mixture was stirred under reflux for 15 h. After the solvent was removed in vacuo, the residue was diluted with water and extracted with pentane. The extract was washed with aqueous $Na_2S_2O_3$, water, and brine, dried, and concentrated. The residue was chromatographed (Al_2O_3, grade II, 50 g, pentane/ether 97.5/2.5) to give a mixture of **3** and **20** (392 mg, 54%). GC [PEG–20 M, 0.25 mm × 50 m glass capillary column, temp 70–220 °C, rate 3°C/min, N_2 pressure 1.2 Kg/cm^2] t_R: **20**, 24.11 min (38.0%); **3**, 24.47 min (49.9%). Preparative GC was performed with a Hitachi 163 gas chromatograph (PEG-20 M, 10 mm × 3 m stainless column) to give **3** (93% pure) and **20** (81% pure. **3**: $[\alpha]^{25}_D$ −41.0° (*c* 0.50, $CHCl_3$); IR (film) 3080, 1660 (sh), 1638, 1450 (br), 1382, 1365, 1185, 1165, 1110, 1090, 1025, 890, 880 (sh), 805 cm^{-1}; NMR (400 MHz) 0.78 (3 H, d, *J* = 7.8 Hz), 0.88 (3 H, d, *J* = 7.8 Hz), 0.96–1.09 (1 H, m), 1.09–1.20 (2 H, m), 1.21–1.32 (1 H, m), 1.34–1.42 (1 H, m), 1.55–1.64 (1 H, m), 1.64 (3 H, br s), 1.82–2.05 (4 H, m), 2.10–2.22 (2 H, m), 2.22–2.35 (2 H, m), 2.55–2.65 (trace, due to the methylene protons of *Z* isomer), 460 and 474 (trace, due to the exocyclic olefin protons of *Z* isomer), 4.81 (1 H, br s, hhw = 6.0 Hz), 4.84 (1 H, br s), hhw = 6.0 Hz), 6.37 (1 H, br t, *J* = 7.8 Hz), no NOE effect was observed between C_2–H and C_1–Me; GC–MS, *m/z* 206 (M^+), 191, 177, 163, 150, 135, 121, 109, 107, 95, 93, 81, 69, 67, 55, 43, 41 (100), 32. **20**: $[\alpha]^{21}_D$ −29.9° (*c* 0.26, $CHCl_3$); IR (film) 3090, 1660 (sh), 1638, 1455 (br), 1382, 1375 (sh), 1365, 1230, 1200, 1170, 1085, 1020, 925, 890, 840, 820, 740 cm^{-1}; NMR (400 MHz) 0.78 (3 H, d, *J* = 7.9 Hz), 0.85 (3 H, d, *J* = 7.9 Hz), 0.98–1.08 (1 H, m), 1.21–1.40 (2 H, m), 1.45–1.68 (3 H, m), 1.60 (3 H, br s), 1.75 (1 H, br d, *J* = 15.5 Hz), 1.96 (4 H, br d, *J* = 15.5 Hz), 2.10–12.35 (4 H, m), 2.52–2.68 (2 H, m), 4.60 (0.85 H, d, *J* = 2.9 Hz), 4.74 (0.85 H, d, *J* = 2.9 Hz), 4.81 and 4.84 (each 0.15 H, due to the exocyclic olefin protons of *E* isomer), 5.10 (0.85 H, d-d, *J* = 4.4 and 11.7 Hz), 5.37 (0.15 H, t, due to the trisubstituted olefin proton of *E* isomer), clear NOE effect was observed between C_2–H and C_1–Me; GC–MS, *m/z* 206 (M^+), 191, 177, 163, 150, 135, 121, 109, 107, 95, 93, 81, 69, 67, 55, 43, 41 (100), 32. Anal. Found: C, 86.58; H, 12.42. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70.

(4*E*,8*R*)-5-Methyl-8-(1-methylethyl)-1-(phenylthio)-4-cyclodecenemethanol (22). The alcoholic fraction **19** (1.1 g) obtained by the procedure described above was rechromatographed by using a Lobar column [prepacked column size C (37 nn × 440 mm), Si 60 (63–125 μm)] to give two fractions, F-I (706 mg) and F-II (217 mg). F-I solidified partly in the refrigerator; the solid was recrystallized from *n*-pentane to give pure *E* isomer **22** (419 mg): mp 87–88 °C; $[\alpha]^{25}_D$ −18.6° (*c* 0.5, $CHCl_3$); IR (nujol) 3530, 3060, 1570, 1220, 1185, 1165, 1075, 1050, 1010, 890, 870, 815, 755, 705, 695 cm^{-1}; NMR (400 MHz) 0.75 (3 H, d, *J* = 7.0 Hz), 0.81 (3 H, d, *J* = 7.0 Hz), 0.80–0.92 (2 H, m), 1.00–1.16 (1 H, m), 1.20–1.63 (9 H, m), 1.77 (3 H, s), 1.81–2.07 (3 H, m), 2.12–2.23 (1 H, m), 2.23–2.37 (1 H, m), 2.56 (1 H, m, OH), 3.20 (1 H, d-d, *J* = 3.0 and 11.0 Hz), 3.38 (1 H, br d-d, *J* = 8.0 and 11.0 Hz), 5.52 (1 H, br t, *J* = 7.0 Hz), 7.30–7.40 (3 H, m), 7.45–7.51 (2 H, m); MS, *m/z* 332 (M^+, 266, 255, 222, 191, 179, 163, 149, 135, 125, 123, 121, 109, 95, 93, 83, 79, 66, 54, 42 (100). Anal. Found: C, 75.57; H, 9.63. Calcd for $C_{21}H_{32}OS$: C, 75.86; H, 9.70.

(−)-Dihydrogermacrene D (3). Crystalline *E* alcohol **22** (348 mg, 1 mmol) was treated in the same manner as described already for the preparation of the mixture of **3** and **20** to give **3** (105 mg, 51%), which was purified with preparative GC. **3** (98% pure): $[\alpha]^{21}_D$ −42.7° (*c* 0.55, $CHCl_3$). IR and GC–MS spectra were completely identical with those described (vide supra). The NMR spectrum (400 MHz) was almost identical with that of **3** (93% pure) except that 98% pure **3** did not show any signals due to the contamination oof *Z* isomer **20**. Anal. Found: C, 87.05; H, 12.76. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70.

