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Asymmetric Synthesis in the Presence of Cyclodextrins

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Abstract

Oxidative couplings of 2-naphthol, 6-bromo-2-naphthol and 2-naphthylamine were achieved at room temperature in the presence of H_2O_2, horseradish peroxidase and a suitable cyclodextrin. 2-Thionaphthol behaved differently, yielding the corresponding disulfide. Yields of binaphthyl derivatives were generally excellent, and a fairly good enantiomeric excess was observed. Under similar reaction conditions methyl 2-(6-methoxy-2-naphthyl) propanoate, when treated with esterase in the presence of cyclodextrin, yielded naproxen (a well-known anti-inflammatory drug) with a good enantiomeric excess. No reaction product was detected in the absence of cyclodextrin. Cyclodextrins do not act as simple transfer agents.

Introduction

Asymmetric processes leading to pure enantiomers are important developments in modern chemistry. It is estimated that about 60% of all known pharmaceuticals are optically active. About 40% of all man-made synthetic drugs are chiral. Not infrequently only one enantiomer shows the desired activity, while the other enantiomer is inactive or harmful to humans or the environment. Thus, expensive separation procedures are needed in order to prepare the preferred enantiomer [1]. Enantiopure compounds have been obtained by synthesis in the presence of an effective chiral catalyst [2], especially enzymes [3]. The enzymatic approach however is severely limited by the low water solubility of the most organic substrates.

Recently, cyclodextrins [4] were shown to act in several organic reactions as inverse phase transfer catalysts [5] allowing water- insoluble molecules to react in an aqueous medium.

We have also reported the positive effect of suitable cyclodextrins in the presence of horseradish peroxidase in bioremediation applications [6]. We wish now to report that a cyclodextrin derivative have a positive role on the chiral discrimination on an enzyme-catalysed oxidative coupling and on the enzymatic hydrolysis of methyl 2-(6- methoxy-2-naphthyl) propanoate in water.

Experimental

2-Naphthol, 6-bromo-2-naphthol, 2-naphthylamine and 2-naphthylthiol (all ACS grade) were purchased from Aldrich (USA); horseradish peroxidase [E:C. 1.11.1.7] and esterase [E:C. 3.1.1.1] from Sigma (USA); diethyl ether, petroleum ether, dichloromethane and ethyl acetate from Merck (Germany). Naproxen was kindly supplied by Farchemia (Treviglio-Italy). Methyl-β-cyclodextrin (D.S = 1.8) was a gift of Wacker Chemie (Germany). Ethyl carbonate of β-cyclodextrin was synthesized as previously reported [7]. *Heptakis*-2,3,6-*O*- trihydroxyethyl-β-CD and *Heptakis*-2,3,6-*O*-tri-2- hydroxypropyl-β-CD were synthesized in our laboratory and described elsewhere [8].

TLC analyses were performed on silica plates (Merck art. 5764), using ethyl acetate/petroleum ether 8:2 v : v as eluent. HPLC analyses were performed on a Daicel chiralpak AD column in a Gilson 133 with RI detector.

Methyl-2-(6-methoxy-2-naphthyl) propanoate

In a three-necked round-bottomed flask equipped with a condenser 90 ml of diethylether, 1.5 g of naproxen and 30 ml of methanol were placed. To the solution 30 ml of BF3/diethyl ether complex were added dropwise and the mixture allowed to react overnight at room temperature. It was subsequently extracted twice with 5% aqueous NaOH to remove the unreacted naproxen and washed with water until the aqueous phase was no longer alkaline. The organic phase was dried with anhydrous sodium sulfate, filtered under vacuum and evaporated to afford 1.31 g of methyl-2-(6-methoxy-2-naphthyl) propanoate (yield: 82.4%).

