Neighboring Group Participation by Sulfur Involving Four-Membered-Ring Intermediates (RS-4)

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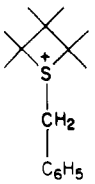
Abstract: The methanolysis and trifluoroethanolysis products and the methanolysis rates of a variety of chain-substituted 3-(alkylthio)- and 3-(arylthio)propyl *p*-toluenesulfonates, RS-C-C-C-OTs, are reported. For R = benzyl, neighboring group participation, resulting in the formation of rearranged product, and anchimeric rate acceleration have been demonstrated for all but the parent 1° and 2° [3-(benzylthio)propyl and 4-(benzylthio)-2-butyl] compounds. The chain substituents promote participation as a result of a Thorpe-Ingold effect. The occurrence of anchimeric assistance without rearrangement in the 3-isopropyl and 3-*tert*-butyl compound has been explained on the basis of the partitioning of the thietanonium intermediate. For para-substituted 3-(arylthio)-3-methyl-1-butyl tosylates, a Hammett σ_p°-ρ relationship has been established, with ρ = -1.58 for k_Δ and ρ = +0.62 for k_s. Steric effects of the substituent on sulfur (R) could not be demonstrated. Rearrangement is promoted by increasing the ionic strength of the solution (by adding $LiClO_4$) or by using a more ionizing, less nucleophilic solvent (CF_3CH_2OH). In the latter case, even the parent $BzSCH_2CH_2CD_2OTs$ solvolyzes via a cyclic intermediate and a common intermediate is demonstrated for $BzSCHMeCH_2CH_2OTs$ and $BzSCH_2CH_2CHMeOTs$.

In the more than 40 years which have elapsed since Winstein first put forth the concept of neighboring group participation,[2] numerous examples of this phenomenon have been studied,[3] including examples of sulfur participation.[4] Most of these examples relate to participation involving three-, five-, or six-membered-ring intermediates; i.e., two, four, or five atoms intervene between the reaction center and the participating group. Not surprisingly, participation involving four-membered rings is much less common, because the formation of such rings is disfavored both enthalpically and entropically. In fact, the only recorded example of neighboring group participation (with or without anchimeric assistance) involving four-membered sulfur-containing rings[5-7] ("S-4") are in relatively rigid polycyclic systems where the sulfur is juxtaposed in space with the leaving group, thus mitigating the entropy problem. Under these circumstances S-4 participation should be about as facile as S-3 since the strain in three- and four-membered rings is about the same. In open-chain systems of the type $RS(CH_2)_nX$ (X = leaving group), it has been shown[8,9] that whereas there is strong anchimeric assistance for n = 2 or 4 and weak assistance for n = 5 in methanolysis, there is no assistance for n = 3.

With this background, we reported in 1980[10] that partial or complete rearrangement occurs in the methanolysis of γ-(benzylthio)propyl *p*-toluenesulfonates, γ-$C_6H_5CH_2S$-C-C-C-OTs, provided there are one or two methyl substituents at the γ position (Table I, entries 1-3). The rearrangement was ascribed to neighboring group participation (RS-4) of the benzylthio group proceeding via an intermediate thietanonium ion (A), and the increasing amount of such participation with increasing substitution of the chain was ascribed to the Thorpe-Ingold effect[11,12]



A

according to which formation of small rings is facilitated by substituents on their open-chain precursors. The findings from the earlier study are summarized in Table I, entries 1-5. A labeling study confirmed the absence of rearrangement in the unsubstituted 3-(benzylthio)propyl *p*-toluenesulfonate (entry 5), and no rearrangement occurs in the (secondary) 4-(benzylthio)-2-butyl analogue (entry 4).

The earlier study left some unresolved questions, the most important of which are as follows: (1) Is the thietanonium intermediate A real or is there a rearrangement of the benzylthio group from position 3 to position 1 not involving a cyclic intermediate? Such a rearrangement might appear plausible since it would involve, in the case of entries 1-3 in Table I, conversion of a primary or secondary carbocation (potentially the first intermediate in solvolysis) to a secondary or tertiary one. It would also account for the absence of rearrangement in cases 4 and 5, where there is no driving force for rearrangement of a primary or secondary to a primary carbocation. (2) If the reaction does, in fact, proceed with neighboring group participation, is there also anchimeric assistance?[13] In other words, does the participating group intervene in the transition state and assist its attainment by lowering its energy? The present work, involving product and rate studies, including studies of solvent and salt effects and of changes in R of the participating group R-S-, was designed to throw light on these questions. (Unfortunately, all attempts to isolate the intermediates A or to synthesize them by independent routes were unsuccessful, so indirect approaches to manifesting their existence had to be devised.)

Product Studies

Methanolysis of $PhCH_2SCH_2CRR'CD_2OTs$ (**1**, R = R' = H) proceeds without rearrangement (Table I, entry 5). If a Thorpe-Ingold effect were in fact operative, as previously postulated,[10] successive introduction of methyl groups into the R and R' positions should promote rearrangement. On the other hand, if the driving force for rearrangement is conversion of a less stable

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(6) Ireland, R. E.; Smith, H. A. *Chem. Ind. (London)* **1959**, 1252.
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(11) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305.
(12) Eliel, E. L. "Stereochemistry of Carbon Compounds", McGraw-Hill: New York, 1962; pp 197-202.
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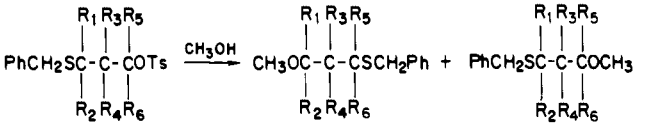
Table I



entry	compound	% rearranged compd
1	$R_1 = R_2 = R_5 = CH_3$; $R_3 = R_4 = R_6 = H$	100
2	$R_1 = R_2 = CH_3$; $R_3 = R_4 = R_5 = R_6 = H$	100
3	$R_1 = CH_3$; $R_2 = R_3 = R_4 = R_5 = R_6 = H$	20
4	$R_1 = R_2 = R_3 = R_4 = R_6 = H$; $R_5 = CH_3$	0
5	$R_1 = R_2 = R_3 = R_4 = H$; $R_5 = R_6 = D$	0
6	$R_3 = CH_3$; $R_1 = R_2 = R_4 = H$; $R_5 = R_6 = D$	12 ± 2
7	$R_3 = R_4 = CH_3$; $R_1 = R_2 = H$; $R_5 = R_6 = D$	49.5 ± 2.3
8	$R_1 = C_2H_5$; $R_2 = R_3 = R_4 = R_5 = R_6 = H$	14
9	$R_1 = (CH_3)_2CH$; $R_2 = R_3 = R_4 = R_5 = R_6 = H$	0
10	$R_1 = (CH_3)_3C$; $R_2 = R_3 = R_4 = R_5 = R_6 = H$	0

Table II. Ratios of Integrals of ^1H, ^2H, and ^{13}C Signals of Methylene Groups in $PhCH_2SCH_2CRR'CD_2OMe/PhCH_2SCD_2CRR'CH_2OMe$ Mixtures[a]

product from	^1H	^2H	^{13}C
$PhCH_2SCH_2CHMeCD_2OTs$	*b*	6.2; 8.6	7.9
$PhCH_2SCH_2CMe_2CD_2OTs$	1.03–1.19	0.98–1.05	0.96–1.18

[a] Ratios are unrearranged to rearranged product. [b] Peaks not adequately resolved for analysis.

carbocation intermediate to a more stable one, the β-methyl (**1**, R = CH_3, R′ = H) and β,β-dimethyl (**1**, R = R′ = CH_3) compounds should not rearrange during solvolysis, since the conversion of one primary carbocation to another, identical one (except for isotopic substitution) is energetically unproductive. Reaction of these compounds (entries 6 and 7 in Table I) thus provides a crucial test for the Thorpe–Ingold hypothesis. As seen in Table I, rearrangement does occur, and, as one would predict, it occurs to a greater extent in the dimethyl than in the monomethyl case. The intervention of the Thorpe–Ingold effect is thus confirmed.