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Registry No. **3**, 64141-33-9; **4**, 1195-31-9; **5**, 91201-40-0; **6**, 91201-41-1; **7**, 91201-42-2; **8**, 91201-43-3; **9**, 91201-44-4; **10**, 91201-45-5; (*R*)-(*E*)-**11**, 91201-46-6; (*R*)-(*Z*)-**11**, 91201-52-4; **12b**, 91201-47-7; **13b**, 91201-48-8; **16**, 91208-70-7; **17**, 91201-49-9; **18**, 91201-50-2; **19**, 91201-51-3; **20**, 91278-65-8; bromocyclopropane, 4333-56-6; (2-pyridylthio)acetonitrile, 7521-19-9; (phenylthio)-acetonitrile, 5219-61-4.

Ionic Bicyclobutane as an Intermediate in the Reaction of PhS^- with 3-Halobicyclobutanecarbonitrile: Comparison between Thio- and Oxycarbenium Ions[1]

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The nucleophilic reaction of PhS^- with 3-chloro- and 3-bromobicyclobutanecarbonitrile (**2**–Cl (Br)) in MeOH and DME was investigated. The products in MeOH are the dithioketal **3** and the two cis–trans isomers of the thiooxoketal **4**. The identity of the element (Cl or Br) in **2** strongly affects the product ratio **3**/**4** but has no effect on the stereodistribution of the two isomers of **4**. It is shown that the mechanism of the reaction of PhS^- with **2** in MeOH is similar to that of an alkoxide reacting with the same substrate (path c, Scheme I). After the cleavage of the central bond by the nucleophile, the thio halo ether group on C-3 expels a halide anion to form thiocarbenium before the negatively charged carbon reacts further. Addition of MeOH or PhSH to the zwitterionic intermediate completes the reaction. In DME, the mechanism is altered and 3-(phenylthio)bicyclobutanecarbonitrile (**2**–SPh) is obtained (path a, Scheme I). By carrying out the reaction at varying concentrations of MeOH in DME it is shown that **2**–SPh is not obtained via a collapse of a zwitterionic intermediate but rather by a γ-elimination step (Scheme II). The γ-elimination mechanism prevails as long as the MeOH concentration in DME is kept below 2 M. Beyond this limit the change in medium polarity induces a gradual changeover in the mechanism and the proportion of the mixed ketal **4** is increased with the concentration of MeOH and follows a sigmoidic curve. A similar sigmoidic curve is obtained for the solubility of KBr in these solvent mixtures, supporting the assumption that the mechanistic changeover is caused by the change in the nature of the medium. Qualitative analysis shows that oxygen is superior to sulfur in enhancing the formation of an adjacent positive center.

Due to geometrical constraints, the internuclear distance between two nonbonded carbon atoms in cyclobutane is only 2.1 Å.[2a] One should therefore expect that the two nonbonded carbons will strongly interact with each other

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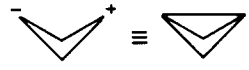
Table I. Element Effect on Product Distribution in the Reaction of PhS^- with 2-Cl(Br) in MeOH[a]

[PhS^- Na^+], M	[PhSH], M	substrate	[2-Cl (Br)], M	product ratio 3/4 (cis + trans)	isomeric ratio 4-*trans*/4-*cis*
0.1	0.02	2-Cl	0.025	0.51	1.8
0.1	0.02	2-Br	0.025	0.94	1.7
0.13	0.025	2-Cl	0.06	0.95	1.41
0.13	0.025	2-Br	0.06	1.82	1.47
0.26	0.05	2-Cl	0.06	2.11	1.56
0.26	0.05	2-Br	0.06	3.78	1.69

[a] The reactions were carried out in pairs according to their entry order.

and that this interaction will manifest itself in the chemical behavior of this compound. Several experimental observations can indeed be attributed to this proximity of the carbons. It was suggested, for example, that the massive interpenetration of the two atoms into each other's van der Waals radii gives rise to a large repulsive interaction.[2b] This repulsive interaction which is estimated to be ca. 10 Kcal/mol for each of the two pairs (1.3 and 2.4 carbon atoms) could be responsible for the high strain energy observed in cyclobutane[2b] (26.9 vs. 28.1 Kcal/mol for clopropane[3]). Another possible manifestation of the proximity effect is the enhanced solvolysis rate of cyclobutyl derivatives.[4] This was interpreted to result from a stabilization of the positive charge on C-1 by the back lobe of the C-3–H bond yielding the so called bicyclobutonium ion.[5] The ease of the 1,3-dehydrohalogenation reaction to form a bond across the ring[6] as well as the formation of a transannular double bond[7] are additional examples of this effect.

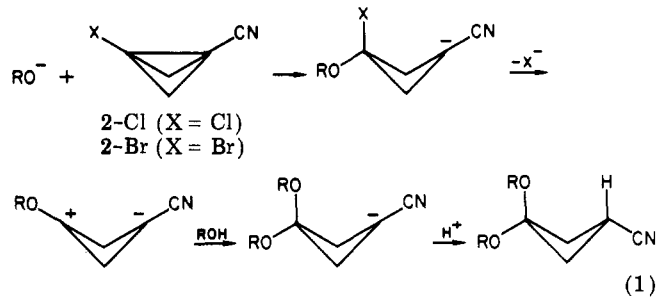
We have recently reported[8] the formation of a derivative of an ionic bicyclobutane (1) in which opposing charges



1

reside on C-1 and C-3. Due to the small separation of these carbons the central line in the schematic description of 1 represents in fact an ionic rather than covalent bond. Needless to say much of its thermodynamic stability is derived from the coulombic cross ring interaction. It was found to exhibit some kinetic stability as well, in that it shows selectivity in its reaction with external nucleophiles. This zwitterionic species does not collapse to the covalent compound. The barrier for such a process includes two components. The first stems from the need to move from the ionic potential surface to the diradical–covalent one. This is in fact the same barrier which prevents the collapse of intimate ion pairs at a vibrational rate. The second derives from the increase in strain energy accompanying such a collapse (the length of the central bond in bicyclobutane is ca. 1.4 Å[2a]) and provides additional height to the barrier.[8]

In our studies, the positive charge was further stabilized by an alkoxy group as an oxycarbenium ion whereas a cyano group was used to stabilize the negative charge at the other bridgehead carbon. This compound was obtained as an intermediate in nucleophilic reactions of alkoxides on 3-halobicyclobutanecarbonitrile (2–Cl, –Br). The mechanism of the reaction was shown to be as follows (eq 1).



