

# THE CONFORMATIONAL ANALYSIS OF SATURATED HETEROCYCLES—XL<sup>1</sup>

## THE STEREOCHEMISTRY OF BASE-CATALYSED HYDROGEN-DEUTERIUM EXCHANGE OF METHYLENE PROTONS ALPHA TO A SULPHONYL GROUP

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**Abstract**—The rates of hydrogen-deuterium exchange of protons alpha to the sulphonyl group in a conformationally rigid sulphone have been measured in aqueous-DMSO. The exchange rate ratio  $k_{eq} : k_{ax}$  is 1.6. The greater kinetic acidity of the equatorial proton is in accord with recent MO calculations on sulphonyl carbanion stability, but does not preclude the intermediary of planar species.

THE stereochemistry of sulphinyl and sulphonyl carbanions formed by the removal of a proton alpha to a sulphoxide or sulphone group has been a subject of recent interest.<sup>2</sup> Cram *et al.*<sup>3</sup> demonstrated that, in non-aqueous solvents, the exchange-epimerisation ratios for the base catalysed proton-deuteron exchange of optically active phenyl 2-octyl sulphoxide are consistent with the view that an ArSO-group does not induce carbanion asymmetry. However, Nishio<sup>4</sup> observed sequential exchange in benzyl-*p*-chlorophenyl sulphoxide in aqueous dioxan. In addition, Wolfe, Rauk and co-workers,<sup>5</sup> had showed earlier that benzyl methyl sulphoxide undergoes exchange in aqueous media via an asymmetric intermediate: they deduced the favoured structure of the sulphinyl carbanion as I on assumptions regarding shielding by the sulphoxide group which may not be valid,<sup>6</sup> although their subsequent molecular orbital calculation<sup>7</sup> also showed decreasing stability in the order I > II > III. In this laboratory,<sup>9</sup> relative exchange ratios of the axial and equatorial protons in the conformationally rigid sulphoxides IV and V differed in D<sub>2</sub>O or MeOD (there was no stereoselectivity to exchange in DMSO or *t*-butanol). The results indicated that the conformations of the carbanion in order of decreasing stability were II > I > III. Recently, Fraser and Schuber<sup>8</sup> reported results for a rigid seven membered ring sulphoxide which again indicate that III is the least stable conformation (without allowing conclusions regarding II and III); however, they have since reversed their earlier NMR assignment<sup>9</sup> and the work now indicates that III is the most stable carbanion.

A *sulphonyl* carbanion frequently behaves as an asymmetric intermediate.<sup>2</sup> Controversy has arisen regarding the origin of this asymmetry and reasoning has followed along two main lines; either the carbanion is pyramidal with a high barrier to inversion or it has an effectively planar asymmetric structure VI in which free rotation into the symmetric form VII is hindered. Cram<sup>10</sup> suggested that the least energetic carbanion structure is pyramidal VIII. Corey however, devised systems<sup>11</sup> in which inversion rather than retention occurred and has argued that the sulphonyl carbanion has sp<sup>2</sup>-hybridised carbon. Recently Bordwell and co-workers<sup>12</sup> after studying the sulphonyl carbanion

derived from optically active  $\text{RCHMeSO}_2\text{R}'$  have concurred with his view, at least for the case where R is phenyl. Cram *et al.*<sup>13</sup> have challenged Corey's conclusions, though from further studies<sup>14</sup> they have concluded that in 5-membered ring sulphones the carbanion carbon atom could prefer a planar structure since the ring system enforces a conformation which destroys the electrostatic driving force for generating a pyramidal anion. They maintain<sup>13</sup> that it is still far from clear whether an open chain carbanion is pyramidal or planar.

