Conformational Analysis of the Thiolane Ring System. II. Proton Magnetic Resonance Spectra and Base-Catalyzed H–D Exchange of Sulfonium Cations and Sulfoxides Derived from 3,3-Dimethylthiolane and *trans*-2-Thiahydrindan

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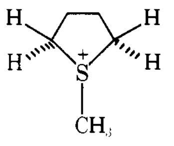
Abstract: Proton NMR spectral analysis of 1,3,3-trimethylthiolanium iodide (III-CH_3) and 3,3-dimethylthiolane 1-oxide (III-O) allows the unambiguous configurational assignment of these five-membered *S* heterocycles. Both systems appear to be conformationally homogeneous; however, while the sulfonium cation adopts a half-chair conformation with maximum twist at C_3–C_4, the sulfoxide has an envelope conformation with sulfur at the tip and the oxygen functionality quasi-axial. In base-catalyzed H–D exchange of the α protons, the two compounds display quite different diastereotopic reactivity patterns, perhaps related to their different ground state conformation. Thus, the exchange is highly stereospecific in the sulfonium cation, but essentially nonstereospecific in the sulfoxide. By contrast, in the *trans*-2-thiahydrindan series where, by virtue of the trans ring fusion, the five-membered heterocycle is rigidly held in the half-chair conformation, the exchange is stereospecific in the sulfoxide as well, though less so than in the sulfonium cation. These results are examined together with those in the literature for comparable systems. However, there seems to be no obvious logical connection between kinetic acidity and geometrical factors.

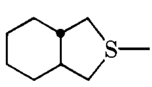
The sulfoxide and sulfonium functions are strongly acid enhancing and C–H protons adjacent to them can be relatively easily abstracted by base. Since these sulfur functions are pyramidal and configurationally stable under ordinary conditions, α-methylene protons are diastereotopic and may display differential acidity, kinetic as well as thermodynamic.

For sulfoxides, a substantial kinetic acidity differential of the diastereotopic protons was first reported in 1965 and involved an acyclic case, benzyl methyl sulfoxide, whose benzylic protons were found to undergo isotopic exchange in D_2O/OD^- at rates differing by a factor of 16.[2] Several other examples have since been reported,[3] often concerning cyclic structures, and sometimes involving diastereotopic reactivity factors on the order of several thousands.[3f]

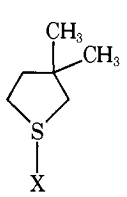
As far as sulfonium cations are concerned, the first example was reported by us in 1971[4] and involved the S–CH_3 derivative of thiolane (I).



I



II(X = CH_3, C_2H_5, O)



III(X = CH_3, O)

In base-catalyzed H–D exchange in D_2O, one pair of α-H's of I was found to exchange faster than the other pair[4] (by a factor of about 30[5]), and the faster pair was later shown to be cis with respect to the S–CH_3 group.[5b] Interestingly, other common-ring sulfonium cations (six- and seven-membered) did not display such an effect to nearly the same extent, their exchange being essentially nonstereospecific.[6]

These findings have prompted an investigation of the configurational and conformational factors which may be responsible for the high diastereotopic reactivity differential in thiolanium cations. It was our hope these studies would contribute to a better understanding of the general problem of stereospecificity in organic reactions. In a recent paper, we have examined the exchange behavior of the S–CH_3 derivative of *trans*-2-thiahydrindan (II-CH_3), a system where the trans ring fusion locks the five-membered heterocycle in the half-chair conformation.[7]

In this paper, we extend our investigation to other derivatives of the rigid structure II (II-C_2H_5 and II-O) as well as to the sulfonium and sulfoxide derivatives of a flexible system, 3,3-dimethylthiolane (III). As we shall see, both derivatives, III-CH_3 and III-O, appear to be conformationally highly homogeneous, though in different conformations, and it was interesting to see how these ground state conformational changes would affect the kinetic acidity of the α protons.

Results

Spectra. The ^1H NMR spectra have been recorded in D_2O and CD_3OD; for the sulfoxides C_6D_6 and $CDCl_3$, solvents were also used. In the tables which follow and throughout this paper, the labeling of the protons corresponds to the order of increasing shielding.

The relevant ^1H NMR parameters for the derivatives of II are reported in Table I, which includes also those previously reported for II-CH_3.[7] The table clearly shows that the low field parts of II-CH_3 and II-CH_2CH_3 match very closely (except for the exocyclic methylene quartet in place of the methyl singlet).

The 100-MHz spectrum of the bicyclic sulfoxide II-O in $CDCl_3$ is reported in Figure 1, lower trace, together with the spectrum obtained in the presence of shift reagent, tris(dipivalomethanato)europium(III), Eu(dpm)$_3$, 0.097 *M* (upper trace). Altogether seven concentrations of Eu(dpm)$_3$ were tested ranging from 0.011 to 0.21 *M*. The chemical shifts of protons H_1–H_5 were obtained directly or extrapolated at zero shift reagent concentration from the linear plots of δ against [Eu(dpm)$_3$]. These and other NMR parameters obtained from first-order analysis are summarized in Table I. The rates of chemical shift change induced by

Table I. ^{1}H NMR Parameters for Derivatives of II[a,b]

Compd	δ_{CH_3}	δ_{H_1}	δ_{H_2}	δ_{H_3}	δ_{H_4}	δ_{H_5}	δ_{H_6}	J_{14}	J_{23}	J_{16}	J_{46}	J_{25}	J_{35}
II-CH_3	2.92	4.02	3.58	3.16	2.96	2.08	1.72	−12.0	−13.0	6.5	12.0	6.0	11.5
II-CH_2CH_3	3.28[c]	3.93	3.60	3.08	2.93			−12.0	−13.5	6.0	12.0	6.0	11.5
II-O		4.01	3.07	2.54	2.10			−12.0	−13.0	7.0	12.0	4.5	12.5
II-O[d]		3.83	2.93	2.18	2.06	2.02							

[a] δ in parts per million with respect to $(CH_3)_3SiCD_2CD_2COONa$ internal standard; J in hertz. [b] The 100-MHz spectra. [c] Exocyclic α-methylene quartet. [d] $CDCl_3$ solvent; reference Me_4Si internal standard.

