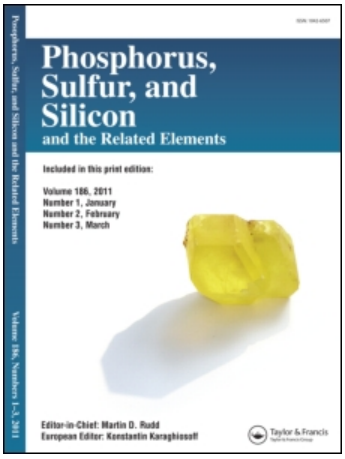

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ASYMMETRIC REDUCTION OF CHIRAL SULFOXIDES BY OPTICALLY ACTIVE LITHIUM ALUMINUM HYDRIDE COMPLEXES WITH ALCOHOLS[1]

by

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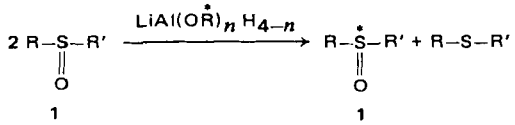
ABSTRACT

Optically active sulfoxides of low optical purity have been obtained by partial reduction of racemic sulfoxides using optically active lithium aluminum hydride–alcohol complexes as reducing agents. The steric course of the asymmetric reductions was found to be dependent on the composition of the complexes and on the configurations of optically active alcohols used. No configurational relationship between chirality at the sulfur and carbon atoms was observed.

Asymmetric syntheses of sulfoxides have recently been reviewed.[2] Most of the reactions described involve an asymmetric chemical or microbial oxidations of unsymmetrical sulfides or chiral sulfoxides. There are only two works published reporting an asymmetric induction by reducing chiral sulfoxides with optically active reagents. In 1964 Balenovic and Bregant[3] described asymmetric reduction of racemic sulfoxides by optically active thiols and a closely related asymmetric reaction of chiral sulfoxides 1 with optically active phosphorus thioacids has recently been reported from our Laboratory.[4]

In these experiments a difference in the rate of reduction of the two sulfoxide enantiomers by the optically active mercapto-reagents has been found, so that if the reduction is taken only part way or an excess of 1 is used the recovered sulfoxide is optically active.

Now we wish to report a new example of asymmetric kinetic destruction of the sulfoxide racemate by optically active complexes of lithium aluminum hydride with alcohols.[5]



1 1

In this study we took advantage of the well-known reduction of sulfoxides to sulfides by lithium aluminum hydride[7] and also of described application of optically active alkoxy lithium aluminum hydrides as the asymmetric reducing agents.[8]

In the first set of experiments the reduction of sulfoxides 1 used in two molar excess was carried out with (+)quinidine-lithium aluminum hydride complex (1 : 1 molar) in boiling ether. After *ca.* 40 hr the unreduced sulfoxides 1 were isolated by the usual method. In most cases they were found to be optically active, although the values of optical rotations were rather low. Optical purity of the recovered 1 was in the range between 0.2 to 2.7%.[15]

Optical rotations and absolute configurations of the sulfoxides 1 obtained are collected in Table I.

Since optically active tertiary phosphinoxides were shown to racemize on treatment with lithium aluminum hydride,[9] it was desirable to prove the optical stability of sulfoxides under experimental conditions employed

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4. M. Mikołajczyk and M. Para, *Chem. Commun.*, 1192 (1969).
5. A similar approach has been used by Holt *et al.*[6] to prepare new optically active organosilicon compounds.
6. A. Holt, A. W. P. Jarvie, and G. J. Jervis, *Tetrahedron Letters*, 4087 (1968); *J. Chem. Soc.*, Perkin II, 114 (1973).
7. F. G. Bordwell and M. H. McKellin, *J. Am. Chem. Soc.*, 73, 2251 (1951); E. N. Karaulova and G. D. Halpern, *Zhur. Obs. Khim.*, 29, 3033 (1959); H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Am. Chem. Soc.*, 88, 1458 (1966).
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TABLE I

Asymmetric Reduction of Sulfoxides by (+)Quinidine–Lithium aluminum hydride complex[a]