Chiral syntheses were carried out in water thanks to the solubilizing effect of the selected cyclodextrin and by adding the required amount of enzyme and reagents. After the reaction was over (10 min for oxidative coupling reaction and 48 h for hydrolysis reaction), the solution was extracted twice with diethyl ether, anhydrified with Na_2SO_4 anhydrous and ana-

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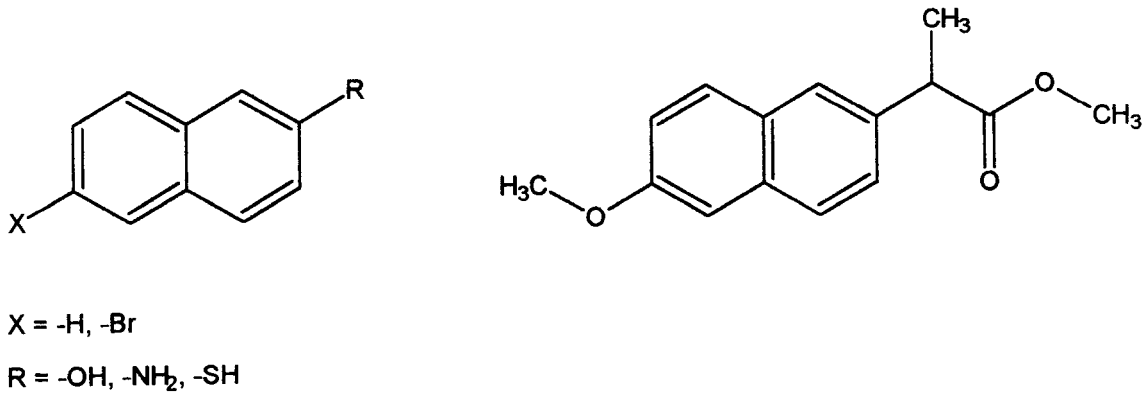
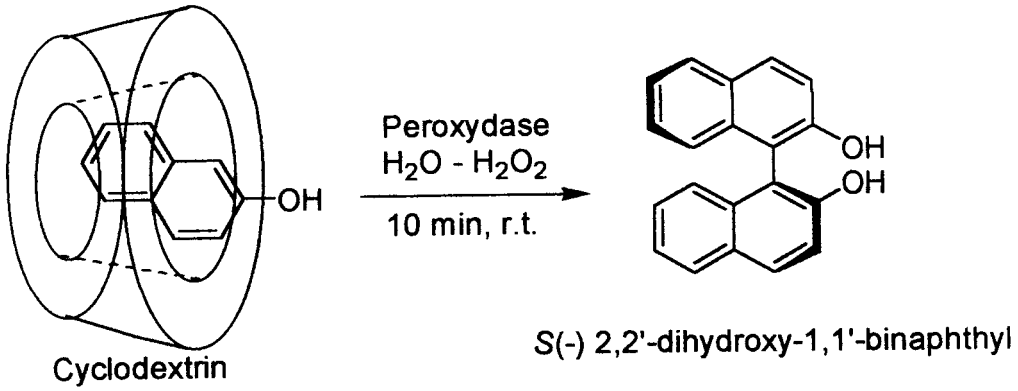


Figure 1. Molecular structures of the studied compounds.



Scheme 1.

lysed by chiral HPLC and/or GC-MS by comparison with authentic samples.

Results and discussion

The production of pure enantiomers through asymmetric processes is an important task of modern chemistry. Enzymes have often been used to catalyse stereoselective organic reactions in the laboratory. However, many potential substrates are poorly soluble in water and will therefore not be converted to products by the enzymes. The use enzymes for reactions in organic solvents is only possible under special conditions and therefore has limited application. We chose to employ a suitable CD as a complexing agent to bridge the water solubility gap between enzymes and the compounds shown in Figure 1, i.e. 2-naphthol, 6-bromo-2-naphthol, 2-naphthylamine, thio-2-naphthol and methyl-2-(6- methoxy-2-naphthyl) propanoate.

They all contain a naphthyl structure and are poorly soluble in water. The solubility could be greatly enhanced by adding suitable cyclodextrin. The solubility of 2-naphthol increased 50-fold, relative to the solubility in pure water, in the presence of 20 wt% of methyl- β-CD, and the solubility of methyl-2-(6-methoxy-2-naphthyl) propanoate increased 210-fold (up to 4.4 g/l) under the same conditions.

