Conformational Analysis of the Thiolane Ring System. I. Stereochemistry of the Base-Catalyzed H–D Exchange, Pyramidal Inversion, and Proton Magnetic Resonance Spectrum of *trans*-3-Methyl-3-thioniabicyclo[4.3.0]nonane Iodide, a Conformationally Rigid Thiolanium Cation

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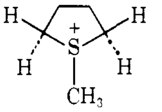
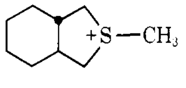
Abstract: The pmr spectrum of the title compound (II) can be analyzed by a first-order procedure. The compound undergoes stereospecific base-catalyzed exchange of the α ring protons, whose reactivities are found to be approximately in the ratio 200:3:3:1. Nuclear Overhauser experiments on specifically deuterated samples indicate the faster proton to be cis to the *S*-methyl group. This stereochemical assignment together with the values of the vicinal coupling constants disclose the stereochemistry of the heterocyclic part of II. Certain consequences of this stereochemistry are discussed. The stereospecificity of the H–D exchange is discussed in relation to its significance in terms of the stereochemistry, retention or inversion, of the exchange, as well as in relation to the Wolfe and Czimadia theory on the conformational energy of species having adjacent lone pairs. Finally, the availability of a specifically deuterated sample has permitted the observation of the occurrence of thermal pyramidal inversion of the sulfur atom, and the measurement of the rate of this process.

Recently we have reported the diastereotopic reactivity of the α ring protons of 1-methylthiolanium iodide (I) in H–D base-catalyzed exchange.[2] One of the pairs of α protons appears to exchange some 30 times faster than the other pair,[2c,3,4] and nuclear Overhauser (nO) experiments have established that the protons undergoing fast exchange are those cis to the *S*-methyl group.[2c] These findings have stimulated our interest in the conformation of the thiolane ring system and prompted a systematic investigation of the nmr spectrum of properly tailored thiolane derivatives.



I



II

A priori one may think of two limiting conformations: (i) "half-chair"[5] with maximum staggering at C$_3$–C$_4$ and (ii) "envelope" with maximum staggering at C$_2$–S–C$_5$. Our approach has been that of studying the pmr spectra of derivatives bearing such substituents as to constrain the ring in one particular conformation and obtain in this way nmr parameters that may be used as guidelines for the analysis of conformationally flexible thiolanes.

We report here our first example, whose pmr analysis has turned out to be particularly straightforward. In the *trans*-3-methyl-3-thioniabicyclo[4.3.0]nonane cation (II) the trans ring fusion constrains the thiolane ring rigidly in the half-chair conformation. This conformational rigidity ensures for each of the α ring protons a fixed torsional angle with respect to the "direction" of the lone pair on sulfur, making this system a very useful model for testing the Wolfe and Czimadia[7,8] theory on the conformational energy of species having adjacent lone pairs (in the present case, a sulfonium ylide). As will be seen below, the H–D exchange has turned out to be highly stereospecific, a feature which has permitted the synthesis of specifically deuterium labeled derivatives of II. These have been instrumental for the stereochemical assignment (by nO experiments) as well as for detecting and measuring the rate of pyramidal inversion of the sulfur atom.

Results

Pmr Spectra. The spectra have been recorded in

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(1) (a) C.E.A.–C.E.N.G.; abstracted from the doctoral thesis ("these d'Etat") of G. B.; (b) Laboratorio C.N.R.; (c) Università di Pisa.

(2) (a) G. Barbarella, A. Garbesi, and A. Fava, *Helv. Chim. Acta*, **54**, 341 (1971); (b) *ibid.*, **54**, 2297 (1971); (c) A. Garbesi, G. Barbarella, and A. Fava, *J. Chem. Soc.. Chem. Commun.*, 155 (1973).

(3) (a) O. Hofer and E. L. Eliel, *J. Amer. Chem. Soc.*, **95**, 8045 (1973). We are indebted to Professor Eliel for letting us know of these results prior to publication. (b) E. L. Eliel, *Angew. Chem., Int. Ed. Engl.*, 11, 748 (1972).

(4) In our earlier reports[2a,b] we have given what now appears to be a grossly inaccurate reactivity ratio (>400). A later publication by Eliel and coworkers,[3a] reporting a ratio of about 30, prompted a reinvestigation of the kinetics of exchange. The newer results indicate that, due to complications arising from a concomitant decomposition, we had[2a] greatly underestimated the reactivity of the slower pair. Starting with 1-methylthiolanium-d_5 nitrate and checking for decomposition, we have now been able to measure, rather than set a limit for, the exchange rate which has turned out to be about 28 times slower than for the other pair (3 *N* D$_2$O–NaOD; 55°) in good agreement with the results of Eliel and Hofer.[3a]

(5) The term "half-chair" actually implies a C_2 symmetry axis and is therefore improper for a sulfonium cation because of the pyramidal geometry around sulfur. Although the term "twist envelope" has been suggested as more appropriate,[6] we will continue to use the more descriptive term "half-chair."

