Supramolecular Catalysis: Enantioselective Oxidation of Thioanisole in Water by Hydrogen Peroxide Catalyzed by Mo(VI) in the Presence of β-Cyclodextrin-Based Ligands

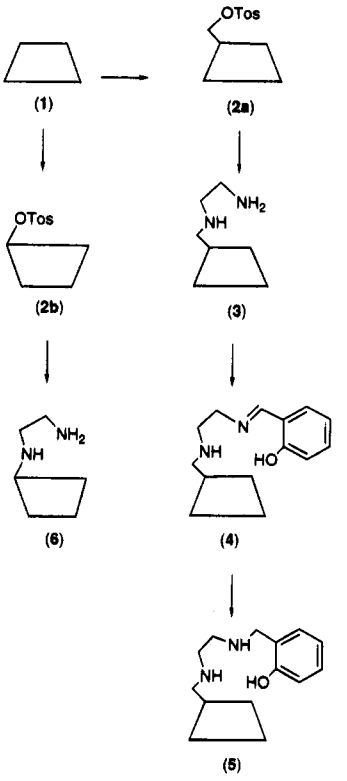
Marcella Bonchio, Tommaso Carofiglio,*,† Fulvio Di Furia, and Roberto Fornasier

Centro Meccanismi Reazioni Organiche del CNR, Dipartimento di Chimica Organica dell'Università and Dipartimento di Chimica Inorganica, Metallorganica ed Analitica, via Marzolo 1, I-35131 Padova, Italy

Received May 10, 1995

Cyclodextrins (CDs), which are water-soluble cyclic oligomers of D-(+)-glycopyranose units, are of interest in supramolecular chemistry owing to their ability to include in a chiral environment various hydrophobic species.[1] This allows CDs to be employed as resolving agents of racemic mixtures[2] and as chiral stationary phases in chromatographic separations.[3] CDs are also useful model compounds which mimic the hydrophobic pockets of enzymes.[4] The use of CDs as chiral auxiliaries in the synthesis of chiral molecules has been reported.[5] As an example asymmetric inductions have been observed in the enantioselective oxidation of aromatic thioethers to the corresponding sulfoxides by various oxidants in the presence of CDs.[6] The best enantiomeric excesses are obtained when CDs behave as "molecular reaction vessels" in which both the substrate and the oxidant are present.[6e] This favorable behavior could be obtained in transition metal catalyzed oxidations by hydrogen peroxide[7] when properly modified CDs capable of binding to the metal were added to the reaction mixture. In this work we have investigated the oxidation of thioanisole by hydrogen peroxide in water in the presence of catalytic amounts of Na_2MoO_4 and of functionalized cycloheptaamyloses (βCDs). Under these conditions an oxodiperoxomolybdenum complex, $MoO(O_2)_2L$, which is the real oxidant,[7,8] is formed. L is the βCD based ligand. Ligands **3**–**6** have been synthesized starting from **2a**[9a] and **2b**,[9b] which in turn are obtained from the unfunctionalized βCD (**1**) as shown in Scheme 1.

Scheme 1. Synthesis of βCD-Based Ligands



By reacting the diamine **3**,[9c] which is already a bidentate ligand, with salicylaldehyde, the Schiff base derivative **4** is obtained.[9d] In **4** an additional anionic binding site, i.e. the phenolic oxygen, is present. Ligand **5** is prepared by reduction of the imino function of **4**. **5** compared with **4** should have the advantage of increased flexibility together with a better stability under hydrolytic conditions. Moreover the 2-diamino-βCD **6** was synthesized[9e] to establish, by comparison with **3**, the relevance of the rigidity of the complex on the stereochemical outcome of the reaction.

The various conditions adopted and the corresponding results are illustrated in Table 1. All the reactions proceed smoothly at 20 °C, so that after ca. 2 h yields of phenyl methyl sulfoxide ranging from fair to good (62–98%) are obtained.[10] Overoxidation to sulfone is not observed. The enantioselectivities are in the range 17–60% (*R*-enantiomer) depending on the nature of the βCD-based ligand and on the experimental conditions.

