The Absolute Stereochemistry of Isotopic Exchange and Methylation in Benzyl Methyl Sulphoxide †

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α-Sulphinyl carbanions generated from diastereomeric monodeuteriobenzyl methyl sulphoxides were quenched with water and methyl iodide and the kinetic isotope effect also determined. Analyses of the isomer distributions and the deuterium content of the resulting mixture revealed that the stereochemical pathway of these reactions consists of three distinct steps, namely (i) the stereochemistry of the formation of the carbanions, (ii) the stereochemistry of the configurational inversion equilibrium, and (iii) the stereochemistry of the approach of the electrophile. It was concluded that the *pro-R* hydrogen in the (*S*)-sulphoxide is abstracted preferentially, *k*(*R*)/*k*(*S*) *ca.* 1·5, and that the equilibrium constant between the configurationally inverted carbanions is *ca.* 20 in favour of the carbanion having the carbon lone pair which bisects the sulphur lone pair and the S–O bond. It is also suggested that the isotopic exchange occurs with retention and the methylation with inversion during the final substitution step in the light of Wolfe's theoretical requirement from extensive non-empirical calculations on α-sulphinyl carbanions.

ELECTROPHILIC substitution at a saturated carbon atom is generally known to proceed with retention of configuration.[1] The stereochemistry at the chiral carbon atom in these reactions has become a subject of controversy due to the fact that inversion is also possible in some reaction.[2–4] In particular, we found that (*SS*)-α-deuteriobenzyl methyl sulphoxide $[^{2}H]$-(I) affords (*RS*)-methyl α-deuterio-α-phenethyl sulphoxide $[^{2}H]$-(II) on quenching its α-lithio-derivative with methyl iodide and suggested that methylation occurs with retention whereas protonation or deuteriation proceeds with configurational inversion.[2] Durst and his co-workers studied the reactions of various α-lithiosulphoxides with alkylating agents and heavy water. They also found that the isomers preferentially produced from methylation and deuteriation have opposite stereochemistry but presented a contrasting interpretation regarding the stereospecificities of the reactions.[3] Since the discrepancy in the interpretations arose from the configuration assigned to the intermediate carbanion, it was important to obtain direct knowledge regarding the acidities of the diastereotopic hydrogens (and deuterons) and the relative stability of the resulting carbanions. We discuss here these features in light of the results obtained from re-protonation experiments of the monodeuteriated sulphoxides (*RR*/*SS*)-$[^{2}H]$-(I) and (*RS*/*SR*)-$[^{2}H]$-(I) and the kinetic isotope effect of the reaction.

EXPERIMENTAL

(*RR*/*SS*)- and (*RS*/*SR*)-α-monodeuteriobenzyl methyl sulphoxides were prepared as described elsewhere,[5,6] the amount of impurities (the isotopically normal and the other diastereomer) being at most 15%. Isotopic and isomer purities of these and the resulting mixtures were analysed by n.m.r. and mass spectral (by monitoring the intense peaks at *m*/*e* 91, 92 and 105, and 106 attributed to $PhCH_2^+$, $PhCHD^+$ and $PhCH^+CH_3$, and $PHCD^+CH_3$ respectively) analyses. N.m.r. and mass spectra were determined with a JEOL–JNM-4H-100 high resolution n.m.r. spectrometer and a JEOL–JMS–O1SG mass spectrometer, the accuracies in the quantitative estimations being within ±5%. The data listed in the Table are average values from at least three experiments and corrected by taking account of the isotopic and isomer purities of the starting materials.

Re-protonation.—To a solution of α-deuteriobenzyl methyl sulphoxide (1 equiv.) in tetrahydrofuran was slowly added 1 equiv. of n-butyl-lithium at −70° under an inert atmosphere. The resulting solution was immediately neutralized with dilute hydrochloric acid and allowed to stand for 30 min. It was repeatedly extracted with chloroform in the presence of saturated sodium chloride. The combined extracts were dried and concentrated to yield an oily material which was distilled (b.p. 108—110° at 0·5 mmHg) and subjected to spectral analyses.

Determination of the Isotope Effect.—A mixture of benzyl methyl sulphoxide (1 equiv.) and α,α-dideuteriobenzyl methyl sulphoxide (1 equiv.) was treated with n-butyl-lithium (1 equiv.) in tetrahydrofuran at −70°. To this solution was added an excess of methyl iodide and this was stirred for 30 min. After standing for a further 1 h at room temperature, this was repeatedly extracted with chloroform in the presence of sodium chloride. Concentration of the combined extracts yielded an oil, which was distilled (b.p. 105—115° at 0·5 mmHg) and submitted to spectral analyses.