(6) P. Haake, J. P. McNeal, and E. J. Goldsmith, *J. Amer. Chem. Soc.*, 90, 715 (1968).

(7) (a) A. Rauk, S. Wolfe, and I. G. Czimadia, *Can. J. Chem.*, 47, 113 (1969); (b) S. Wolfe, A. Rauk, L. M. Tel, and I. G. Czimadia, *J. Chem. Soc. B*, 36 (1971); (c) S. Wolfe, L. M. Tel, J. H. Liang, and I. G. Czimadia, *J. Amer. Chem. Soc.*, 94, 1361 (1972).

(8) S. Wolfe, *Accounts Chem. Res.*, **5**, 102 (1972).

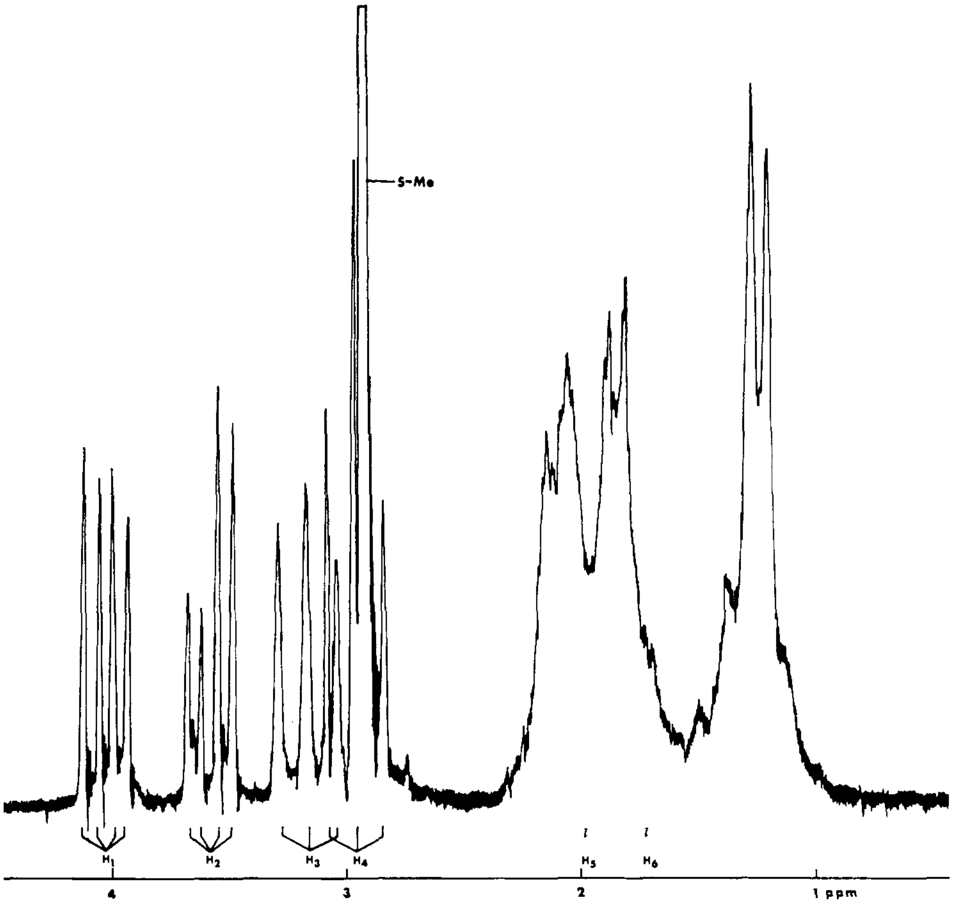


Figure 1. Pmr spectrum of *trans*-3-methyl-3-thioniabicyclo[4.3.0]nonane iodide (II) in D_2O (100 MHz).

Table I. Pmr Parameters for Cation II[a]

	δ_{CH_3}	δ_{H_1}	δ_{H_2}	δ_{H_3}	δ_{H_4}	δ_{H_5}	δ_{H_6}	$J_{H_1 \cdot H_4}$	$J_{H_2 \cdot H_3}$	$J_{H_1 \cdot H_6}$	$J_{H_4 \cdot H_6}$	$J_{H_2 \cdot H_5}$	$J_{H_3 \cdot H_5}$
D_2O	2.92	4.02	3.58	3.16	2.96	2.08	1.72	−12.0	−13	6.5	12.0	6.0	11.5
D_2O–pyridine	3.24	4.19	3.75	3.33	3.14	2.15	1.82	−12.0	−13	6.5	12.0	6.0	11.5

[a] δ in ppm with respect to $(CH_3)_3SiCD_2CD_2COONa$ internal standard; J = Hz.

