The Thermal β-Cis-Elimination Reaction of Cyclic Sulfoxides and Subsequent Ring Expansion Reactions

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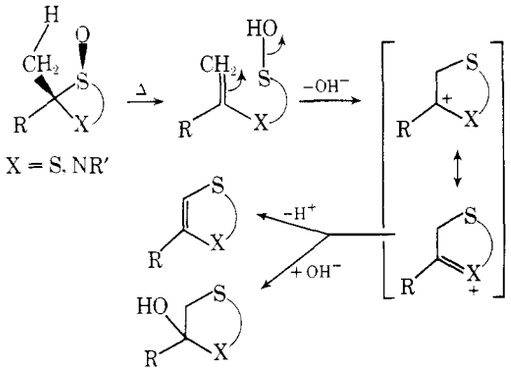
Received September 21, 1976

A two-step process has previously been identified for the ring expansion which occurs on heating cyclic and spirocyclic sulfoxides in solution, a β-cis elimination to form sulfenic acid and olefin moieties, followed by an intramolecular electrophilic addition reaction between these functional centers with ring closure yielding a heterocyclic sulfide with one more member than the original sulfoxide. It is found that either step can be rate determining depending on the ground state geometry of the substrate undergoing reaction. The geometric factors that determine the rates of the β-cis elimination step are examined in some detail through variation of the structural features of the sulfoxides. Study of the kinetic deuterium isotope effect by applying the criterion of the temperature dependence of k_H/k_D discloses that tunneling is an important factor in the pseudopericyclic process by which β-cis-elimination is effected in sulfoxides. Moreover, such tunneling is correlated directly with the distance of separation of the carbon and oxygen centers between which hydrogen is transferred in the course of forming olefin and sulfenic acid.

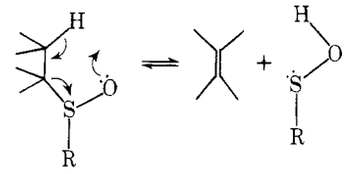
Thermolysis of sulfoxides containing β hydrogen atoms is a well-known method of preparing olefins; the established stereo- and regiospecificity of the reaction[1] is an important feature. The application of this reaction to cyclic sulfoxides, however, has been practiced infrequently in the past. A well-documented example occurs in the penam–cephem conversion of penicillin *S*-oxides;[2] the initial step of this reaction apparently is the thermal ring opening to a sulfenic acid intermediate via an assumed β-cis-elimination process.[1]

The subsequent intramolecular interaction of the sulfenic acid and olefin centers arising from this thermolytic cleavage of a cyclic sulfoxide can take place either through a cis addition which is the reverse of the cleavage reaction, or an electrophilic addition equivalent to the attack of a sulfur cation on the double bond. Typical cases of the cis addition are the ring contraction of thiepane 1-oxide to 2-methylthiane 1-oxide[3] and the thermal isomerization of penicillin *S*-oxides.[4] The electrophilic addition appears to be operative when the cationic intermediate is stabilized by a heteroatom substituent on the olefin center. Two cases of this type have recently been reported[5,6] to take place according to the following scheme.[7]



There are indications that the electrophilic addition mode requires acid catalysis.

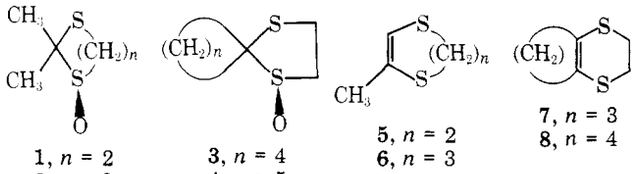
The rearrangement of 1,3-dithiolane 1-oxides into dihydro-1,4-dithiins reported recently[5] was independently characterized by us. However, the valuable synthetic applications of this reaction pointed out by Chen[5] have not been our main concern. Here we have undertaken to elucidate the kinetic characteristics of the sequence of steps involved in the overall rearrangement process. The elimination of sulfenic acid on thermolysis of sulfoxides is generally regarded as a concerted process. Though conceived to have a planar structure, some charge separation in the transition state has been alleged.[8] Since unshared pairs on the heteroatoms must be involved in the synchronism of bond making and breaking it is possible to consider this a pseudopericyclic[9,10] process as represented in the following equilibrium:



The principal focus of our studies has been on the geometry of the sulfoxide ring expansion controlling the kinetic factors of the overall reaction process.