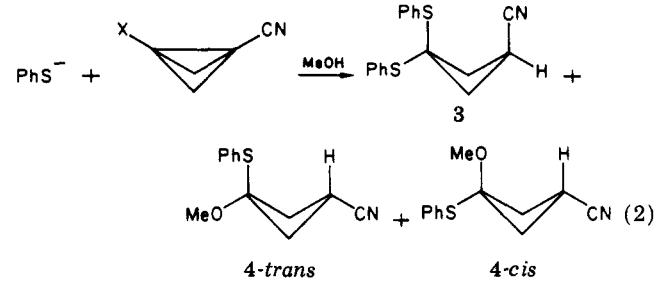
2-Cl (X = Cl)
2-Br (X = Br)

(1)

The key point in this mechanism is that the solvolysis of the halo ether moiety to give the oxycarbenium is faster than any of the reactions which the neighboring carbanion can undergo. The carbanion can be annihilated either by protonation or via a γ-elimination reaction which will lead to the formation of a covalent alkoxybicyclobutane. The rate order of the various processes in the system was found to be: solvolysis to form the oxycarbenium > γ-elimination > protonation.[8] This reaction rate order was found to prevail in alcohols as well as in THF. Since the oxygen atom of the alkoxide plays a primary role in this mechanism we have addressed ourselves in the present study to the possible mechanistic consequences of substituting this oxygen with sulfur. As will be shown later this variation has a pronounced effect on the mechanism of the reaction.

Results

Reaction of 2–Cl (Br) with PhS^- in MeOH. The reactions were performed at room temperature and were followed by gas chromatography. The reactions are relatively fast and at concentrations of ca. 0.1 M in each of the reactants is completed in a matter of minutes. Three products are obtained (eq 2): the dithioketal (3); the two



3

4-*trans* 4-*cis*

(2)

geometrical isomers, cis and trans S,O ketals 4. 3-(Phenylthio)bicylobutanecarbonitrile (2–SPh) was not obtained in the reactions in MeOH, even when PhS^- concentrations (0.04 M) were much lower than that of the substrate (0.15 M). The ratio of the two isomers does not remain constant due to a post isomerization reaction. Isomerization experiments of 2–SPh in MeOH–MeO^- showed that one isomer (4-*cis*, see discussion) is more stable than the other (K = 1.7). In order to suppress the isomerization reaction, PhSH was added to the reaction mixtures. Under these conditions, the less stable isomer (4-*trans*) was preferentially obtained. The effect of changing the leaving group from Cl to Br on the product distribution (3 vs. 4) as well

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Table II. The Effect of MeOH Concentration in DME on the Yield of 4 (cis + trans in percent)[a] in the Reaction of PhS^-[b] with 2-Cl[c] and on the Solubility of KBr

[MeOH]	0	0.62	1.56	1.86	3.12	4.68	6.24	7.8	9.36	12.48	18.72	24.7[d]
4, %	0	0	0		10	35	49	60	88		97	97
[KBr][e]	$<10^{-3}$	$<10^{-3}$		0.01	0.016	0.027	0.048		0.07	0.11	0.167	0.172

[a] Within ±4%. [b] Concentration 0.11 M. [c] Concentration 0.1 M. [d] 100% MeOH. [e] Saturation concentration.

as on the stereodistribution of 4 is given in Table I. The following points are of interest: (a) As the concentration of PhS^- + PhSH is increased, 3 is obtained in larger proportion. (b) Replacement of Cl by Br strongly affects the product distribution (3/4). (c) There is practically no element effect on the stereodistribution within 4.

Reactions of PhS^- with 2-Cl in Aprotic Solvents. The reaction of PhS^-Na^+ with 2-Cl in DME at room temperature is very fast. The precipitation of NaCl is observed almost immediately upon mixing the reactants at concentrations of ca. 0.1 M each. When 2-Cl was reacted in DME with 2–3 equiv of PhS^-, in the presence of PhSH, the major product (>90%) was the dithio ketal 3. When equivalent concentrations of the nucleophile and substrate are used, the major product is 3-(phenylthio)-bicyclobutanecarbonitrile (2-SPh). Attempts to obtain

2-SPh

this compound in a pure state by preparative gas chromatography and column chromatography were unsuccessful since decomposition occurs under the separation conditions. However, its stability in solution enabled the performance of the following experiments which unambiguously proved its structure. Catalytic hydrogenation of the reaction mixture resulted in a high yield of the 3-(phenylthio)cyclobutanecarbonitrile which was easily separated by gas chromatography. Addition of an equal volume of MeOH to the DME solution of 2-SPh did not induce any reaction and none of the isomers of 4 was obtained. When 3 volumes of a 0.15 M solution of MeO^-–MeOH were added to a 0.2 M solution of 2-SPh in DME the two isomers of 4 are obtained in their equilibrium ratio (the MeO^- present catalyzes the isomerization reaction). This reaction is ca. 10-fold slower than the reaction of 2-Cl with PhS^- in MeOH at similar concentrations. Addition of PhS^- (0.2 and 0.015 M) in MeOH to the DME solution (volumes 3:1, respectively) yielded only the dithio ketal 3. Addition of methanolic HCl (0.05 M) to the DME solution (volume ratio 3:1, respectively) gave the two isomers of 4, trans and cis in a 1:24 ratio, respectively. Finally, 2-Cl (0.28 mmol) was allowed to react with PhS^- (0.265 mmol) in $CDCl_3$ at room temperature for 24 h. After filtration of the solids the ^1H NMR obtained showed the typical pattern of bicyclobutanes—two singlets (in addition to the aromatic peak), one for the endo and one for the exo protons.[9]