Most of the experiments were carried out by suspending thioanisole in a buffered aqueous solution (note a, Table 1) in which the peroxomolybdenum complex is completely soluble. Under these conditions **1** has almost no effect (compare entries 1 and 4) and racemic sulfoxide is obtained. These results confirm previous reports that, in similar systems, at least stoichiometric amounts of **1** are required to achieve appreciable enantioselections.[6] By contrast, in the presence of ligands **3**–**6** both catalysis and asymmetric induction are observed. This is evidence

† Dipartimento C.I.M.A.

(1) (a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: Berlin, 1978. (b) Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344. (c) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803.

(2) Mikolajczyk, M.; Drabowicz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2510.

(3) Li, S.; Purdy, W. C. *Chem. Rev.* **1992**, *92*, 1457.

(4) (a) Breslow, R. *Science* **1982**, *218*, 532. (b) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66. (c) Tabushi, I. *Tetrahedron* **1984**, *40*, 269.

(5) Takahashi, K.; Hattori, K. *J. Incl. Phenom.* **1994**, *17*, 1.

(6) (a) Czarnik, A. W. *J. Org. Chem.* **1984**, *49*, 924. (b) Drabowicz, J.; Mikolajczyk, M. *Phosphorous Sulfur* **1984**, *21*, 245. (c) Fornasier, R.; Scrimin, P.; Tecilla, P.; Tonellato, U. *Phosphorous Sulfur* **1988**, *35*, 211. (d) Rama Rao, K.; Sattur, P. B. *J. Chem. Soc., Chem. Commun.* **1989**, 342. (e) Sakuraba, H.; Natori, K.; Tanaka, K. *J. Org. Chem.* **1991**, *56*, 4124. Enantiomeric excesses in the range 1–15% (*S*) are reported for the enantioselective oxidation of thioanisole.

(7) (a) Conte, V.; Di Furia, F. In *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Strukul, G., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992; Chapter 7, pp 223–252. (b) Conte, V.; Di Furia, F.; Modena, G. In *Organic Peroxides;* Ando, W., Ed.; John Wiley and Sons: Chichester, 1992; Chapter 11.2, pp 559–598.

(8) (a) Di Furia, F.; Modena, G.; Curci, R. *Tetrahedron Lett.* **1976**, 4637. (b) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325. (c) Schurig, V.; Hintzer, K.; Leyrer, U.; Mark, C.; Pitchen, P.; Kagan, H. B. *J. Organomet. Chem.* **1989**, *370*, 81 and references cited therein.

(9) (a) Petter, R. C.; Salek, J. S.; Sikorsky, C. T.; Kumaravel, G.; Lin, F.-T. *J. Am. Chem. Soc.* **1990**, *112*, 3860. (b) Ueno, A.; Breslow, R. *Tetrahedron Lett.* **1982**, *23*, 3451. (c) Tabushi, I.; Shimizu, N.; Sugimoto, T.; Shiozuka, M.; Yamamura, K. *J. Am. Chem. Soc.* **1977**, *99*, 7100. (d) Shen, B.-J.; Tong, L.-H.; Jin, D.-S. *Synthetic Commun.* **1991**, *21*, 635. (e) Wenzel, T. J.; Bogyo, M. S.; Lebeau, E. L. *J. Am. Chem. Soc.* **1994**, *116*, 4858.

(10) Under the experimental conditions adopted but in the absence of Na_2MoO_4, negligible amounts of sulfoxide (<1%) are formed in 2 h.