Results and Discussion

The cyclic and spirocyclic sulfoxides **1–4** were prepared from the corresponding sulfides by oxidation with hydrogen peroxide in acetic acid.[11] Upon heating in *o*-dichlorobenzene or Me_2SO at 110–130 °C, **1, 3,** and **4** rearrange smoothly into the corresponding dithiins **5, 7,** and **8,** respectively, identified by their NMR and mass spectral features.[12,13] In Me_2SO-d_6



1, *n* = 2
2, *n* = 3

3, *n* = 4
4, *n* = 5

5, *n* = 2
6, *n* = 3

7, *n* = 3
8, *n* = 4

at 110 °C, **1, 3,** and **4** were converted to the extent of 50% after 13, 2.5, and 20 h, respectively, as monitored by NMR spectroscopy. However, **2** decomposed much more slowly—50% after ~50 h—and less cleanly; dihydrodithiepin, **6,** was formed only in low yield (<20%), and the only other low-boiling product identified was 2,2-dimethyl-1,3-dithiane.

The unexpected course taken in the thermolysis of **2** may be a consequence of both the high $\Delta G^{\ddagger}$ for closure of a seven-membered ring and a ground-state structure which does not completely fulfill the geometric requirements for cis elimination. On the other hand, inspection of models reveals that **1** and **3** possess the geometry that is very favorable for the cis cleavage, with **3** being almost locked into the ideal positioning. It can also be seen with the aid of models that the S–O bond in **2** is disposed equatorially.[14,15] These circumstances, wherein the distance between the oxygen and the methyl is unusually long and coplanarity is difficult to achieve, are decidedly unfavorable for the cis-concerted elimination process. The situation in the spirocyclic sulfoxide **4** is somewhat more

Table I. Kinetic Parameters[a] for the Decomposition of *tert*-Butyl Ethyl Sulfoxide (11) and Its d_9 Analogue (12)

Substrate	$10^5 k^{112.5°C}$, s^{-1}	Temp range, °C	E_a, kcal mol^{-1}	A (10^{-12})
11	3.8[c]	102–135	29.4 ± 0.9	11.7
12	0.74[b]	112–143	32.6 ± 0.7	24

$[\Delta E_a]_D^H$ = 3.2 kcal mol^{-1}; A_H/A_D = 0.07

[a] Calculated from rate data plotted in Figure 1. [b] Data not corrected for incomplete deuteration of <5%. [c] Compare with *tert*-butyl methyl sulfoxide data[10] (toluene solvent) $k_{100°C} = 0.63 \times 10^{-5}$ s^{-1}.

complex, but study of its model construction discloses that its geometry is slightly more favorable for the cis elimination than is the case in **2**. Thus, the observed order of overall rearrangement rates, **3** > **1** > **4** > **2**, appears to parallel the order deduced on the basis of ground-state structural considerations which determine the ease of attainment of the geometric requirements of an essentially planar, cis-concerted elimination process.

The question which then presents itself is whether the ring opening is indeed the rate-determining step of the overall rearrangement, for, if not, it is reversible. To test reversibility and stereospecificity of the ring-opening step under the reaction conditions, substrates **1** and **2** were heated in Me_2SO-d_6 containing a large molar excess of D_2O. If the intermediate sulfenic acid existed for a finite interval prior to the product forming step it must suffer H/D exchange. Assuming its formation to be rapidly reversible, the substrate molecule must become deuterated and, if this step is stereospecific, the deuterium incorporation is to be expected at the cis methyl.[4] Consequently, the uptake of a measurable amount of deuterium in the starting material after a half-life of reaction under these circumstances is indicative of a rate-determining, product-forming step of electrophilic ring closure. The converse result, i.e., no deuterium incorporation into the substrate, is also to be taken as an indication of rate-determining cis elimination to form irreversibly a sulfenic acid which is very rapidly transformed to product.

