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SULFUR PARTICIPATION IN SOLVOLYSIS INVOLVING FOUR-MEMBERED RING INTERMEDIATES

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Summary. Neighboring group participation *via* four-membered ring intermediates resulting in complete rearrangement occurs in the methanolysis of $R_1R_2C(SCH_2C_6H_5)CH_2\dot{C}H(R_3)OTs$ when $R_1=R_2=R_3=Me$ and when $R_1=R_2=Me$, $R_3=H$. No rearrangement is found for $R_1=R_2=R_3=H$ or $R_1=R_2=H$, $R_3=Me$. The case of $R_1=Me$, $R_2=R_3=H$ is intermediate.

Cases of neighboring group participation by sulfur involving four-membered rings are extremely rare.[1,2] Paquette, Meehan and Wise[3] have observed rate enhancement by nearly four orders of magnitude in solvolysis of a tosylate in a caged system where a sulfur atom was rigidly positioned so as to be able to participate through formation of a four-membered ring. Ireland and Smith[4] have found exclusive formation of the *endo* alcohol in solvolysis of either *exo*- or *endo*-8-thiabicyclo[3.2.1]-3-yl *p*-toluenesulfonates without significant rate differences, suggesting sulfur participation after the transition state was reached. There is also some evidence of S-4 participation in steroid systems.[5] In simpler systems, however, Bordwell and Brennan[6] found no palpable evidence of anchimeric assistance in the reaction of 3-phenylthiopropyl chloride with either methanol or potassium iodide in acetone (Table 1).

Table 1

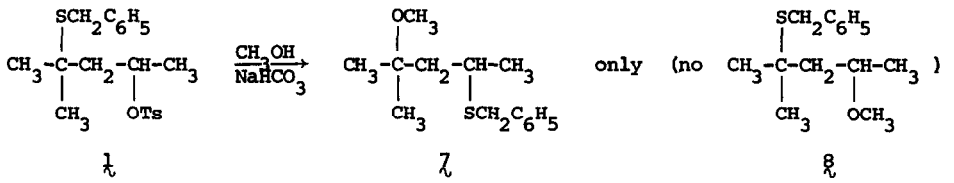
Relative Rates[a] of Reactions of $C_6H_5S(CH_2)_nCl$ with KI and with Methanol[6]

n	1	2	3	4	5
Rate, KI[b]	540	0.79	*3.1*	1.8	1.4
Rate, CH_3OH	33000	150	*1.0*	130	4.3

[a]Relative to *n*-butyl chloride (KI) or *n*-hexyl chloride (MeOH) taken as unity.
[b]In acetone at 75°C.

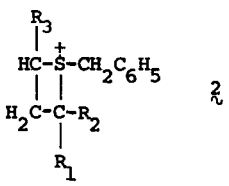
Results. We now report several cases of simple γ-benzylthioalkyl tosylates which clearly proceed with neighboring group participation (formation of four-membered sulfonium ring intermediates) as evidenced by the nature of the products. The difference between these cases and earlier ones studied appears to be methyl substitution of the carbon chains involved, which evidently facilitates ring formation by the classical Thorpe-Ingold effect.[7] In the absence of such substitution, e.g. in $C_6H_5CH_2SCH_2CH_2CH_2OTs$, there is no evidence of participation.

The salient results are shown in Schemes 1-4. The reaction of 4-benzylthio-4-methyl-2-pentyl *p*-toluenesulfonate (1) with methanol at reflux in the presence of solid sodium

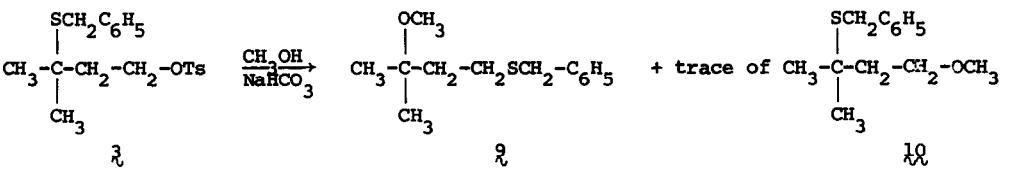


Scheme 1

bicarbonate gave 4-benzylthio-2-methyl-2-pentyl methyl ether (7, Scheme 1) in 57% yield.[8] Gas chromatographic and NMR analysis (see below for reference compounds) using either the ^{1}H or ^{13}C spectrum indicated essential absence (<5%) of the unrearranged 4-benzylthio-4-methyl-2-pentyl methyl ether (8). Use of other weak bases (either homogeneous or heterogeneous), such as thiourea, ethylene diamine or potassium carbonate gave essentially the same result; but with a stronger base, such as potassium thiolacetate, the main product is 4-benzylthio-2-methyl-1-pentene, $CH_3-CH(SCH_2C_6H_5)-CH_2-C(CH_3)=CH_2$. Both this rearranged olefin and the rearranged ether (Scheme 1) are presumably formed *via* a cyclic sulfonium salt intermediate, 2, $R_1=R_2=R_3=CH_3$. Similarly, the reaction of 3-benzylthio-3-methyl-1-butyl *p*-toluenesulfonate (3) with methanol