Table II. ^{1}H NMR Parameters for III-CH_3 in CD_3OD[a,b]

δ_{CH_3}	δ_{H_1}	δ_{H_2}	δ_{H_3}	δ_{H_4}	δ_{H_5}	δ_{H_6}	$\delta_{CH_3(b)}$	$\delta_{CH_3(a)}$[c]	
2.95	3.77	3.58	3.51	3.09	2.32	2.24	1.34	1.14	
J_{13}	J_{24}	J_{56}	J_{35}	J_{16}	J_{36}	J_{15}	$^4J_{26}$	$^4J_{4}CH_3(a)$	$^4J_{5}CH_3(a)$
−13.6	−12.5	−13.4	6.6	6.6	3.6	11.0	±1.25	~0.3	~0.3

[a] δ in parts per million from $(CH_3)_3SiCD_2CD_2COONa$ internal standard; J in hertz. [b] The 250-MHz spectrum. [c] Broad singlet ($W_HCH_3^{(a)} - W_HCH_3^{(b)} \simeq 1$ Hz).

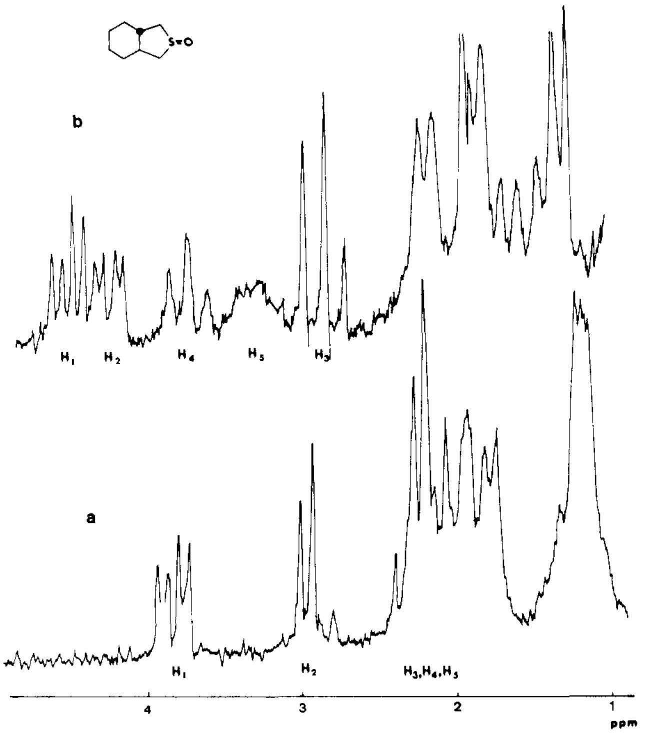


Figure 1. (a) The 100-MHz spectrum of II-O 0.5 M in $CDCl_3$. (b) In the presence of $Eu(dpm)_3$ 0.097 M.

the shift reagent for the various protons are the following (ppm mol^{-1} for 0.5 M solutions in $CDCl_3$): H_1, 7.8; H_2, 14.5; H_3, 8.2; H_4, 18.4; H_5, 14.8.

The 250-MHz spectrum of III-CH_3 is first order and yields the parameters reported in Table II. The regions of the spectrum corresponding to the six ring protons are reported in Figure 2, upper trace.

The 250-MHz spectrum of III-O is also first order. The relevant NMR parameters are reported in Table III, together with the values of the aromatic solvent induced shifts (chloroform-benzene). $Eu(dpm)_3$ induced shifts were also determined and are as follows (ppm mol^{-1} for 0.5 M solution in $CDCl_3$): H_1, 1.8; H_2, 1.8; H_3, 2.9; H_4, 2.9; H_5, 1.8; H_6, 1.4; CH_3^a, 1.3; CH_3^b, 0.9. The low field region of the spectrum is reported in Figure 2, lower trace.

Base-Catalyzed H-D Exchange. In our previous paper,[7] the rates of exchange were reported for the individual α ring protons of II-CH_3 in D_2O-NaOD. In this solvent, however, one of the protons, H_1, is so unreactive that pyramidal inversion of the S atom may occur competitively.[7] Since this process results in scrambling of atoms across the ring (e.g., $H_1 \rightleftharpoons H_2$),[7] it was only possible to set an upper limit for the exchange rate of H_1. To make the slowest proton accessible to rate measurement, a 50:50 v/v, D_2O-Me_2SO-d_6 solvent mixture has now been used. In this medium, exchange is greatly accelerated while pyramidal inversion is not.[8] The results are given in Table IV. The table also reports the exchange data for II-O and the derivatives of III.