Since the carbon skeletons of $PhCH_2SCH_2CRR'CH_2OTs$ (**1**) are end-over-end symmetrical, so that rearrangement cannot be detected, it was necessary to synthesize the α,α-dideuterated analogues. The pertinent alcohols, $PhCH_2SCH_2CRR'CD_2OH$ were obtained by lithium aluminum deuteride reduction of the corresponding acids or esters. $PhCH_2SCH_2CH(CH_3)CO_2CH_3$ was synthesized by addition of benzyl mercaptan to methyl methacrylate, $PhCH_2SC(CH_3)_2CO_2H$ by treatment of chloropivalic acid[14] with sodium benzylmercaptide.

The products ($PhCH_2SCH_2CRR'CD_2OMe$ or $PhCH_2SCD_2CRR'CH_2OMe$) were anlyzed by proton (^1H), deuteron (^2H), and carbon (^{13}C) NMR spectroscopy. The resonance frequency of the SCH_2 group in the dimethyl compound is at 2.45 ppm in the ^1H and ^2H spectra and at 41.67 ppm in the ^{13}C spectrum; the frequencies for CH_2O are 3.12 ppm (^1H) and 80.35 ppm (^{13}C). The corresponding data for monomethyl are 2.22, 2.49 ppm (diastereotopic protons), 35.5 ppm, 3.11, 3.20 ppm, and 76.6 ppm. The amount of rearrangement is inferred directly from the integration of the two pertinent peaks in the ^1H and ^2H spectra; the ^2H spectrum for the methanolysis product of $PhCH_2SCH_2CMe_2CD_2OTs$ is displayed in Figure 1. Perhaps less obviously, the ratio of the integrals of the two ^{13}C peaks also gives the product ratio; this follows from the fact that the ^{13}C signal of a CD_2 peak is essentially obliterated (at least on short pulsing of the spectrum) through the combination of the absence of a nuclear Overhauser effect, dissipation of the signal into a quintet, long *T*, and quadrupole broadening by deuterium. Pertinent integration data for the various nuclei are shown in Table II. From these data, the percentage of rearrangement is 12 ± 2% for the monomethyl compound and 49 ± 2.3% for the dimethyl compound. However, since the intermediate (A) is, except for

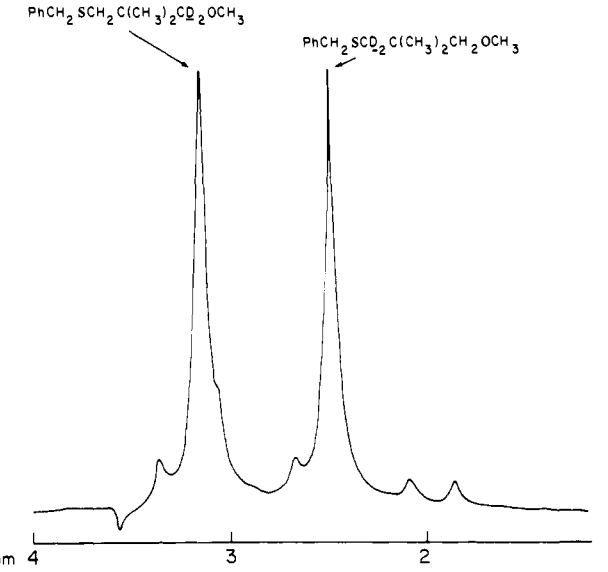


Figure 1. ^2H NMR spectrum of methanolysis product of $PhCH_2SCH_2CMe_2CD_2OTs$.

isotopic substitution, symmetrical, it will, except for a very small secondary isotope effect, be opened equally from the two sides and attack from one side leads back to the isotope distribution of the starting material. Hence one must multiply the percent rearrangement by 2 to obtain the portion of the reaction which has gone through the cyclic intermediate. This portion is thus 24 ± 4% for the monomethyl compound and 99 ± 4.6% for the dimethyl. In the latter case, the solvolysis evidently takes place essentially entirely with neighboring group participation, whereas in the former only about a quarter of the reaction proceeds by this path, the other three-quarters involving direct solvolytic displacement.

An alternative way of demonstrating a cyclic intermediate is by solvolyzing an optically active starting material.[3] Since the intermediate A is achiral, to the extent that the reaction proceeds through it, optical activity will be lost. (*R*)-(+)-$PhCH_2SCH_2CHMeCH_2OH$ is readily prepared from commercially available (*R*)-(−)-*S*-acetyl-3-mercaptoisobutyric acid, (−)-$AcSCH_2CHMeCO_2H$, by lithium aluminum hydride reduction followed by monobenzylation. Methanolysis of its tosylate led to partially racemized methyl ether whose rotation was compared to that of a sample prepared from the alcohol directly by methylation. In three solvolysis runs, the percentages of racemization (which are equal to percent participation, since each time the reaction goes via the symmetric intermediate A, the product is racemized) were 40%, 22%, and 22%. The two latter percentages agree closely with that (24 ± 4%) found in the labeling study; in fact the third run was carried out with substrate that was both optically active and labeled, and the fractions of reaction proceeding via A found by the two techniques agreed. The discrepancy in the first run was eventually traced to the presence of water in the methanol (see below under solvent effects).

Having established neighboring group participation in the reaction under study, we decided to investigate the effect of changing substituents on the propyl backbone as well as on sulfur. The first series studied was of the type $PhCH_2SCHRCH_2CH_2OTs$ with R = methyl, ethyl, isopropyl, and *tert*-butyl. The results (Table I, entries 3 and 8–10) show a drop-off of rearranged product in this series; in fact, no rearrangement at all occurred with isopropyl and *tert*-butyl. This result was surprising until it was recognized that the absence of rearrangement in this case did not signify absence of participation. We shall come back to this point in the section on kinetics.

Next, 3-(arylthio)-3-methyl-1-butyl tosylates, $ArSCMe_2CH_2CH_2OTs$ were investigated, with Ar = *p*-XC_6H_4 (X = CH_3O, CH_3, H, Cl, and F). It was anticipated that the inductive and electromeric electron withdrawal from sulfur caused by the phenyl substituent would reduce sulfur participation.

(14) Kharasch, M. S.; Brown, H. C. *J. Am. Chem. Soc.* **1940**, *62*, 925.

Table III. First-Order Rate Constants for Methanolysis at 60 °C

entry	compound	10^5k_1, s^{-1}	k_{rel}
1	$PhCH_2SCH_2CH_2CH_2OTs$	0.76	1
2	$PhCH_2SCH(CH_3)CH_2CH_2OTs$	2.51	3.3
3	$PhCH_2SC(CH_3)_2CH_2CH_2OTs$	21.4	28.2
4	$PhCH_2SCH_2CH_2CH(CH_3)OTs$	3.05	4.0[a]
5	$PhCH_2SC(CH_3)_2CH_2CH(CH_3)OTs$	49.4	65.0[a]
6	$PhCH_2SCH_2CH(CH_3)CH_2OTs$	0.28	0.37
7	$PhCH_2SCH_2C(CH_3)_2CH_2OTs$	0.085	0.11
8	$PhCH_2SCH(C_2H_5)CH_2CH_2OTs$	5.18	6.2
9	$PhCH_2SCH(i\text{-}C_3H_7)CH_2CH_2OTs$	13.2	17.4
10	$PhCH_2SCH(t\text{-}C_4H_9)CH_2CH_2OTs$	133	175

[a] k_{rel}(entry 5)/k_{rel}(entry 4) = 16.3.