Reactions of 2-Cl with PhS^- in DME–MeOH Mixtures. These experiments were designed in order to examine the effect of medium composition on the relative amounts of 4. The main product in the reaction of 2-Cl with PhS^- in a medium poor in MeOH was 2-SPh. In high molarity of MeOH, the major products were the two isomers of 4. As can be seen from Table II and Figure 1, when the concentration of MeOH is below 2.5 M, no 4 is obtained. Above this concentration there is a steep rise in the percent of 4 in the products which levels off around 10 M MeOH. In this region the product composition is about the same as in pure MeOH, namely, the major products are the two isomers of 4. For comparison, the solubility of KBr was also measured in the various solvent compositions (Table II).

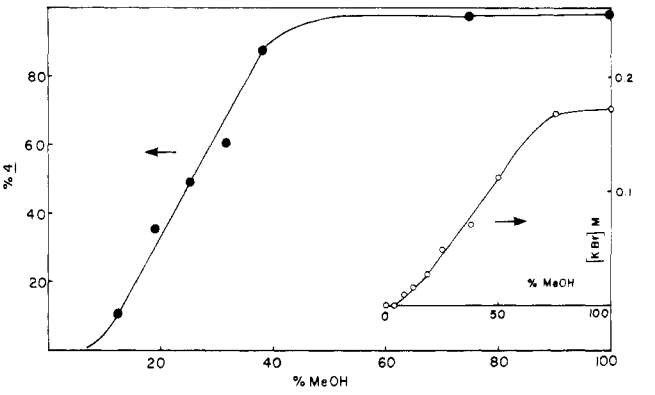

Figure 1. Percent of 4 obtained in the reaction of PhS^- with 2-Cl in DME–MeOH mixtures (●). Solubility of KBr as a function of MeOH in DME (○).

Discussion

Reactions in Methanol. The first step of the reaction of thiophenoxide with 2 is no doubt a nucleophilic attack at C-3 of 2. This process may be coupled with the cleavage of the carbon–halogen bond to give 3-(phenylthio)bicyclobutanecarbonitrile (2-SPh) or with the cleavage of the central bond of 2-Cl (Br). For the reactions of alkoxides with 2-Cl (Br), we have advanced[8] four arguments in favor of the latter possibility: (a) kinetic element effect (k_{Cl}/k_{Br}), (b) element effect (Cl/Br) on product distribution, (c) theoretical considerations of the driving forces of the two alternative processes (which include the ability of the cyano group to stabilize a neighboring negative charge as well as the energy gained due to relief to steric strain), and (d) analogies with olefinic compounds. The study of reactions of 2-Cl with thiophenoxide provides an additional and most powerful argument against the direct displacement of the leaving group in these reactions. From the reactions in DME we were able to obtain 2-SPh. If 2-SPh is indeed obtained as an intermediate in the reactions in MeOH, by a direct displacement of the halide ion, the following two conditions must be fulfilled.[10] First, the product distribution must be identical with that displayed by the reaction of 2-Cl under the same reaction conditions. Second, the rate by which 2-SPh is converted to products must be at least identical if not faster to that observed for 2-Cl. As can be seen from the Results section, none of these conditions is met. The cis and trans isomers of 4 are not obtained from 2-SPh. On the contrary, the latter yields only 3 and does not add methanol under the reaction conditions. The rate of methoxide-mediated conversion of 2-SPh to give 4 is slower than the overall reaction by a factor of 5–10. Thus it is clear that the central bond of 2 is cleaved in the first step of the reaction and the ex-

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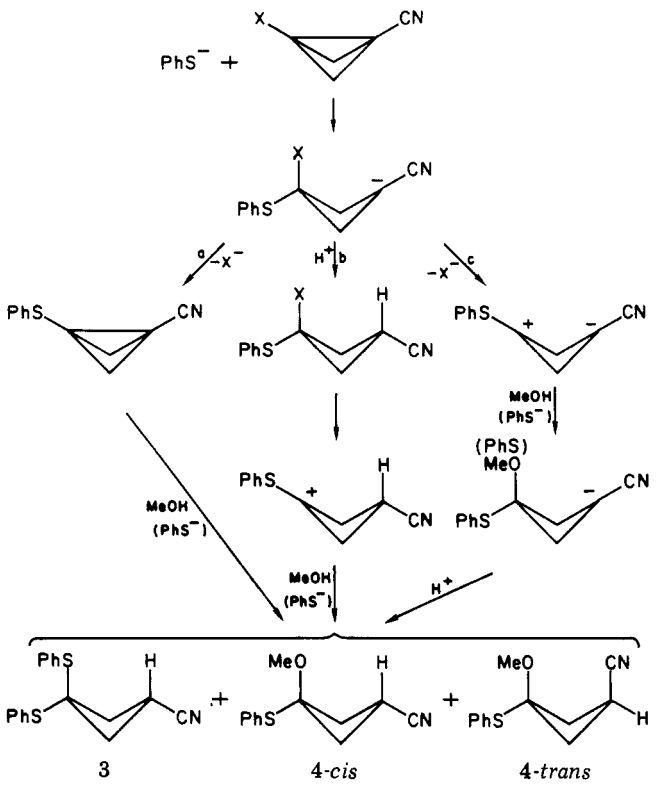
Scheme I



pulsion of the leaving group takes place at a later stage.

Having established the identity of the first step, let us now turn to various mechanistic possibilities by which the reaction may proceed. Three possibilities are shown in Scheme I. The first (path a) can be immediately excluded since it involves the formation of 2–SPh which has already been shown not to be an intermediate in this reaction. The two other mechanisms (paths b and c) involve similar processes, namely, protonation of the carbanion on C-1, solvolysis of the halo thio ether moiety to give the thiocarbenium, and its trapping by either PhS^- or MeOH. However, they differ significantly in the sequence of these steps. In path b, protonation is the fastest step and is the first to occur, whereas in mechanism c, the two other steps come first, followed by protonation as the slowest process.