In the NMR spectra of **1** and **2** the cis methyl groups appear at lower field than the trans. On heating at 100 °C the cis/trans ratio of the methyl groups of **1** is dramatically decreased; the spectrum of **2**, however, remained unchanged after 4 days of such heating. At 120 °C heating, **2** slowly decomposed but the cis/trans ratio of its methyl groups remained essentially unaltered. Clearly, sulfenic acid formation is rapidly reversible and stereospecific in the conversion of the cyclic sulfoxide **1** to its rearrangement product **5**, but in the corresponding reaction of **2** this is the slow step. Reversibility of ring opening as shown by deuterium incorporation into the starting material was also demonstrated in the course of conversion of **3** to **7**, whereas there was no significant D incorporation in **4** during its conversion to **8** (see Experimental Section).

The deuterium exchange experiment was also performed in the reverse manner; the 2,2 dimethyl-d_6-1,2-dithiolane 1-oxide (**1**-d_6) was prepared and heated in Me_2SO-d_6 in the presence of H_2O. Some hydrogen was taken into the cis methyl group (i.e., cis to the sulfoxide oxygen) but quite slowly, the overall rate of rearrangement also being considerably slower than that for the nondeuterated substrate **1**. According to the NMR analysis the product contained some vinylic hydrogen but no $-CH_3$ could be detected. The results appear to be consistent with a large kinetic deuterium isotope effect in the initial cis-elimination step, sufficient to reduce the rate differences between the two reaction steps and thereby shorten the lifetime of the sulfenic acid intermediate. Direct evidence

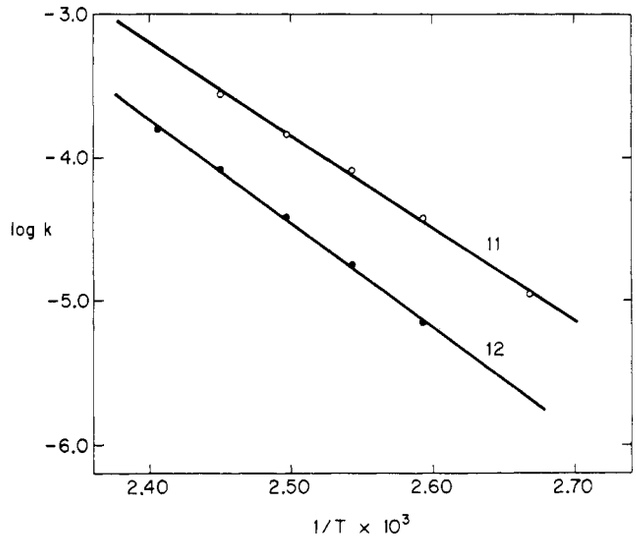
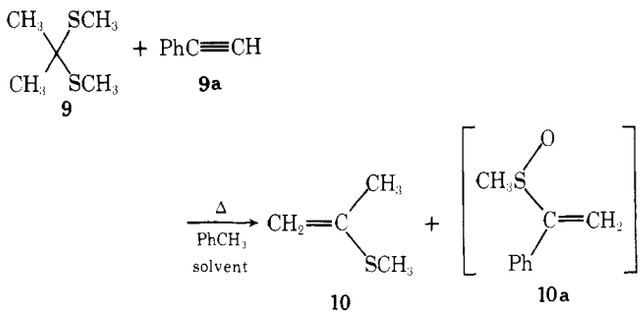


Figure 1. Arrhenius plots, thermolysis of *tert*-butyl ethyl sulfoxide and deuterated analogue.

of a large k_H/k_D in sulfoxide thermolysis is discussed in the following section.