As far as II-CH_2CH_3 is concerned, we were only interested in determining the rate of the most reactive ring proton and that of the exocyclic methylene hydrogens. In D_2O-NaOD, 1.7 M at 75°, the pseudo-first order specific rate is 7.5×10^{-4} sec^{-1} for the most reactive ring proton (H_2) and 1.4×10^{-3} sec^{-1} for the exocyclic α protons. Under the same conditions, the corresponding ring proton of II-CH_3 exchanges at almost the identical rate, 8.5×10^{-4} sec^{-1}.[7]

Nuclear Overhauser Experiments. The differential exchange rate of the α ring protons of III-CH_3 provides an easy route to stereospecific deuterium labeling. Two specifically deuterated derivatives were prepared, III-CH_3-d_3 (A) and III-CH_3-d_2 (B). Sample A had 98% deuterium at H_1 and H_2, 80% deuterium at H_4, and 80% protium at H_3. Sample B had 99% deuterium at H_3, 90% deuterium at H_4, and 80% protium at H_1 and H_2. When irradiated at the S^+-CH_3 resonance, A gave a 13 ± 2% enhancement of the H_3 resonance while, for sample B, the enhancement of the H_1 and H_2 resonances was essentially nil.

Discussion

Stereochemical Assignment and Conformation. The NMR spectra, coupled with the nuclear Overhauser experiments for the sulfonium cation III-CH_3, the aromatic solvent, and the lanthanide-induced shifts for the sulfoxides, allow the complete stereochemical assignment of the heterocyclic protons and establish unequivocally the conformation of the flexible systems III-CH_3 and III-O.

***trans*-Thiahydrindan *S*-Oxide (II-O).** From their chemical shifts and coupling patterns, the protons α to S(O) are readily identified as H_1–H_4 (Figure 1 and Table I). Proton H_5 must be one of the bridgehead protons, while the second bridgehead proton cannot be resolved and remains under the envelope of the alicyclic protons. In this rigid system, the trans ring fusion determines the quasi-axial setting of the bridgehead protons. Consequently those of the α protons which have the larger vicinal coupling are also pseudoaxial.

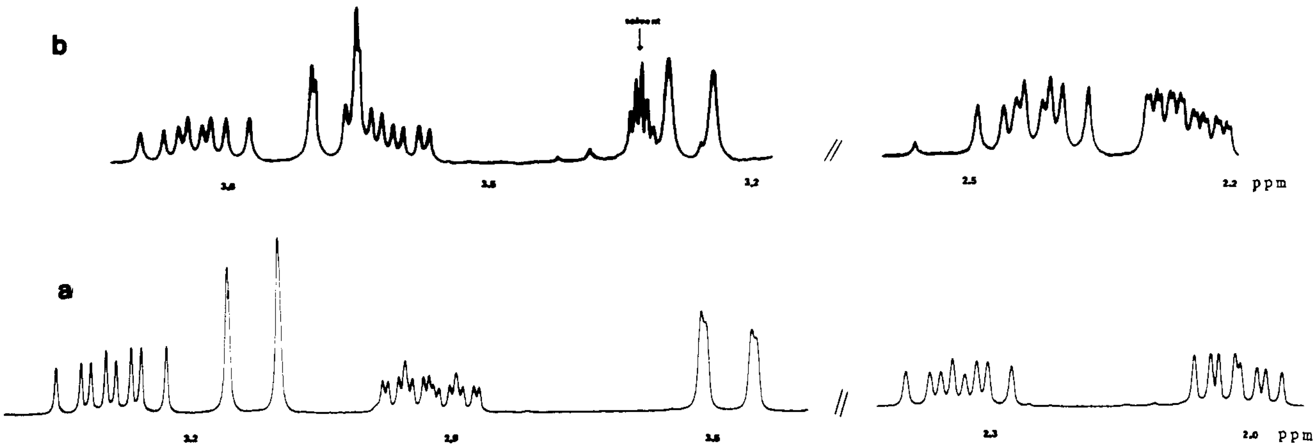


Figure 2. (a) Low field part of the 250-MHz spectra of III-O in D_2O. (b) III-CH_3 in CD_3OD.

Table III. ^1H NMR Parameters for III-O[a, b]

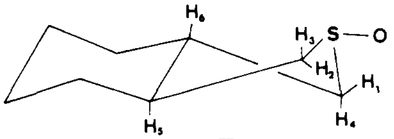
	δH_1	δH_2	δH_3	δH_4	δH_5	δH_6	$\delta CH_3(a)$	$\delta CH_3(b)$
D_2O	3.36	3.19	3.00	2.66	2.33	1.99	1.32	1.07
$CDCl_3$	3.20	3.00	2.94	2.62	2.44	1.88	1.37	1.07
C_6D_6	2.47	2.26	2.40	2.12	1.95	1.10	1.02	0.47
$(\delta_{CDCl_3} - \delta_{C_6D_6})$	0.73	0.74	0.54	0.50	0.49	0.78	0.35	0.60

J_{13}	J_{24}	J_{56}	J_{35}	J_{16}	J_{36}	J_{15}	$^4J_{34}$
-13.7	-14.0	-13.5	5.1	7.1	6.9	9.5	±1.4

[a] δ in parts per million from Me_4Si ($CDCl_3$ or C_6D_6 solvent) or $(CH_3)_3SiCD_2CD_2COONa$ (in D_2O) internal standards; J in hertz in $CDCl_3$. [b] The 250-MHz spectrum.