It is noteworthy that in the related reaction of 2–Cl (Br) with alkoxides it was found that the solvolysis of the halo ether on C-3 to give the oxycarbenium paired with the halide anion was faster than protonation on C-1. This is analogous to path c of Scheme I above. In the following discussion it will be shown that in spite of the fact that the solvolysis of chloro thio ether is slower than that of the analogous chloro ether, by at least two orders of magnitude,[11a,b] it is still faster than protonation of the carbanion and path c is the prevailing one in this case as well.

In order to do so let us first discuss the stereochemistry of the reaction. The two isomers of 4 differ slightly (ca. 0.3 Kcal/mol) in their stability as is determined by the equilibrium experiments. Most probably the more stable isomer is the one in which the two bulky groups SPh and CN can simultaneously assume equatorial positions (4-*cis*).[2a] However, under the reaction conditions, it is the less stable isomer which is preferentially obtained. Clearly, in both path b and c, the stereodistribution is determined by the last step of the reaction, which is protonation of the carbanion in path b and nucleophilic attack on the thiocarbenium in path c. However, the product distribution determining step, namely, the step in which it is determined whether the thiocarbenium will be trapped by PhS^- to give 3 or by MeOH to give 4, is one and the same as the stereochemistry controlling step only in path b and not in c. Therefore, if the reaction indeed occurs via path b where both the stereochemical distribution as well as the product distribution are determined by the same process, any perturbation which induces a change in the product distribution (3/4 ratios) would be expected to also affect the stereodistribution of 4. On the other hand, in path c, these two steps are uncoupled and therefore a change in one should not be reflected by the other. As can be seen from Table I, varying the leaving group from Cl to Br induces a very pronounced effect on the product composition. This is probably due to an element effect of the halide ion within the formed ion pair. Nevertheless the stereodistribution of 4 was found to be completely insensitive to the identity of the leaving group. This dichotomous behavior of the element effect on the two basic features of the reaction, the product and stereodistributions, is clearly in favor of path c where the two features are not determined in the same step.[12]

Table III. Percent of Protonation and Elimination in 3-R-3-Chlorocyclobutane-3-carbonitrile-1-anion

R	% protonation	% elimination
H[a]	50	50
CN[b]	30	70
PhS	?	?

[a] Reference 6. [b] Reference 13.

That path c is indeed the actual course of the reaction can also be inferred from the following kinetic arguments. Let us compare the rates of protonation of the cyano stabilized carbanion on C-1 (path b) with rates of 1,3-eliminations in derivatives of cyclobutanecarbonitrile-1-anion.

As can be seen from Table III, the internal nucleophilic displacement of Cl^- (γ-elimination) is similar in rate to the protonation of the carbanion for both R = H and R = CN. The question at hand is what will be the relative proportions for R = PhS. To a first approximation one can assume the protonation rate is not affected by variation of substituents at the γ-position. However nucleophilic displacements on α-halo thio ethers are known to be faster by ca. three orders of magnitude than the same reactions on analogous alkyl halides.[14] Thus it is clear that for R = PhS, which is the first intermediate in our reaction, the carbanion, given enough time, will preferentially γ-eliminate the chloride to give 2–SPh and will not undergo protonation. This, in terms of Scheme I, means that moving along path a (γ-elimination) is faster than following path b (protonation of the carbanion). Path b should therefore be discarded. Since we have already unambiguously shown that 2–SPh of path a is not an intermediate in the reaction, one has to conclude that the nucleophilic reaction of PhS^- with 2–Cl (Br) proceeds along path c. In other words the solvolysis of the α-halo thio ether which is probably largely enhanced by the neighboring negative charge is faster than elimination of the leaving group by

(11) (a) Jones, T. C.; Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 4863. (b) Modena, G.; Scorrano, G.; Venturello, P. *J. Chem. Soc., Perkin Trans. 2* **1979**, 3.

(12) An alternative explanation based on different proportions of free, solvent separated or intimate ion pairs can in principle also be invoked. However, this explanation was rejected in the previous paper and the arguments will not be repeated here.

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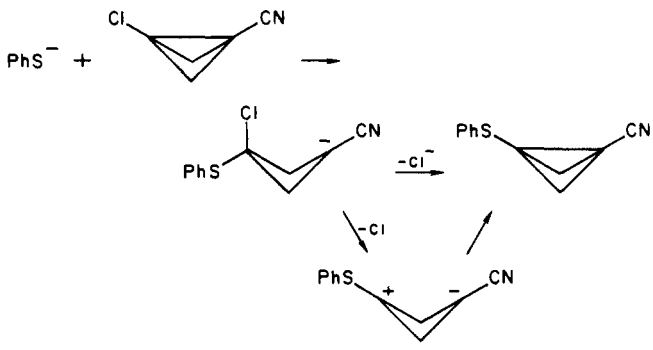
Scheme II



the carbanion to give 2–SPh which on the other hand is faster than protonation of the same carbanion.

It should be pointed out that the upper limit for the rate of solvolysis of the α-halo thio ether to give the thiocarbanion is that of a molecular vibration while the theoretical upper limit for the rate of protonation by the solvent could be the same as that for a molecular rotation. These two upper limits may be within an order of magnitude of each other. However, it is well-known that for cyano-stabilized carbanions such as substituted malononitrile,[15] the eigenplot levels at about 10^8 M^{-1} s^{-1}. It was also found that protonation of a carbanion stabilized by only a single cyano group is well below the diffusion controlled limit.[16] Thus the life span of the carbanion on C-1 is apparently long enough to enable both solvolysis as well as the capture of the oxycarbenium ion to occur before it undergoes protonation. Thus, mechanistically the reaction of 2–Cl with thiophenoxide in CH_3OH is completely identical with that of alkoxides. However, these considerations relate only to reactions in methanol. In the following section we will show that in dipolar aprotic solvents the similarity ends and the reaction with PhS^- takes a different course.