The Kinetic Deuterium Isotope Effect in β-Cis Elimination of Sulfoxides. For these studies 3,3-dimethyl-2,4-dithiapentane 2-oxide (**9**) and its 3,3 dimethyl-d_6 analogue were considered to be suitable model substrates. When **9** was refluxed in toluene (~10 h) in the presence of ethynylbenzene (**9a**) to trap the methylsulfenic acid formed,[16] isopropenyl methylsulfide (**10**) was indeed isolated alongside of the



product (**10a**) of sulfenic acid addition to **9a**. However, the sulfoxide **9**, which is known to be very sensitive toward acids,[17] including probably methylsulfenic acid, proved to be too unstable to permit accurate kinetic analysis. Consequently the isotope effect studies were carried out using a somewhat less attractive model, but one which did not have the limitations of **9**, namely, *tert*-butyl ethyl sulfoxide (**11**) and its d_9 analogue **12**.

The temperature dependence of k_H/k_D (TIC)[18] has proven to be a much more valuable approach to elucidating mechanistic factors in H-transfer reactions than the common practice of estimating the nature of the isotope effect from a single temperature measurement of k_H/k_D. With this understanding the first-order rates of decomposition of **11** and **12** in inert (*n*-decane) solvent were determined over a ca. 30 °C temperature range. These rate data have been plotted in Figure 1 and the computed activation parameters are compiled in Table I. The large kinetic deuterium isotope effect invoked earlier to explain the slow and incomplete exchange of deuterium in **1**-d_6 on reaction in the presence of a large molecular excess of water is verified by these results; $k_H/k_D \approx 5$ at the same temperature.

A number of pericyclic H-transfer reactions, involving a

six-membered transition state structure, exhibit a maximum, (exclusively) zero-point energy controlled isotope effect.[18a,b] No evidence for hydrogen tunneling[19] has been observed in these cases. The (above) results for the five-membered pericyclic transition state involved in sulfoxide thermolysis clearly show a $[\Delta E_a]_D^H$ which is much larger than the value (~1.1 kcal mol^{-1}) characteristic for H-transfer from carbon when determined only by zero point energy differences. In fact, the large magnitude of $[\Delta E_a]_D^H$ and the correspondingly small value of the frequency factor ratio, A_H/A_D, strongly suggest the incursion of hydrogen tunneling,[19,20] which, as stated earlier, is most unusual among the pericyclic processes studied by application of the TIC.[18a]

Shelton et al.[10] have identified a significant degree of steric strain acceleration by *tert*-butyl substitution on the sulfoxide center, as well as considerable curvature of the activation plot for the decomposition rates of di-*tert*-butyl sulfoxide. Such effects may also be correlated[19] with the occurrence of hydrogen tunneling. A major factor controlling the incidence of tunneling is the thickness of the activation barrier;[18d,19,21] a relatively tall and narrow barrier, of course, creates the most favorable circumstances.[22] In the retroene reactions previously studied,[18a,b] where tunneling is totally absent, the distance between the centers across which the hydrogen is linearly transferred in the course of reaction is quite large. This makes for a barrier top of low curvature and relatively broad width, i.e., a reflection of the ground state geometry from which the double minimum activation curve is structured. However, in the five-membered pseudopericyclic transition state of *tert*-butyl sulfoxides, it can readily be seen with the aid of models that the oxygen atom is always close to one of the β(C–H) bonds. This situation must result in a narrow barrier and the consequent increased possibilities for tunneling.

