Hydrogen–Deuterium Exchange in 2-Thiabicyclo[2.2.1]heptane Derivatives

By **Ugo Folli,*** **Dario Iarossi**, (Miss) **Irene Moretti**, **Ferdinando Taddei**, and **Giovanni Torre**, Istituto di Chimica Organica, Università, Via Campi 183, 41100 Modena, Italy

The rate constants for deuterium exchange of protons α to the sulphinyl or sulphonyl group in the 2-thiabicyclo-[2.2.1]heptane derivatives (1)—(6) were determined in MeONa–MeOD at 100°. Electronic and steric effects on the facility of carbanion formation in these systems and the stereochemistry of exchange are discussed.

As shown theoretically [1,2] for the hypothetical models $H-SO-CH_2^-$ and $H-SO_2-CH_2^-$, the stability of α-sulphinyl and -sulphonyl carbanions is dependent on the stereochemical relation between the sulphinyl or sulphonyl group and the carbanion electron pair. Consequently, the facility of proton abstraction α to a sulphinyl or sulphonyl group in base-catalysed hydrogen–deuterium exchange is also expected to be a function of proton orientation relative to these groups.

In diastereoisomeric sulphoxides, the *exo*-isomers (2) and (5) and the *endo*-isomers (3) and (6) of the 2-thiabicyclo[2.2.1]heptane series, three definite orientations can be recognized for the α-protons, which are derived from the restricted conformational mobility of the bicyclic system: *cis* to the SO bond, *cis* to the sulphur lone-pair, and the bisector of the oxygen–sulphur lone-pair angle. Two of these orientations are also present in the corresponding sulphones (1) and (4). Substrates (1)—(6) therefore appeared useful model compounds for an experimental study of α-sulphinyl and -sulphonyl carbanions as intermediates in isotopic exchange reactions.

While approximate exchange data for the α-protons of sulphoxides (5) and (6) have been already reported,[3] the present results do not support some of the conclusions [3] about the relative stability of α-sulphinyl carbanions of the type involved here and suggest that exchange with inversion of configuration is probably the prevailing mechanism when the less stable of two diastereomeric carbanions is generated by α-proton abstraction.

RESULTS AND DISCUSSION

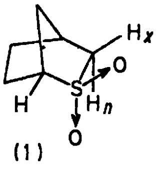
0·5M Solutions of compounds (1)—(6) were subjected to deuterium exchange by treatment with 1·18M-MeONa in MeOD at 100°. The product was isolated and the extent of deuterium exchange of α-protons determined from a comparison of the residual areas of their n.m.r. signals with those of other protons of the substrate not exchanged under these conditions. To follow the exchange of both *exo*- and *endo*-α-protons (H_x,H_n) with this technique it was necessary to simplify the ^1H n.m.r. spectra by using the hexadeuteriated substrates (4)—(6), while for the isotopically normal substrates (1)—(3) exchange at the bridgehead α-proton could be followed. Good first-order plots were obtained in each case from at least five experimental measurements, and from them the pseudo-first-order rate constants of the Table were derived.

Rates of deuterium exchange [a] of α-protons in compounds (1)—(6)

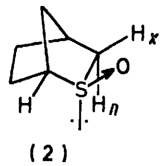
Comp.	(4)	(1)	(5)	(2)	(6)	(3)
H_x	23,160		540		2·7	
H_n	2900		9·4		24	
1-H		7400		6·0		5·8
k_x/k_n	8 : 1		57 : 1		1 : 9	

[a] Pseudo-first-order rate constants ($\times 10^7$ s^{-1}) for 1·18M-MeONa and 0·5M-substrate in MeOD at 100°.