0022-3263/95/1960-5986$09.00/0

Table 1. Asymmetric Oxidation of Thioanisole (0.55 mmol) with H_2O_2 (0.55 mmol) Catalyzed by Na_2MoO_4 (0.025 mmol) in the Presence of Various βCD-Based Ligands under Heterogeneous (HE), Inverse Phase Transfer (IPT), or Homogeneous (H) Reaction Conditions[a]

entry	βCD deriv	mmol	reactn conditn	T, °C	yield (%)[b] of PhS(O)Me	ee, %[c] (confign)
1			HE	20	68	0
2			IPT	20	9	0
3			H	20	82	0
4	1	0.025	HE	20	69	0
5	3	0.025	HE	20	91	59 (*R*)
6	3	0.085	HE	20	62	53 (*R*)
7	3	0.025	HE	0	87	57 (*R*)
8[d]	3	0.025	HE	20	85	54 (*R*)
9	3	0.025	IPT	20	44	53 (*R*)
10	3	0.025	H	20	98	60 (*R*)
11	4	0.025	HE	20	76	24 (*R*)
12	5	0.025	HE	20	89	20 (*R*)
13	6	0.025	HE	20	90	17 (*R*)

[a] See Experimental Section. [b] Yields based on substrate conversion and determined by ^1H NMR ($CDCl_3$, 200 MHz) after 2 h reaction time. [c] Determined by ^1H NMR ($CDCl_3$, 200 MHz) in the presence of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol. [d] Reaction carried out in 2.5 mL of aqueous HEPES buffer solution.

of an interaction between the peroxomolybdenum complex and the hydrophobic recognition site of βCD. A further more direct evidence has been provided by spectroscopic experiments. The reaction mixture in the absence of βCD-based ligands exhibits the typical electronic absorption band of peroxomolybdenum species[11] (λ_{max} = 315nm, ϵ_{max} = 800) (Figure 1a). No optically active bands are, of course, observed by circular dichroism. Upon addition of **3**, while the absorption at 315 nm is not significantly modified, two negative induced circular dichroism (ICD) bands are observed (Figure 1b). This is a clear indication that the catalytic center is located in the proximity of the chiral βCD cavity.[12] The possible modes of interaction between the metal catalyst and the βCD-based ligand are shown in Scheme 2, in which the terminology adopted in the following discussion is also explained.

The finding that the highest enantioselections are obtained with the *holohost* **3** (entries 5−10) suggests that the primary hydroxylic functions of βCD play an important role by interacting with molybdenum. An interaction with the nitrogen atoms of the diamine is also possible.[13] This interaction causes a decrease of the degrees of freedom of the system, leading to the formation of an effective metal-capped *apohost* (Scheme 2). The presence of the phenolic oxygens in **4** and **5**, which may compete with the hydroxylic functions of βCD, lowers the enantioselection likely because a less effective metal-appended *apohost* conformation (Scheme 2) is reached. Furthermore, the observation that the diamine **6** provides the lowest enantioselection may be rationalized by pointing out that, in this case, the catalytic center is located above the secondary hydroxylic functions on the larger side of the βCD molecule. This again reduces the rigidity of the system.

As additional pieces of information, we have observed that the enantioselection is scarcely dependent on the temperature (entry 7), on the total concentration of the