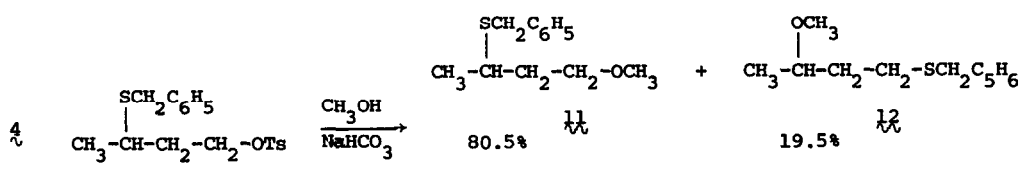


gives nearly exclusively the rearranged ether (9, Scheme 2) containing but a trace of the unrearranged 3-benzylthio-3-methyl-1-butyl methyl ether (10). Presumably the intermediate here is again 2, $R_3=H$, $R_1=R_2=CH_3$.



Scheme 2

Much less rearrangement is seen in primary-secondary (as distinct from secondary-tertiary, Scheme 1 and primary-tertiary, Scheme 2) systems as shown in Scheme 3. The primary tosylate -



Scheme 3

secondary thioether (4) undergoes rearrangement only to the extent of *ca* 20% and the secondary tosylate - primary thioether 5 hardly rearranges at all. Clearly intermediate 2 with R_1=CH_3, R_2=R_3=H is not so readily formed; its formation cannot compete at all with the direct solvolysis (without participation) of a secondary tosylate (5) and it competes poorly with the direct solvolysis of a primary tosylate (4).[9]

Finally, as shown in Scheme 4 by means of deuterium labeling, no cyclic intermediate (2, R_1=R_2=R_3=H or D) intervenes in the solvolysis of a di-primary thioether - tosylate (6).

$$\underset{6}{C_6H_5CH_2S\text{-}CH_2\text{-}CH_2\text{-}CD_2\text{-}OTs} \xrightarrow[NaHCO_3]{CH_3OH} \underset{\text{only}}{C_6H_5CH_2S\text{-}CH_2\text{-}CH_2\text{-}CD_2\text{-}OCH_3} \quad 13$$

Scheme 4

Materials. The tosylates and unrearranged methyl ethers corresponding were synthesized from the appropriate alcohols with *p*-toluenesulfonyl chloride - pyridine[10] and sodium hydride - methyl iodide,[11] respectively. The precursor alcohols were generated by reduction of the corresponding ketones (secondary alcohols) or esters (primary alcohols) with lithium aluminum hydride. The required β-benzylthio esters or ketones were prepared, in turn, by base-catalyzed addition of benzyl mercaptan to an α,β-unsaturated ester or ketone in the presence of sodium ethoxide.[12] Thus addition of benzyl mercaptan to $(CH_3)_2C{=}CHCOCH_3$ followed by hydride reduction gives the precursor of 1 and 8, a similar procedure starting with $(CH_3)_2C{=}CHCO_2C_2H_5$ gives the precursor of 3 and 10, an analogous procedure starting with ethyl crotonate gives the alcohol corresponding to 4 and 11 and, starting with methyl vinyl ketone, the alcohol corresponding to 5 and 12 is obtained. The precursor of 6 and 13 results from benzylation of methyl β-thiopropionate with benzyl chloride and base followed by reduction with lithium aluminum deuteride.

The rearranged products were similarly synthesized by methylation (*vide supra*) of the appropriate alcohols. The alcohol precursor of 7 (Scheme 1) was synthesized from the adduct of benzyl mercaptan and ethyl crotonate plus methylmagnesium iodide. Similarly, the precursor of 9 (Scheme 2) arose from methyl or ethyl β-benzylthiopropionate (*vide supra*) and methylmagnesium iodide. Finally, $C_6H_5CH_2SCD_2CH_2CH_2OCH_3$ (14) was made by converting commercial γ-methoxypropionitrile to $CH_3OCH_2CH_2CO_2C_2H_5$,[13] reducing with lithium aluminum deuteride, tosylating and treating with benzyl mercaptide.