For hydrogen–deuterium exchange in sulphoxides (5) and (6) a rate ratio $k_x/k_n \geqslant 12:1$ (CD_3OD-CD_3ONa; 120°) and 1 : 2·5 (CD_3OD-CD_3ONa; 110°), respectively, has been reported previously,[3] derived in both cases from one-experimental point kinetics. The latter results agree qualitatively with those in the Table, showing that in both sulphoxides (5) and (6) the methylene proton *cis* to SO exchanges more readily with deuterium in the presence of a basic catalyst than its diastereotopic partner *cis* to the sulphur lone-pair, quite apart from its *exo*- or *endo*-location in the bicyclo[2.2.1] system, the *exo*-side of which is expected to be less sterically hindered and more accessible to an attacking reagent. On the hypothesis that the intermediates of the base-catalysed exchange reaction are tetrahedral α-sulphinyl carbanions (electron pair on one sp^3 hybrid orbital), which seems reasonable in the absence of possible p–π conjugative interaction and supported by theoretical findings,[1] these experiments clearly indicate that carbanion (7), in which the electron pair is eclipsed by the SO bond, is more stable, because



(1)



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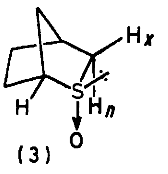

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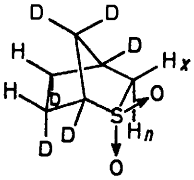

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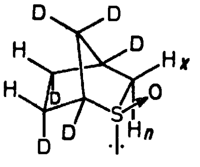

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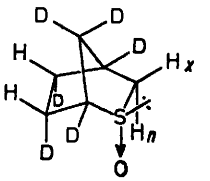

(6)

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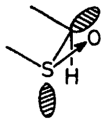
[1] S. Wolfe, A. Rauk, and I. G. Csizmadia, *Canad. J. Chem.*, 1969, **47**, 113.

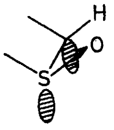
[2] S. Wolfe, A. Rauk, and I. G. Csizmadia, *J. Amer. Chem. Soc.*, 1969, **91**, 1567.

[3] R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, *J. Amer. Chem. Soc.*, 1972, **94**, 8795.

of more favourable electronic interactions, than (8) which contains two eclipsed electron pairs.



(7)



(8)

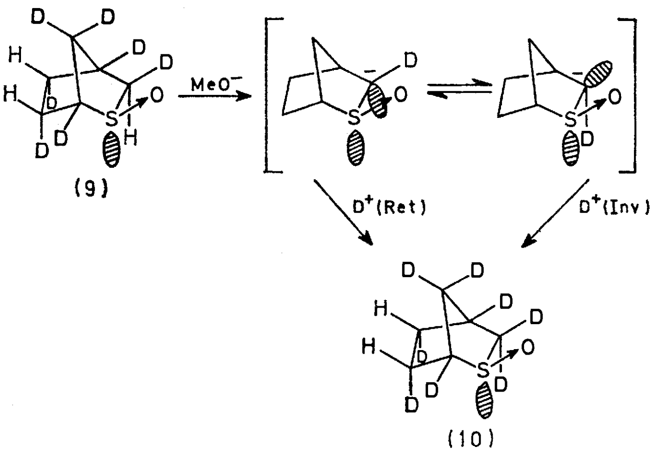
Since for ketones of the bicyclo[2.2.1]heptan-2-one series such as camphor and norbornanone *exo*-abstraction prevails over *endo* in the ratio 20 : 1 and 715 : 1, respectively,[4] the suggestion was made [3] that *exo*-proton abstraction in sulphoxides (5) and (6) should be sterically favoured over *endo*-abstraction by some intermediate value, say, at least 100 : 1. Consequently in sulphoxide (6), where steric and electronic effects are in competition and the latter is 2·5 times greater, the electronic preference for abstraction of the *cis* to SO over the *cis* to lone-pair proton was evaluated [3] as at least 250 : 1. This would also imply that the rate ratio $\geqslant 12:1$ reported [3] for compound (5), where both effects favour *exo*- over *endo*-proton abstraction, would actually be $>25{,}000:1$.

The experimental results reported in the Table clearly do not support the estimated [3] magnitude of steric as well as of electronic factors affecting carbanion formation in these systems. For sulphoxide (5) a k_x/k_n ratio of 57 : 1 was measured in an extensive kinetic run, and for the corresponding sulphone (4), where only steric effects are expected to play a role in *exo–endo*-selectivity in exchange, a k_x/k_n ratio of 8 : 1 was measured, *i.e.* much lower than in camphor. It follows that the electronic preference arising from carbanion (7) being more stable than (8) cannot be as large as had been estimated.[3]