Indeed, whereas the amount of rearranged product with a benzyl substituent on sulfur in this series is 100% (Table I, entry 2), this percentage is lowered to 82% with phenyl. Corresponding percentages for phenyl groups with para-substituents are *p*-CH_3O, 91%, P-CH_3, 92%, *p*-F, 70%, *p*-Cl, 58%. If one plots log (rearranged/unrearranged product) vs. the σ_p° of the substituents,[15] one obtains a straight line (r = 0.996) with ρ = −2.09. We shall come back to this observation later; suffice it to say at this point that the formation of thietanonium intermediate A should be inhibited by an electron-withdrawing group such as aryl, that this effect should be enhanced by electron-withdrawing substituents in the para position (such as F and Cl) and diminished by electron-donating substituents (CH_3O and CH_3), and that the more the formation of A is inhibited, the less rearrangement should occur. This is exactly what is observed.

Finally, to investigate steric effects of substituents on sulfur, the amount of rearranged product from $RSCMe_2CH_2CH_2OTs$ where R = *n*-butyl, *sec*-butyl, *tert*-butyl was examined. In all cases, only rearranged product was found, just as in the case of R = benzyl. The conclusion is that steric effects of the sulfur substituents (at least within the range examined) do not impede formation of A, presumably because the R–S bond is long enough to effectively isolate the sulfur from such effects.

Kinetic Studies

Neighboring group participation can occur either before or after the transition state is reached. If it occurs before, the activation energy will necessarily be lower than it would be in the absence of participation in the transition state (or else the reaction would proceed through a transition state not involving participation). The rate enhancement caused by participation in the transition state is called "anchimeric assistance".[13] The kinetic studies to be described were designed to probe for such assistance.

In order to decide whether a reaction is anchimerically accelerated, one must know what the rate constant would be in the absence of such acceleration. This requires study of model compounds. We chose, as models for the 3-benzylthio-substituted compounds $PhCH_2SCR^1R^2CR^3R^4CR^5R^6OTs$, the corresponding butyl compounds, $CH_3CR^1R^2CR^3R^4CR^5R^6OTs$ (methyl in place of benzylthio). Whether these are good models depends mainly on whether the inductive effect of sulfur (which is absent in the models) affects the rate. For primary tosylates ($R^5 = R^6$ = H), there seems to be little inductive effect; in earlier work[8] $RSCH_2CH_2CH_2X$ (R = C_2H_5, X = Cl) was found to solvolyze at the same rate as $CH_3CH_2CH_2CH_2X$, and in the present study, γ-(benzylthio)propyl tosylate (R = $PhCH_2$, X = OTs; Table III, entry 1) solvolyzed at 85% of the rate of *n*-butyl tosylate (Table IV, entry 1). For secondary tosylates ($R^5 = CH_3$, R^6 = H), the matter is not quite so clear since 2-amyl tosylate (Table IV, entry 4) solvolyzes about 2.5 times as fast as 4-(benzylthio)-2-butyl tosylate (Table III, entry 4). Assuming the latter to react without anchimeric assistance (no rearrangement occurs, cf. Table I, entry 4), the inductive effect of the γ-benzylthio group on the rate of solvolysis of a secondary tosylate would correspond to a rate reduction by a factor of ca. 2.5.

(15) Taft, R. W.; Ehrenson, S.; Lewis, I. C.; Glick, R. E. *J. Am. Chem. Soc.* **1959**, *81*, 5352.

Table IV. First-Order Methanolysis Rates of Model Compounds at 60 °C

compound	10^5k_1, s^{-1}
$CH_3CH_2CH_2CH_2OTs$	0.89
$CH_3CH(CH_3)CH_2CH_2OTs$	0.70
$CH_3C(CH_3)_2CH_2CH_2OTs$	0.24
$CH_3CH_2CH_2CH(CH_3)OTs$	8.61
$CH_3C(CH_3)_2CH_2CH(CH_3)OTs$	6.19
$CH_3CH_2CH(CH_3)CH_2OTs$	0.08,[a] ref 16
$CH_3CH_2C(CH_3)_2CH_2OTs$	0.0027,[a] ref 16

[a] Estimated rates in the absence of participation. See ref 16.

Table V. First-Order Methanolysis Rates at 60 °C Relative to Those of Model Compounds

		k_{rel}		
entry		X = SCH_2Ph	X = CH_3	A[a]
1	$X\text{-}CH_2CH_2CH_2OTs$	1	1	0.85
2	$X\text{-}CH(CH_3)CH_2CH_2OTs$	3.3	0.79	3.6[b]
3	$X\text{-}C(CH_3)_2CH_2CH_2OTs$	28.2	0.26	90.8[b]
4	$X\text{-}CH_2CH_2CH(CH_3)OTs$	4.0[e]	9.63[f]	
5	$X\text{-}C(CH_3)_2CH_2CH(CH_3)OTs$	65.0[e]	6.92[f]	8.0[c]
6	$X\text{-}CH_2CH(CH_3)CH_2OTs$	0.37	0.09[d]	3.5[b]
7	$X\text{-}CH_2C(CH_3)_2CH_2OTs$	0.11	0.003[d]	31.5[b]

[a] k_{SCH_2Ph}/k_{CH_3}. [b] If corrected for the inductive retardation in entry 1, these values would be 4.2, 106.8, 4.1, and 37.1, respectively. [c] If corrected for the inductive retardation in entry 4, this value would become 22.8. [d] Estimated values; see ref 16. [e] k_{rel}(entry 5)/k_{rel}(entry 4) = 16.3. [f] k_{rel}(entry 5)/k_{rel}(entry 4) = 0.72.

Table III displays the methanolysis rates of the *p*-toluenesulfonates for which product data were shown in Table I. Relative to $PhCH_2S(CH_2)_3OTs$ (entry 1), which probably reacts without participation and therefore without anchimeric assistance, the γ-substituted and γ,γ-disubstituted homologues (entries 2, 3, and 8–10) all react faster; i.e., their solvolysis is anchimerically accelerated. The acceleration is relatively modest for a single, unbranched γ-substituent (entries 2 and 8) but becomes increasingly marked as the substituent becomes more branched (entries 9 and 10) or when there are two γ-substituents (entry 3). The occurrence of anchimeric assistance is, of course, strong evidence for the existence of intermediate A (which begins to form in the transition state) especially when taken in conjunction with the formation of rearranged products (Table I). It is of particular interest that the γ-ethyl, -isopropyl, and -*tert*-butyl compounds (entries 8–10, Table III) experience considerably more rate acceleration than the corresponding methyl compound (entry 2), even though the amount of rearrangement falls off in this series (to zero for the isopropyl and *tert*-butyl compounds, cf. entries 3 and 8–10 in Table I). This observation may be explained in one of two ways: (1) Participation occurs in the transition state so as to produce rate acceleration, but intermediate A is never fully formed and the substrate falls back to an unrearranged solvolysis product. We find this explanation unattractive, since it provides no rationale for the countertrend in amount of rearrangement (Me > Et > *i*-Pr > *t*-Bu) and specific solvolysis rate (*t*-Bu > *i*-Pr > Et > Me). (2) Intermediate A is formed in all cases—more rapidly for the larger substituents because the Thorpe–Ingold effect is larger for them—but is opened to an increasingly lesser extent from the secondary (RCH<) as distinct from the primary (CH_2<) side because of steric factors. The fact that the logarithms of the solvolysis rates of the four 3-alkyl-substituted tosylates (Table 3, entries 2, 8–10) were found to correlate linearly with Taft's steric parameters[17] E_s of the substituents (correlation coefficient r = 0.989, slope −0.939) supports the latter explanation.