Analysis. All authentic products were characterized by proton and ^{13}C NMR spectroscopy and their gas chromatographic retention times ascertained. Appropriate analytical data are summarized in Table 2. Reaction products from Schemes 1, 2 and 3 were inspected by NMR and then analyzed by gas chromatography; the product from Scheme 4 was analyzed by proton and ^{13}C NMR. Compound 13 is transparent in the proton NMR at 3.30 ppm ($\underline{CH}_2O$) and in the ^{13}C NMR at 70.9 ppm ($\underline{CH}_2O$) signal (not seen in $\underline{CD}_2O$ because of lack of NOE and of adequate dipole-dipole relaxation); 14, correspondingly, is transparent at 1.70 ppm ($SC\underline{H}_2$) in the proton and 27.9 ($S\underline{CH}_2$) in the carbon NMR spectrum; the methanolysis product (Scheme 4) has spectra corresponding to 13 with no detectable amount of 14.

Conclusion. Neighboring group participation is prominent in β-benzylmercaptopropyl tosylates with two or three methyl substituents, presumably because formation of the cyclic intermediate is furthered by the Thorpe-Ingold effect.[7] In the absence of methyl substitution no such intermediate is formed and only the unrearranged solvolysis product results. With a

Table 2

Characteristics of Methyl Ether Products

Compound	Proton NMR[a]	^{13}C NMR[a]	Retention time[b]
7	1.10(s),1.11(s),1.33(d),1.7(m),2.8(m),3.14(s)	22.9,24.9,25.7,35.5,46.8,48.9,74.5	16.6
8	1.10(d),1.34(s),1.37(s),1.7(m),3.32(s),3.6(m)	20.2,28.4,30.1,45.6,49.3,55.4,74.4	15.8
9	1.1(s),1.7(m),2.5(m),3.11(s)	24.9,26.0,39.7,49.1,74.2	34
10	1.34(s),1.87(t),3.32(s),3.55(t)	29.3,41.4,44.9,58.5,69.8	37.5
11	1.28(d),1.65(g),2.75(m),3.1(s),3.3(t)	21.5,34.9,36.6,58.3,70.0	54
12	1.1(d),1.6(m),2.4(t),3.15(s),3.3(g)	18.8,27.3,36.1,55.8,75.2	60
13	1.70(t),2.4(t),3.19(s)	58.2,29.1,27.9	-
14	2.69(t),3.18(s),3.30(t)	70.9,58.2,29.2	-

[a] In ppm from TMS. The signals of the $C_6H_5CH_2S$ moiety (both aromatic and benzylic) are omitted, since they are not distinctive. All peaks in the proton spectra were integrated and were in the proper area ratios.

[b] On 20% Carbowax 20M plus 10% KOH on 60-80 mesh Chromosorb A at 180-190°C. In mins.

single methyl substituent, partial rearrangement occurs when the *p*-toluenesulfonate is primary but not when it is secondary. It remains to be shown through rate studies whether anchimeric assistance (rate enhancement) occurs and whether the intermediate synthesized in independent fashion undergoes ring opening in the direction required.[14]

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References and Footnotes

1. E. Block, "Reactions of Organosulfur Compounds", Academic Press, Inc., New York, NY, 1978, chapter 4.
2. B. Capon and S.P. McManus, "Neighboring Group Participation", Plenum Press, New York, NY, Vol. 1, 1976, chapter 5.
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7. See E.L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill Book Co., Inc., New York, NY, 1962, pp. 197-202.
8. About 20% of the product was high-boiling; of the material distilling below 125°/0.2 mm (80%) approximately 30% represented olefinic products. With the other *p*-toluenesulfonates only solvolysis products (ethers) and starting tosylates were recovered.
9. Alternatively (but less likely) the product mixture from 4 may reflect the fate of the intermediate 2, R_1=CH_3, R_2=R_3=H; in any case 5 does not form this intermediate at all.
10. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley & Sons, Inc., New York, NY, 1967, Vol. 1, p. 1180.
11. cf. R. Méric and J.-P. Vigneron, Bull.Soc.Chim.Fr., 327 (1973).
12. cf. H.J. Backer and G.J. deJong, Recl.Trav.Chim.Pays-Bas, 70, 377 (1951).
13. cf. R.H. Kimball, G.D. Jefferson and A.B. Pike, Org.Syn.Coll., Vol. II, 284 (1943).
14. A 1,3-benzylthio shift might be contemplated as an (unlikely) alternate mechanism.

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