Reactions in DME. As we have stated in the previous section, the two fastest processes that the first carbanionic intermediate can undergo are solvolysis to give the zwitterionic intermediate and elimination to give 2–SPh. In methanol it was found that solvolysis is more rapid than elimination. However, decreasing the polarity of the medium is likely to diminish the rate of the first processes and increase that of the latter. Such a trend will eventually lead to a changeover in the mechanism of the reaction from path c to a. Performing the reaction in DME with an equivalent amount of PhS^-, 2–SPh was indeed obtained as the major reaction product. (In higher PhS^- concentrations, 2–SPh reacts further with PhS^- to give 3.) While this is completely in accord with our expectations, it is clear that the formation of 2–SPh does not provide an unambiguous proof for the validity of path a in DME. As shown in Scheme II, an alternative route to the formation of 2–SPh is the collapse of the zwitterionic intermediate formed by the solvolysis of the halo ether moiety.

In order to explore the possible occurrence of the solvolysis process in DME we have performed a series of experiments in which increasing amounts of MeOH were added to the reaction mixture. If 2–SPh is indeed obtained from a collapse of the zwitterionic intermediate then the amount of 4 formed should correlate approximately linearly with the concentration of MeOH. On the other hand if 2–SPh is formed by an elimination process, then addition of MeOH will not cause the formation of 4 as long as the nature of the medium is not sufficiently altered.

The effect of added MeOH is illustrated in Figure 1. It is clear that below a concentration of ca. 2 M in MeOH no 4 is formed at all. Thus, in this region 2–SPh is formed via the γ-elimination mechanism (path a). This is also strongly supported by the absence of 3 in the reaction at low PhS^- concentration in DME. When the MeOH concentration exceeds 2 M, a changeover in the mechanism due to the change in the polarity[17] of the medium takes place and more of the zwitterionic intermediate is formed until at the end, the reaction behaves as if conducted in pure MeOH (path c, Scheme I). The sigmoidic nature of the plot in Figure 1 is typical of a solvent effect.[18] This can also be inferred from the similar behavior of the solubility of KBr as a function of solvent composition. (It should be pointed out however that the activity of KBr in the solvent is affected to a certain extent by the concentration of KBr itself and can therefore serve only as a rough criteria for solvation properties at high KBr concentrations.)

Sulfur vs. Oxygen, Stabilization of the Carbenium Center. Earlier in this paper we have pointed out that the upper limit for the rate of the solvolytic step is that of a molecular vibration. This holds for the thio as well as for the oxo derivative. The question at hand is whether the two species indeed react at the same upper rate limit or whether one of them is faster than the other.

Gas-phase experiments as well as theoretical calculations indicate that sulfur is more effective than oxygen in stabilizing a neighboring carbenium center in the gas phase.[19] However, results from condensed-phase studies are not so conclusive and some contrasting pieces of evidence are reported.[11,20] It is worth noting that while solvolysis is always faster than γ-elimination in the reaction of alkoxides with 2–Cl (Br), even in aprotic solvents, for thiophenoxide the relative rate order of the two processes is inverted upon moving from MeOH to DME. Yet, as will become clear from the following discussion, these observations do not suffice to answer our question. A clearer insight into this problem can be gained from a qualitative analysis of medium effects on the pertinent reaction rates.

In general, solvolytic reactions in which the overall charge is increased will be slowed down as a result of a decrease in the polarity of the medium. On the other hand, nucleophilic reactions in which the charge is more diffused at the transition state will exhibit the opposite behavior due to a diminished demand for solvation of the transition state.[21] These trends are shown in Figure 2 for the solvolysis and the γ-elimination reactions, respectively. A changeover from one mechanism to the other will take place at the intersection zone of the two lines describing (the sensitivity of the rates to the polarity of the medium (Figure 2). Having arbitrarily drawn the lines for the

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(16) Jencks, W. P., private communication.

(17) Throughout the following text the term polarity will be used to express those solvent features which facilitate the formation of charges.
(18) See for example: Kosower, E. M.; Kanety, H. *J. Phys. Chem. (N.Y.)* **1982**, *86*, 3776.
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(21) Ingold, C. K. "Structure and Mechanism in Organic Chemistry", 2nd ed.; Cornell University Press: Ithaca, NY, 1969; Chapter 7.

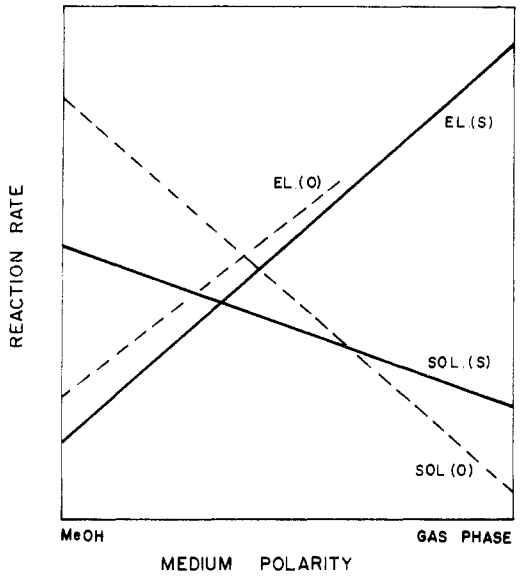

Figure 2. The effect of medium polarity on the solvolysis (sol) and elimination (el) of halo thio and oxo ethers (S and O, respectively).

reaction with the thio nucleophile (sol(S) and el(S)), we will try to locate the respective lines for the alkoxide reactions ((sol(O) and el(O)) with respect to those of the former nucleophile.