If the steric effect favouring *exo*- over *endo*-proton abstraction can be assumed * to be almost constant in all the *S*-oxides (4)—(6), a rate ratio of *ca.* 8 : 1 is expected to favour *exo*-proton abstraction in both *S*-oxides (5) and (6), as measured for the corresponding *S*-dioxide (4). The k_x/k_n ratio enhancement from 8 : 1 to 57 : 1 (see Table) which is observed on passing from *S*-dioxide (4) to *exo*-*S*-oxide (5) can be ascribed to the superimposition of an electronic effect favouring *exo*- over *endo*-proton abstraction by a rate ratio of 7 : 1, which is nearly of the same magnitude as the steric factor. On the other hand, the rate ratio 1 : 9 observed for *endo*-*S*-oxide (6) would imply that the electronic factor is nine times stronger than the steric factor, if hydrogen–deuterium exchange with retention of configuration at the α-carbon of the intermediate carbanion (7) or (8) is the stereochemistry of the process. However, carbanion (7) or (8), initially formed by α-proton abstraction, could equilibrate to some extent by pyramidal inversion before its electrophilic capture. In this case, exchange through initial formation of the less stable carbanion (8) is expected to occur with a high degree of inversion of configuration, since a lower energy barrier must be associated with the pyramidal inversion of the less stable carbanion.

Exchange in sulphoxide (6) mainly with inversion of configuration as a result of *exo*-proton abstraction (sterically favoured) and retention associated with *endo*-proton abstraction (electronically favoured) could then account for the appearance of deuterium at the *endo*-position faster than would be expected if the reaction always proceeded by retention.

Similarly, in sulphoxide (5), exchange with retention of configuration is expected as a result of *exo*-proton abstraction, which produces the more stable carbanion besides being sterically favoured; *endo*-proton abstraction, on the other hand, is expected to be much slower and the stereochemistry of the exchange to be mainly inversion. However, since deuterium at the *endo*-position of sulphoxide (5) ($k_x/k_n = 57:1$) becomes experimentally detectable when the substrate is almost completely deuteriated at the *exo*-position [compound (9)], *endo*-proton abstraction followed by deuteriation can lead only to the *exo–endo*-dideuteriated product (10), *i.e.*, to the appearance of deuterium at the *endo*-position, whatever the stereochemical fate of the initially formed carbanion might be (Scheme 1). Thus, in sulphoxide (5) the measured rate of deuterium exchange should closely reflect the rate of α-proton abstraction.



SCHEME 1

We tried to gain more direct evidence about the stereochemistry of the exchange in sulphoxides of this series by α-carbanion generation in the presence of equimolar amounts of n-butyl-lithium in tetrahydrofuran (THF) at −70° and subsequent quenching with D_2O or MeI, but the attempts were only partly successful.

While sulphoxide (3) gave mainly decomposition products in these conditions, sulphoxide (2) gave a clean sequence of highly selective α-methylation and α-deuteriation reactions (Scheme 2). The first α-methyl-

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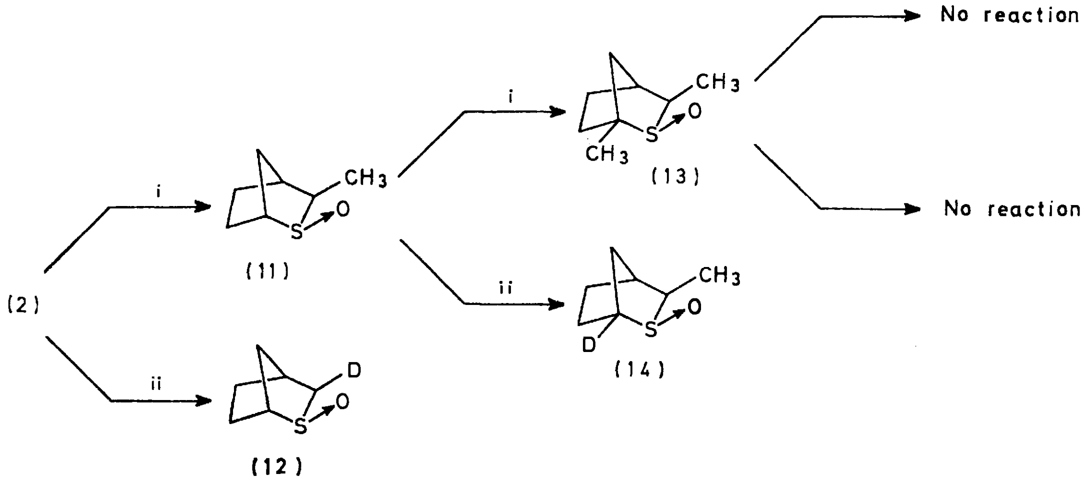
* The validity of this assumption can hardly be assessed, since it implies that no appreciable difference in molecular geometry exists between substrates (4)—(6) and that the steric requirements of a sulphur lone-pair are equal to those of an SO bond.