D_2O and in D_2O–pyridine. Figure 1 reports the 100-MHz pmr spectrum of II in D_2O. As for all sulfonium cations[2b] the protons α to the cationic heteroatom are downfield and can be easily identified (H_1–H_4). The bridgehead protons (H_5 and H_6) are hidden behind the broad resonance of the alicyclic protons. Their identification was obtained through double resonance experiments. The decoupled spectra at 60 MHz are shown in Figure 2. First-order analysis of the spectra yields the relevant pmr parameters which are summarized in Table I.

Base-Catalyzed H–D Exchange. Under conditions of base catalysis, sulfonium cations are known to undergo readily H–D exchange at the α positions.[2b] Integration of the pmr absorption of individual protons at given time intervals allows the determination of exchange rates. As found previously[2b] the *S*-methyl group of II exchanges its hydrogens much faster than the S–CH_2 groups. However, of the latter four H's, cation II exchanges relatively rapidly only one of them, H_2. In D_2O–NaOD (1.7 *M*) the pseudo-first-order specific rates are 1.5×10^{-4} and 8.5×10^{-4} sec^{-1} at 59 and 75°, respectively. These values are in the same range as that for the more reactive pair of ring protons in the 1-methylthiolanium cation under the same conditions.[2a,b] Of the remaining protons, two, H_4 and H_3, which overlap somewhat in the pmr spectrum, appear to have approximately the same reactivity, as shown by the fact that the pseudo-first-order plot obtained from the change of their overall signal intensity does not show any important curvature. The pseudo-first-order specific rates are approximately 1.2×10^{-5} and 3.5×10^{-5} sec^{-1} at 75 and 85°, respectively. Thus, the rate ratio between H_2 and H_3 (or H_4) is about 70. No appreciable decomposition of the sulfonium salt appears to take place within the time required to measure the exchange rates for H_2 and H_3, H_4.

The fourth hydrogen atom, H_1, is less reactive still. Its apparent exchange rate is about three times slower than that of H_3 or H_4, hence some 200 times slower than H_2. It appears, however, that the observed rate is an upper limit, as pyramidal inversion (which interchanges H_1 with H_2, see below) becomes competitive and may actually account for a large fraction if not all of the exchange. Moreover, there may be some unaccounted for decomposition of the sulfonium cation, which would add to the apparent exchange rate.

