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CONFIGURATIONAL ASSIGNMENT TO ARYL-ALKYL-SULPHOXIDES BASED ON ASYMMETRIC SYNTHESIS

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Several papers dealing with attempts to establish absolute configurations in dissymmetric sulphoxides appeared in the last few years (1-8). Although the absolute configuration of some natural sulphoxides was unequivocally established by X-ray analysis (1,6b), the aim of many investigations was to find general and possibly simple methods of configurational correlations. A few of these (2,3) are based on the asymmetric synthesis of sulphoxides.

The key for the final solution of the problem was Andersen's synthesis of optically active sulphoxides from diastereoisomeric sulphinates and Grignard reagents (4). It was shown by ORD measurements (4c,8b) that nucleophilic substitution at sulphur in sulphinates is stereospecific and proceeds with inversion of configuration. On these bases it was possible to Mislow, after determining the absolute configuration of diastereoisomeric sulphinates by X-ray technique (9), to assign the absolute configuration to dissymmetric sulphoxides (8): in the case of aryl-alkyl-sulphoxides (8b), this assignment of configuration [(R)(+), (S)(-)] agrees with that suggested by us in 1961 (2b) from the results of asymmetric synthesis.

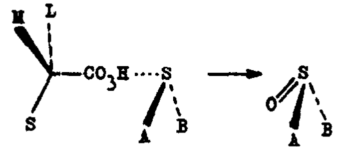
Since Mislow et al. (8b,c) are of the opinion that the coincidence is purely fortuitous, this makes necessary a survey of the validity and limits of our method of correlation.

i) The oxidation of phenyl-alkyl-sulphides by (1S)(+)percamphoric acid (I) in chloroform at -5° usually yields optically active sulphoxides. At the

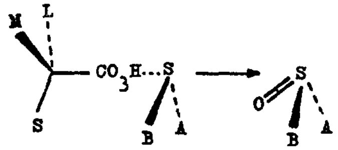
D-line these are always dextrorotatory for normal or β-branched alkyl chains (Me, Et, n-Pr, n-But, i-But), inactive or nearly inactive for α-branched chains (i-Pr, s-But), laevorotatory for doubly branched chains in α (t-But) (2a). The same results are obtained in the oxidation of the corresponding m-COOCH$_3$-phenyl-alkyl-sulphides by peracid (I) and (S)(+) perhydratropic acid (II) (2b).

ii) With an extension to oxidation of sulphides of the empirical correlations expressed by Cram and Prelog (10) for the asymmetric induction at carbon, we proposed (2) that the stereochemical trend of the reaction is considered to be regulated by the balance between two conformations when the attack of the reagents takes place, a) more favoured, b) less favoured, in which the largest group A of the sulphide respectively faces the less hindered region (S, M) and the medium hindered region (S, L) of the peracid.

a)



b)



The rule indicated above is also based on the logical assumption that the electrophilic attack on sulphur (11) takes place in the direction of maximum charge density in the lone pair of sulphur. It is assumed that the staggered conformations a) and b) are relatively more favoured with respect to the other staggered ones in which groups A or B face the most hindered region (L, M) of the peracid, and with respect to all eclipsed conformations.

In agreement with Cram's and Prelog's rules (10), this line of reasoning does not pretend to give any detailed or rigorous interpretation of the transition state in the oxidation of sulphides to sulphoxides by peracids.

iii) Other effects beside steric induction (electrostatic, solvation, etc.)

are neglected in the above scheme; this must imply several and important limitations. Thus, strongly polar groups (NO_2, SO_2R, etc.) bonded to the peracid or solvents different from chloroform may determine erratic results, so that the correlation may not be valid anymore (12); from this point of view the choice of chloroform, made by analogy with the normal oxidations by peracids, clearly revealed to be advantageous.

On the other hand the distance between the inducing asymmetric centre and the reaction centre, which is larger than that normally found in the asymmetric syntheses at carbon, should restrict by itself the amount of asymmetric synthesis (in the cases so far examined it does not exceed 5%).

iv) The proposed model accounts for the inversion of rotation (and of absolute configuration) with the same peracid, passing from aryl-methyl- to aryl-t-butyl-sulphoxides (methyl $\ll$ aryl $<$ t-butyl), and for the very low or negligible yield in asymmetric synthesis in the case of i-propil- and s-butyl-aryl-sulphoxides, in which sizes of groups bonded to sulphur are comparable. Steric differences in positions farther from sulphur seem to be irrelevant (methyl $\approx$ n-alkyl).

v) Checked on methyl- and t-butyl-phenyl-sulphoxide, the stereochemical trend of the asymmetric synthesis was constantly observed in the oxidations in chloroform by the following peracids (13): (S)(+)hydratropic (II) (2b,12), (S)(+)α-cyclohexyl-propionic (III) (2d), (R)(+)endo-norbornane-carboxylic (IV) (2c), (S)(+)exo-norbornane-carboxylic (V) (2c). All these peracids yielded methyl- and t-butyl-phenyl-sulphoxide of opposite sign, and always in agreement with the proposed scheme [with the only exception of (V) which, together with the expected (+)methyl-phenyl-sulphoxide, afforded an optically inactive t-butyl-phenyl-sulphoxide].