[4] T. T. Tidwell, *J. Amer. Chem. Soc.*, 1970, **92**, 1448.

ation and α-deuteriation of sulphoxide (2) produced the *exo*-derivatives (11) and (12) as the only detectable products. Both electrophilic reactions followed the same stereochemical course (retention), while an opposite stereochemistry was observed for open-chain sulphoxides.[5] The observed *exo*-selectivity may be considered a proof of the greater stability of a type (7) over type (8) carbanion under equilibrating conditions.

Compound (11) was considered a useful model to establish the stereochemistry of the exchange at the *endo*-α-proton, but it decomposed rapidly on treatment in MeONa–MeOD solution at 100°. However, by reaction with Bu^nLi at −70° and subsequent quenching (Scheme 2), the only detectable product involved carbanion formation at C-1. Carbanions at C-1 in compounds (1)—(6) have approximately the orientation of the bisector of the angle oxygen–sulphur–oxygen, for which theory [1,2] predicts maximum stability in the case of $H-SO-CH_2^-$ or $H-SO_2-CH_2^-$. From the exchange data in the Table it can be seen that the kinetic acidity of 1-H compared with that of *exo*- and *endo*-protons at C-3 (neglecting isotope effects) has an intermediate value in the case of (4),(1) and (6),(3), and is the lowest in (5),(2), in apparent contradiction to theoretical predictions. It is to be observed, however, that carbanions at C-3 are secondary, while at C-1 they are tertiary, and, other things being equal, the latter are less stable.[6] When, as in compound (11) (Scheme 2), both carbanions at C-1 and -3 are tertiary, the first shows greater stability [comparison however is not available for α-methyl derivatives isomeric with compound (11)].

Finally, attention is drawn to the unexpected inertness of compound (13), which was recovered unaltered after treatment with five mol. equiv. of Bu^nLi at −70°, or with Bu^nLi in the presence of *NNN'N'*-tetramethylethylenediamine [7] at −40°, and subsequent quenching with D_2O or MeI.



SCHEME 2 Reagents: i, Bu^nLi–MeI; ii, Bu^nLi–D_2O.

EXPERIMENTAL

^1H N.m.r. spectra were recorded on a JEOL JNM-C-60HL spectrometer.

2-Thiabicyclo[2.2.1]*heptane and* 1,4,5-endo,6-endo-7,7-*Hexadeuterio-2-thiabicyclo*[2.2.1]*heptane*.—These were obtained by employing a modification of previously reported methods [8-10] and details will be reported elsewhere.

Sulphoxides and Sulphones (1)—(6).—These were obtained from the corresponding sulphides by a reported procedure.[8] Physical and spectroscopic properties were in agreement with those in the literature.[8-10]

3-exo-*Methyl-* (11) *and* 3-exo-*Deuterio-2-thiabicyclo*[2.2.1]-*heptane* 2-exo-*Oxide* (12).—n-Butyl-lithium (1 mol. equiv.) (prepared [11] and titrated [12] as described) in THF cooled at −70° was added dropwise by means of a syringe to a stirred solution of sulphoxide (2) (4 g) in THF (120 ml) cooled at −70° under nitrogen. After 5 min a solution of MeI (9 g) in THF was added at such a rate that the temperature did not exceed −60°. The mixture was stirred for 1 h at −70° and then allowed to reach room temperature. The solvent was evaporated at reduced pressure and water added to the residue. Extraction with CH_2Cl_2 gave an oily product in 100% yield, some of which was distilled at 60° and *ca.* 0·01 mmHg, n_D^{17} 1·5352 (Found: C, 58·4; H, 8·3; S, 21·9. $C_8H_{12}OS$ requires C, 58·3; H, 8·4; S, 22·2%). ^1H N.m.r. analysis of the crude product was compatible with the selective replacement of 3-*exo*-H in the starting material by a methyl group, *i.e.*, compound (11) was formed. This was confirmed by substituting D_2O for MeI in the above reaction. ^1H N.m.r. analysis of crude (12) showed the selective disappearance of the *exo*-proton