RESULTS AND DISCUSSION

α-Sulphinyl carbanions generated from (*RR*/*SS*)-$[^{2}H]$-(I)[5] and (*RS*/*SR*)-$[^{2}H]$-(I)[6] were quenched with excess of water. Careful work-up followed by spectral analyses of the total crude products revealed the isomer ratios and the deuterium content as listed in the Table.

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† Presented at the 22nd Symposium of Organic Reaction Mechanisms (Japan), Nagoya, Oct., 1971, Abstracts, p. 114.

[1] (*a*) D. J. Cram, 'Fundamentals of Carbanion Chemistry,' Academic Press, New York, 1965, p. 116 ff; (*b*) F. R. Jensen and B. Rickborn, 'Electrophilic Substitution of Organomercurials,' McGraw-Hill, New York, 1968; (*c*) D. S. Matteson, *Organometallic Chem. Rev. A*, 1969, **4**, 263.

[2] K. Nishihata and M. Nishio, *Chem. Comm.*, 1971, 958.

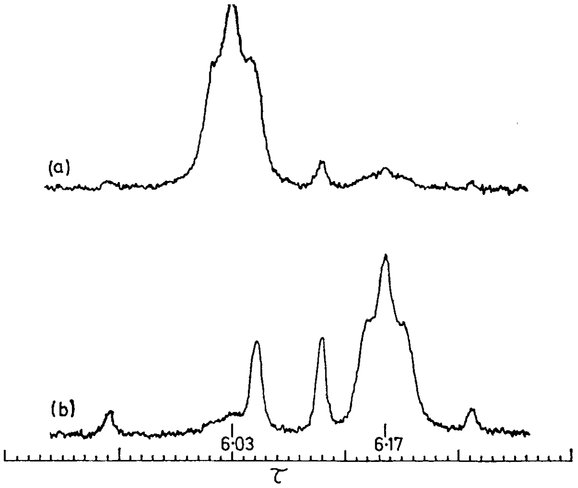
[3] T. Durst, R. Viau, and M. R. McClory, *J. Amer. Chem. Soc.*, 1971, **93**, 3077.

[4] (*a*) H. C. Brown and C. F. Lane, *Chem. Comm.*, 1971, 521; (*b*) R. Lett, S. Bory, B. Moreau, and A. Marquet, *Tetrahedron Letters*, 1971, 3255; (*c*) F. R. Jensen and D. D. Davis, *J. Amer. Chem. Soc.*, 1971, **93**, 4048.

[5] (*a*) M. Cinquini, S. Colonna, and F. Montanari, *Chem. Comm.*, 1969, 607; (*b*) T. Durst, R. R. Fraser, M. R. McClory, R. B. Swingle, R. Viau, and Y. Y. Wigfield, *Canad. J. Chem.*, 1970, **48**, 2148.

[6] (*a*) A. Rauk, E. Buncel, R. Y. Moir, and S. Wolfe, *J. Amer. Chem. Soc.*, 1965, **87**, 5498; (*b*) J. E. Baldwin, R. E. Hackler, and R. M. Scott, *Chem. Comm.*, 1969, 1451.

The most interesting of these results is an apparent configurational inversion observed in the re-protonation of (*RR*/*SS*)-[^{2}H]-(I). The substrate, consisting mostly of the (*RR*/*SS*)-diastereomer (86%), was converted to a mixture which consists of 81% (*RS*/*SR*)-[^{2}H]-(I) (Figure).



Methylene protons of the n.m.r. spectra (100 MHz, in D_2O, tetramethylsilane as external reference) of (a), (*RR*/*SS*)-[^{2}H]-(I) before exchange and (b) after exchange

The high deuterium content in the resulting mixture indicates the preferential abstraction of the *pro-R* hydrogen in the (*S*)-sulphoxide.[2] The observed values for isomer distribution, however, cannot be explained without considering a rapid configurational inversion of the intermediate carbanions,[4b,7] with one of the epimers existing in an overwhelming predominance. This is consistent with Wolfe's theoretical results[8] from extensive non-empirical M.O. calculations on the hypothetical carbanion $HMeSO^-$ (hydrogen methyl sulphoxide) that there is no barrier to inversion of the carbanions.