If entry 4 is taken as the solvolysis rate constant for a secondary tosylate without anchimeric assistance, entry 5 indicates that

(16) Cf.: Ingold, C. K. "Structure and Mechanism in Organic Chemistry"; Cornell University Press: Ithaca, NY, 1969; pp 455 and 555.

(17) Taft, R. W. "Steric Effects in Organic Chemistry"; Newman, M. S., Ed.; Wiley: New York, 1984; pp 556–675.

Table VI. First-Order Rate Constants[a] for Methanolysis of p-$XC_6H_4SCMe_2CH_2CH_2OTs$ and Percentage of Rearranged (RAR) Product

X compd	%RAR	k_t[a,b]	k_Δ[a,c]	k_s[a,d]	$\sigma_p°$
OCH_3	91	2.32	2.11	0.21	−0.15
CH_3	92	2.15	1.98	0.17	−0.15
H	82	1.57	1.29	0.28	0
F	70	1.02	0.71	0.32	0.17
Cl	58	0.80	0.46	0.34	0.27

[a] $\times 10^5$, s^{-1}. [b] Global rate constant. [c] $k_\Delta = k_t \times (\%RAR/100)$; see text. [d] $k_s = k_t \times [(100 - \%RAR)/100]$; see text.

γ,γ-disubstitution once again causes anchimeric rate acceleration although the effect is less compared to entries 3 and 1. Presumably anchimeric assistance from sulfur is less important in the more S_N1-like transition state for the solvolysis of the secondary tosylate than for the more S_N2-like transition state of the primary one.

Entries 6 and 7 cannot be directly compared to entry 1 because of steric factors due to the β-substituents. However, if we pass now to Table V in which the sulfur compounds are compared with sulfur-free models (cf. Table IV), we see clear evidence for anchimeric assistance in the dimethyl compound (entry 7) though the effect for the monomethyl analogue (entry 6) is only marginal. For the other cases (entries 1–5), the conclusions are similar to those based on the data in Table III.

Rate studies for the earlier-mentioned arylthio-substituted systems are summaried in Table VI. k_t is the total rate measured; k_Δ is the presumed anchimerically assisted rate obtained by multiplying k_t with the fraction (%100) of rearranged material and $k_s = k_t - k_\Delta$. This treatment is based on the assumption that unrearranged product is produced entirely by direct solvolytic displacement rather than by formation of a thietanonium intermediate A followed by opening of the four-membered ring from the less hindered side (cf. earlier discussion). The justification for this assumption comes from the computed k_s values themselves: they are all very close to the k_s value of the model compound (CH_3 in place of ArS; cf. Table IV, entry 3).[18] $\log k_\Delta/k_\Delta^H$ was plotted against σ_p, σ_p^+, and $\sigma_p°$; as one might surmise from the similarity of the k_Δ values for p-methyl and p-methoxy substituents (Table VI, entries 1 and 2), only the plot against $\sigma_p°$ gave a good straight line ($r = 0.998$) with $\rho = -1.58$. That the correlation is best with $\sigma_p°$ suggests that resonance overlap of the p electrons on sulfur with the aromatic π-orbitals is of minor importance (perhaps because it would involve overlap of 2p and 3p orbitals) and is somewhat surprising in view of the contrary observation[19] that in three-membered (thiiranium) sulfur-containing intermediates, the rate constants correlate with σ^+.

The k_s values correlate less well with $\sigma_p°$ ($r = 0.926$ for a plot of $\log k_s/k_s^H$ vs. $\sigma_p°$), and ρ is small and positive (+0.62) as might be expected for an S_N2-like reaction in which the inductive effect is fairly far removed from the reaction center.[20]

The rates of methanolysis at 25 °C for $RSCMe_2CH_2CH_2OTs$ for R = n-Bu, 59.81×10^{-5} s^{-1}, s-Bu, 51.50×10^{-5}, and t-Bu, 76.87×10^{-5} are similar to the rate for R = $PhCH_2$, 28.20×10^{-5} s^{-1}. Since in all four cases only rearranged product is isolated, it may be assumed that anchimeric assistance occurs in all four. A small inductive effect is seen for t-Bu (favorable) and $PhCH_2$ (unfavorable).

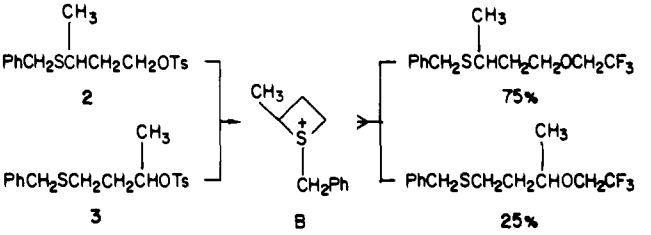
Solvent Effects

It was mentioned earlier that in the solvolysis of $PhCH_2SCH_2CHMeCH_2OTs$, the amount of rearranged product increased from 12% to 24% when the solvent was changed from dry methanol to methanol containing 3% water. This substantial change led us to investigate the effect of using highly polar solvents in product studies of solvolysis. We chose trifluoroethanol, CF_3CH_3OH, because of its high Y value[21] (1.74[22]) and low nucleophilicity[23] ($N = -2.67$[22]). Product studies for the trifluoroethanolysis of p-toluenesulfonates for some of the compounds which gave only little or no rearrangement in methanolysis (Table I, entries 3–6) are summarized in Table VII. It is evident that the amount of rearranged product in trifluoroethanolysis is consistently greater than for methanolysis. In trifluoroethanolysis, even the straight chain, unsubstituted 3-(benzylthio)propyl tosylate (entry 1) undergoes 43% rearrangement, indicating that at least 86% of the reaction proceeds via intermediate A; the 2-methyl-substituted homologue (entry 2) now proceeds entirely via cyclic intermediate A. For the 3-methyl- and 1-methyl-substituted homologues (entries 3 and 4), rearrangement is evidently not complete even in CF_3CH_2OH. However, 25% rearrangement for the 3-methyl (entry 3) and 75% rearrangement for the 1-methyl (entry 4) compound imply that the product composition is the same for the two cases (cf. Scheme I). It would therefore appear that the two substrates react via one and the same cyclic intermediate (B) which then partitions itself to give a 3:1 ratio of products of opening at the primary and secondary sites, respectively (Scheme I). It is particularly gratifying that this common intermediate can be manifested in trifluoroethanolysis, whereas in methanolysis it cannot be seen because the secondary compound **3** apparently undergoes direct nucleophilic displacement by methanol too fast for the cyclic intermediate to have a chance to form. It is also of interest that the intermediate B (Scheme I) undergoes opening at the primary site more rapidly than at the secondary one. In contrast, the product data in Table I, entries 1 and 2, indicate that in the competition of a tertiary site in intermediate C with either a primary or secondary site, opening at the tertiary site occurs exclusively or nearly so (Scheme II). This suggests that the opening of the intermediate A involves the usual S_N2–S_N1

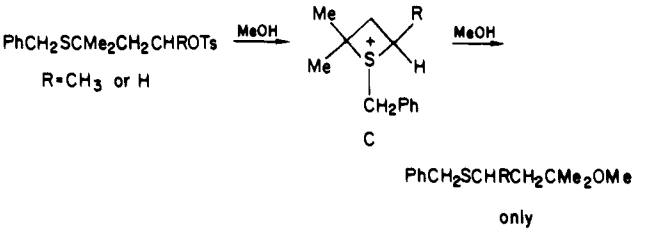
Table VII

compound	% rearranged prod CH_3OH	% rearranged prod CF_3CH_2OH
$PhCH_2SCH_2CH_2CD_2OTs$	0	43
$PhCH_2SCH_2CH(CH_3)CD_2OTs$	12	50
$PhCH_2SCH(CH_3)CH_2CH_2OTs$	20	25
$PhCH_2SCH_2CH_2CH(CH_3)OTs$	0	75

Scheme I



Scheme II



(18) As expected, there is a small inductive effect of the substituent; see text. The literature value[8] for the solvolysis rate of $PhSCH_2CH_2CH_2Cl$ is about 50% of that of n-BuCl. Even if one assumed that half the unrearranged product was formed via intermediate A, the kinetic argument given in the sequel of the text would not be palpably affected.