It has been suggested<sup>7</sup> that Corey's results can be interpreted in terms of either highly asymmetrical solvation of an asymmetric planar anion or by spontaneous inversion of an initially generated pyramidal anion to another with the electron pair directed along the bisector of the OSO bond, IX. If the latter was the case, then by implication IX would be the most stable conformation of the sulphonyl carbanion. In a subsequent paper Wolfe *et al.*<sup>15</sup> extended their MO calculations to the hypothetical  $\text{CH}_2\text{SO}_2\text{H}$  system and deduced that conformation IX is the most stable for this system. They also concluded that of the planar carbanions, VI was more stable than VII. More recently Fraser and Schuber<sup>16</sup> have studied the base catalysed H/D exchange of the sulphone derived from their sulphoxide used earlier.<sup>8</sup> The approach of the base is sterically hindered and the relative rate of exchange of the alpha protons is dependent upon the catalyst used. Stabilisation by the aryl group of the anions derived by loss of the different protons unfortunately varies. The authors have attempted to allow for this and to derive a quantitative value of the  $\Delta G^\circ$  between sulphonyl carbanions of different configurations. It is concluded that the MO theory is qualitatively correct but appears to over-estimate energy differences. We now report our own studies on the exchange of the  $\alpha$  axial and equatorial protons in a conformationally rigid six membered ring sulphone.

#### *Preparation of compounds and spectral assignment*

The sulphone derived from the sulphoxides IV and V was unsatisfactory for the present purposes in that the equatorial and axial C-2 protons displayed the same chemical shift; thus H/D exchange of the individual protons could not be followed. The sulphone XI obtained via X shows a poorly resolved ABC multiplet with two protons of similar chemical shifts about 50 Hz downfield from the third. Exchange of the C-3(5) protons for deuterium, using pyridine/ $\text{D}_2\text{O}$  gave XII which shows a 53 Hz separation between the AB system found for the two C-2 protons, so assigning the high field signal in XI to one of these. Decoupling of the high field proton in XI gave an AB pattern with  $J_{23} = 13.6$  Hz, showing that the low field C-2 proton is axial.

The base catalysed exchange XI  $\rightarrow$  XII showed no detectable AB pattern assignable to the C-2 protons of the thermodynamically less stable trans-isomer which has been observed in other systems.<sup>17</sup> However, since even a small concentration of this conformationally mobile compound would confuse results of H/D exchange studies for the C-2 protons the CO group of XI was reduced with LAH under conditions which left the sulphone group intact. Recrystallisation afforded the hydroxy sulphone XIII. The equatorial configuration of the OH group was established by following the exchange of the C-2 protons for deuterium in NaOD/ $\text{D}_2\text{O}$ / $\text{DMSO-d}_6$  to give XIV, which shows an  $A_2B$  spectrum ( $J = 10.5$  Hz). The large coupling constant is consistent with an equatorial OH group, *trans* to both phenyl groups which fix the ring in one conformation, which we assume to be a chair by analogy to other systems.