From Table I, these are identified to be H_3 and H_4 ($^3J_{HH}$ = 12 and 12.5 Hz). On the other hand, H_1 and H_2 are pseudo-equatorial ($^3J_{HH}$ = 4.5 and 7.0 Hz, respectively). The geometric relation of the various heterocyclic ring protons with the S=O function can be established on the basis of the lanthanide induced shifts.

The europium shift reagent is known to cause a dramatic differentiation of protons neighboring a sulfoxide function.[9] This is believed to arise from complexation of the sulfinyl oxygen with the metal atom causing greater paramagnetic shifts for those protons which are closer to oxygen.[10] In cyclic or more generally in conformationally restricted systems, protons cis to oxygen suffer greater downfield shifts than trans protons at the same position, and their configuration can be accordingly assigned.[10b,11] On these bases, H_2, H_4, and H_5 are recognized to be cis to S=O. The stereochemical assignment arising from these considerations is shown:[12]



II·O

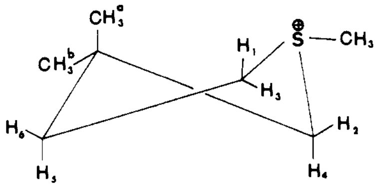
1,3,3-Trimethylthiolanium Cation. As for all sulfonium cations,[6a] the α protons are downfield and can be easily identified (H_1-H_4), while the S^+-CH_3 resonance is the more downfield methyl singlet (δ 2.92). Particularly informative are the vicinal coupling constants for protons H_1, H_3, H_5, and H_6 (Talbe II), situated on the C_4-C_5 fragment; their values, one "large", one "medium", and one "small", suggest that the ring is largely conformationally homogeneous. Moreover, H_1 and H_5, having one large and one medium coupling, are trans to each other and pseudo-axial, while H_3 and H_6, with one small and one medium coupling, are trans to each other and pseudo-equatorial. More informative still is the observation of a long range coupling ($^4J_{HH}$ = 1.25 Hz) between H_2 and H_6 (at C_2 and C_4, respectively) requiring a nearly planar setting of the $H_2C_2C_3C_4H_6$ fragment. This is only possible if: (i) both H_2 and H_6 are quasi-equatorial; (ii) maximum ring puckering occurs at C_3; and (iii) the ring is conformationally highly homogeneous.

These observations would be consistent with either of two nonequivalent twist-envelope conformations, A and A′, which imply opposite configurational assignments.

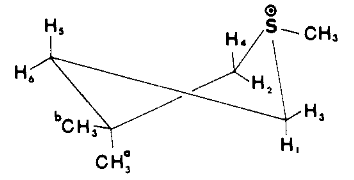
Table IV. Relative Rates of Base-Catalyzed H–D Exchange of α Ring Protons in Five-Membered Cyclic Sulfonium Cations and Sulfoxides[a]

		Proton			
Compd		H_1	H_2	H_3	H_4
		e,t	e,c	a,t	a,c
II-CH_3	D_2O	⩽1	200[b]	3	3
	D_2O–Me_2SO	1	700[c,d]	90	90
		a,t	e,t	e,c	a,c
III-CH_3	D_2O	1	1	80[e]	12
	D_2O–Me_2SO	1	1	28[e,f]	14
		e,t	e,c	a,t	a,c
II-O	D_2O	⩽1	7.2[g,h]	5.4	3.5
	D_2O–Me_2SO	1	15[i,j]		
		a,t	a,t	e,c	e,c
III-O	D_2O	1	1.4	1.7[g,k]	1.7

[a] To facilitate the appreciation of the results, for each compound the stereochemistry of each proton (see Discussion) is specified by a set of two letters, indicating the conformational setting, quasi-axial or quasi-equatorial (a or e), and the geometric relation, cis or trans (c or t) with respect to the substituent at sulfur. [b] Pseudo-first-order specific rate, $k_1 = 9.6 \times 10^{-5}$ sec^{-1} in NaOD 1.7 M at 55°. [c] NaOD 1 M at 50°. [d] $k_1 = 3.8 \times 10^{-3}$ sec^{-1}. [e] $k_1 = 8.4 \times 10^{-5}$ sec^{-1}, NaOD 2.5 M at 55°. [f] $k_1 = 3.8 \times 10^{-3}$ sec^{-1}. [g] NaOD 3 M, 89.5°. [h] $k_1 = 2.1 \times 10^{-5}$ sec^{-1}. [i] $k_1 = 9.6 \times 10^{-5}$ sec^{-1}. [j] NaOD 1.1 M, 89.5°. [k] $k_1 = 5.9 \times 10^{-5}$ sec^{-1}.

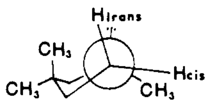


A

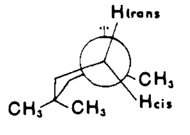


A′

Several arguments concur to indicate the correct choice to be A. Let us first consider the NOE evidence. Granted that maximum puckering occurs at C_3, scale model shows that, independently of which twist-envelope conformation the ring adopts, A or A′, of the geminal protons at C_α, that which is cis to S-CH_3 will always be closer to the S-CH_3 group than the trans proton. The Newman projections shown for A and A′, taken along the C_5-S bond, illustrate this.