It is well known that the entiopure binaphthyl is the core structure of many efficient auxiliares, ligand and catalysts for asymmetric syntheses, chiral shift reagents, materials for resolution of racemates etc. Thus there is a considerable interest in developing enantioselective syntheses of the above mentioned atropoisomers.

The more common routes exploit an intermolecular Ullman coupling [9], a nucleofilic aromatic substitution [10] an oxidative dimerization with a variety of oxidants [11] and electrocatalysis [12]. However, practical method for enantiopure synthesis has not yet been developed and the desired enantiomers are therefore usually obatained by resolution of racemates [13].

Working at room temperature with a H_2O_2-horseradish peroxidase system in the presence of suitable cyclodextrin we obtained directly in few minutes the oxidative coupling of 2-naphtol, 2-bromo-2- naphthol and 2-naphthylamine, as sketched in scheme 1. The binaphthyl derivatives were generally obtained in high yields and with a fairly good enantiomeric excess (Table 1).

For instance, in the preparation of 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) we employed a series of both native and chemically modified CDs. The enantioselectivity of BINOL synthesis in a peroxydase – H_2O_2 system increased greatly (entries 6–7) in the presence of methyl-β-CD.

On the other hand, poor yields and a negligible enantiomeric excess (e.e.) were seen in the absence of CDs or in the presence of native, unmodified CDs. Our results clearly show that CDs do not act exclusively as solubilising agents. Indeed, β-CD ethylcarbonate, in spite of its good solubilising effect on 2-naphthol, induced but a poor yield of BINOL, and no enantiomeric enrichment. BINOL yields

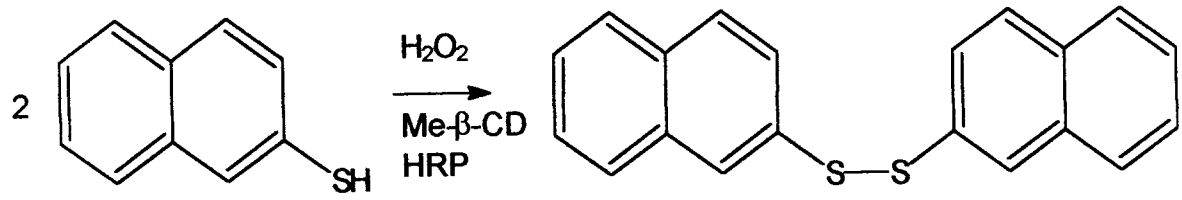


Figure 2. Oxidative coupling of thio-2-naphthiol.

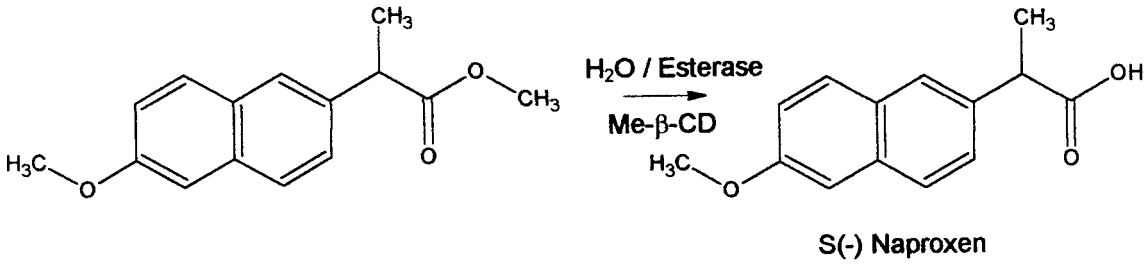


Figure 3. Chiral hydrolysis reaction of methyl-2-(6-methoxy-2-naphthyl) propanoate.