The isomer distribution and the deuterium content obtained in the re-protonation experiments

		Products (%)			
Substrates		(*RR*/*SS*)-[^{2}H]-(I)	(*RS*/*SR*)-[^{2}H]-(I)	Total deuterium	(I)
(*RR*/*SS*)-[^{2}H]-(I)	N.m.r.	6	81	87	13
	M.s.			81	19
(*RS*/*SR*)-[^{2}H]-(I)	N.m.r.	5	71	76	24
	M.s.			74	26

The high values of deuterium content observed in the experiment with (*RS*/*SR*)-[^{2}H]-(I) suggest that an appreciable isotope effect is operating at this temperture in the rate-determining proton abstraction step;* superimposed on this effect are differential abstraction rates dependent on the geometry of the molecule. The ratios for the second order rate constants $k_h(R)/k_d(S)$ and $k_h(S)/k_d(R)$ are estimated from the above data to be 9 and 4 respectively.† Similar values were obtained from the quenching experiments with methyl iodide.

A mixture of non-deuteriated (I) (1 equiv.) and α,α-dideuterio-(I) (1 equiv.) was treated with 1 equiv. of n-butyl-lithium in THF at −70°, followed by quenching with excess of methyl iodide. N.m.r. and mass spectral analyses of the total crude product revealed that it consists of methyl α-phenethyl sulphoxide (II) (80%) and methyl α-deuterio-α-phenethyl sulphoxide [^{2}H]-(II) (20%) along with unchanged (I) and [$^2H_2$]-(I). From this the kinetic isotope effect at −70° is estimated to be 7. The ratios for $k_h(R) : k_h(S) : k_d(R) : k_d(S)$ are thus roughly estimated to be 9 : 6 : 1·5 : 1. A considerably smaller k_h/k_d value at a higher temperature (2·1 at 0°) suggests that competition for lithium cation between the generated carbanions and the surviving substrate molecules occurs, and this may mask the genuine kinetic term of the isotope effect and consequently lead to under-estimations.

If Wolfe's theoretical result concerning the stability of α-sulphinyl carbabion[8] and the conformational preference of this molecule[6a,11] is adapted to the present problem, it suggests that the carbanion prefers a pyramidal structure in which *gauche*-interaction[12] between adjacent electron pairs ‡ and the polar S–O bond are maximized (carbanion of the type *b*, see Scheme), and consequently, that the protonation proceeds with retention with high stereospecificity, and that the methylation with MeI occurs with inversion.[3] An alternative mechanism for the α-methylation,[2,3] less likely however,[3] is that the methyl cation prefers the less populated type *a* carbanion (in this case the substitution occurs with retention). This possibility cannot be excluded at this time.

Adopting the forementioned Wolfe's postulate,[12] the predominant pathway of the experiments can be summarized as shown in the Scheme. Preferential abstraction of H_R, $k_h(R)/k_h(S)$ *ca.* 1·5, followed by inversion–retention for isotopic exchange (inversion

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* For cases where smaller isotope effects have been observed (in these cases, the rate-controlling step involves a carbanion–solvent reorganisation rather than a breaking of the carbon–hydrogen covalent bond) see refs. 1*a* (pp. 28 and 29) and 9.

† The kinetic data reported in this paper were obtained from following relationship: $k_1/k_2 = \ln(1 - p_1)/\ln(1 - p_2)$, where k_1 and k_2 stand for rate constants and p_1 and p_2 are mole fractions of the resulting isomers in a competive reaction (see ref. 10).

‡ Hartmann and Eliel have very recently reported an interesting result suggestive of this effect in deuteriation and methylation of 2-lithio-1,3-dithians which proceed with remarkable stereoselectivity.[7] See also for a similar observations on 1,3,5-trithians, M. Fukunaga, T. Sugawara, and M. Ōki, *Chem. Letters*, 1972, 55.

[7] A. A. Hartmann and E. L. Eliel, *J. Amer. Chem. Soc.*, 1971, **93**, 2572.

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

[9] (*a*) D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Amer. Chem. Soc.*, 1961, **83**, 3688; (*b*) D. J. Cram and S. H. Pine, *ibid.*, 1963, **85**, 1096; (*c*) B. J. Hutchinson, K. K. Andersen, and A. R. Katritzky, *ibid.*, 1969, **91**, 3839; (*d*) J. N. Roitman and D. J. Cram, *ibid.*, 1971, **93**, 2225.