(19) Harris, J. M.; Paley, S. M.; Hovanes, B. M. McManus, S. P., unpublished results. We thank Prof. McManus for providing us with a copy of the manuscript.

(20) Cf.: Jaffé, H. *Chem. Rev.* **1953**, *53*, 191.

(21) Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 846.

(22) The Y and N values are from: Allard, B.; Casadevall, A.; Casadevall, E.; Largeau, C. *Nouv. J. Chim.* **1979**, *3*, 335. See also: Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667.

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Table VIII. Percent Rearranged Product in Presence and Absence of 0.1 N $LiClO_4$

entry	substrate	% rearranged product in MeOH	% rearranged product in MeOH + 0.1 N $LiClO_4$	E_s
1	$PhCH_2SCH_2CHMeCD_2OTs$	12	31	
2	$PhCH_2SCHMeCH_2CH_2OTs$	20	55	0
3	$PhCH_2SCHEtCH_2CH_2OTs$	14	51	−0.07
4	$PhCH_2SCH(i\text{-}Pr)CH_2CH_2OTs$	0	10	−0.47

spectrum of mechanisms leading to relative rates of ring opening at 1° > 2° < 3° sites.[24]

When the nucleophilic character of the medium is enhanced by adding sodium trifluoroethoxide, $CF_3CH_2O^-Na^+$, to the trifluoroethanol solvent, the amount of rearranged product becomes less, as might have been expected. For $PhCH_2SCH_2CH_2CD_2OTs$, the amount of rearrangement drops from 43% in pure CF_3CH_2OH to 36% in 0.5 N Na salt to 15% in 1.5 N salt. The drop for $PhCH_2SCH_2CHMeCD_2OTs$ is less, from 50% to 39% rearrangement as the salt concentration goes from 0 to 1.5 N.

Salt Effects

Salt effects have been extensively studied in solvolysis. In the present case, it was to be expected that the addition of a nonnucleophilic salt, such as lithium perchlorate, should enhance rearrangement, similarly as does a more ionizing solvent. A brief examination of product composition in the presence of 0.1 N lithium perchlorate (Table VIII) supports this assumption. It is of interest that the 3-isopropyl-substituted compound (entry 4) which showed no rearrangement (Table I, entry 9) but substantial anchimeric assistance (Table III, entry 9) did produce 10% of rearranged product in the presence of 0.1 N $LiClO_4$. Since it was hypothesized earlier that the isopropyl compound, in view of its substantially enhanced rate, reacted largely or entirely via intermediate A, one must assume that lithium perchlorate, in addition to furthering the formation of this intermediate by increasing the ionic strength of the medium, also influences the direction of its opening. Thus, the more "S_N1-like" ring opening at the secondary site (cf. B in Scheme I; the alkyl group may be methyl, ethyl, or isopropyl) would gain over the "S_N2-like" opening at the primary site in the presence of the lithium salt. In addition one might expect the ratio of these two modes of ring opening of A to reflect the steric effect of the substituent: the larger the substituent, the less opening at the secondary site. This is certainly true qualitatively (Table VIII, entries 2–4) and it even turns out that a plot of log (rearranged/unrearranged) reaction products vs. E_S is again a straight line with a correlation coefficient r = 0.997, though, since only three points are available, this correlation may be somewhat fortuitous.

Synthesis and Analysis

Except as already noted, the alcohols needed in this study were prepared by addition to thiolates to α,β-unsaturated esters, followed by reduction with lithium aluminum hydride. The alcohols were converted to their *p*-toluenesulfonates and to their methyl ethers (for reference) by standard methodology. The solvolysis products were analyzed by proton and/or carbon-13 NMR spectroscopy.

Conclusion

The combination of product and rate studies presented here, including the Hammett correlations for k_Δ and k_s in the ArS-4 series and the effect of solvent and added salt on product ratio leave little doubt that RS-4 participation in solvolysis of branched 3-(alkylthio)- and 3-(arylthio)propyl *p*-toluenesulfonates is real and that a marked Thorpe–Ingold effect is in evidence in these compounds. This experimental conclusion parallels that recently published[25] for four-membered ring chloronium ions on the basis of MINDO/3 calculations which suggest that such cyclic ions are greatly stabilized by substituents in the α-position on the four-membered ring.

Experimental Section

Proton NMR spectra were recorded on Bruker WM-250 (250 MHz), Varian XL-100, or Perkin-Elmer R27B (60 MHz) spectrometers; ^{13}C NMR spectra were recorded at 62.9 MHz on the Bruker WM-250 instrument. Both ^1H and ^{13}C spectra are referenced to internal TMS. Fluorine-19 NMR spectra were recorded at 94.1 MHz and are referenced to C_6F_6. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Methanol for both kinetic and preparative solvolysis runs was freshly distilled from magnesium turnings. Trifluoroethanol was used as received and solvolyses were carried out at reflux in the presence of solid sodium bicarbonate.

The reduction of alkylthio esters (see below) to alcohols was carried out with lithium aluminum hydride (cf. the reduction of methyl 3-(benzylthio)-2-methylpropanoate with lithium aluminum deuteride below). Alcohols were converted to *p*-toluenesulfonates as described in the literature.[26] Unrearranged methyl ether products were prepared from the corresponding alcohols with NaH and CH_3I in tetrahydrofuran.[27] Authentic rearranged products, where required, were synthesized as described below. $C_6H_5CH_2SCH_2CH_2CD_2OTs$, $C_6H_5CH_2SCH(CH_3)CH_2CH_2OTs$, $C_6H_5CH_2SCH_2CH_2CH(CH_3)OTs$, and the methanolysis products from these compound have been previously reported.[10]

Methyl 3-(benzylthio)-2-methylpropanoate (4) was synthesized by base-catalyzed addition of benzyl mercaptan to methyl methacrylate as previously described.[10] The ester was pure according to NMR and was used in subsequent steps without further purification: ^1H NMR (60 MHz) δ 3.10 (d, J = 6 Hz, 3 H), 2.20–2.90 (overlapping multiplets, 3 H), 3.50 (s, 3 H), 3.60 (s, 2 H), 7.16 (s, 5 H).