vi) The ORD curves in the 300-600 mμ region suggest that for equal sign of rotation at the D-line the aryl-alkyl-sulphoxides examined have the same absolute configuration: from the results of asymmetric syntheses, this should be (R)(+), (S)(-), in agreement with the results of X-ray analysis (8b,9).[x]

vii) The asymmetric synthesis of benzyl-alkyl-sulphoxides by the same method gave results of more difficult interpretation; moreover, strong solvent effects may change the sign of rotation and the ORD curve of the sulphoxides, at least in the region above 350 mμ.[xx]

Summing up the situation, there is no doubt that the extension, technically impossible till recently, of ORD spectroscopy under 300 mμ region, and the easy conversion of diastereoisomeric sulphides into optically active sulphoxides (4) have opened new possibilities of investigation and synthesis of the latter compounds. However it must be emphasized that, within the limits stated above, and for the compounds that we have investigated, the simple correlation employed by us (2) between the configurations of optically active peracids and those of aryl-alkyl-sulphoxides retains so far its validity. Therefore it is believed that, notwithstanding low optical yields, the constant trend of correct results descending from our working hypothesis may hardly be attributed to a constant trend of casual events (8b).

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REFERENCES

1. R. Hine and D. Rogers, *Chem. and Ind.* 1428 (1956); R. Hine, *Acta Cryst.* **15**, 635 (1962).

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[x] The oxidation of optically active esters of o-methylthio-benzoic acid with symmetric oxidizing agents gives optically active o-methylsulphinyl-benzoic acid (2b). A more detailed account of this asymmetric synthesis will be given in a forthcoming paper.

[xx] A tentative hypothesis put forward on the possible absolute configuration of benzyl-alkyl-sulphoxides (2a) has been arbitrarily interpreted by Mislow *et al.* (8c) as definitive assignment.

2. a) A. Mayr, F. Montanari, and M. Tramontini, *Gazz. Chim. Ital*. **90**, 739 (1960); b) A. Maccioni, F. Montanari, M. Secci, and M. Tramontini, *Tetrahedron Letters* 607 (1961); c) G. Barbieri, U. Folli, F. Montanari, and G. Torre, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 47 (1965); d) A. Maccioni, *ibid*. **23**, 41 (1965).

3. K. Balenović, I. Bregovec, D. Francetić, I. Monković, and V. Tomašić, *Chem. and Ind*. 469 (1961); see also: K. Balenović, N. Bregant, and D. Francetić, *Tetrahedron Letters* 20 (1960); K. Balenović and N. Bregant, *Chem. and Ind*. 1577 (1964).

4. a) K. K. Andersen, *Tetrahedron Letters* 93 (1962); b) *J. Org. Chem*. **29**, 1953 (1964); c) K. K. Andersen, W. Gaffield, N.E. Papanikolau, J. W. Foley, and R. I. Perkins, *J. Amer. Chem. Soc*. **86**, 5637 (1964).

5. D. J. Cram and S. H. Pine, *J. Amer. Chem. Soc*. **85**, 1096 (1963).

6. a) W. Klyne, J. Day, and A. Kjaer, *Acta Chem. Scand*. **14**, 215 (1960); b) K. K. Cheung, A. Kjaer, and G. A. Sim, *Chem. Comm*. 100 (1965); c) B. W. Christensen and A. Kjaer, *ibid*. 225 (1965).

7. W. Gaffield, F. F. Wong, and J. F. Carson, *J. Org. Chem*. **30**, 951 (1965).

8. a) K. Mislow, M. M. Green, P. Laur, and D. R. Chisholm, *J. Amer. Chem. Soc*. **87**, 665 (1965); b) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, *ibid*. **87**, 1958 (1965), and references cited therein; c) K. Mislow, M. M. Green, and M. Roban, *ibid*. **87**, 2763 (1965).

9. E. B. Fleischer, M. Axelrod, M. M. Green, and K. Mislow, *J. Amer. Chem. Soc*. **86**, 3395 (1964).

10. E. L. Eliel, *Stereochemistry of Carbon Compounds*, p. 68. McGraw-Hill, New York (1962).

11. a) C. G. Overberger and R. W. Cumming, *J. Amer. Chem. Soc*. **75**, 4250 (1956); b) G. Modena *et al*., *Gazz. Chim. Ital*. **89**, 834 (1959) and following papers.

12. F. Montanari *et al*., researches in progress.

13. For a mild conversion of optically active carboxylic acids into peracids, see: G. Barbieri and F. Montanari, *Ricerca Sci. Rend. A*. **3**, 1233 (1963).