Reduction of XI with LAD afforded XV. The chemical shift of the C-3 proton

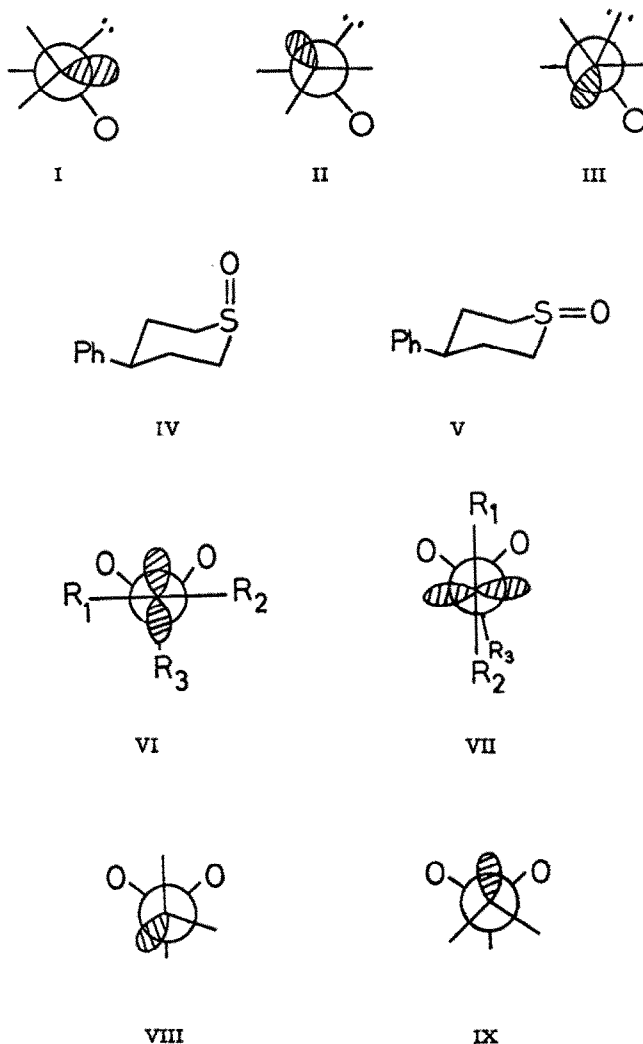


FIG. 1.

determined from the spectrum of XIV is similar to one of the C-2 protons but some 60 Hz upfield from the other. The lowfield C-2 proton in XV was shown to be axial, as in XI, by partially exchanging the C-2 protons for deuterium in NaOD. The appearance of a doublet,  $J=11$  Hz, at lowfield was consistent with a *trans* coupling to the axial C-3 proton. Furthermore, decoupling of the lowfield proton simplified the highfield multiplet to an AB,  $J=3.5$  Hz, though one doublet was obscured by secondary oscillations of the irradiating frequency. Further support was forth-coming on reduction of XII with LAD to give XVI which shows an AB pattern chemical shift difference of 76 Hz, in which the downfield proton showed the broader peaks due to larger coupling to the C-3 deuterium.

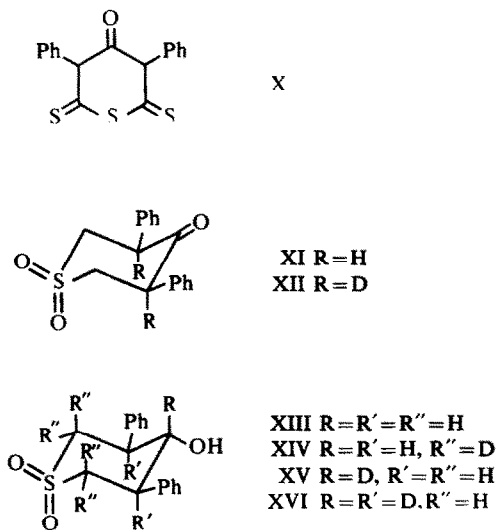


FIG. 2

### Kinetic study

Insolubility of XIII and overlap of solvent peaks precluded the use of many solvents but a convenient medium was found to be DMSO- $d_6$ /D $_2$ O/NaOD. The conditions chosen represented a large excess of deuterons over replaceable protons. Exchanges were performed on XV and XVI in an NMR tube, and spectra were recorded at various intervals. Integration of the peaks against a standard was unnecessary because the recorder accurately reproduced spectra over the time of the exchange. Direct measurements of the peak areas involved serious errors arising from the uncertainty of the base line, an HDO peak, and overlap with the C-3 proton in the case of XV. For the latter reason, exchange studies on XVI were preferred and the remaining sources of error were minimised through the use of the LORENTDECOMP computer programme<sup>18</sup> which fits the observed spectra to that obtained by the overlapping of a number of theoretical Lorentzian curves. The error involved in integration of peak area by this technique is difficult to estimate but is believed to be small.

### EXPERIMENTAL

*Cis*-3, 5-Diphenyltetrahydrothiopyran-4-one-1, 1-dioxide. Zinc dust (60 g) was added to 3,5-diphenyltetrahydrothiopyran-4-one-2,6-dithione<sup>19</sup> (15 g) in boiling AcOH (600 ml). HCl (75 ml) was added gradually and the resulting soln was refluxed for 15 min, after which time similar amounts of Zn and HCl were added. The whole was refluxed for a further 45 min, filtered hot, and poured into cold water (1.5 l.). After 24 hr, the crude 3,5-diphenyltetrahydrothiopyran-4-one was filtered off and washed with water (20 ml). 27% H $_2$ O $_2$  (35 ml) was added to this crude sulphide in AcOH (150 ml). The resulting soln was maintained at ca 50° for 45 min, then cooled, and 20% NaOH aq (125 ml) was added slowly with cooling. Most of the solvent was removed by distillation under reduced pressure, then water (200 ml) was added to the remaining material and the whole allowed to stand for 1 hr. The crude sulphone was collected by filtration, washed with water (2 × 10 ml), dried and recrystallised twice from benzene to yield *cis*-3, 5-