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[5] (*a*) T. Durst, R. R. Fraser, M. R. McClory, R. B. Swingle, R. Viau, and Y. Y. Wigfield, *Canad. J. Chem.*, 1970, **48**, 2148; (*b*) T. Durst, R. Viau, and M. R. McClory, *J. Amer. Chem. Soc.*, 1971, **93**, 3077; (*c*) K. Nishihata, and M. Nishio, *Chem. Comm.*, 1971, 958; (*d*) K. Nishihata, and M. Nishio, *J.C.S. Perkin II*, 1972, 1730; (*e*) R. Viau, and T. Durst, *J. Amer. Chem. Soc.*, 1973, **95**, 1346.

[6] D. J. Cram, 'Fundamentals of Carbanion Chemistry,' Academic Press, New York, 1965, ch. 1.

[7] J. M. Mallan, and R. L. Bebb, *Chem. Rev.*, 1969, 693.

[8] C. R. Johnson, H. Diefenbach, J. E. Keiser, and J. C. Sharp, *Tetrahedron*, 1969, **25**, 5649.

[9] R. R. Fraser, T. Durst, M. R. McClory, R. Viau, and Y. Y. Wigfield, *Internat. J. Sulphur Chem.*, 1971, **A1**, 133.

[10] R. R. Fraser, and Y. Y. Wigfield, *Chem. Comm.*, 1970, 1471.

[11] H. Gilman and B. J. Gay, *J. Org. Chem.*, 1965, **22**, 1165.

[12] R. A. Ellison, R. Griffin, and F. N. Kotsonis, *J. Organometallic Chem.*, 1972, **36**, 209.

signal consequent upon its replacement with a deuterium atom.

1,3-exo-*Dimethyl-* (13) *and* 1-*Deuterio*-3-exo-*methyl*-2-*thiabicyclo*[2.2.1]*heptane* 2-*Oxide* (14).—In three separate experiments, sulphoxide (11) was treated in THF solution with Bu^{n}Li at $-70°$ as described above, followed by the addition of a THF solution of MeI, D_2O, and H_2O, respectively. An oily product was obtained in quantitative yield in each case, which, omitting any purification, was identified by ^{1}H n.m.r. analysis as compounds (13), (14) (selective disappearance of 1-H signal), and unaltered (12), respectively. Sulphoxide (13) was recovered unaltered when it was treated in turn with 5 mol. equiv. of Bu^{n}Li and *NNN'N'*-tetramethylethylenediamine in THF at $-40°$, followed by MeI or D_2O addition.

Kinetic Measurements of Isotopic Exchange.—For compounds (1)—(6), 10 separate samples were prepared by placing in a Pyrex glass tube (15 cm × 0·8 cm) 1M-substrate in MeOD (0·4 ml) and 2·37M-MeONa in MeOD (0·4 ml). The tube was chilled in an acetone–dry ice bath and sealed. At time zero the samples were placed in a bath at 100° (boiling water). After suitable intervals the samples were withdrawn, chilled to below 0°, opened, and immediately acidified with dilute HCl. The aqueous solution was saturated with NaCl and extracted with $CHCl_3$ (× 10). The $CHCl_3$ solution was dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The white solid residue was dissolved with 0·5 ml of the solvent used for subsequent ^{1}H n.m.r. analysis [D_2O for (2) and (5), CF_3CO_2H for (3) and (6), and C_6H_6 for (1) and (4)]. In the graphical derivation of the rate constants of the Table, the integrated pseudo-first-order rate equation ($\log c/c_0 = -0{\cdot}43\, kt$) was applied, the initial concentration c_0 being substituted with A_0/n (A_0 is the intensity of the n.m.r. signals of n non-exchangeable protons in the substrate, selected as reference) and the concentration c being substituted with A (area measured at time t for the α-proton signal under consideration). Proton assignments were derived from those already reported.[9,10]

We thank the Italian CNR for financial support.

[4/464 *Received*, 11*th March*, 1974]