No.	Sulfoxide	Sulfoxide recovered (%)[b]	$[\alpha]_{589}$ (neat)	$[\alpha]_{589}$ (c)[c]	Abs. conf.[d]
1a	CH_3–SO–C_2H_5	24	–	–	–
1b	CH_3–SO–C_3H_7–*n*	40	−2.02°	−2.04° (10.1)	R
1c	CH_3–SO–C_3H_7–*i*	40	−0.12°	−0.12° (10.2)	R
1d	CH_3–SO–C_4H_9–*n*	50	−2.06°	–	R
1e	CH_3–SO–C_4H_9–*i*	35	−0.95°	−0.96° (5.2)	R
1f	CH_3–SO–$CH_2C_6H_5$	72	–	–	–
1g	CH_3–SO–C_6H_4–CH_3–*p*	45	–	−0.35° (3.2)	S

[a] Boiling ether; 40 hr, 1 : 1 : 2 ratio of $LiAlH_4$: quinidine : sulfoxide.

[b] Based on the weight of the sulfoxide isolated.

[c] Rotations refer to solvent ethanol.

[d] For absolute configuration and optical activity of sulfoxides see ref.[10–13]

for the reduction. Thus, we carried out the reduction of (−)methyl *n*-butyl sulfoxide 1d, $[\alpha]_{589}$ −2.85°, with a half-molar amount of lithium aluminum hydride in boiling ether. The recovered excess of 1d had $[\alpha]_{589}$ −2.73°, so its optical rotation was practically unchanged. This result clearly demonstrates that racemization of 1d did not take place and therefore the order of asymmetric kinetic destruction of the sulfoxide racemate during the reduction studied is very low.

In the second step of this study the effect of various optically active alcohols on steric course of the reduction of (±)sulfoxide 1d was investigated. The results are shown in Table II. Of the alkaloids tested, the reducing reagent from (+)quinidine led to the highest optical purity (2.7%) of 1d. With (−)cinchonidine and (−)quinine the optical purity was lower.

It is of interest to compare the absolute configurations of the optically active methyl *n*-butyl sulfoxide 1d obtained after the incomplete reduction by optically active lithium aluminum alkoxy hydrides. An inspection of Table II reveals that the reduction of (±) 1d by complexes from (+)quinidine and (−)cinchonidine having enantiomeric relationship at C_8 and C_9 led to the same R configuration of 1d. On the other hand, the reagents from (−)cinchonidine and (−)ephedrine, which possess

TABLE II

Asymmetric Reduction of Methyl-*n*-Butyl Sulfoxide 1d by Optically Active Lithium Aluminum Hydride Complexes with Alcohols[a]

Optically Active Hydroxy-Compounds	Sulfoxide 1d recovered %[b]	$[\alpha]_{589}$ (neat)	Abs. Configuration[c]
(−)Quinine	54	+0.15	S
(+)Quinidine	50	−2.06	R
(−)Cinchonidine	67	−0.90	R
(−)Ephedrine	55	+1.67	S
(−)Menthol	42	+1.08	S

[a] Boiling ether, 40 hr, 1 : 1 : 2 ratio of $LiAlH_4$: alcohol : sulfoxide.

[b] Based on the weight of sulfoxide isolated.

[c] See footnote c in Table I.

comparable S,R-"erythro" configurations on the amino alcohol centres, gave the sulfoxide 1d of the opposite configurations (R and S, respectively). The complexity of the stereochemical course of the reduction studied is further illustrated, if the results of the reduction of 1d by complexes formed from (−)quinine and (−)-cinchonidine and $LiAlH_4$ are compared. Complexes of (−)quinine and (−)cinchonidine, which differ only in the substitution of a methoxy group for hydrogen at position 6 of the quinoline nucleus afforded the enantiomeric (+)S and (−)R sulfoxides 1d.

In addition, a reversal of the steric course of the reduction was observed with the change in the composition of the reducing complexes. Whereas, the

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13. W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, 90, 6250 (1968).

partial reduction of (±)1d by the complex with 1 : 1 molar ratio of $LiAlH_4$ and (−)menthol was found to give (+)S 1d, $[\alpha]_{589}$ +1.08°, the (+)R sulfoxide 1d, $[\alpha]_{589}$ −1.07° was obtained, if two equivalents of (−)menthol were used.