A



A′

Hence H_{cis} is expected to experience a greater nuclear Overhauser enhancement than H_{trans}. Considering now the geminal pair at C_5, H_1 and H_3, the observation of a 13% enhancement for H_3 and none for H_1 gives a strong indication that H_3 is cis to S-CH_3, in agreement with the configurational and conformational assignment depicted in A above. It is noteworthy that the magnitude of the NOE (13%) is very close to that found previously for the bicyclic system II-CH_3 (15%),[7] where the thiolanium ring is held rigidly in a twist-envelope conformation. This near coincidence may be a further indication that the geometries of II-CH_3 and III-CH_3 are indeed very close.

That conformation A is highly favored over A′ is not surprising and could have been expected a priori on the basis of the effective relaxation of steric compression which obtains when the *cis*-methyl group at C_3 is quasi-equatorial (A) with respect to when it is quasi-axial (A′). Carbon-13 NMR studies, which are recognized to be very informative about steric effects, unquestionably confirm the absence of any important steric compression in III-CH_3.[13]

The comparatively large value of $^4J_{HH}$ indicates that the thiolane ring must be very considerably puckered,[15] a notion confirmed by the value of the vicinal couplings relative to the C_4-C_5 fragment (Table II). Application of the Karplus[16a] equation (with $J^{180°}$ = 13.8 Hz) yields a dihedral angle ϕ_{ac} on the order of 47°. Even though this value may be highly inaccurate,[16b] there is no question about the high degree of puckering of this cycle.

The configurational picture of III-CH_3 is completed by the observation of two additional small four-bonds couplings ($\simeq$0.3 Hz) between the high field methyl (δ 1.14, broad singlet) and both H_4 and H_5. These couplings, consistent with the quasi-axial setting of either proton, allow for the assignment of the high field singlet to the quasi-axial methyl (trans to S^+-CH_3).

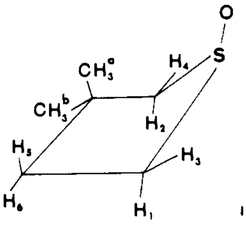
3,3-Dimethylthiolane 1-Oxide. The assignment of the ^{1}H NMR spectrum is straightforward; the quartet due to H_2 and H_4 (Figure 2, lower trace) identifies the isolated methylene protons at C_2. Of the remaining protons, the two most downfield, H_1 and H_3, are the α-methylene protons at C_5, while H_5 and H_6 are the β-methylene protons at C_4. From the lanthanide induced shifts, H_3, H_4, H_5, and CH_3^a are recognized to be cis to oxygen. This assignment is fully confirmed by the aromatic solvent induced shift (Table III).

According to this test, the protons trans to the S-O bond are the more strongly shielded in benzene. This rule, which is often rationalized on the basis of a specific interaction of the aromatic solvent molecules with the positive end of the S^+-O^- dipole,[17] has been widely applied and appears to be generally valid at least in the absence of extraordinary steric hindrance to solvation.[11,18]

Several pieces of evidence suggest the prevailing conformation of III-O to be radically different from that of the sulfonium cation, III-CH_3. In the latter, as well as in II-CH_3 and II-O, the geminal coupling constants for the α-methylene protons at C_2 and C_5 differ by about 1 Hz, which is likely to derive from the different orientation, at the two sides of the S-O or S-CH_3 function, of the HCH bisectors with respect to the lone pair. In III-O instead, they differ slightly (0.3 Hz), suggesting that the two bisectors are similarly oriented.

A second indication is provided by the pattern of vicinal couplings relative to the C_4-C_5 fragment. In III-CH_3, the axial-axial coupling, J_{15} = 11.0 Hz, is just slightly smaller than the corresponding coupling in the rigid counterpart, II-CH_3, J_{35} = 11.5 Hz. For the sulfoxides on the other hand, the corresponding coupling is considerably smaller in III-O (J_{15} = 9.6 Hz) than in II-O (J_{35} = 12.0 Hz). It seems legitimate to conclude that the torsional angle at C_4-C_5 is significantly smaller in III-O than in the rigid system II-O or the potentially flexible III-CH_3.

The most compelling piece of evidence, however, is provided by the observation of a long range interaction (four bonds) between two α protons, H_3 and H_4, which necessarily occurs through the S atom. This coupling cannot be something peculiar to the SO function since it is not observed in II-O but is likely to arise from the near coplanarity of the $H_3C_5SC_2H_4$ fragment. This geometry is only compatible with a conformation where maximum puckering occurs at the S atom, such as in an envelope conformation with S at the tip. It is noteworthy that the interacting protons, H_3 and H_4, are both cis to oxygen; henceforth the oxygen substituent must be quasi-axial. The stereochemical assignment and the conformation suggested by the above observations are depicted for III-O.



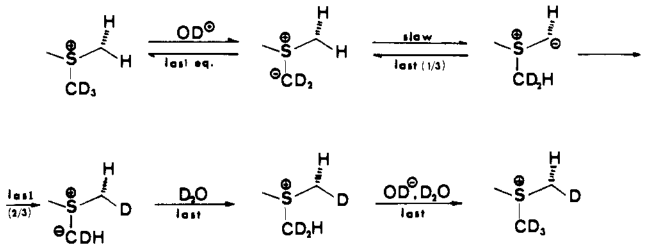
III-O

This conformation is supported by yet another observation. In III-O, the geminal coupling constants are considerably more negative than in II-O (−13.7 and −14.0 against −12.0 and −13.0 Hz). This is significant in view of the observation by Lambert and Keske[19] that, in thiacyclohexane 1-oxide, the geminal constant for protons α to SO is about 2 Hz more negative in the axial than in the equatorial conformer (−13.7 against −11.7 Hz). Indeed in the axial conformer, the bisectors of the α-methylenes very nearly eclipse the lone pair, which is expected[20] to make ^2J more negative. This criterion has been widely applied[11a,21] and its general validity as a conformational guide has been very recently confirmed.[11e] It is remarkable that the mere replacement of O for CH_3 at the S atom produces such dramatic conformational change from half-chair to envelope. While this may perhaps be due to the conformations of five-membered systems having relatively small energy differences, it is nevertheless a striking phenomenon which calls for further investigations.

