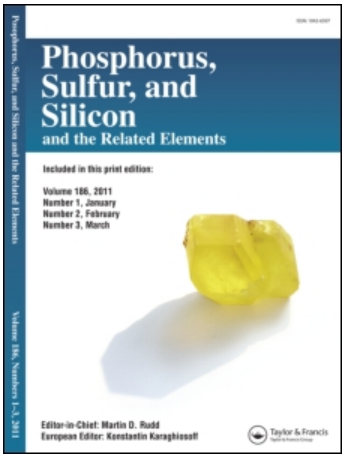

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SHORT COMMUNICATION
Asymmetric Oxidation of Sulfides to Sulfoxides Catalyzed by β-Cyclodextrin

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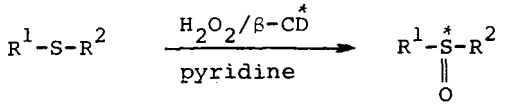
Cyclodextrins are naturally occurring doughnut-shaped molecules composed of 6,7 and 8 D-glucose units and are known to be able to form inclusion complexes with a wide variety of molecules.[1-3] Due to these properties cyclodextrins (CD) have been widely used as a model of enzymes because they form molecular complexes with substrates prior to chemical transformations. From the point of view of stereochemistry it is interesting to point out that cyclodextrins are chiral molecules and show enantioselection in many reactions. This feature has been utilized for the optical resolution of racemic compounds and in asymmetric synthesis, although the application of CDs as chiral catalysts or reagents for asymmetric synthesis has been limited to a small number of reactions as yet.[4]

Previously, the authors succeeded in the optical resolution of a series of sulfoxides, sulfinates, thiosulfinates nd sulfinamides via their inclusion complexes with β-cyclodextrin.[5-8] This paper describes the use of β-cyclodextrin as a chiral auxiliary reagent in asymmetric oxidation of sulfides to sulfoxides.[9] The oxidation of dissymmetric dialkyl sulfides, **1**, alkyl benzyl sulfides, **2**, alkyl phenyl sulfides, **3**, and alkyl *p*-tolyl sulfides, **4**, to the corresponding sulfoxides **5–8** was carried out in a pyridine solution containing β-cyclodextrin using hydrogen peroxide as oxidizing agent. The advantage of the use of pyridine as solvent is that the oxidation reactions can be performed under homogeneous conditions.



1–4 **5–8**

*Denotes optically active center.

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TABLE I

Asymmetric oxidation of sulfides **1–4** to sulfoxides **5–8** with hydrogen peroxide in the present of β-cyclodextrin (β-CD)[a]

Sulfide			Reagents Ratio Sulfide/H_2O_2/ β-CD	Time /hr/	Sulfoxide				
No.	R^1	R^2			No.	Yield[c]	$[\alpha]_{589}$ (c, solvent)	Opt. [%] purity	Abs.[e] conf.
1a	Me	Pr^n	4 : 10 : 1	12	**5a**	50	−1.20 (2.50 EtOH)	0.90	R
1b	Me	Bu^n	3 : 10 : 1	6	**5b**	50	+0.30 (3.53 EtOH)	0.25	S
2a	Bz[b]	Me	2 : 10 : 1	12	**6a**	50	+3.00 (2.51 EtOH)	2.80	S
2b	Bz	Et	2 : 10 : 1	14	**6b**	68	−1.10 (8.80 $CHCl_3$)	1.10	S
2c	Bz	Pr^n	2 : 10 : 1	24	**6c**	58	±0.00 (5.20 EtOH)	0.0	—
2d	Bz	Pr^i	2 : 10 : 1	13	**6d**	58	+2.70 (2.71 EtOH)	2.10	S
3a	Ph[b]	Me	2 : 10 : 1	18	**7a**	38	−0.40 (5.00 EtOH)	0.03	S
3b	Ph	Et	2 : 10 : 1	16	**7b**	42	+3.80 (5.50 EtOH)	2.10	R
3b	Ph	Et	1 : 5 : 1	61	**7b**	54	+4.60 (6.00 EtOH)	2.60	R
3b	Ph	Et	1 : 10 : 1	72	**7b**	69[j]	+17.40 (1.50 EtOH)	9.80	R
3c	Ph	Bu^n	1 : 5 : 1	160	**7c**	23[d,k]	−48.00 (1.00 EtOH)	27.20	S
3c	Ph	Bu^n	1 : 5 : 1	214	**7c**	12[f,k]	−53.01 (2.01 EtOH)	30.00	S
3c	Ph	Bu^n	1 : 20 : 1	156	**7c**	73[h]	−0.30 (5.01 EtOH)	0.40	S
3c	Ph	Bu^n	1 : 10 : 1	144	**7c**	60[i]	+0.80 (2.08 EtOH)	0.40	R
3d	Ph	Bu^i	1 : 5 : 1	156	**7d**	12[d]	−4.00 (3.50 EtOH)	1.70	S
4a	Tol[b]	Me	1 : 10 : 1	66	**8a**	32	−3.20 (5.00 EtOH)	2.00	S
4b	Tol	Et	1 : 5 : 1	96	**8b**	61	+5.50 (3.00 EtOH)	3.10	R
4c	Tol	Bu^n	1 : 5 : 1	140	**8c**	109[g]	−16.20 (1.50 EtOH)	8.90	S

[a] All reactions were carried out by using 1–2 mmol of sulfide **1–4**; 10 ml of pyridine was used for 1 mmol of sulfide.