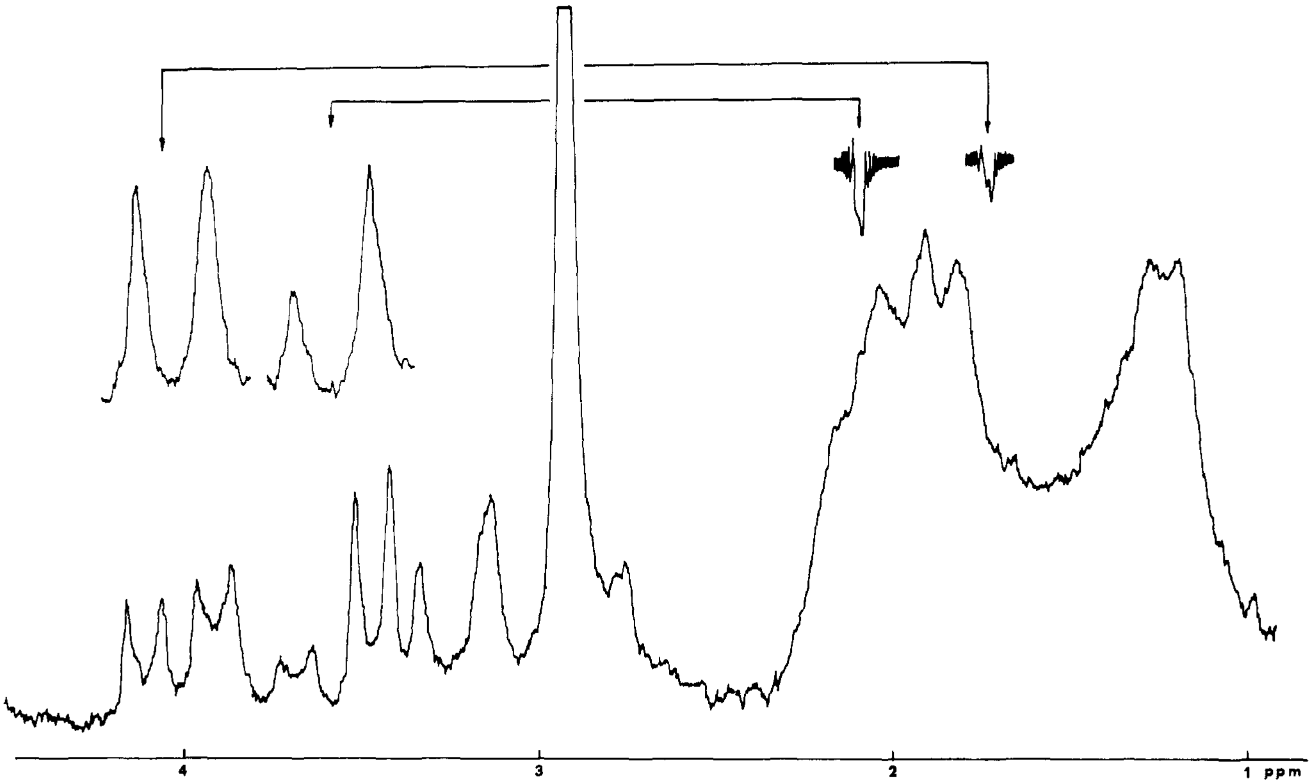


Figure 2. Pmr spectrum of II in D_2O (60 MHz) and decoupling experiments.

It is remarkable that exchange of H_2 and H_4 is accompanied by a gradual change of the signals for H_3 and H_1, respectively, which eventually become doublets, indicating that H_1,H_4 and H_2,H_3 are geminal pairs.

Nuclear Overhauser Experiments. By taking advantage of the differential exchange rate of α protons, it has been possible to prepare a sample of II with 98% deuterium at H_1, H_3, H_4, 15% deuterium and 85% protium at H_2 (II-d_3). Nuclear Overhauser experiments have been performed with this derivative which, upon irradiation of the *S*-methyl group, gave a nO enhancement of 15 ± 1% for H_2. Similar experiments were carried out on a sample prepared from II-d_3 above by stereomutation at sulfur (see below) which had about 48 and 37% protium at H_2 and H_1, respectively. For this sample the nO was 16 ± 2% for H_2 and essentially zero for H_1. These results match closely those for the parent ring cation I[2c]. On this basis it may be concluded that, in II, H_2 and S–CH_3 are cis with respect to each other.

Thermal Stereomutation at Sulfur. The iodide of II-d_3 used in the nO experiment was heated at 90° in D_2O (in the absence of base) for various periods of time. As seen in Figure 3, the pmr spectrum in the region 3.3–4.4 ppm shows that the intensity of the signal of the 3.58 signal (H_2) decreases, while that of the 4.02 signal (H_1) increases correspondingly, until they become equally intense. No significant proton signal appears in the 2.7–3.3-ppm region (H_3–H_4). The rate of change of signal intensity is $k = 1.4 \times 10^{-5}\ \text{sec}^{-1}$ at 90°.

Discussion

Pmr Spectrum and nO Experiment. The values of the vicinal coupling constants and the results of the nO experiments allow the unambiguous assignment of all the protons of the five-membered ring.

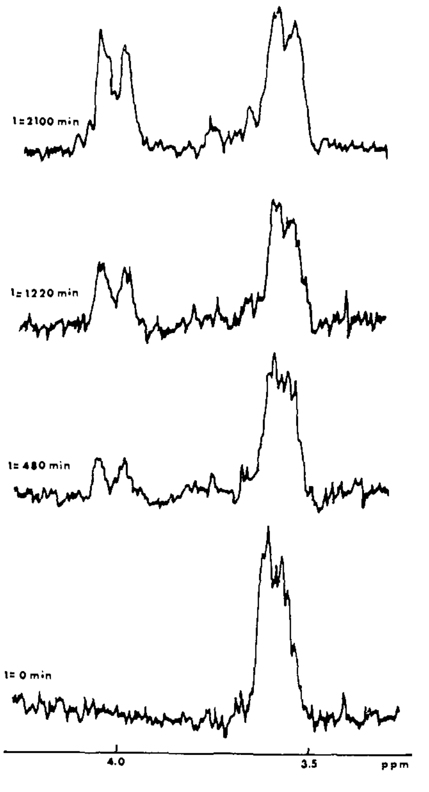
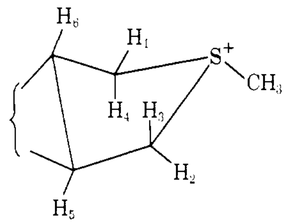


Figure 3. Variation of the pmr spectrum (D_2O) of II-d_3 upon heating at 90° for various lengths of time.