These observations clearly show that there is no simple way to correlate the chirality at the sulfur and carbon atoms. However, in this context it is worthwhile to notice that the reduction of racemic methyl alkyl sulfoxides 1b-e with (+)quinidine-lithium aluminum hydride complex afforded in each case the unreduced sulfoxides containing (−)R enantiomer in excess.

Experimental Section

IR spectra were recorded with a Perkin-Elmer Infracord 237 Spectrometer. The optical activity measurements were made with a Perkin-Elmer 141 photopolarimeter (sensitivity ±0.002°). The following optically active alcohols were used:

(−)quinine, mp 172–173°, $[\alpha]_{589}$ −155° (4.2, ethanol);

(+)quinidine, mp 169–170°, $[\alpha]_{589}$ +238 (3.3, ethanol);

(−)cinchonidine, mp 204°, $[\alpha]_{589}$ −103.7° (3,4, ethanol);

(−)ephedrine, bp 122–123°/4 mm Hg, $[\alpha]_{589}$ −5.02 (7.9 ethanol);

(−)menthol, mp 42–44°, $[\alpha]_{589}$ −48.73, (2.73, ethanol).

The racemic sulfoxides 1a–g were prepared by oxidation of the appropriate sulfide with hydrogen peroxide in acetone solution.[14] Synthesis of methyl isobutyl sulfoxide 1e, which has, not as yet, been reported in the literature, is given below.

14. S. Hunig, and O. Boes, *Ann.*, 579, 23 (1953); D. Jerchel, L. Dippelhofer, and D. Renner, *Chem. Ber.*, 87, 947 (1954).

Methyl isobutyl sulfoxide 1e

To a solution of methyl isobutyl sulfide (10.4 g, 0.1 mole) in acetone (90 ml) hydrogen peroxide (12 ml, 30%) was added. The reaction mixture was left to stand at room temperature for 24 hr. Then, acetone was evaporated and water (25 ml) added. The water solution was extracted with chloroform (4 x 30 ml). Evaporation of the dried ($MgSO_4$) extract left the crude product which was distilled to give methyl isobutyl sulfoxide 1e (10.0 g, 82%) bp 40°/0.1 mm Hg, n_D^{20} 1.4640.

IR: 2910 cm^{-1}, νC–H; 2820 cm^{-1}, ν_{sym}C–H; 1460 cm^{-1}, δ_{as}C–H; 1380 cm^{-1}, δ_{as}C–H; 1080 cm^{-1} and 1030 cm^{-1} νS=O

^{1}H-NMR (benzene, 60 MHz): 0.81 ppm (d, J = 6 Hz, 3H) and 0.84 ppm (d, J = 6 Hz, 3H) $CH_3{}^A CH_3{}^B$–CH–CH_2; 1.7–2.5 ppm (m, 3H), $(CH_3)_2CH$–CH_2 2.03 ppm (s, 3H) CH_3–SO.

Anal. Calcd. for $C_5H_{12}SO$ (120.16): C, 49.95; H, 10.06; S, 26.67%.
Found: C, 49.76; H, 10.17; S, 26.31%.

General procedure for asymmetric reduction of sulfoxides by optically active lithium aluminum alkoxy hydrides

The complex was prepared *in situ* by the addition of the optically active alcohol (11 mmole) to a suspension of lithium aluminum hydride (0.42 g, 11 mmole) in ether (100 ml). The mixture was refluxed for 20–30 min and then sulfoxide (22 mmole) was added. After refluxing for 40 hr, the reaction mixture was hydrolysed with aqueous ammonium chloride and the organic layer was washed with water. The combined aqueous layers were saturated with sodium chloride and extracted with chloroform. The organic extracts were dried over $MgSO_4$ and evaporated to give the unreduced sulfoxide which was purified by distillation and then by chromatography on silica gel using a methylene chloride–ether (1 : 1) mixture as eluent. IR spectra of the sulfoxides were identical with those of authentic samples.

15. Negative result obtained with the sulfoxides 1a and 1f may be due to small differences in the reactivity of enantiomers towards the chiral reducing complex.