*diphenyltetrahydrothiopyran-4-one 1,1-dioxide* (1.98 g, 14%) m.p. 213.5°. (Found: C, 68.2; H, 5.3.  $C_{17}H_{16}SO_3$  requires: C, 68.0; H, 5.4%); IR (Nujol)  $\nu_{max}$  1732, 1297, 1125, 897, 714, 700, 682  $cm^{-1}$ ; NMR 100 MHz (12% solution in DMSO- $d_6$ ).  $\delta = 3.60-4.15$  (m, 2H);  $\delta = 4.40-5.15$  (m, 4H);  $\delta = 7.38$  (m, 10H); mass spectrum: No molecular ion, main fragments at  $m/e$  78 and 77.

*cis-3,5-Dideuterio-3,5-diphenyltetrahydrothiopyran-4-one 1,1-dioxide*. *cis-3,5-Diphenyltetrahydrothiopyran-4-one 1,1-dioxide* (0.60 g) in pyridine (25 ml) and  $D_2O$  (6.0 ml) was maintained at room temp for 12 hr. Removal of the solvent afforded *cis-3,5-dideuterio-3,5-diphenyltetrahydrothiopyran-4-one 1,1-dioxide*, the structure was shown by NMR.

*cis-3,5-Diphenyl-trans-4-hydroxytetrahydrothiopyran 1,1-dioxide*. *cis-3,5-diphenyltetrahydrothiopyran-4-one 1,1-dioxide* (0.600 g) in dry THF (70 ml) was added rapidly to LAH (0.150 g) under dry  $N_2$ . The soln was stirred for 40 min at 35°, then THF (20 ml) and water (10 ml) was added slowly followed by 50% HCl (15 ml). The resulting soln was extracted with ether (4  $\times$  100 ml), the extract washed with water (10 ml), dried ( $MgSO_4$ ), and the ether was distilled off under reduced pressure to yield the crude product (0.580 g). Repeated recrystallisations from benzene gave *cis-3,5-diphenyl-trans-4-hydroxytetrahydrothiopyran 1,1-dioxide* (0.434 g, 72.1%) m.p. 247.5°. (Found: C, 67.7; H, 5.8.  $C_{17}H_{16}SO_3$  requires: C, 67.5; H, 6.0%); IR (Nujol)  $\nu_{max}$  3510 (s), 1604 (w), 1495 (m), 1304 (s), 1120 (s), 695 (s), 683 (s), 671 (s)  $CM^{-1}$ ; NMR 60 MHz (12% soln in DMSO- $d_6$ )  $\delta = 2.9-4.3$  (m, 8H),  $\delta = 7.39$  (m, 10H); mass spectrum: no molecular ion, two main fragments at  $m/e$  78 and 77.

*Kinetic studies*. *cis-3,5-Diphenyl-trans-4-hydroxy-3,4,5-trideuterotetrahydrothiopyran 1,1-dioxide* (0.035 g) was dissolved in perdeuteriodimethyl sulphoxide (0.35 ml) and  $D_2O$  (0.030 g). The 100 MHz, NMR spectrum was run on a Varian Associates HA 100 spectrometer at 36.5°. 10% NaOD/ $D_2O$  (6  $\mu$ l) were added and the NMR spectrum scanned at various times up to 2 hr. The areas of individual peaks were determined using the LORENTDECOMP computer program.<sup>18</sup>

## RESULTS AND DISCUSSION

The rate of the exchange is highly dependent upon the base concentration: 6  $\mu$ l of 10% NaOD/ $D_2O$  in 0.35 ml gave a convenient rate and the results quoted are for this concentration. The variation of the NMR spectrum with time is shown in Fig 3.

The Table shows the area  $A^s$  of one half of the AB pattern arising from the starting sulphone at various times and the total area of the peaks due to the unexchanged axial protons  $A^{ax}$  and unexchanged equatorial protons  $A^{eq}$  at various times. The results are reported up to about 50% exchange, for both protons; results at greater exchange are affected by large errors in the determination of small areas.