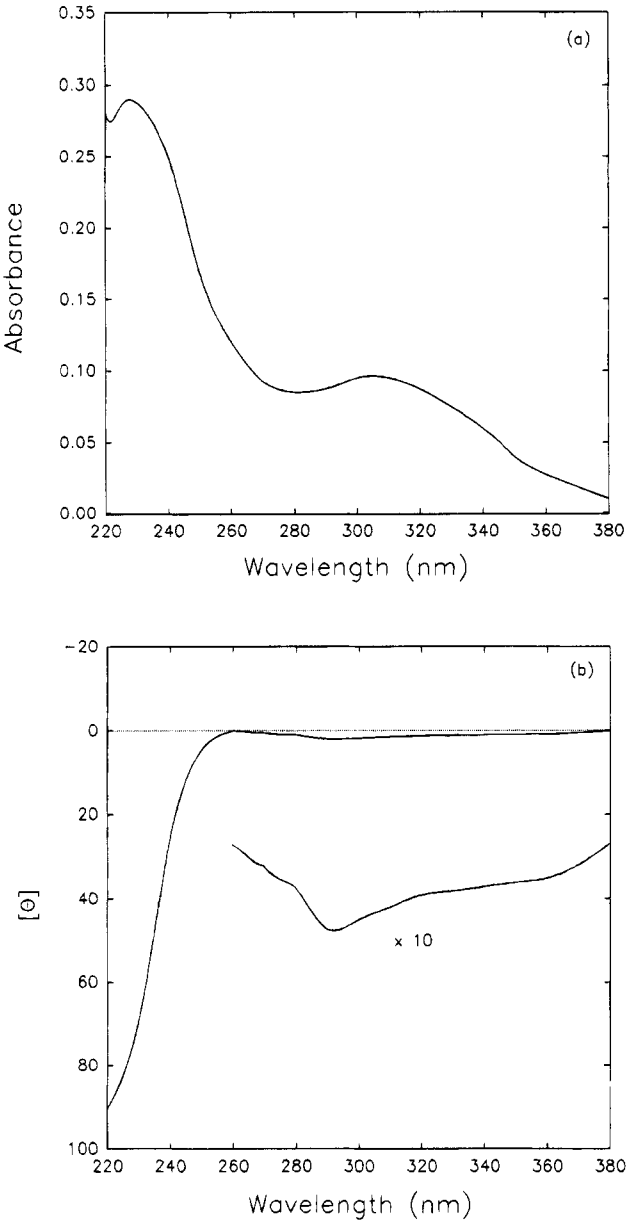


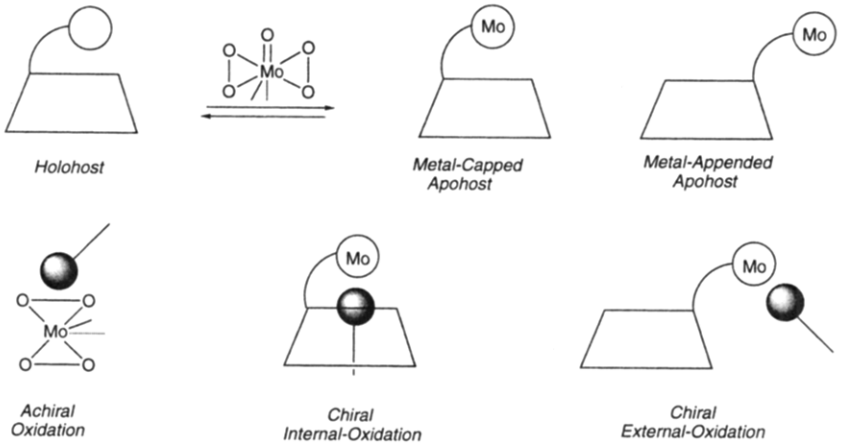
Figure 1. Electronic (a) and circular dichroism (b) spectra of Na_2MoO_4 (0.00125 M) in the presence of H_2O_2 (0.0275 M) and of **3** (0.00125 M) in HEPES buffer aqueous solution (0.05 M, pH = 7).

reactants (entry 8), and on the ligand−molybdenum ratios (entry 6).[14] An important point has been addressed concerning the relevance of the achiral oxidation of thioanisole, e.g. the reaction which takes place in the absence of the βCD-based ligands. This process, likely due to the fact that thioanisole is present, though in small concentration, in water, occurs also when **3** is added, providing racemic sulfoxide. To minimize the achiral path, we have carried out the oxidation in a biphasic (H_2O−DCE) system, taking advantage of the inverse phase transfer capability of βCD which may extract the substrate from DCE. Under these conditions the oxidation in the absence of ligand **3** is almost suppressed (entry 2), as expected since the two reagents are not in contact. However when **3** is added (entry 9), the enantioselectivity is similar to that obtained under heterogeneous conditions (entry 5), thus indicating that the achiral oxidation