With regard to cyclic sulfoxides, the results considered above suggest that a small distance of separation between the sulfoxide oxygen and the cis methyl is prerequisite for a low energy, concerted pathway. In **1** and **3**, as well as most penicillin *S*-oxides, where this distance is ~2 Å,[2b] barriers of ≤1 Å thickness are of great likelihood and engender high probability for H tunneling. This also has recently been illustrated for thermal cleavage of *tert*-butyl ethers which take place via a cyclic mechanism.[18d]

Experimental Section[23]

Preparation of Sulfides. Dithioketals were prepared from their corresponding ketones by reaction with the appropriate bismercaptans in the presence of boron trifluoride etherate.[24] Acetone-d_6 (99+ %) was used for the preparation of 2,2-dimethyl-d_6-1,3-dithiolane. *tert*-Butyl ethyl sulfide was prepared from *tert*-butyl alcohol and ethanethiol in sulfuric acid (75%); *tert*-butyl-d_9 ethyl sulfide was prepared from *tert*-butyl alcohol-d_{10} (99%) and ethanethiol in D_2SO_4–D_2O. The latter product was purified by preparative GLC; all other sulfides were purified by simple distillation.

Preparation of Sulfoxides. The general procedure[11] involved oxidation of the corresponding sulfides with approximately 0.9 equiv of 30% hydrogen peroxide in glacial acetic acid at 5–15 °C. After additional stirring for about 30 min at room temperature, the sulfoxide product was worked up by dilution with methylene chloride, neutralization of the acid with sodium carbonate and, after drying, evaporation of the solvent. Unless otherwise indicated, the sulfoxides were purified by distillation under high vacuum.

2,2-Dimethyl-1,3-dithiolane 1-Oxide (1): bp 84 °C (0.015 mm) [lit.[5] 83–84 °C (1 mm); NMR ($CDCl_3$) δ 3.9–3.1 [m, $+CH_2+_2$], 1.7 (s, 3, cis CH_3), and 1.55 (s, 3, trans CH_3).

2,2-Dimethyl-d_6-1,3 dithiolane 1-Oxide (1-d_6): bp 104 °C (0.9 mm); NMR ($CDCl_3$) δ 3.8–3.0 [m, 4, $+CH_2+_2$]; no CH_3 detected.

2,2-Dimethyl-1,3 dithiane 1-Oxide (2): bp 102 °C (0.2 mm) [lit.[14] 98–100 °C (0.15 mm); NMR ($CDCl_3$) δ ~3–2 [m, 6, $+CH_2+_3$], 1.65 (s, 3), and 1.60 (s, 3, CH_3).

1,4-Dithiaspiro[4.4]nonane 1-Oxide (3): bp 122 °C (0.05 mm) [lit.[13] 53.5 °C (8 μ); NMR ($CDCl_3$) δ 3.8–3.1 (m, 4, $-SOCH_2CH_2S-$), ~2.6 (m, 1), and ~1.8 (m, 7) both equivalent to $+CH_2+_4$; the multiplet at ~2.6 ppm probably can be ascribed to the β hydrogen atom in the carbocyclic ring cis–cis with respect to the S=O bond.

1,4-Dithiaspiro[4.5]decane 1-Oxide (4): recrystallized from heptane, mp 83–85 °C (lit.[13] 82.8 °C); NMR ($CDCl_3$) δ 3.7–3.1 (m, 4, $-SOCH_2CH_2S-$) and ~2.2–1.5 [m, 10, $+CH_2+_5$].

3,3-Dimethyl-2,4-dithiapentane 2-Oxide (9): bp 60 °C (0.5 mm); NMR ($CDCl_3$) δ 2.6 (s, 3, $-SOCH_3$), 2.2 (s, 3, SCH_3), 1.60 (s, 3) and 1.55 (s, 3) both CH_3's.

***tert*-Butyl ethyl sulfoxide (11)** was purified by preparative GLC on an SE-30 column at 130 °C: NMR ($CDCl_3$) δ 2.5 (double quartet, 2, CH_2), 1.4 (t, 3 CH_2CH_3), and 1.3 [s, 9, $C(CH_3)_3$]; mass spectrum *m/e* 134 (M^+).

***tert*-Butyl-d_9 ethyl sulfoxide (12)** was also purified by preparative GLC (SE-30), 130 °C): NMR ($CDCl_3$) δ 2.5 (m, 2, CH_2) and 1.4 (t, 3, CH_2CH_3), but no $C+CH_3+_3$; mass spectrum ~94% d_9 and ~6% d_8.