The exchange reaction is expected to be pseudo-first order in sulphone and a plot of  $\log(A^o/A^s)$  against time, is a straight line. The slope gives a value of  $k(ax) + k(eq) = 4.55 \times 10^{-4} sec^{-1}$ , where  $k(ax)$  and  $k(eq)$  are the rate constants for the H-D exchange of axial and equatorial protons respectively of the starting material. If we now assume that there is no secondary deuterium isotope effect then it can be shown that the slopes of the individual plots of  $\log(A^o/A^{ax})$  and  $(A^o/A^{eq})$  versus time correspond to  $k(ax)$  and  $k(eq)$  respectively. The sum of these rate constants,  $1.8 \times 10^{-4}$  and  $2.9 \times 10^{-4} sec^{-1}$  respectively, corresponds well with that obtained earlier. The results indicate a stereoselectivity towards exchange of 1.6:1, equatorial to axial. The error in the ratio is estimated to be  $\pm 0.2$ .

Dominant factors expected to affect the ratio of equatorial exchange to axial exchange are effects of solvation of the generated carbanions, steric effects, extent of inversion of the carbanion if pyramidal, and inherent stability of the carbanion arising from its configuration. The first three effects are difficult to estimate quantitatively and thus conclusions about the fourth factor are only of a tentative nature.

The calculations of Rauk *et al* on the  $CH_2SO_2H$  anion indicate that the pyramidal configuration IX should be some 4 kcal/mole more stable than the alternative structure

