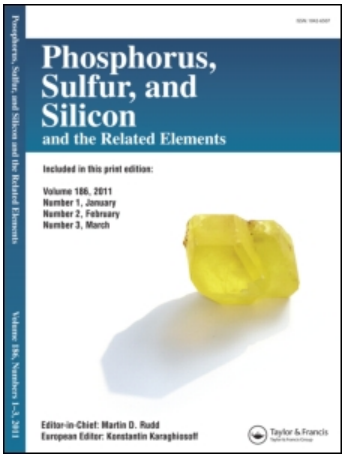

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ASYMMETRIC OXIDATION OF SULFIDES IN THE PRESENCE OF CYCLODEXTRINS: EFFECT OF THE PRECOMPLEXATION OF THE REACTANTS

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The asymmetric induction due to cyclodextrins in the oxidation of thioanisols with *m*-chloroperbenzoic acid in water is enhanced by using preformed 1:1 complexes of the reactants under heterogeneous conditions.

The asymmetric oxidation of aryl alkyl sulphides to the corresponding chiral sulfoxides which can be successfully used as synthone in asymmetric syntheses[1] has been recently reported to occur in the presence of bovine serum albumin with excellent optical yields.[2] Cyclodextrins (CD) which may somehow mimic the effect of the binding site of complex biological domains, have also been used as chiral reaction vessels for the asymmetric oxidation of aryl alkyl sulfides by Drabowicz and Mikolajczyk[3] in the oxidation with H_2O_2 in pyridine and by Czarnik[4] with a variety of oxidants in water, reporting moderate to poor enantiometric excesses (ee).

Following the finding that optical induction in the reduction of prochiral ketones could be improved by carrying out the reaction under heterogeneous conditions and using preformed CD-substrate complexes[5] we carried out a number of experiments aimed at verifying the optimal yields in the oxidation of simple aryl alkyl sulfides (mainly thioanisol) using *m*-chloroperbenzoic acid (m-ClPBA) as oxidant. This was reported by Czarnik[4] to be rather effective (up to 20% ee at 25°) in the chiral oxidation of a specifically designed substrate (*m*-*t*-butylphenyl ethyl sulfide) in the presence of excess β-CD. Preliminary experiments showed that no appreciable ee's (<1%) could be observed in the resulting sulfoxides by using, in the presence of CDs, either other oxidants such as H_2O_2, NaClO, $NaIO_4$ and PhIO in water or *m*-ClPBA in homogeneous solutions in DMF.

The results reported in Table I were obtained under the following conditions: 0.80 mMol of substrate (S) and 0.87 mMol of *m*-ClPBA (Ox) either in preformed complexes with CD or simply mixed with variable amounts of CD in 20 ml of H_2O were allowed to react under vigorous stirring (the reaction mixture was in each case heterogeneous due to precipitation of insoluble CD complexes) and the reaction mixture analyzed, after a carefully checked standard workup, for

TABLE I

Asymmetric oxidation of prochiral sulfides with *m*-ClPBA(Ox) in water at 25°C

Entry	Reagents[a]	Time/h	Yield %	$[\alpha]_D^{25}$	O.Y.[c]	Config.
1	S + Ox	2	94			—
2	[S · β-CD] + [Ox · β-CD]	2	45	−18.5	12.4	S
3	S + [Ox · β-CD]	2	86	−15.9	10.7	S
4	[S · β-CD] + Ox	2	78	−3.4	2.3	S
5	S + Ox + 1β-CD	2	67	−3.2	2.1	S
6	S + Ox + 3β-CD	2	70	−18.3	12.3	S
7	S + Ox + 3β-CD	72[b]	54	−14.8	9.9	S
8	S + Ox + 5β-CD	12	77	−13.1	8.4	S
9	S + Ox + 8β-CD	12	49	−11.4	7.7	S
10	S + Ox + 3α-CD	62	60	+9.0	6.0	R
11	S′ + Ox + 3β-CD	12	57	−8.9	7.2	—
12	S″ + Ox + 3β-CD	62	62	−5.3	8.8[d]	—

[a] S = Ph—S—Me; S′ = *p*—Cl—C_6H_4—S—Me; S″ = *p*—Br—C_6H_4—S—*t*Bu; the figure preceding the CD indicates the molar ratio relative to the substrate; [ ] indicates the use of preformed and isolated 1:1 complexes. Other conditions: see text.

[b] At 0°C.

[c] Based on the maximum $[\alpha]^{25}$ reported in the literature for the resulting enantiomeric sulfoxide (−105. in the case of S; −114. in the case of S′).

[d] As determined by ^{1}H NMR (a Bruker WP200 SY instrument) using Eu(hfc)$_3$ as shift reagent.

chemical and optical purity. In the presence of β-CD no sulphone was detected in the reaction mixture. The results may be summarized as follows: a) the oxidation reaction proceeds slower as the amount of added CD increases; b) in the case of preformed complexes (runs 2–4) the largest ee values are observed when either both S or Ox or just the peracid were added as preformed complexes; c) in the case of simple mixtures (runs 4–12), the ee first increases by addition of increasing amounts of CD up to value of 12.3 when the molar ratio CD/S/Ox is *ca.* 3/1/1 and then decreases; d) *para*-substituents in the thioanisol phenyl ring generally decrease the ee; e) α-CD (run 9) is less effective than β-CD and induces excess of the enantiomer of opposite configuration.

Although there is not much room for mechanistic speculation, the results seem to indicate that the asymmetric oxidation of the sulfides at least under our conditions involves complexation of the peracid: as indicated by the data (run 4), when only the sulfide is added as a preformed complex the ee drops sharply. Apparently, the asymmetric oxidation occurs mainly within crystalline CD complexes which may provide either discrete small cages or channels[6] in which the reagents can not only penetrate but also move in such a way as to come to useful contact for reaction in a stereochemically controlled way. Czarnik's results obtained in homogeneous aqueous solutions in which both sulfide and peracid are complexed could also involve microaggregate[7] of complexes particularly at high CD concentration and at lower temperatures where the largest optical yields were observed.

Clearly, the present method, otherwise experimentally quite simple, affords sulfoxides with ee's of little practical interest in view of the effectiveness of other recently reported procedures.[8]

However, when the ee here obtained with a "poor" substrate are compared

with the small values reported in the literature[3,4] for similar systems in the presence of cyclodextrins as chiral vessels, it appears that the effect of induced asymmetry is again[5] magnified by using *performed* 1:1 complexes under heterogeneous solutions.

Optimization of substrates and conditions may lead to substantial improvements.

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