Thermolysis of Cyclic Sulfoxides. 1 was heated in *o*-dichlorobenzene solution (20%) at 130 °C for 40 h. The formation of 2-methyl-5,6-dihydro-1,4-dithiin (**5**) as the only product was shown by GLC and NMR;[25] **5** was isolated by preparative GLC (SE-30 column). The NMR ($CDCl_3$) showed δ 5.9 (m, 1, C≡CH), 3.15 [m, 4, $+CH_2+_2$], and 1.9 (d, 3, CH_3); mass spectrum *m/e* 132 (M^+).

2 was heated in *o*-dichlorobenzene solution (20%) at 130 °C for ca. 15 h. The resulting dark brown solution was concentrated and the residue distilled under reduced pressure. The isolated fraction consisted of 2-methyl-5,6-dihydro-1,4-dithiepin (**6**) and 2,2 dimethyl-1,3-dithiane in a ~3:1 ratio as indicated by GLC and NMR.[25] GLC/mass spectral analysis, *m/e* 148 (M^+, 2,2 dimethyl-1,3-dithiane) and 146 (M^+, **6**)

3 was heated in *o*-dichlorobenzene solution (8%) at 130 °C for ca. 17 h. Essentially the only product present in the resulting brown solution was 2,3-trimethylene-5,6-dihydro-1,4-dithiin (**7**) by NMR analysis. This was isolated by distillation: bp 85 °C (0.4 mm) [lit.[26] 64 °C (0.2 mm)]; NMR ($CDCl_3$) δ 3.15 (s, 4, $-SCH_2CH_2S-$), ~2.5 (m, 4) and 2.0 (m, 2) carbocyclic protons.

4 was heated in Me_2SO solution (8%) at 110 °C for ca. 17 h. Essentially the only product present in the reaction mixture as indicated by NMR analysis was 2,3-tetramethylene-5,6-dihydro-1,4-dithiin (**8**). This was isolated by extraction with petroleum ether: NMR ($CDCl_3$) δ 3.2 (s, 4, $-SCH_2CH_2S-$), ~2.1 (m, 4) and 1.7 (m, 4) both carbocyclic protons.

Deuterium exchange experiments in **1** and **2** were carried out by heating sealed NMR tubes containing solutions of the sulfoxides (~0.3 M) in Me_2SO-d_6 which was ~8 M in D_2O and also contained an internal standard (benzophenone). The tubes were removed at intervals from a thermostated oil bath and examined in the NMR. Incorporation of deuterium into **3** was studied as follows.

A solution of 300 mg of **3** in a mixture of 5 mL of THF and 1 mL of D_2O was refluxed (bp 65 °C) for 90 h; the resulting solution was concentrated, diluted with acetone/water (1:1), washed with pentane to remove the rearrangement product, and concentrated again. The NMR spectrum showed *decreased* intensity of the 2.6 ppm multiplet; mass spectral analysis showed a strongly *increased* intensity of the M + 1 peak ($M^+/M + 1^+ = 2$)

Compound **4** was also refluxed in THF/D_2O (5:1) for ~150 h; mass spectral analysis showed an essentially unaltered $M^+/M + 1^+$ ratio as compared to an untreated sample of **4**; ($M^+/M^+1^+ = \sim 7$.

Hydrogen exchange experiments in 2,2 dimethyl-d_6-1,3-dithiolane 1-oxide (1-d_6) were carried out in the same manner as the deuterium exchanges described above, only H_2O was used in place of D_2O.

Thermolysis of 3,3-Dimethyl-1,4-dithiapentane 1-Oxide (9). A solution of 1 g of **9** and 2 mL of ethynylbenzene in 10 mL of toluene was refluxed for 5 h. The reaction mixture was then distilled. The fraction bp 90–102 °C consisted of toluene and isopropenyl methyl sulfide **10** (lit.[27] bp 91 °C) confirmed by NMR analysis.