H-D Exchange. For the sulfonium cations, a solvent change from D_2O to Me_2SO-D_2O 1:1 produces a large acceleration of the exchange (on the order of two powers of ten). The various protons are not affected equally, but the reactivity spread diminishes. The reactivity order remains unchanged, however.[22] For II-CH_3, the ratio k_{H_2}/k_{H_1}, which is 700 in D_2O-Me_2SO, is likely to become greater in pure D_2O, and a reasonable extrapolation from the data of Table IV and ref 7 would indicate this ratio to be on the order of 1300, which makes this one of the most stereospecific nonenzymatic reactions reported yet.

Although the stereospecificity must be related to some geometrical factor, it is difficult to say which factor is the important one. There are, however, a number of regularities worth noting. In the parent ring sulfonium cation, I-CH_3, the protons cis to S^+-CH_3 are more reactive than the trans ones.[4,5] The same appears to be true for II-CH_3 and III-CH_3; for these cations, however, it is possible to make a further specification—within the cis pair, the quasi-equatorial proton is more reactive than the quasi-axial one, while the opposite is true for the trans pair. In either compound, the largest reactivity differential is exhibited by the quasi-equatorial protons.

The observation that the cis protons are more easily abstracted by base suggested the possibility of the incursion of what may be called the "α,α'-mechanism". In every case so far investigated, in fact, the exocyclic *S*-alkyl group was CH_3, whose H's are known to have considerably larger kinetic acidity (by a factor $\geq 10^2$)[6a] than methylene or methine hydrogens. Actually the S^+-CH_3 protons have been almost completely replaced by deuterons before the ring protons have appreciably reacted. It was then conceivable that the ring H's may undergo intramolecular exchange via rapid deuteron abstraction from S^+-CD_3, followed by 1,3-proton shift occurring preferentially with the cis proton:



This mechanism is difficult to prove; however, if it does not operate, it can be ruled out straightforwardly by carrying out exchange experiments on sulfonium derivatives (for example of II) whose exocyclic *S*-alkyl substituent carries at C_α either no hydrogen (Ph, *t*-Bu) or relatively unreactive hydrogens [CH_3CH_2, $(CH_3)_2CH$-]. In such cases, if the α,α' mechanism were at work, one should expect a drastic drop of the exchange rate for the fastest ring hydrogens. An ancillary requirement for such a test is that the exocyclic substituent must not, by virtue of its bulk, affect significantly the geometry of the five-membered ring. A good compromise was reached with the *S*-ethyl derivative, II-CH_2CH_3, whose NMR parameters match almost exactly those of II-CH_3 (Table I), guaranteeing that the two systems very nearly have the same geometry.[23] The exchange data show that, in both II-CH_3 and II-CH_2CH_3, the more reactive ring hydrogen is H_2 (quasi-equatorial and cis to S-R), the exchange rate being very nearly the same in both compounds in spite of the fact that the exocyclic protons exchange at widely different rates in the two cases.[6a] This finding allows us to rule out the α,α' mechanism to be responsible for the higher reactivity of the cis protons in base-catalyzed exchange.

Therefore the diastereotopic reactivity differential must be in some way connected with the angular relation of the C-H bond with the adjacent asymmetric sulfur function (lone pair and bonding pair). When this point is examined more closely, however, severe inconsistencies come to light. Considering II-CH_3, the diastereotopic protons to be compared are those similarly oriented with respect to the dissymmetric ring system but differing for their orientation relative to the sulfur function, i.e., H_1 vs. H_2 (quasi-equatorial) and H_3 vs. H_4 (quasi-axial). If the dihedral angles at C_α-S were the all important factors (as implied in the so called "gauche effect" theory),[24] the two pairs would be expected to display very similar reactivity factors since the angular relations for H_3 and H_4 are the same as those for H_1 and H_2, respectively. The striking observation instead is that H_1,H_2 have widely different reactivities (corresponding to an energy difference between the diastereomeric transition states for proton abstraction $\delta\Delta G^\ddagger_e$ = 4.3 kcal mol^{-1}) while H_3,H_4 have closely similar reactivity ($\delta\Delta G^\ddagger_a \sim 0$).

Similar behavior, though less pronounced, is exhibited by the conformationally fixed sulfoxide II-O. Here again the equatorial pair exhibits considerably greater stereospecificity than the axial pair (Table IV). Moreover, the reactivity order is inverted, insofar as, within the equatorial pair, it is the proton cis to oxygen which is the more reactive, while the opposite is true for the axial pair.[25]

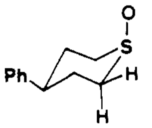
In conclusion, in either the sulfonium and sulfoxide derivatives of II, the data are inconsistent with any theory (e.g., the gauche effect theory[24,26]) based on the idea that the all important factor may be the dihedral angle at C_α-S.[27]

In discussing the conformationally homogeneous but flexible systems, III-CH_3 and III-O, it must be considered that the ground state conformation may not be an unambiguous guide to the transition state geometry, insofar as exchange could take place more favorably via conformations other than the ground state.