As can be deduced from the reactions of methoxymethyl chloride and its sulfur analogue with a nucleophile, the oxygen derivative is expected to undergo the γ-elimination reaction faster than the thio derivative (rate el(O) > rate el(S)). The studies of Thornton[11a] and Scorrano[11b] also indicate that the sensitivity of the rate ratio of these S_N2 reactions to solvent variation is practically identical. (At 80% dioxane–20% H_2O and at 95% dioxane–5% H_2O the rate ratios are 114 and 113, respectively.) While this tendency may be inverted in the gas phase, it is highly likely to hold for our reactions which were run in similar solvents (DME and THF). Thus the el(O) line must be located above that of the el(S) line at least in this region of medium polarity. Since no changeover in the mechanism was observed for the reactions of alkoxides with 2–Cl (Br) it is clear that *the intersection of the el(O) and s(O) lines must occur at lower polarity than for S* where this changeover was actually observed. Since the sol(O) in the gas phase must be below the sol(S) point, the only way by which this can be achieved is by locating the sol(O) in MeOH higher than this point for sol(S). Thus, the solvolytic process in our case is faster for an oxycarbenium than for thiocarbenium formation. This is in agreement with the majority of the observations made in this field.[20]

Conclusions

We have shown in this and the preceding paper[8] that nucleophilic substitution on 2–Cl (Br) by alkoxides and thiophenoxide in MeOH proceeds by a hitherto unknown and unexpected mechanism (path c, Scheme I) in which an ionic bicyclobutane is obtained as an intermediate. Due to the reduced ability of sulfur as compared to oxygen to stabilize a neighboring positive charge, a mechanistic changeover is observed in the reactions of PhS^- as a nucleophile upon moving from MeOH to DME (path a, Scheme I).

Somewhat similar 1–3-zwitterionic intermediates were previously reported in the literature. These include ylids of the structure $R_2C = X^+–C^-R_2$ containing first and second row central atoms[22] (X = O, N, S) where direct interaction at the π level via the central atom exists between the two terminal carbons. In a series of stimulating papers Cram has demonstrated[23] that suitably substituted cyclopropane can undergo heterolytic rather than homolytic ring opening. In this process, 1–3-zwitterionic intermediates are obtained with carbon as the bridging atom. The coulombic bonding between the two termini in this case is smaller than in the cyclobutanic system since the separation of the 1,3-carbons is larger by ca. 0.4 Å than that in cyclobutane. In light of the similarity between the central bond of bicyclobutane and the π bond in an olefin, an interesting question arises as to whether an ionic olefin can in fact exist. Due to the short distance between the two carbon atoms (ca. 1.5 Å length of the σ bond), the electrostatic interaction will further increase and is therefore expected to substantially stabilize such a molecule. In order for such a molecule to be observed, two basic conditions must be fulfilled. (a) The covalent component of the π level must be completely reduced and (b) the zwitterionic configuration has to be more stable than the diradicaloid one. The first condition can be met by rotating an olefin by 90° so that the p orbitals on the two carbon atoms will be orthogonal. This can be achieved for example by a bulky substitution or by confinement within a strained ring system. The use of push–pull substituents can provide a satisfactory solution to the second condition. Thus, in fact, obtaining an ionic olefin might not be all that impossible a task and indeed we believe that partial success has been achieved by the work of Sandstrom et al.[24] They have prepared a variety of olefinic compounds exhibiting large dipole moments and deviating significantly from planarity. Thus in general, the similarity between bicyclobutanes and olefins seems to be retained.

Experimental Section

General Methods. ^1H NMR (in $CDCl_3$) spectra were recorded on a Varian EM 360A spectrometer. Mass spectra were taken with a Finnigan 4021 mass spectrometer. For analytical purposes a Packard Model 878 (FI detector) gas chromatograph was used whereas for preparative separation, a Varian 920 gas chromatograph (TC detector) was used. In both cases, the column was 3–5% Xe60 on Chromosorb W.

Solvents and Starting Materials. Methanol (Frutarom, analytical) was dried by the magnesium method.[25] DME (Fluka) was treated with KOH for 24 h and distilled over CaH_2. Sodium thiophenoxide was prepared by mixing 3.3 g of PhSH (30 mmol) and 0.6 g of Na (26 mmol) in 100 mL of dry ether. After the completion of the reaction (end of gas evolution), the salt was filtered, washed with dry ether, and stored in a desiccator. 3-Chlorobicyclobutanecarbonitrile (2-Cl) and the bromoderivative (2-Br) were prepared according to published procedures.[8,9]

Preparation of Products. 3-Methoxy-3-(phenylthio)-cyclobutanecarbonitrile (4). A solution of 0.12 M thiophenoxide with 0.02 M thiophenol was prepared by addition of weighed amounts of thiophenol to a 0.12 M solution of MeO^- in MeOH. The substrate 2–Cl was added to this solution up to a concentration of 0.1 M. After 1 h at room temperature the reaction mixture was treated with ether and water. The etheral phase was separated, washed with water, and dried over $MgSO_4$ and the ether was removed by evaporation. GC analysis revealed that the two

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isomers 4-*cis* and 4-*trans* were obtained in 75% yield in a 1:17 ratio, respectively. The dithioketal **3** was also obtained in these reactions in a ca. 20% yield. The two isomers were separated by preparative gas chromatography (the cis isomer had a smaller retention time than the trans isomer). The two isomers showed the same NMR and MS spectra: ^{1}H NMR δ 7.33 (m, 5 H), 3.35 (s, 3 H), 2.8–2.4 (m, 5 H); MS (CI) 204, 188, 110. Satisfactory CHNS analysis was obtained for the two isomers.

3,3-Bis(phenylthio)cyclobutanecarbonitrile (3). A solution of 0.25 M PhSH and 0.15 M PhSNa was prepared in DME. To this solution 2-Cl was added at room temperature up to a concentration of 0.1 M. After 12 h the reaction was quenched with water and extracted with ether and the etheral phase was dried over $MgSO_4$ and evaporated. The yield of **3** was 95% (GC). The product was purified by preparative gas chromatography: ^{1}H NMR δ 7.4 (m, 10 H), 3.5–3.2 (m, 1 HCCN), 2.9–2.6 (m, 4 H);[26] H); MS (CI) 298, 220, 188, 187, 110, 109, 78. Satisfactory CHNS analysis was obtained.