Thermolysis of *tert*-Butyl Ethyl Sulfoxide (11) and Its d_9 Analogue 12. Measurement of k_H/k_D. Thin-walled tubes containing ~0.075 M solutions of the sulfoxide, and *p*-di-*tert*-butylbenzene as the internal standard, in freshly distilled *n*-decane as solvent were heated in a thermostated bath. Samples were removed at regular intervals and analyzed by GLC; column, 10% OV-101 on Gas-Chrom Q, direct on column injection. The relative amounts of sulfoxide present in the samples were calculated from peak areas. Arrhenius plots were constructed using a least-squares method; activation parameters were calculated by standard procedures.

Registry No.—**1**, 59176-95-3; 1-d_6, 61558-89-2; **2**, 41893-06-5; **3**, 59796-90-6; **4**, 59796-91-7; **5**, 5769-49-3; **6**, 5769-50-6; **7**, 35156-14-0; **8**, 23285-17-8; **9**, 35493-34-6; **9a**, 536-74-3; **11**, 25432-20-6; **12**,

61558-90-5; 2,2-dimethyl-1,3-dithiolane, 6008-78-2; 2,2-dimethyl-d_6-1,3-dithiolane 61558-91-6; 2,2-dimethyl-1,3-dithiane, 6007-22-3; 1,4-dithiaspiro[4.4]nonane, 176-39-6; 1,4-dithiaspiro[4.5]decane, 177-16-2; hydrogen peroxide, 7722-84-1.

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Conformational Analysis. 36. Preferred Conformations of 5-Substituted 1,3-Dioxanes with Sulfur-Containing and Ether Functions in the Side Chain[1,2]

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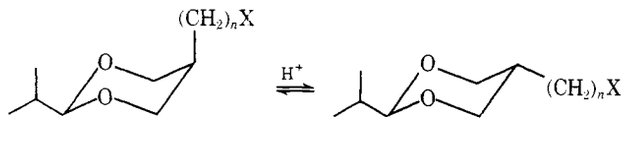
Received October 14, 1976

The conformational preferences of 2-isopropyl 5-substituted 1,3-dioxanes in which the 5 substituent is $-(CH_2)_nSCH_3$, $-(CH_2)_nSOCH_3$, $-(CH_2)_nSO_2CH_3$, $-(CH_2)_nS(CH_3)_2^+$, or $-(CH_2)_nOCH_3$ and n = 0, 1, 2 have been determined. The results may be interpreted in terms of the amount of positive charge on the atom attached to C(5) of the ring: the greater the positive charge, the higher the axial preference.

In a previous publication[3] we have reported the conformational preference of compounds of the type shown in Scheme I where n = 0 and X is a polar substituent, such as

Scheme I



SCH_3, $SOCH_3$, SO_2CH_3, or NO_2, or a charged species, such as SMe_2^+, NH_3^+, NMe_2H^+, or NMe_3^+. We have now extended these measurements to the cases where n = 1 or 2 and X is SCH_3, $SOCH_3$, SO_2CH_3, or $S(CH_3)_2^+$. For comparison, the cases where X = OCH_3 are reported also. The results contribute to our as yet meager knowledge of *intra*molecular polar effects.

Synthesis, Configurational Assignment, Analysis, and Results. The synthesis of the required compounds from *cis*- and *trans*-5-hydroxymethyl-1,3-dioxane[4] is shown in Scheme II. It was found convenient to start with a mixture of diastereomeric 2-isopropyl-5-hydroxymethyl-1,3-dioxanes and separate the final cis–trans mixtures of ethers or thioethers by gas chromatography. Configurational assignments of the ethers and thioethers rest on the ^1H NMR signals of $H(4)_e$ and $H(4)_a$. In the trans (equatorial) isomers, these protons appeared as a nearly first-order AA'BB'X system, with $H(4)_a$ the upfield, slightly distorted triplet and $H(4)_e$ the downfield, narrow doublet of broad doublets. In the cis (axial) isomers