The trans ring fusion determines the pseudoaxial setting of the bridgehead protons, H_5 and H_6. Hence α ring protons that are characterized by the larger vicinal coupling constant are also pseudoaxial. From Table I these can be recognized as H_3 and H_4. Consequently, H_1 and H_2 are pseudoequatorial. Examination of models (see also the perspective formula III)



III

shows that one of these is cis to the *S*-methyl group, and the nO indicates this to be H_2. Hence it is possible to assign the stereochemistry of all the protons of the five-membered ring, which is shown in the perspective structure III. The assignment is fully consistent with the evidence stemming from the exchange experiments (H_1,H_4 and H_2,H_3 geminal pairs) as well as from the pyramidal inversion experiments (interconversion $H_1 \rightleftarrows H_2$).

This stereochemistry allows a number of observations. First of all it appears that the method of assigning the stereochemistry of protons adjacent to lone pairs on the basis of their chemical shifts[9] is not reliable. According to this method the chemical shifts should be $\delta_{H_3} > \delta_{H_2}$ and $\delta_{H_1} > \delta_{H_4}$ while we observe $\delta_{H_2} > \delta_{H_3}$. Neither can the chemical shifts of protons adjacent to heteroatoms be quantitatively assessed on the basis of their steric relation to lone pairs.[10]

Hydrogen–Deuterium Base-Catalyzed Exchange. In discussing the differential rate of exchange of diastereotopic protons it is useful to consider geminal protons first. Very recently Fraser and coworkers have convincingly argued that, whenever stereospecific exchange is observed, the more reactive proton must exchange with predominant retention.[11] Nothing can be said *a priori* about the slower proton, whose stereochemistry of exchange depends on whether the interconversion of the diastereomeric carbanions is slow or fast with respect to reprotonation.[11] However, the rates of exchange, being uniquely determined by the energies of the respective transition states for proton abstraction, are completely independent of the stereochemical pathways actually involved.[11] This conclusion is very important insofar as it disposes of the objection[3b,7b] that the stereochemistry of exchange may affect the rate ratios, and establishes that the observed ratios can be used at face value.

Turning to our own results, we find a reactivity factor of about 70 for the H_2,H_3 geminal pair, while for the other pair we can only set a minimum ratio of about 3. This is due to the observed rate of H_1 which is not much faster, under the conditions of the experiments, than pyramidal inversion of the sulfur atom. As this process interconverts H_1 and H_2 (see below), *i.e.*, the slowest with the fastest exchanging hydrogen, its occurrence results in the appearance of deuterium at position 1, while the corresponding protium appearing at position 2 would be rapidly exchanged. Thus the significance of the observed value of k_{H_1} is doubtful, except for its meaning as an upper limit. More experiments are necessary to settle this point, which we plan to do in follow-up research primarily concerned with the medium effects on the diastereotopic reactivity factors.

Of greater interest are the reactivity factors pertaining to the pairs H_2,H_1 and H_3,H_4. The protons of each pair differ in their orientation only with respect to the *S*-methyl function, being otherwise identical. These pairs are then best suited for a test of the so-called "gauche effect."[8] Diastereotopic reactivity in H–D base-catalyzed exchange of protons α to a heteroatom carrying a lone pair has been explained within the framework of the theory of the gauche effect,[8] *i.e.*, in terms of the conformational energy of carbanions in relation to the torsional angle between the "directions" of lone pairs on the adjacent atoms. For the pair of pseudoequatorial protons H_1 and H_2 the theory[7,8] predicts that the carbanion obtained by abstraction of H_2 should be more stable since the torsional angle between the lone pairs is about 120°, while in that obtained by removal of H_1, the lone pairs nearly eclipse each other. On this basis, and within the limit of a reasonable parallelism between kinetic and thermodynamic acidities (see below), H_2 should exchange faster than H_1. This is precisely what is observed. The other pair, however, that of the pseudoaxial protons H_3 and H_4, does not display any important reactivity differential, although the angular relations to the lone pair on sulfur are similar to those of H_1 and H_2, respectively. Thus the two pairs of diastereotopic protons offer a conflicting response, which adds considerable doubt to the value of the kinetic acidity as a test of the gauche effect.