3-(Phenylthio)bicyclobutanecarbonitrile (2-SPh). Attempts to isolate and purify this product by a variety of chromagraphic methods were unsuccessful because of its fast decomposition on the columns. Therefore this product was prepared and further reacted as DME solution. A solution of PhSNa (0.21 M) in DME was gradually added to a solution of 2-Cl (0.2 M) in DME at room temperature until all the substrate had reacted. NaCl precipitated and 2-SPh was obtained as the major product (>90%): MS (GC–MS, CI) 188, 110, 109, 78. In order to obtain the NMR spectrum of 2-SPh, the reaction was performed in $CDCl_3$. 2-Cl (0.03 g, 0.265 mmol) was mixed with PhSNa (0.037 g, 0.28 mmol) in 1 mL of $CDCl_3$ for 24 h at room temperature. GC analysis showed that 2-SPh was obtained in over 90% yield. The salt was removed by filtration and the solvent was partly evaporated to give the product in a suitable concentration. Me_4Si was added as an internal standard. NMR δ 7.4 (m, 5 H), 2.25 (s, 2 H), 1.7 (s, 2 H).

Reactions of 2-Cl and 2-Br with PhS^- in MeOH. To a solution of 0.1–0.3 M CH_3ONa in CH_3OH was added PhSH up to the needed concentrations (see Table I). (For these reactions an excess of PhSH over MeONa was added in order to prevent the post isomerization induced by the basic medium. The reactions are completed within 30 min.) The substrate 2-Cl was injected into 2 mL of these solutions and the reactions were analysed by gas chromatography. In order to study the element effect on the stereochemistry and product distribution, the reactions of the two substrates (2-Cl, 2-Br) were carried in pairs. Product distribution data were obtained by GC analysis with calibration curves. The relative proportions of the products **3** and **4** depended on the reaction conditions (see Table I). The bicyclic product 2-SPh was not obtained in these reactions.

Reaction of 2-Cl with PhS^-Na^+ in DME. Reaction mixtures were prepared by dissolving known amounts of PhSNa in DME and mixing it with a previously prepared DME solution of 2-Cl. NaCl precipitated almost immediately and the formation of the products 2-SPh and **3** was monitored by analytical GC. in the presence of excess of PhS^-Na^+ and prolonged reaction periods (see product preparation) the initially formed 2-SPh was converted to **3**.

Reaction of 2-Cl with PhS^-Na^+ in DME–MeOH Mixtures. A series of DME-MeOH solutions with variable amounts of MeOH (see Table II) were prepared. These solutions (1 mL) were added to volumetric flasks each containing 0.015 g of (0.11 mmol) PhS^-Na^+. The reactions were initiated by injection of ca. 0.011 g, (0.1 mmol) of 2-Cl to each of the reaction vessels. GC analysis after 1 h showed that 2-Cl had reacted completely. The product ratio was determined by gas chromatography with calibration curves.

Solubility of KBr in DME–MeOH Solutions. To 12 mL of each of the above solutions was added 1 g of KBr. After 24 h of stirring at room temperature, the mixtures were centrifuged. Clear aliquots of 6 mL each were taken from each of the solutions and the solvent was removed by evaporation. The solubility of KBr was determined from the weight of the remaining solid.

Reactions of 3-(Phenylthio)bicyclobutanecarbonitrile (2-SPh). The substrate 2-SPh was prepared in DME in a concentration of ca. 0.2 M as previously described. **Hydrogenation**: ca. 30 mL of the solutions containing 2-SPh was transferred to a 250-mL pressure bottle containing 0.3 g of 5% Pd/C. After 12 h under 70 psig of H_2 the reactions were analyzed by gas chromatography. The product 3-(phenylthio)cyclobutanecarbonitrile was obtained in a 90% yield (GC). This product was separated on a preparative GC and was identified by its NMR and MS spectra.[27] **Reaction in MeOH**: addition of 3 mL of MeOH to 1 mL of the mother liquor of 2-SPh in DME did not induce any reaction of 2-SPh after incubation for 12 h. **Reactions with MeO^-**: to 1 mL of 2-SPh in DME was added 3 mL of 0.15 M MeO^- in MeOH. After ca. 3 h the two isomers of **4** were obtained in their equilibrium ratio (1:1.5). **Reactions of 2-SPh with PhS^-Na^+**: to 1 mL of the mother liquor of 2-SPh in DME was added a 3-mL solution of 0.2 M PhS^-Na^+ in MeOH at room temperature. The reaction mixture was analyzed by GC. The only product was the dithio ketal **3**. None of the isomers of **4** was obtained. **Reactions of 2-SPh with methanolic HCl**: an 0.05 M solution of HCl in MeOH was prepared by bubbling gaseous HCl into MeOH. A volume of 3 mL of this solution was added to a 1-mL solution of 2-SPh in DME. The reaction was followed by gas chromatography. The major products (>90%) were the two isomers of **4** in a 1:2.4 ratio (cis–trans, respectively).

Isomerization of 3-Methoxy-3-(phenylthio)cyclobutanecarbonitrile. The isomerization experiments were conducted in a 0.1 M solution of MeO^- in MeOH at room temperature. Starting with each of the isomers (**4** cis and **4** trans) separately the reactions (0.02 M in each isomer) were allowed to reach equilibrium (ca. 4 h). The isomer ratio was determined by GC analysis.

Registry No. 2-Cl, 23745-75-7; 2-Br, 87712-20-7; 2-SPh, 91003-31-5; **3**, 91003-30-4; *cis*-**4**, 91003-32-6; *trans*-**4**, 91003-33-7; 3-(phenylthio)cyclobutanecarbonitrile, 91003-34-8; PhSNa, 930-69-8.

(26) A referee had pointed out that the chemical shift of the two isomers of **4** appears at a higher field (δ 2.4–2.8) compared to that of **3**. The reason for this is probably due to the fact that the bulky PhS group prefers to adopt the equatorial position in **4** whereas in **3** where there are two PhS groups, a 1,3-diaxial interaction with the H–C–CN hydrogen is unavoidable. The anisotropic effect of the Ph group induces the downfield shift observed for **3**.

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