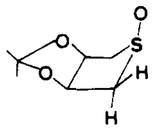
It is interesting in this connection to examine the kinetic acidities of III-CH_3, whose ground state geometry matches very closely that of the rigid system II-CH_3. However, the former is flexible and could adopt a different transition state conformation *if that allowed for a lower overall energy barrier to exchange.* Examination of the data (Table IV, footnotes *d* and *f*) reveals that the more reactive protons of each system, H_2 for II-CH_3 and H_3 for III-CH_3, have the same geometry (cis and quasi-equatorial) and *are abstracted at essentially the same rate.* This is a strong indication that, at least for the more reactive proton of III-CH_3, the transition state conformation is very nearly the same as the ground state. For the less reactive protons, however, the finding that the reactivity pattern, although similar to II-CH_3, is nevertheless less spread out (Table IV) suggests that some minor conformational adjustment may occur at the transition state.

As far as sulfoxide III-O is concerned, the envelope conformation makes the quasi-equatorial protons gauche to both the S-O bonding pair and the lone pair, while the quasi-axial protons are gauche to the lone pair and anti to the bonding pair. The gauche effect theory would predict greater reactivity for the former pair;[26] actually their slightly greater reactivity, though real, is so exiguous that, to all intents and purposes, the system is nonstereospecific.

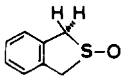
Unfortunately there is no rigid model available for a sound comparison. The literature reports, however, two examples of conformationally biased sulfoxides where the angular relation of the α-methylene H's to the S-O bond may be similar to that prevailing in III-O. These are the six-membered sulfoxide *cis*-4-phenylthiane 1-oxide (**IV**)[3d] and the acetone derivative of *cis*-3,4-dioxathiolane 1-oxide (V) which appear to have the conformations shown.[29]



IV



V



VI

For IV, considerable stereospecificity was found in water or methanol (but not in *tert*-butyl alcohol), with the axial proton (trans to oxygen) reacting some eight times faster than the equatorial one.[3d] Similar behavior was found for V, whose trans-axial protons appear to be considerably more reactive than the cis-equatorial ones.[28,30] These findings would appear to be at odds with those pertaining to III-O, which shows little stereospecificity if any. There may be several reasons for this, however. In the first place in either IV and V, the protons concerned are diastereotopic because of their relation not only to the S-O function but also to other structural features of their respective systems, whose influence on reactivity is unknown. On the other hand, the lack of stereospecificity in III-O may be due to the system being sufficiently mobile to be able to adjust the conformation at the transition states so as to minimize at nearly the same level the overall energy barriers for exchange.[31] It is interesting in this connection to consider another five-membered sulfoxide, 3,4-benzothiolane 1-oxide (VI). Although this ring must have only envelope conformations, its geometry is probably not comparable to that of the other thiolane rings considered here, as it has no out-of-plane groups at C_3-C_4. However, the tip of the envelope may be expected to be mobile. Yet this system is highly stereospecific, the pair of protons trans to oxygen being 67 times more reactive (in D_2O) than the cis pair.[3g]

In conclusion, it is difficult to organize the results obtained for II-O, III-O, and IV-VI in a unique coherent picture. It would seem that sulfoxides having comparable geometrical features may exhibit different patterns of diastereotopic reactivity even in a solvent, water, which minimizes ion pairing.[32] We feel that further systematic studies are necessary to gain a better understanding of these phenomena.

Experimental Section

***trans*-2-Ethyl-2-thiahydrindan Tetrafluoborate** (**II-CH_2CH_3**) was prepared by treatment of the corresponding sulfide[7] with commercial triethyloxonium fluoborate in CH_2Cl_2 at room temperature for 12 hr under stirring. The resulting solid was very hygroscopic, and no reliable melting point could be taken. The ^1H NMR spectrum (Table I) leaves no doubt about the identity of the product obtained.

***trans*-2-Thiahydrindan 2-Oxide (II-O)** was obtained (70% yield) from the sulfide[7] by oxidation with H_2O_2 in acetone according to the procedure by Johnson and McCants.[33] The hygroscopic solid was purified by distillation [bp 125-126° (1.5 mm)] (ir 1015 cm^{-1}, S-O stretch). For the ^1H NMR spectrum see Figure 1 and Table I.

1,3,3-Trimethylthiolanium Iodide (III-CH_3) was prepared from commercial (Fluka) 2,2-dimethylsuccinic acid through the following sequence: (1) $LiAlH_4$ reduction to the diol (91% yield) [bp 127-131° (11 mm)]; (2) conversion of the diol to the ditosylate with *p*-toluenesulfonyl chloride in pyridine (85% yield) and cyclization with $Na_2S{\cdot}9H_2O$ (molar ratio ditosylate-sodium sulfide 1:2) to give the cyclic sulfide (64% yield) [bp 146-148° (760 mm) (lit.[34] 144-145° (755 mm))]; (3) methylation of the sulfide with CH_3I in absolute ethanol to the title sulfonium salt (mp 134-135° dec).

3,3-Dimethylthiolane 1-Oxide (III-O) was obtained by H_2O_2 oxidation in acetone[31] of the corresponding sulfide [bp 103-104° (3 mm); ir (film) 1010, 1035 (S-O stretch)].