In the very recent literature several cases have been reported where this test has proven to give, at best, equivocal results. To remain within the class of cyclic sulfonium ylides, the five-membered ring (I) appears to give results in agreement with theory.[2c] However, the six-[2b,3a] and seven-membered[2b] rings exchange with little or no stereospecificity, against the predictions of the theory;[7,8] a similar behavior has been found for both *cis*- and *trans*-1,2-dimethylthianium cations.[3] It may be argued that lack of stereospecificity may be only apparent insofar as a highly stereospecific proton abstraction followed by deuteration with inversion would appear as nonstereospecific exchange. However, at least in protic solvents, this possibility appears to be physically unplausible. This contention follows from the consideration that, neglecting isotope effects and assuming reorganization of the protic solvent to be fast with respect to interconversion of the carbanions, protonation of the carbanion must be the microscopic reverse of its formation by proton abstraction. Hence, inversion necessarily implies that the transition state for reprotonation with inversion be of lower energy than that for reprotonation with retention. But, if it were so, and since the ground state is the same, the former transition state would be reached more readily from the "retention side," *i.e.*, exchange would have occurred with retention. Thus the hypothesis that the faster proton may exchange with configurational inversion is self-defeating.

The unreliability of the kinetic acidity as a test of the operation of the gauche effect is even more dramatically

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[9] R. F. Fraser and F. I. Schuber, *Can. J. Chem.*, 48, 663 (1970).

[10] C. C. Price, *Tetrahedron Lett.*, 47, 4527 (1971); C. C. Price, *J. Org. Chem.*, 38, 615 (1973).

[11] R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, *J. Amer. Chem. Soc.*, 94, 8794 (1972).

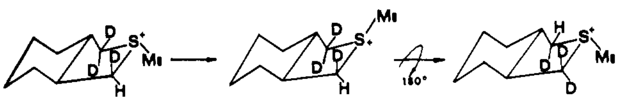
illustrated by the recent results obtained by Fraser, Durst, and coworkers on α-sulfinyl carbanions.[11,12] These authors have shown that the diastereotopic reactivity ratio in methyl benzyl sulfoxide or in 1,1-dimethyl-5,7-dihydrothiepin *S*-oxide is strongly dependent on the solvent–base system, to the point where a change from D_2O–OD^- to CH_3OD–CH_3O^- may change the reactivity ratio from 1:4 to 250:1.[11]

The failure of the kinetic acidity test to support the theory of the gauche effect does not necessarily imply that the theory is unsound. In fact the validity of the test implicitly rests on two assumptions: (i) that the carbanion's conformational energies at *equilibrium* (the quantities obtained from calculation) are directly related to the energies of the quasicarbanionic transition states (the quantities obtained experimentally), and (ii) that the relative gas-phase conformational energies may not be substantially altered by solvation phenomena.

The first of these assumption is equivalent to assuming a linear free energy relation (Brønsted) between rates and acidity constants of carbon acids: $\log k = \alpha \log K_a + C$. It is therefore a completely reasonable assumption, since, though Brønsted relations are known to fail not infrequently,[13] when such failures do occur, it is because one attempts to fit to the same regression line acids of widely varying structure covering a large pK_a range.[13] This is unlikely to be the case of the carbon acids under consideration here, where the structural variation involved is minor and implies a small pK_a range.[14] The second assumption, concerning solvation effects, is probably a gross oversimplification, and the above mentioned[11,12] solvent–base effects indicate it to be unwarranted. However, exactly what role the solvent–base system performs in changing the diastereotopic reactivity factor is not clear; this calls for more systematic experimental work in this field.

Thermal Stereomutation at Sulfur. To understand the results illustrated in Figure 3 it should be considered that cation II-d_0 is an asymmetric species existing as a *d,l* pair. Pyramidal inversion of the sulfur atom does not change the configuration of the molecule, as can be easily verified by rotation of the species, obtained by inversion at sulfur, of 180° around an axis passing through the sulfur atom and bisecting the C_1–C_5 bridge. However, inversion of the sulfur atom changes the relation of the *individual* ring hydrogens to the *S*-methyl function. Thus hydrogen atom H_2 becomes H_1,H_3 becomes H_4, and *vice versa*. Therefore, for the cation II-d_3 discussed above, where deuterium replaces protium at positions 1, 3, and 4, inversion at sulfur produces isomerization, insofar as protium appears at position 1 while deuterium appears at position 2.

This is precisely the significance of the experiment described above which, while allowing for the determination of the thermal pyramidal inversion rate, lends further support to the stereochemical assignment insofar as it confirms that H_1,H_2 and H_3,H_4 are the pairs of hydrogens which differ in their orientation with respect to the *S*-methyl function, being otherwise equivalent.



The rate of stereomutation, $k = 2.10^{-5}$ sec^{-1}, at 90° is on the order expected on the basis of the rates previously measured by a completely independent method (racemization of optically active substrates) for other five-membered cyclic sulfonium cations.[16] It is remarkable that this nmr study definitively confirms the nature of the thermal stereomutation of sulfonium cations as being that of a pyramidal inversion. The results in fact rule out the possibility that stereomutation may be achieved *via* fission of the ring carbon to sulfur bond, followed by recombination, since the latter process would bring about scrambling of H_2 with H_3 rather than H_2 with H_1 as observed.