[b] Bz = $C_6H_5CH_2$; Ph = C_6H_5; Tol = p − CH_3 − C_6H_4.

[c] Yield of the product after isolation; pure by TLC analysis.

[d] Yield determined by GLC analysis of the crude reaction product.

[e] Optical purity values were calculated on the basis of the highest values reported in the same solvent: $[\alpha]_D$ = −139.02 for R—**5a** and $[\alpha]_D$ = +109.9 for S—**5b** from K. K. Andersen, B. Bujnicki, J. Drabowicz, M. Mikołajczyk and J. B. O'Brien, *J. Org. Chem.*, in press; $[\alpha]_D$ = +106.08 for S—**6a**, $[\alpha]_D$ = −106.6 for S—**6b**, $[\alpha]_D$ = +130.0 for S—**6d** from K. Mislow, M. M. Green and M. Raban, *J. Amer. Soc.*, **87**, 2761 (1965); $[\alpha]_D$ = −149.0 for S—**7a** from J. Jacobus and K. Mislow, *J. Amer. Chem. Soc.*, **89**, 5227 (1967); $|\alpha|_D$ = −177.1 for S—**7c**, $[\alpha]_D$ = −234.6 for S—**7d** from M. Mikołajczyk and J. Drabowicz unpublished results $[\alpha]_D$ = +163.0 for S—**8a** from G. Solladie, *Synthesis*, **1981**, 185; $[\alpha]_D$ = +176.5 for R—**8b**, $[\alpha]_D$ = +187.0 for S—**8c** from K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons and A. L. Ternay, *J. Amer. Chem. Soc.*, **87**, 1958 (1965).

[f] 41% of sulfide **3c** was recovered.

[g] 45% of sulfide **4c** was recovered.

[h] *n*-Butyl phenyl sulfone was formed in 19% yield.

[i] *n*-Butyl phenyl sulfone was formed in 35% yield.

[j] The crude product was contaminated with 4% of ethyl phenyl sulfone.

[k] During the reaction time the precipitation of β-cyclodextrin was observed.

A typical experimental procedure applied in the present work is as follows. Sulfide and a solution of hydrogen peroxide (conc. 30%) were added to a pyridine solution of β-cyclodextrin. After the proper time (see Table I) pyridine was removed under vacuum and the residue was treated with ether. The precipitated β-cyclodextrin was filtered off. Then, the ethereal solution was evaporated and the residue was dissolved in chloroform. The chloroform phase was washed with potassium carbonate solution and water, dried over anhydrous magnesium sulfate and chromatographed (Silicagel 60 silanisiert, 70–230 mesh, Merck; pentane-hexane, chloroform) to give the pure sulfoxide. The results obtained and some experimental details are summarized in Table I.

An inspection of the results in Table I shows that oxidation of sulfides **1–4** to sulfoxides **5–8** was stereoselective in almost all the cases. The only exception was the oxidation of *n*-propyl benzyl sulfide **2c** which resulted in the formation of racemic sulfoxide **6c**. In the majority of cases the optical purity of sulfoxides was rather low. The best result was obtained with *n*-butyl phenyl sulfide, **3c**, which was oxidized to the corresponding sulfoxide, **7c**, with 30% op. Analysis of the optical purity values of sulfoxides **5–8** and their chirality at sulfur shows that there is no simple relationship between the stereoselectivity of oxidation and the nature of substituents in the starting sulfides. It is interesting to note that both the optical purity and absolute configuration at sulfur in sulfoxides strongly depend on the molar ratio of reagents i.e. sulfide, hydrogen peroxide and β-cyclodextrin.

Finally, we would like to note that the formation of optically active sulfoxides **5–8** is caused, in fact, by asymmetric oxidation process induced by β-cyclodextrin and is not due to an eventual partial, optical resolution of racemic sulfoxides formed after oxidation of sulfides with hydrogen peroxide. The latter possibility was quite probable in view of our earlier results on the optical resolution of racemic sulfinyl compounds by means of their β-cyclodextrin inclusion complexes. First of all, it was observed that the formation of the solid inclusion β-CD-sulfoxide complexes occurs in a pyridine solution in much lower yields as compared with a water solution. Moreover, the enantiospecificity of the inclusion process in a pyridine solution was observed to be very low. Thus, for example, the inclusion of ethyl benzyl sulfoxide, **6b**, into β-CD was completely non-stereospecific. In the case of *n*-butyl phenyl sulfoxide, **7c**, the included sulfoxide recovered from its β-CD-inclusion compound exhibited a very low optical rotation, $[\alpha]_{589}$ −1.5° (ethanol) whereas the non-includes sulfoxide **7c** had $[\alpha]_{589}$ +0.3°.

Further studies aimed at the increasing the degree of asymmetric induction in the oxidation of sulfides to sulfoxides in the presence of cyclodextrins as well as on the role of cyclodextrins in this process are under way.

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9. A very recent report[10] on the cyclodextrin-mediated chiral sulfoxidation, which appeared after our experiments had been completed, prompted us to publish the results from our Laboratory, especially in view of the fact that there are marked differences in the experimental conditions employed for oxidation. Moreover, in contrast to the results of Czernik, we have observed a higher degree of asymmetric induction with hydrogen peroxide as oxidizing reagent.
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