3-(Benzylthio)-2-methylpropanol-*1,1*-d_2 (5). To a solution of lithium aluminum deuteride (0.61 g, 14.5 mmol) in THF (4.5 mL) in a 100-mL three-neck flask equipped with a dropping funnel, reflux condenser, and nitrogen inlet tube the above ester (5.5 g, 26.4 mmol) in 10 mL of THF was added over a 30 min period. The solution was refluxed for 8 h and then cooled, quenched with 5% aqueous KOH solution, and filtered through a fritted glass funnel with the aid of Celite. The retained salts were rinsed with several portions of diethyl ether to help dissolve any residual alcohol. The combined organic solution was washed with 2 × 25 mL of saturated brine, dried over $MgSO_4$, filtered, and concentrated, and the resulting oil was distilled; yield 2.8 g (54%); bp 121–123 °C/0.5 torr. The proton NMR spectrum of the deuterio compound indicates quantitative ^2H incorporation (>99%): ^1H NMR (protio analogue, obtained by substituting lithium aluminum hydride for the deuteride) δ 0.93 (d, J = 6 Hz, 3 H), 1.78 (sextet, J = 6 Hz, 1 H), 2.20 (q, J = 7.5 Hz, 1 H (diastereotopic S–C*H*)), 2.42 (q, J = 6.8 Hz, 1 H (diastereotopic S–C*H* proton)), 3.29 (br, 1 H (–OH)), 3.42 (d, J = 6 Hz, 2 H), 3.63 (s, 2 H), 7.11–7.37 (multiplet, 5 H); ^{13}C NMR ($CDCl_3$, 62 MHz) (protio analogue) δ 16.73, 35.45, 35.61, 37.03, 66.00, 126.97, 128.48, 129.00, 138.78; ^2H NMR ($CDCl_3$, 38.4 MHz) δ 3.44.

3-(Benzylthio)-2,2-dimethylpropanoic acid (6) was prepared from 3-chloro-2,2-dimethylpropanoic acid[14] by adaptation of the literature procedure[28] for 3-(thioalkyl)-2,2-dimethylpropanoic acid derivatives. The acid was recrystallized from boiling pentane: yield 78%; mp 50.5–51 °C; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.25 (s, 6 H), 2.65 (s, 2 H), 3.70 (s, 2 H), 7.25 (s, 5 H), 10.3 (br s, 1 H). Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.20. Found: C, 64.16; H, 7.13.

3-(Benzylthio)-2,2-dimethylpropanol-*1,1*-d_2 (7). This compound was prepared from the acid **6** by the procedure described above for its monomethyl analogue except that refluxing of the reaction mixture was extended to 16 h: ^1H NMR (60 MHz) (protio analogue) δ 0.91 (s, 6 H), 2.39 (s, 2 H), 2.90 (br s, 1 H), 3.26 (s, 2 H), 3.62 (s, 2 H), 7.20 (s, 5 H); ^{13}C NMR (62.9 MHz) (protio analogue) δ 24.02, 36.49, 37.93, 41.29, 69.57, 127.00, 128.47, 128.91, 138.71; ^2H ($CDCl_3$, 38.4 MHz) δ 3.62.

3-(Benzylthio)-2-methyl-1-propyl-*1,1*-d_2 (8) and 3-(benzylthio)-2,2-dimethyl-1-propyl-*1,1*-d_2 toluenesulfonate (9) were prepared by standard methodology.[26]

Compound **8**: yield, 84%; ^1H NMR ($CDCl_3$) (protio analogue) δ 0.92 (d, J = 6.4 Hz, 3 H), 1.94 (sextet, J = 7.2 Hz, 1 H), 2.25 (d of d, J = 13.6, 7.5 Hz, 1 H), 2.40 (d of d, J = 13.6, 6.8 Hz, 1 H), 2.41 (s, 3 H),

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3.60 (s, 2 H), 3.92 (d of d, J = 1.5, 4.9 Hz, 2 H), 7.12–7.81 (AA'BB' quartet + multiplet, 9 H); ^{2}H NMR ($CDCl_3$, 38.4 MHz) δ 3.91. Anal. (protio analogue) Calcd. for $C_{18}H_{22}O_3S_2$: C, 61.67; H, 6.34. Found: C, 61.76; H, 6.30.

Compound **9**: yield, 58%; ^{1}H NMR ($CDCl_3$) (protio analogue) δ 0.92 (s, 6 H), 2.38 (s, 2 H), 2.43 (s, 3 H), 3.62 (s, 2 H), 3.70 (s, 2 H), 7.17–7.83 (AA'BB' quartet + multiplet, 9 H); ^{2}H NMR ($CDCl_3$, 38.4 MHz) δ 3.72. Anal. (protio analogue) Calcd. for $C_{19}H_{24}O_3S_2$: C, 62.59; H, 6.65. Found: C, 62.58; H, 6.56.

Methanolysis of 8 and 9: 3-(Benzylthio)-2-methylpropyl-*1,1-d*$_2$ Methyl Ether (10) and 3-(Benzylthio)-2,2-dimethylpropyl-*1,1-d*$_2$ Methyl Ether (11). Compounds **6** and **7** were solvolyzed under the conditions already described.[10] Pertinent data are reported below. The deuterium NMR spectrum from the solvolysis of **7** is shown in Figure 1; signals below correspond to the appropriate protio compounds.

10-H: yield, 88%; ^{1}H NMR δ 0.94 (d, J = 7.5 Hz, 3 H), 1.89 (sextet, J = 7.1 Hz, 1 H), 2.26 and 2.41 (2 d of d, J = 7.5, 12 Hz, 2 H (diastereotopic S–C*H* protons)), 3.20 (m, 2 H), 3.24 (s, 2 H), 3.63 (s, 3 H), 7.11–7.31 (m, 5 H); ^{13}C NMR δ 16.73, 33.67, 35.41, 36.85, 58.58, 76.61, 126.81, 128.34, 128.87, 138.69.

11-H: yield, 59%; ^{1}H NMR δ 0.94 (s, 6 H), 2.45 (s, 2 H), 3.12 (s, 2 H), 3.30 (s, 3 H), 3.68 (s, 2 H), 7.15–7.33 nm, 5 H); ^{13}C NMR δ 24.40, 36.06, 38.08, 41.67, 59.08, 80.35, 126.87, 128.42, 128.96, 138.87.

(*R*)-(+)-3-Thio-2-methylpropanol (12). In a 100-mL three-neck round-bottom flask equipped with a dropping funnel, reflux condenser, and N_2 inlet tube, 80 mg (2.1 mmol) lithium aluminum hydride was dissolved in 40 mL of THF. (*R*)-(−)-*S*-acetyl-3-mercaptoisobutyric acid in 10 mL of THF was added over 30 min and the solution refluxed 12 h. To the cooled solution was added 3% aqueous H_2SO_4 until the alumina gel dissolved. The contents of the flask was transferred to a separatory funnel and extracted with 6 × 40 mL portions of diethyl ether. The ether extracts were combined, dried over $MgSO_4$, filtered, and concentrated, and the resulting liquid was distilled; yield, 1.18 g (72%); bp 92 °C 16/torr; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.00 (d, J = 7.5 Hz, 3 H), 1.86 (sextet, J = 7.5, 6.00 Hz, 1 H), 2.41 (eight-line pattern, 2 H, (SH and one diastereotopic hydrogen from adjacent CH_2 unit)), 2.65 (quintet, 1 H, other diastereotopic hydrogen), 3.51 (d, J = 7.5 Hz, 2 H), 4.17 (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$, 62.89 MHz) δ 15.09, 27.42, 37.92, 65.18 $[\alpha]^{25}_D$ 19.14° (*c* 3.146, THF).