Experimental Section

***trans*-3-Methyl-3-thioniabicyclo[4.3.0]nonane iodide (II)** was prepared from commercial (Aldrich) *trans*-1,2-cyclohexanedicarboxylic acid anhydride by following the method of Mislow:[17] (1) $LiAlH_4$ reduction to the diol (76% yield); (2) conversion of the diol to the ditosylate (80%) with *p*-toluenesulfonyl chloride in pyridine; (3) reaction of the ditosylate with $Na_2S \cdot 9H_2O$ (molar ratio 1:2) in 95% EtOH, to give the cyclic sulfide (55%), bp 219–220° (lit.[18] bp 104.4–105.6° (20 mm)); (4) methylation with CH_3I of the sulfide to the title sulfonium salt (95%), mp 169–170° (lit.[18] mp 164.5–166.5°).

All intermediate products had ir and pmr spectra consistent with the expected structure.

***trans*-3-Methyl-3-thioniabicyclo[4.3.0]nonane-*2,2,4,4d₄* iodide** was prepared following the procedure by Siegl and Johnson.[19] (1) The bicyclic sulfide (25 mmol) was oxidized with H_2O_2 in acetic acid to the corresponding sulfone (80%): mp 104–105° (lit.[18] mp 105–105.5°); nmr ($CDCl_3$) δ 3.27 (q, 2 H), 2.73 (t, 2 H), 1.90 (m, 6 H), 1.27 (m, 4 H). (2) The sulfone was treated with 1 *N* NaOD in D_2O–dioxane (molar ratio D_2O/sulfone 40:1) under stirring for 26 hr, neutralized with HCl, and evaporated to dryness. The sulfone was extracted with CH_2Cl_2 and analyzed for residual α protons by pmr. After four treatments as above the sulfone gave no appreciable pmr signal in the α-proton region (2.5–3.5 ppm). (3) The sulfone-d_4 above (12 mmol) was reduced to the corresponding sulfide (80%) with $LiAlH_4$ (44 mmol) in ether. The crude sulfide-d_4 was methylated with CH_3I to yield the title compound (90%).

***trans*-3-Methyl-3-thioniabicyclo[4.3.0]nonane-d_3 iodide** was prepared from the corresponding α,α′-tetradeuterio derivative by selective D–H exchange with 2 *N* NaOH in H_2O (10 hr at 50°). Under these conditions only one of the four α deuteriums is substantially replaced by protium. The sample thus obtained, which was used in the nO experiments, appeared to have 85% protium at the H_2 position of the pmr spectrum, using as reference the S–CH_3 signal (2.92 ppm).

Kinetics. The rate of exchange of the various protons was determined by following the intensity of their signals in the pmr spectrum, relative to that of a suitable standard ($(CH_3)_3SiCD_2CD_2COONa$, *ca.* 0.02 *M*) added to the reaction medium. Solutions were made up directly in the nmr tube by dissolving 50-mg samples in 0.8 ml of D_2O containing 1.7 *M* NaOD. The tube was sealed and kept in a thermostated bath at 59, 75, or 85° except for taking the nmr spectra after each period of time. The kinetic runs comprised at least five points each and were followed up to 90 and 40%

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(12) T. Durst, R. R. Fraser, M. R. McClory, R. B. Swingle, R. Viau, and Y. Y. Wigfield, *Can. J. Chem.*, **48**, 2148 (1970).

(13) L. Senatore, E. Ciuffarin, A. Fava, and G. Levita, *J. Amer. Chem. Soc.*, **95**, 2918 (1973).

(14) The case recently reported[15] by Eliel and coworkers, of *cis*-4,6-dimethyl-1,3-dithiane, a carbon acid with two acidic diastereotopic hydrogens, supports this view. The equatorial proton, which is removed faster (by a factor of 9),[15b] also gives rise to the more stable carbanion (by a factor of >100).[15a] This finding implies a small but not unreasonable Brønsted coefficient, $-\alpha \leqslant 0.45$.

(15) (a) A. A. Hartmann and E. L. Eliel, *J. Amer. Chem. Soc.*, **93**, 2572 (1971); (b) E. L. Eliel, A. Abatjoglou, and A. A. Hartmann, *ibid.*, **94**, 4786 (1972).

(16) A. Garbesi, N. Corsi, and A. Fava, *Helv. Chim. Acta*, **53**, 1499 (1970).

