.57. Calcd for $C_{11}H_{11}O_2BrS$: C, 46.00; H 3.86. Found: C, 54.33; H, 4.71.

D. With Thiourea.—A solution of 243 mg of **3**, 254 mg (3.33 mmol) of thiourea, and 7 ml of absolute methanol was refluxed 3 hr. Cooling and filtering gave 72.5 mg of thiourea, mp 165–177° dec. A second fraction amounted to 192 mg (79%), mp 134–142°; the mixture melting point with authentic **3** was 135.5–144°. A similar result was obtained in acetonitrile.

Reaction of 3-(α-Bromoethyl)benzo[b]thiophene 1,1-Dioxides (2b) with Thiophenoxide Ion in Absolute Methanol.—A mixture of 100 mg (0.366 mmol) of 3-(α-bromoethyl)benzo[b]thiophene 1,1-dioxide, 1.5 ml (205 mg, 1.83 mmol) of absolute methanol, and 0.85 ml of 0.21 *M* sodium methoxide solution (1.8 mmol) was dissolved and heated at reflux for 9 hr. The solution was evaporated with a stream of nitrogen and extracted with three 10-ml portions of benzene. The mixture was filtered and the filtrate was evaporated, leaving 125 mg of a yellow oil: nmr ($CDCl_3$), δ 7.5–8.25 (aromatic), 4.58 (quartet, 1.4), 4.35 (broad singlet), 2.34 (triplet, 1.4), and 2.09 (broad singlet). Because of the absence of absorptions in the δ 5–7.5 region (vinyl region), it was possible to rule out structures corresponding to the abnormal displacement product, its SNi′ rearrangement product, starting material, and the normal displacement product. Because of the absence of absorption in the region δ 0.5–2, it was possible to rule out 2-phenylthio-3-ethylbenzo[b]thiophene 1,1-dioxide as the structure. The chemical-shift data and coupling constants were consistent with a mixture of geometric isomers of 3-(phenylthio)ethylene-2,3-dihydrobenzo[b]thiophene 1,1-dioxide. Integration of the spectrum showed the ratio of methyl absorptions (2.34, 2.09) to methylene absorptions (4.58, 4.35) to aromatic was 3.0:2.2:14. Thus about 20% by weight was benzenethiol. The remainder (*ca.* 110 mg, 99%) was attributed to displacement products. Trituration with methanol failed to give a solid.

Anal. Calcd for $C_{16}H_{14}O_2S_2$: C, 63.55; H, 4.67. Found: C, 63.80; H, 4.63.

Registry No.—**9**, 16958-52-4; **10**, 16958-53-5.

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(40) Microanalyses were by Micro-Tech Laboratories, Inc., Skokie, Ill.