(*R*)-(+)-3-(Benzylthio)-2-methyl-1-propanol (13). To a solution of 452 mg of NaH (50% oil dispersion, washed with pentane, 9.4 mmol of active hydride) in 15 mL of THF in a three-neck round-bottom flask equipped with a dropping funnel, N_2 inlet, and reflux condenser, compound **12** (1 g, 9.4 mmol) in 5 mL of THF was added over 15 min. The solution was refluxed 1 h to ensure formation of the sodium thiolate; then benzyl bromide (1.69 g, 9.9 mmol) was added, and refluxing continued overnight. After the solution cooled, water (2 mL) was added, and the contents of the flask were transferred to a separatory funnel and diluted with an additional 75 mL of diethyl ether. After removal of the water layer, the ether layer was washed twice with 10 mL of 10% aqueous NaOH followed by 10 mL of saturated NaCl solution. The ether layer was dried over $MgSO_4$, filtered, and concentrated. The product is identical in all ways with that obtained by hydride reduction of **2** (vide supra); $[\alpha]^{25}_D$ +28.7° (*c* 4.754, THF).

(*R*)-(+)-(Benzylthio)-2-methylpropyl *p*-toluenesulfonate (14) was made from **13** as previously described (see compound **8**). Spectral characteristics were in agreement with those of **8**: $[\alpha]^{25}_D$ 33.04° (*c* 2.260, THF).

(*R*)-(+)-3-(Benzylthio)-2-methylpropyl Methyl Ether. Authentic optically pure methyl ether was made from precursor chiral alcohol (**14**) and methyl iodide.[27] Spectral data (^{1}H, ^{13}C NMR) agreed with those of the solvolysis product described earlier; $[\alpha]^{25}_D$ 14.96° (*c* 2.868, THF).

Ethyl 3-(Benzylthio)pentanoate, ethyl 3-(benzylthio)-4-methylpentanoate, and ethyl 3-(benzylthio)-4,4-dimethylpentanoate were prepared[10] by a base-catalyzed 1,4-conjugate addition of sodium benzylmercaptide to the appropriate unsaturated esters[29-36] and were reduced, by lithium aluminum hydride, to the corresponding alcohols which, in turn, were converted to the *p*-toluenesulfonates in the usual way.[26,37]

3-(Arylthio)propyl *p*-toluenesulfonates and the isomeric 3-(butylthio)-propyl *p*-toluenesulfonates were prepared analogously.[37]

Solvolysis Products. Unrearranged products from methanolysis of the above tosylates were obtained by Williamson methylation[27] of the precursor alcohols. Authentic rearranged products encountered in the first two solvolysis reactions were prepared by reaction of 3-(benzylthio)-1-propanal with ethyl- and isopropylmagnesium bromide, respectively, followed by Williamson methylation.[27]

Solvolyses with $Na^+OCH_2CF_3^-$. Reactions were carried out on a 0.75 mmolar scale in 8 mL of CF_3CH_2OH (TFE). The $Na^+OCH_2CF_3^-$ was prepared by washing the required amount of sodium hydride (36 mg of a 50% oil dispersion) with pentane and then suspending it in approximately 2 mL of tetrahydrofuran under N_2. An equivalent amount of TFE (75.5 mg) was then slowly injected so as to generate the alkoxide after which the solvent was pumped off and 5 mL of TFE added. Next, the tosylate (0.75 mmol) in 3 mL of TFE was added, and the reactions were refluxed 8–10 h. Workup consisted of the addition of 1 mL of water followed by removal of the TFE under reduced pressure. The residue was dissolved in ether, which was dried over $MgSO_4$, filtered, and removed under reduced pressure, and the oily residue was distilled on a Kugelrohr to separate the ether from unchanged tosylate. In each case, the products were compared with authentic materials made by different routes. In general, good spectral data were obtained in ^{1}H and, where applicable, ^{2}H NMR. In the cases of the 3-methyl and 1-methyl compounds ^{1}H, ^{13}C, and ^{19}F NMR were used to identify products. The appropriate tosylate (200–300 mg) dissolved in tetrahydrofuran (THF) was injected into a suspension of sodium trifluoroethoxide in THF under N_2 atmosphere. The sodium trifluoroethoxide was normally used in threefold excess and was generated by injecting TFE into a suspension of NaH in THF. The reaction mixture was refluxed for 12 h and workup accomplished by adding 1 mL of water, distilling the THF under reduced pressure, taking up the compound in ether (25 mL), washing with NaCl solution, drying over $MgSO_4$, filtering, and distilling the solvent. The products were then distilled on a Kugelrohr. Pertinent analytical data for the ethers are listed below.

3-(Benzylthio)propyl Trifluoroethyl Ether. Yield, 83%; bp 114–122 °C/0.2 torr; ^{1}H NMR δ 1.71 (quintet, J = 7.0 Hz, 2 H), 2.40 (t, J = 7.0 Hz, 2 H), 3.49 (t, J = 5 Hz, 2 H), 3.58 (s, 2 H), 3.60 (q, $J_{^{19}F-^1H}$ = 9.5 Hz, 2 H), 7.05–7.27 (m, 5 H); ^{13}C NMR δ 27.84, 29.42, 36.43, 68.35 (q, $J_{^{19}F-^{13}C}$ = 34 Hz), 71.19, 124.49 (q, $J_{^{19}F-^{13}C}$ = 280 Hz), 127.17, 128.69, 129.11, 138.88; ^{19}F NMR Φ = 74.4 ± 0.1. Anal. Calcd. for $C_{12}H_{15}OSF_3$: C, 54.52; H, 5.73. Found: C, 54.17; H, 5.63.

3-(Benzylthio)-2-methylpropyl Trifluoroethyl Ether. Yield, 78%; bp 120–131 °C/0.15 torr; ^{1}H NMR δ 0.95 (d, J = 6 Hz, 3 H), 1.88 (sextet, J = 6 Hz, 1 H), 2.26 (d of d, J = 6 Hz, 1 H), 2.48 (d of d, J = 6, 13 Hz, 1 H), 3.41 (overlapping d of d, J = 2, 6 Hz, 2 H), 3.63 (s, 2 H), 3.66 (q, $J_{^{19}F-^{13}C}$ = 9 Hz, 2 H), 7.08–7.30 (m, 5 H); ^{13}C NMR δ 16.50, 33.84, 35.10, 36.98, 68.62 (q, $J_{^{19}F-^{13}C}$ = 34 Hz), 76.44, 124.24 (q, $J_{^{19}F-^{13}C}$ = 280 Hz), 127.06, 128.57, 129.01, 138.72; ^{19}F NMR Φ = 74.4 ± 0.1. Anal. Calcd. for $C_{13}H_{17}OSF_3$: C, 56.09; H, 6.17. Found: C, 56.13; H, 6.32.

3-(Benzylthio)butyl Trifluoroethyl Ether. Yield, 72%, bp 125–139 °C/0.2 torr; ^{1}H NMR δ 1.28 (d, J = 7.5 Hz, 3 H), 1.77 (q, J = 5.5 Hz, 2 H), 2.79 (sextet, J = 5.5 Hz, 1 H), 3.58–3.76 (overlapping multiplets, 6 H), 7.16–7.35 (m, 5 H); ^{13}C NMR δ 21.65, 35.09, 36.42, 36.64, 68.48 (q, $J_{^{19}F-^{13}C}$ = 32 Hz), 70.30, 124.10 (q, $J_{^{19}F-^{13}C}$ = 280 Hz) 127.02, 128.56, 128.90, 138.78; ^{19}F NMR Φ = 68.4 ± 0.1.

4-(Benzylthio)-2-butyl Trifluoroethyl Ether. Yield, 57%, bp 128–139 °C/0.1 torr; ^{1}H NMR δ 1.11 (d, J = 6 Hz, 3 H), 1.50–1.84 (m, 2 H), 2.46 (m, 2 H), 3.52–3.82 (overlapping, 5 H), 7.12–7.32 (m, 5 H); ^{13}C NMR δ 19.26, 27.33, 36.18, 36.46, 66.33 (q, $J_{^{19}F-^{13}C}$ = 34 Hz), 76.40, 124.17 (q, J = 278 Hz), 127.05, 128.56, 128.90, 138.60; ^{19}F NMR Φ = 68.0 ± 0.1.