(11) Schwane, L. M.; Thompson, R. C. *Inorg. Chem.* **1989**, 28, 3938 and references cited therein.
(12) Kodaka, M. *J. Am. Chem. Soc.* **1993**, *115*, 3702.
(13) Bonomo, R. P.; Cucinotta, V.; D'Allessandro, F.; Impellizzeri, G.; Maccarrone, G.; Rizzarelli, E.; Vecchio, G. *J. Incl. Phenom.* **1993**, *15*, 167.

(14) A competitive oxidation of the ligand is observed when ligand−molybdenum ratios larger than stoichiometric are employed.

Scheme 2



path is not responsible for the incomplete enantioselectivity achieved. A further evidence supporting the latter conclusion is the fact that, under homogenous conditions (aqueous methanol solution), which definitively favor the achiral oxidation (entry 3), we obtained the highest yield and enantiomeric excess (entry 10). At this stage of the work at least two hypothesis could be considered; either homogeneous conditions do not repress the inclusion of the substrate in the βCD cavity or a chiral external oxidation is taking place which proceeds with a similar enantioselectivity as the chiral internal oxidation (Scheme 2). The results obtained, though not yet synthetically significant, are of interest because they are among the first examples of supramolecular catalysis in oxidation reactions.[15] Furthermore, the information collected should allow an improvement of the efficiency of the chiral oxidazing system.

Experimental Section

General. Deionized water was purified with a Milli-Q apparatus (Millipore). Methanol and dichloromethane (HPLC grade, Aldrich) were used as received. 1,2-Dichloroethane (Aldrich, 99%) was washed with concentrated sulfuric acid, dried over $CaCl_2$, and distilled over P_2O_5. Thioanisole (Aldrich) was purified by distillation under reduced pressure. β−Cyclodextrin (Fluka) was recrystallized from water and dried under vacuum overnight at 100 °C. Na_2MoO_4 (Fluka), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES, Aldrich), and (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol (Aldrich) were used as purchased. The purity of hydrogen peroxide (30% wt solution in water, Aldrich) was determined by iodometric titration. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker WP-200 spectrometer. IR spectra were recorded on a FT-IR Perkin-Elmer 1600 instrument. UV−vis and CD spectra were obtained respectively on a Lambda 5 Perkin-Elmer instrument and on a Jasco Model J-500 automatic recording spectropolarimeter equipped with a Jasco DP-501 N data processor.

Oxidation Procedures. All the oxidation reactions were carried out in a jacketed glass reactor with the temperature control better then ±0.05 °C. Heterogeneous oxidations (HE): thioanisole was suspended in 5 mL of aqueous HEPES buffer solution (0.05M, pH = 7) in which the appropriate amounts of Na_2MoO_4 and of βCD or a βCD-based ligand had been previously dissolved. To this mixture, thermostated at 20 °C, was added hydrogen peroxide. Inverse phase transfer oxidations (IPT): thioanisole was dissolved in 2 mL of a DCE solution which was added, under vigorous stirring, to 5 mL of aqueous HEPES buffer solution (0.05M, pH = 7) containing H_2O_2, Na_2MoO_4, and βCD or a βCD-based ligand. Homogeneous oxidations (H): 3 mL of a HEPES buffer water solution (0.05M, pH = 7) and 4mL of CH_3OH were used to dissolve thioanisole in the presence of both the catalyst and the oxidant. After 2 h all oxidation reactions were extracted with CH_2Cl_2 (5 mL) and the organic phase was washed with a saturated solution of $Na_2S_2O_5$ and subsequently with water, dried over anhydrous $MgSO_4$, and concentrated under vacuum.