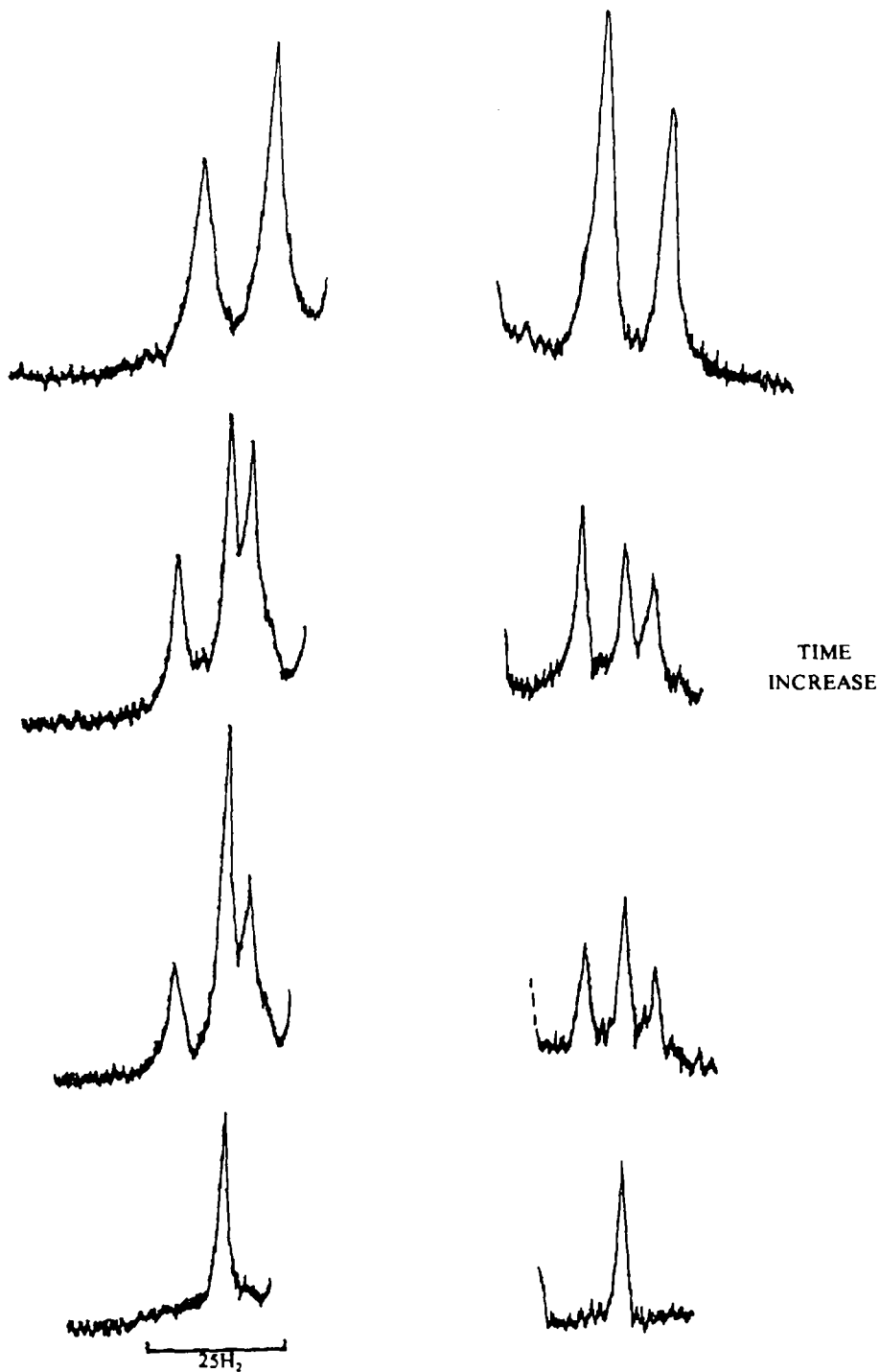


FIG. 3

TABLE I

Time (min)	A <sup>ac</sup>		A <sup>ac'</sup>	log <sub>10</sub> A°/A <sup>ac'</sup>		log <sub>10</sub> A°/A <sup>ac''</sup>	log <sub>10</sub> A°/A <sup>ac'''</sup>
	Axial doublet	Equatorial doublet	A <sup>ac'</sup>	log <sub>10</sub> A°/A <sup>ac'</sup>	log <sub>10</sub> A°/A <sup>ac''</sup>	log <sub>10</sub> A°/A <sup>ac'''</sup>	log <sub>10</sub> A°/A <sup>ac'''</sup>
0.0	153	153	153	0.0	0.0	0.0	0.0
7.6	116	141	141	0.12	0.03	0.03	0.10
12.6		113	121	0.13		0.17	
34.7	63		104	0.38			
39.7		50	77	0.48			
55.5	34		69	0.65		0.34	

<sup>a</sup> A<sup>ac</sup> is area of one half of the AB pattern arising from unexchanged sulphone

<sup>b</sup> A<sup>ac'</sup> is total area of signal from axial protons

<sup>c</sup> A<sup>ac''</sup> is total area of signal from equatorial protons

<sup>d</sup> A<sup>ac'''</sup> is area of signal of one doublet of the AB at zero time

VIII, for that system. Extrapolation of these results to the present case predicts that the carbanion directly generated by removal of the equatorial proton should be more stable than the corresponding carbanion derived by abstraction of the axial proton. Cram's model predicts the reverse. The most stable trigonal configuration of the  $\text{CH}_2\text{SO}_2\text{H}$  carbanion was calculated to be VI which is some 2.5 kcal/mole less stable than IX; other trigonal carbanion configurations are as much as 5 kcal/mole less stable than IX. In the present case the ring would impose a constraint on a trigonal carbanion, preventing it from adopting configuration VI. An examination of a molecular model reveals that on conformational grounds the likely configuration of trigonal carbanion would be intermediate between VI and VII. Such a configuration for the  $\text{CH}_2\text{SO}_2\text{H}$  carbanion was calculated to be about 4 kcal/mole less stable than configuration IX.

In the present work there is only a small preference for exchange of the equatorial proton and the system does not therefore demonstrate any large intrinsic stability of carbanion IX over carbanions with other configurations. Indeed the result can be adequately explained by invoking either pyramidal carbanion intermediates (VIII and IX) having similar stabilities (assuming a correlation between kinetic acidity and carbanion stability) or participation by an asymmetrically solvated trigonal intermediate. If pyramidal carbanions are in fact involved, further discussion about small differences in their stabilities based on an exchange ratio of 1.6:1 does not seem meaningful when contributions from other effects cannot be estimated.

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