Kinetics. The rate of exchange of the various protons was determined by following the intensity of their signals in the ^1H NMR spectrum relative to that of a suitable standard [$(CH_3)_3SiCD_2CD_2COONa$, ca. 0.02 *M*] added to the reaction medium. Solutions in D_2O were made up directly in the NMR tube by dissolving 1-mmol samples in 2 ml of NaOD solution of suitable concentration (specified in the footnotes to Table IV). The D_2O-Me_2SO solutions were made up by dissolving 1-mmol samples in 1 ml of Me_2SO-d_6 and adding 1 ml of NaOD, 2 *M* in D_2O. The concentrations reported in the footnotes to Table IV are therefore only approximate. The slowest reacting proton of II-O (H_1) gave us serious experimental problems since the drastic conditions required for exchange caused substantial corrosion of glass with attendant loss of base. Thus we report only an upper limit for the exchange rate of H_1 in D_2O. The situation improved somewhat in D_2O-Me_2SO; however, this solvent obscures the region of H_3,H_4 whose rates could not be measured in this solvent. Normally the kinetic runs comprised at least four points, the exchange being followed to 60% or more. Standard deviations are on the order of ±10%.

^1H NMR spectra were recorded at 100 MHz on Varian H-100 and/or Jeol PS-100 for the derivatives of II and at 250 MHz (Cameca) for III-CH_3 and III-O. The kinetic measurements for II-O and III-O were carried out with the 250-MHz instrument.

The NOE were carried out on the H-100 instrument, following the procedure described by Bell and Saunders.[35] The enhancements reported are the percent difference in the integrated intensities of a given signal caused by double irradiation at the S-CH_3 signal and at a blank region of the spectrum, consecutively and using the same irradiating power. The enhancements reported are the average of ten comparisons.

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(14) G. Barbarella, unpublished.

(15) To our knowledge this is one of the largest four bonds coupling reported for a five-membered ring. See, for example, L. A. Sternson and A. W.

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(31) It is worth noting in this connection that the α protons of III-O are all more reactive, though by a small factor, than the fastest reacting proton of II-O (see Table IV, footnotes *g*, *h*, and *m*).

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Radical Chain Reductive Dehalogenation of Hetaryl Halides Promoted by Methoxide Ion

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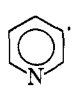
Abstract: 3-Iodopyridine and 4-bromoisoquinoline rapidly react with $NaOCH_3$ at 165° to give mixtures consisting of pyridine and isoquinoline, respectively, as the major products along with the substitution products 3-methoxypyridine and 4-methoxyisoquinoline. Reduction of 3-iodopyridine in $NaOCH_3$-CH_3OD takes place without the incorporation of a significant amount of deuterium at the 3 position of pyridine. Reduction of both the iodo and bromo compounds is inhibited by nitrobenzene, azoxybenzene, and 1,1-diphenylethylene but not by oxygen and is believed to take place by a radical chain process which involves the formation of 3-pyridyl and 4-isoquinolyl radical intermediates. Low concentrations of copper(II) chloride accelerate the methoxydehalogenation of both hetaryl halides so that substitution becomes the major reaction. In the presence of the radical initiator azobisisobutyronitrile (AIBN) and $NaOCH_3$, the two halogenated reactants as well as 2- and 4-iodopyridines undergo at 100° rapid reductive dehalogenation. Kinetic studies carried out with the three isomeric iodopyridines show that the rate of the reduction reaction is limited by the decomposition of AIBN and is independent of the identity of the iodide. In the presence of AIBN-$NaOCH_3$-CH_3OD 3-iodopyridine gives pyridine largely free of deuterium at position 3, indicating the formation of the 3-pyridyl radical intermediate. Reactions involving $NaOCH_3$ and AIBN-$NaOCH_3$ represent new ways to generate hetaryl radicals.

We wish to report that 3-iodopyridine and 4-bromoisoquinoline react with methoxide ion in methanol to give the dehalogenated compounds pyridine and isoquinoline as major products. These reactions are shown to be radical chain processes. Reduction may be initiated by the radical initiator azobisisobutyronitrile (AIBN) acting in the presence of $NaOCH_3$ and inhibited by various radical and electron trapping agents. 3-Pyridyl (I) and 4-isoquinolyl (II) radicals are intermediates. Our results show that hetaryl halides are a new source of hetaryl free radicals, especially under highly basic conditions. We previously have shown that radical II may be trapped by thiophenoxide ion in methanol to give 4-phenylthioisoquinoline substitution product by a new route.[1] Others have demonstrated that aryl and hetaryl radicals may be trapped by a variety of nucleophiles, giving rise to new and useful routes to aromatic substitution products.[2-6] Indeed, trapping of radicals under basic conditions represents a promising new method of nucleophilic aliphatic and aromatic substitution.[7-9]



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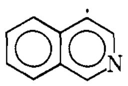
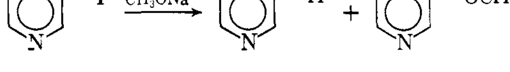


II

Results

Iodopyridines. The results of ten experiments involving 3-iodopyridine and $NaOCH_3$ in methanol are summarized in Table I. Pyridine is the major product; yields range from 73 to 90% when the reaction is complete. Other heterocyclic products include 3-methoxypyridine and the anion of 3-hydroxypyridine. The hydroxy compound is produced from the 3-methoxy compound in an ether cleavage reaction with methoxide ion, $k = 4.7 \times 10^{-5}\ M^{-1}\ sec^{-1}$ at 165°,[10] eq 1



(1)