Compounds **2a**,[9a] **2b**,[9b] **3**,[9c] and **6**[9e] were prepared according to the literature. Compound **4**[9d] has been synthesized according to a literature procedure modified as follows: the diamine derivative **3** (1.03 g, 0.875 mmol) was suspended in dry ethanol (10 mL) and a 5-fold excess of salicylaldehyde (0.53 g, 4.37 mmol) was added. The suspension was stirred overnight. The yellow solid obtained was filtered off, washed with diethyl ether, and dried in vacuo (yield 0.6 g, 54%). ^{1}H NMR (DMSO-d_6, δ): 8.52 (s, broad, 1H, −HC=N−), 7.42−6.82 (m, 4H, phenyl), 5.72 (s, broad, 14H, OH), 4.82 (s, broad, 7H, C1H), 4.46 (s, broad, 6H, OH), 3.94−3.09 (m, 42H, C2H−C6H), 3.00−2.69 (m, 4H, $-NCH_2-CH_2N-$). ^{13}C NMR (DMSO-d_6, δ): 166.7 (N=CH); 161.7, 132.5, 131.9, 118.7, 118.3, 116.9 (phenyl); 102.2, 81.8, 73.3, 72.7, 72.3, 60.1 (unsubstituted glucose moieties); 83.4, 70.9, 50.0 (substituted glucose moiety); 58.2 ($-CH_2N=$); 49.2 ($-NHCH_2-$). Anal. Calcd for $C_{51}H_{80}O_{35}N_2{\cdot}8H_2O$: C, 42.7; H, 6.74; N, 1.95. Found: C, 42.7; H, 6.24; N, 1.91. IR characterization of compound **4** through its C=N stretching band, which is the most significative parameter for such a class of compounds, was hampered by the presence of a strong absorption at 1635 cm^{-1} due to water of crystallization. A similar strong band at 1641 cm^{-1} is observed also in the IR spectrum of the parent βCD.

Compound **5** was obtained by reduction of compound **4** (0.5 g, 0.39 mmol) with a 10-fold excess of $NaBH_4$ (0.147 g, 3.9 mmol) in dry methanol (50 mL). The yellow reaction mixture was stirred overnight. After this time a white suspension was formed. Addition of water (10 mL) gave a clear solution which was neutralized using 10% HCl. A white solid precipitated upon addition of acetone (1 L). This crude product was desalted by inclusion chromatography (Sephadex G15, water eluent) (yield 0.35 g, 70%). ^{1}H NMR (D_2O, δ): 7.23−6.89 (m, 4H, phenyl), 4.95 (s, broad, 7H, H-1), 3.80−3.36 (m, 42H, H-2−H-6), 3.28−2.77 (m, 6H, $-NCH_2CH_2NCH_2-$). ^{13}C NMR (D_2O, δ): 157, 132.2, 132.0, 121.2, 120.0, 116.8 (phenyl); 103.2, 82.3, 74.4, 74.3, 73.2, 61.2 (unsubstituted glucose moieties); 102.8, 84.6, 71.1 (substituted glucose moiety); 49.8, 48.8, 46.2, 45.3 ($-CH_2NCH_2CH_2-NCH_2Ph$). Because of the variable amount of water molecules of crystallization contained in cyclodextrin compounds, elementary analysis of compound **5** is of little help in establishing the extent of imine reduction. This information is provided by the disappearance of the ^{1}H-NMR signal at 8.55 ppm ($-CH=N-$) and of the ^{13}C-NMR signal at 166.7 ppm ($-CH=N-$).

Acknowledgment. This research was carried out in the frame of "Progetto Finalizzato Chimica Fine II" of CNR. Financial support by MURST is also gratefully acknowledged. The instructive discussions with Professor Giorgio Modena are greatly appreciated.

JO950870C

(15) It should be emphasized that the stereochemical outcome of the reaction is just the opposite to that reported in other CD-mediated chiral oxidations of thioanisole, with in our case the (*R*)-(+)-phenyl methyl sulfoxide being the enantiomer in excess.