Kinetics

All kinetic runs were carried out in thermostated baths by using Sargent-Welsh thermonitors with the corresponding heaters and circulators. Temperature calibration of the baths was accomplished by using primary standard thermometers. Reliability of the thermometers is ±0.05 °C. Approximately 1 mmol of the *p*-toluenesulfonate was dissolved in 50 mL of methanol. Methanolysis was followed by titrating 5-mL aliquots of the reaction solution with hydroxide (ca. 0.2 N) to a methyl red end point using a buret with an accuracy of ±0.01 mL. Kinetic plots gave correlation coefficients of $r \geq 0.99$. Infinity titers were taken after ten theoretical half-lives and were within 2–3% of expected values.

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Acknowledgment. Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Army Research Office (ARO) for partial support of this research under Grant PRF 12420-AC4 and Contract DAAG29-82-K-0184, respectively.

Supplementary Material Available: Proton NMR spectra and, in some instances, analyses and Kugelrohr boiling points of ethyl 3-(benzylthio)pentanoate, ethyl 3-(benzylthio)-4-methylpentanoate, ethyl 3-(benzylthio)-4,4-dimethylpentanoate, 3-(benzylthio)-1-pentanol, 3-(benzylthio)-4-methyl-1-pentanol, 3-(benzylthio)-4,4-dimethyl-1-pentanol, 3-(benzylthio)-1-pentyl *p*-toluenesulfonate, 3-(benzylthio)-4-methyl-1-pentyl *p*-toluenesulfonate, 3-(benzylthio)-4,4-dimethyl-1-pentyl *p*-toluenesulfonate, ethyl-3-methyl-3-(phenylthio)butanoate, ethyl 3-methyl-3-(*p*-tolythio)butanoate, ethyl 3-[(*p*-methoxyphenyl)thio]-3-methylbutanoate, ethyl 3-[(*p*-fluorophenyl)thio]-3-methylbutanoate, ethyl 3-[(*p*-chlorophenyl)thio]-3-methylbutanoate, ethyl 3-(*n*-butylthio)-3-methylbutanoate, ethyl 3-(*sec*-butylthio)-3-methylbutanoate, ethyl 3-(*tert*-butylthio)-3-methylbutanoate, 3-methyl-3-(phenylthio)-1-butanol, 3-methyl-3-(*p*-tolylthio)-1-butanol, 3-methyl-3-[(*p*-methoxyphenyl)thio]-3-methyl-1-butanol, 3-[(*p*-fluorophenyl)thio]-3-methyl-1-butanol, 3-[(*p*-chlorophenyl)thio]-3-methyl-1-butanol, 3-(*p*-butylthio)-3-methyl-1-butanol, 3-(*sec*-butylthio)-3-methyl-1-butanol, 3-(*tert*-butylthio)-3-methyl-1-butanol, 3-methyl-3-(phenylthio)-1-butyl *p*-toluenesulfonate, 3-methyl-3-(*p*-tolylthio)-1-butyl *p*-toluenesulfonate, 3-(*p*-methoxyphenyl)-3-methyl-1-butyl *p*-toluenesulfonate, 3-[(*p*-fluorophenyl)thio]-3-methyl-1-butyl *p*-toluenesulfonate, 3-[(*p*-chlorophenyl)thio]-3-methyl-1-butyl *p*-toluenesulfonate, 3-(*n*-butylthio)-3-methyl-1-butyl *p*-toluenesulfonate, 3-(*sec*-butylthio)-3-methyl-1-butyl *p*-toluenesulfonate, 3-(*tert*-butylthio)-3-methyl-1-butyl *p*-toluenesulfonate, 3-(benzylthio)pentyl methyl ether, 3-(benzylthio)-4-methylpentyl methyl ether, 3-(benzylthio)-4,4-dimethylpentyl methyl ether, 1-(benzylthio)-3-pentyl methyl ether, 1-(benzylthio)-4-methyl-3-pentyl methyl ether, 3-methyl-3-(phenylthio)-1-butyl methyl ether, 3-methyl-3-(*p*-tolylthio)-1-butyl methyl ether, 3-[(*p*-methoxyphenyl)thio]-3-methyl-1-butyl methyl ether, 3-[(*p*-fluorophenyl)thio]-3-methyl-1-butyl methyl ether, 3-[(*p*-chlorophenyl)thio]-3-methyl-1-butyl methyl ether, 3-(*n*-butylthio)-3-methyl-1-butyl methyl ether, 3-(*sec*-butylthio)-2-methyl-1-butyl methyl ether, 3-(*t*-butylthio)-3-methyl-1-butyl methyl ether, 4-[(*p*-methylphenyl)thio]-2-methyl-2-butyl methyl ether, 4-[(*p*-methoxyphenyl)thio]-2-methyl-2-butyl methyl ether, 4-[(*p*-fluorophenyl)thio]-2-methyl-2-butyl methyl ether, 4-[(*p*-chlorophenyl)thio]-2-methyl-2-butyl methyl ether (10 pages). Ordering information is given on any current masthead page.

Theoretical Investigation of Acidity and Isotope Exchange in Purine Nucleotide Cations

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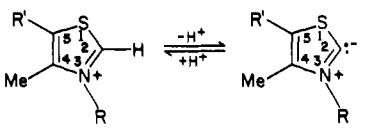
Abstract: The protonation of purine nucleotide models at N(7) and the C(8)H acidity of the purine cations have been explored by semiempirical (INDO) and ab initio (STO-3G) molecular orbital calculations performed on neutral, N(7)-protonated, and C(8)-deprotonated purine species. Factors associated with relative rates of C(8)H isotope exchange among different nucleotides were investigated. Substituent effects for natural nucleotides, such as electron-donation or -withdrawal, stabilization or destabilization, etc., were analyzed in the context of effects from the other common electron-withdrawing and -releasing groups at C(2) and C(6). The calculated N(7) basicity of neutral purines shows guanine, adenine, and hypoxanthine to be among the strongest bases along with methyl- and methoxypurines. Xanthine and fluoro- or nitropurine are computed to be among the weakest bases of the group. Ionization of C(8)H was predicted to be the most facile for xanthine and fluoro- and nitropurines and least facile for adenine, guanine, hypoxanthine, dimethyladenine, and dimethylguanine. The predicted thermodynamic ordering (xanthine > purine > hypoxanthine > adenine) is consistent with the observed exchange rate constants for the nucleosides and nucleotides, but guanine is predicted to be thermodynamically the least susceptible to exchange. Analysis of charge distributions in the N(7) protonated species reveals that approximately 35% of the positive charge appears at C(8)H. The magnitude of the charge appears to be a good indicator of the effect of substituents on C(8)H lability. The C(8)-deprotonated purines appear to be ylides, stabilized by π polarization, with little zwitterionic character. Both calculated proton affinities and C(8)H charges for the various C(2)- and C(6)-substituted purines show remarkably good correlations with standard Hammett σ values.

Relatively facile hydrogen isotope exchange in heterocyclic cations is a widespread, well-documented phenomenon with important biochemical implications. The earliest attention, motivated by Breslow's observations,[1] was focused on the ionization at C(2)H of the thiazolium ring due to its importance in the mechanism of thiamine-dependent enzyme processes.[2]



Subsequently this ionization/exchange has been observed in many other heterocyclic systems, such as thiazoles,[3] isothiazoles,[4] oxazoles,[3b] tetrazoles,[5] pyrazoles,[5] imidazoles,[3b,6] pyridines,[7] and purines.[6b,8-14]

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