Table 1. The effect of the CD (type and concentration) on the enzymatic oxidative coupling at room temperature

Entry	CD (wt%)	Substrate (mg/100 mL)	Products mg (yield %)	e.e. (%)
1	–	2-naphthol (65)	5 (7.6%)	–
2	α-CD (1.8)	2-naphthol (104)	10 (9.6%)	–
3	β-CD (1.8)	2-naphthol (67)	6 (8.9%)	–
4	γ-CD (1.8)	2-naphthol (15)	0	–
5	Me-βCD (18)	2-naphthol (73)	58 (79.5%)	5.4
6	Me-βCD (1.8)	2-naphthol (309)	236 (76.4%)	42.7
7	Me-βCD (2.5)	2-naphthol (366)	347 (95.0%)	42.4
8	Me-βCD (5.0)	2-naphthol (496)	200 (40.3%)	32.5
9	Me-β-C (7.5)	2-naphthol (588)	244 (41.5%)	6.2
10	Me-β-C (18)	2-naphthol (1632)	155 (9.5%)	3.0
11	EtCaCD (1.8)	2-naphthol (230)	66 (28.7%)	–
12	Me-βCD (2.5)	2-naphthylamine (166)	149 (89.7%)	41.0
13	Me-βCD (2.5)	6-Br-2-naphthol (334)	301 (90.0%)	41.2
14	Me-β-CD (2.5)	thiol-2-naphthol (36)	35 (97.2%)	–
15	THP-β-CD (1.8)	2-naphthol (148)	137 (93.1%)	42.5
16	THE-β-CD (1.8)	2-naphthol (235)	216 (92.1%)	43.2

Table 2. Hydrolysis of naproxen methyl ester at room temperature

CD (%)	Naproxen ester (mg)	Esterase (mg)	e.e.
–	0.1	0.5	–
Me-β-CD (2.5)	5	0.5	46
Me-β-CD (2.5)	5	1.0	34
Me-β-CD (5.0)	8	0.5	8

were greatly influenced by the cyclodextrin concentration. Almost quantitative yields (entry 7) were obtained by using 2.5wt% of methyl- β-CD.

2-Naphthylamine (entry 12) behaved similarly although less soluble than 2-naphthol. Similar results were obtained with 6-bromo-2-naphthol (entry 13). Among reaction products TLC detected the presence of structural isomers of BINOL, but no polymers. The horseradish peroxidase (HRP) that was recovered from the reacted mixture showed only a modest loss of enzymatic activity. To test the feasibility of enzyme recycling we used four times over the same reaction bath, in which only the saturated substrate-CD solution was replaced: nearly the same results were obtained. Rather surprisingly, with thiol-2-naphthol no oxidative coupling was seen, the only reaction product being the corresponding disulfide (Figure 2). Evidently, the thiol radicals immediately paired with each other and the delocalisation of the unpaired electron onto the aromatic ring, that was prevalent in the case hydroxyl and amino groups, did not occur.

Radical formation on the hetero atom is a prerequisite. In fact, when the mobile hydrogen atom on 2-naphthol was blocked by etherification with methyl iodide, the resulting methoxy naphthalene did not react with hydrogen peroxide and horseradish peroxidase.

Naproxen is a well known and much used antiinflammatory, antipyretic and analgesic drug. However, only the S(-) enantiomer has the therapeutic activity.

We found that esterase acting in aqueous solution on methyl 2-(6- methoxy-2-naphthyl) propanoate in the presence of modified cyclodextrins yielded the desired product with a good enantiomeric excess (Figure 3).

No product could be detected when cyclodextrin was not present (Table 2). The enzyme reaction was not completed in 48 h. This is unusual for enzyme- catalysed reactions. It is therefore possible that the enzymatic conversion is inhibited by complexation of the compound with cyclodextrin. We speculate that, unlike the case of the oxidative coupling, the inclusion compound formed with the ester is much too cumbersome for the esterase, so that and the ester group find a more difficult access to the catalytic site of the enzyme.

Conclusions

Cyclodextrins greatly enhance the water solubility of hydrophobic compounds, allowing poorly soluble substrates to undergo enzyme- catalysed reactions. High yields were achieved in the oxidative coupling and ester hydrolysis reactions and in some cases a considerable enantiomeric excess was obtained. Because the results were greatly influenced by CD concentration and structure, optimisation work is in progress to improve yields and e.e. by using other chemically modified CDs.

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