(17) P. Laur, H. Häuser, J. E. Gurst, and K. Mislow, *J. Org. Chem.*, **32**, 498 (1967).

(18) S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Org. Chem.*, **19**, 1449 (1954).

(19) W. O. Siegl and C. R. Johnson, *J. Org. Chem.*, **35**, 3657 (1970).

for H_2 and H_3,H_4, respectively; standard deviations were on the order of ±10%. For H_1, the slowest reacting proton, the upper limit given is based on one point only. Decomposition of the sulfonium cation appears not to be a problem in the determination of the exchange rates for H_2 and H_3,H_4. In fact, within the time required (up to 800 min at 75° 1.7 *M* NaOD), the intensity of the H_1 signal (relative to the standard) does not decrease appreciably. On the other hand, for H_1, the decrease of the signal intensity may be due to exchange, or to pyramidal inversion, as well as to decomposition of the substrate. The latter is likely not to be important, however, as no new signal appears in the pmr spectrum.

The thermal stereomutation experiments were performed on a 50-mg sample of II-d_3 (see above) dissolved in 0.8 ml of D_2O directly in the nmr tube, which was sealed and put in a thermostated bath at 90°. The kinetic run comprised eight points between 2 and 50 hr. After each time interval the sample was quenched and the pmr spectrum recorded. Aside from the aforementioned decrease of the 3.58-ppm and increase of the 4.02-ppm signals, no other spectral change was observed in the 2.5–4.5-ppm region. In particular, no significant proton signal appeared in the 2.7–3.3-ppm region (H_3–H_4), while the overall signal intensity in the 3.5–4.1-ppm region (H_1–H_2) remained constant relative to that of the 2.92-ppm signal (S–CH_3).

Pmr spectra were recorded on a Varian H-100 and/or a Jeol PS-100. The nO experiments were carried out on both instruments, following the procedure described by Bell and Saunders.[20] The enhancements reported are the per cent differences in the integrated intensities of a specific 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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Conformation of (−)-Menthone Lactam and *N*-Methylmenthone Lactam[1]

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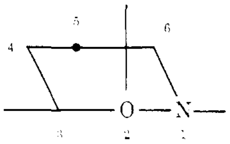
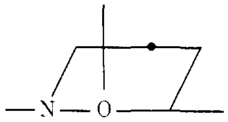
Abstract: A regularity about the n–π* Cotton effect of the seven-membered lactam ring (lactam rule) was applied to (−)-menthone lactam and *N*-methyl-(−)-menthone lactam. Conformational equilibrium of a simple seven-membered lactam ring was discussed on the basis of the lactam rule.

Recently, we suggested[1] that the sign of the n–π* Cotton effect of a seven-membered lactam ring depends solely on classification into two types (A (−Ve) and B (+Ve)) from the CD and ORD data of *A*-azatetrahydro-α-santonins[2] and *A*-azasteroids[3] derived from their oximes by the Beckmann rearrangement.



A



B

Rehling and Jensen[4] reported the relationship between the CD spectra and absolute configuration of β-lactam substituted azetidinones. The azetidinone ring showed coplanarity from its X-ray analysis,[5] and coplanarity of the lactam ring means similarity of the seven-membered lactam ring. Application of the lactam rule to azetidinones should solve problems about the absolute configuration. In this case, the model is so placed that the substituents are above the octant plane. When the substituent R^1 and/or R^3 is above the plane of the octant, corresponding to model B, the compounds should have a positive Cotton effect. On the other hand, when the substituent R^2 and/or R^4 is above the plane of the octant, corresponding to model A, the compounds would be expected to exhibit a negative Cotton effect. The data are summarized in Table I which clearly indicates that the azetidinone derivatives (**1–15**) are present in two types, A and B.

When the substituent is two or more and in mixed positions (R^1 and/or R^3 and R^2 and/or R^4), the decision of the sign of n–π* Cotton effect may be made from the substituent effect. For example, in compounds **8** (R^1 = CH_3, R^2 = $CH{=}CH_2$) and **15** (R^1 = $CH{=}CH_2$, R^2 = CH_3), the $CH{=}CH_2$ group may decide the sign of the Cotton effect.

The quadrant rule given by Schellman[6] for the amide chromophor shows that the rotation is dominated by the nearest substituent to carbonyl group oxygen. From the quadrant rule a positive Cotton effect for compound **3** (Table I) is anticipated by a positive quadrant substituent (R^4). For the same reason, a negative Cotton effect for compound **11** is anticipated by a negative quadrant substituent (R^3). Thus the same substituent is attached to the same side of the octant plane, and prediction of the sign of the Cotton effect cannot be decided from the quadrant rule. In this case, application of the lactam rule resolves the

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