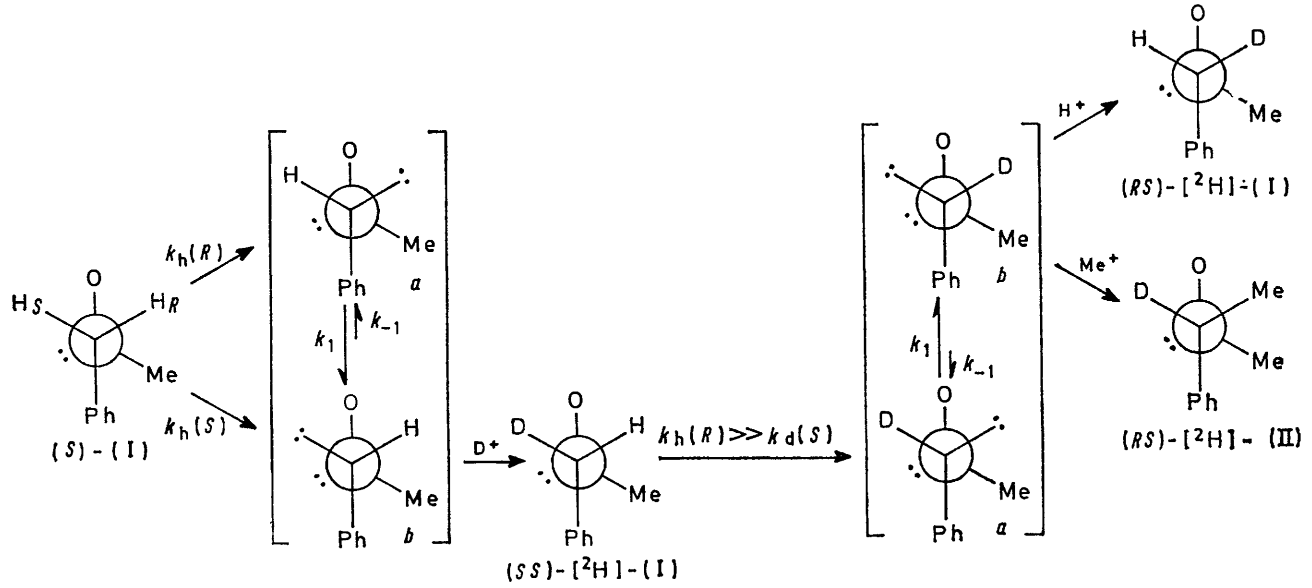
[10] N. Inamoto, 'Introduction to Kinetics in Organic Reactions,' Hirokawa Publishing Co., Tokyo, 1969, p. 11.

[11] S. Wolfe and A. Rauk, *Chem. Comm.*, 1966, 778.

[12] S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc.* (*B*), 1971, 136.

at the equilibration stage and retention at the substitution step: overall inversion) and inversion–inversion or retention–retention for the methylation (formal retention).

The finding of Wolfe[6a] that the predominant formation of (*RS*)-[^{2}H]-(I) from competitive base catalysed exchange of (*S*)-(I) in deuteriated protic solvents can be rationalized by considering the relative stabilities of the transition states leading to the carbanions[3] where the Curtin–Hammett principle will directly apply, with a reasonable assumption that protonation occurs with retention.[1] This does not conflict with the present conclusion regarding the quenching experiments which reflects a blend of effects due to the stereochemistry of (i) the abstraction step (kinetically controlled S_E2 mechanism), (ii) the configurational inversion equilibrium, and (iii) the kinetically controlled step of electrophilic attack.



SCHEME

We now concur with Durst that protonation occurs with retention[3] and that removal of either the *pro-R* or -*S* hydrogen has little bearing on the stereochemistry of the products,[13] in at least this case, since it is apparent from present results that equilibrium between the carbanions is reached before quenching ($k_1/k_{-1} = K$ is *ca.* 20 assuming 100% stereospecificity at step iii) and that the difference in the acidities of the diastereotopic hydrogens (step i) is much smaller than presumed earlier.[2]

It is not certain why a small structural change in the electrophile causes such a dramatic effect on the stereospecificity at the final substitution step. However chemical intuition suggests that the size of the electrophile and the accompanying anion play an important role. Apart from the clarification of these points, it is certain that these sulphoxides will provide potential means of preparing optically active compounds by hydroxyalkylation,[14] carbonation,[15] or successive alkylations, due to their ready availability in an optically active state[16] and the excellent stereoselectivity. We would further predict that an interchange of the reaction sequence can alter the stereochemical result.

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[13] T. Durst, personal communication.

[14] (*a*) C. R. Johnson and C. W. Schroeck, *J. Amer. Chem. Soc.*, 1971, **93**, 5304, 5305; (*b*) T. Durst, R. Viau, R. van den Elsen, and H. Nguyen, *Chem. Comm.*, 1971, 1334.

[15] K. Nishihata and M. Nishio, unpublished data.

[16] (*a*) K. K. Andersen, *J. Org. Chem.*, 1964, **29**, 1953; (*b*) F. Wudl and T. B. K. Lee, *Chem. Comm.*, 1972, 61.