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Stereoselective sulfoxidation catalyzed by achiral Schiff base complexes in the presence of serum albumin in aqueous media

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ABSTRACT

Four coordination complexes **ML** derived from an achiral Schiff base ligand (H_2L = 2,2′-[(1,2-ethanediyl) bis(nitrilopropylidyne)]bisphenol) have been synthesized and characterized. A method is described for the enantioselective oxidation of a series of aryl alkyl sulfides using the coordination complexes in the presence of serum albumins (SAs) in an aqueous medium at ambient temperature. The mixture of metal complexes with serum albumins is useful for inducing asymmetric catalysis. The complex, albumin source and substrate influence stereoselective sulfoxidation. At optimal pH with the appropriate oxidant, some of **ML**/SA systems are identified as very efficient catalysts, giving the corresponding sulfoxides in excellent chemical yield (up to 100%) and good enantioselectivity (up to 94% *ee*) in certain cases. UV–visible spectroscopic data provide evidence that stronger binding between the complex and serum albumin lead to higher enantioselectivity.

1. Introduction

Enantioselective oxidation of prochiral sulfides is a current focus of asymmetric oxidative transformations[1–3] in organic, synthetic and biological chemistry.[4–6] This is a consequence of the increasing application of the products as chiral auxiliaries,[7–9] ligands,[10] organocatalysts[11] and intermediates for the synthesis of biologically active compounds.[12,13] Chiral sulfoxides have also been used in pharmaceuticals[14,15] such as antifungal, antiatherosclerotic, antibacterial, and antihypertensive agents.[16,17] The asymmetric catalytic oxidation of sulfides is a straightforward and frequently used method to obtain optically active sulfoxides.[18]

Schiff base ligands have played an important role in the development of coordination chemistry, especially their metal complexes, and have found wide application in biological and industrial systems.[19] Among the metal complexes, transition metal complexes of Schiff bases, including titanium,[20,21] iron,[22–24] manganese,[22,25] chromium,[26] cobalt,[19,22] vanadium,[27,28] and copper,[19] have been used for the development of a variety of efficient, easily synthesized, catalysts for asymmetric sulfoxidation. The reaction proceeds via the formation of a high valency metal–oxygen complex intermediate.[9,15,21,29–35] However, in such catalytic enantioselective oxidations, the asymmetric induction is usually provided by a chiral ligand or organic chiral auxiliary.[36] Many of these systems also suffer from one or more limitations, such as high cost, the requirement for a co-catalyst,[27] less environmentally friendly chlorohydrocarbon solvents[21,22,27,37] or complicated synthetic steps to obtain chiral complexes.[23] These deficiencies are becoming more apparent in view of growing environmental concerns in recent years. Thus, exploiting novel, more efficient, cost-effective and environmentally benign catalytic asymmetric sulfoxidation systems for green sustainable chemistry are still key challenges in the synthesis of enantiopure sulfoxides.

Serum albumins (SA), natural globular proteins that provide a chiral environment, possess well-defined binding sites for hydrophobic organic molecules.[38] Anchoring of ligand-bound metal complexes to proteins noncovalently provides conjugates that have potential as enantioselective catalysts: the metal complex is responsible for catalysis and the protein acts as a chiral auxiliary.[39–44] Reetz and Jiao[42] have shown that a 1:1.2 copper-complex of a Schiff base ligand and bovine serum albumin (BSA) functions as a catalyst in asymmetric Diels–Alder reactions, affording enantioselectivity of up to 98% *ee*. In a novel and systematic study, Mahammed and Gross[43] mixed Fe(III) and Mn(III) complexes of amphiphilic corroles with serum albumins, utilizing hydrogen peroxide for asymmetric sulfoxidation in up to 74% *ee*, but only obtaining 16% yield.

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It is therefore reasonable to assume that SAs coupled with transition-metal Schiff base complexes could have advantages for enantioselective sulfoxidation to obtain higher activity and enantioselectivity. Additionally, SAs are available in large quantities in enantiomerically pure form[45] and are generally robust, readily available, inexpensive and nontoxic.[38]

Inspired by these observations and considering the remaining challenges, in the present work we have endeavored to generate a catalyst system for the sulfoxidation of sulfides that combines high catalytic efficiency and excellent enantioselectivity under mild reaction conditions (water as reaction solvent and hydrogen peroxide [H_2O_2] as primary oxidant). In addition to the previously reported complex CoL **5**,[46] we synthesized another four coordination complexes: CuL **1**, MnL **2**, VL **3** and FeL **4**, derived from an achiral Schiff base ligand (H_2L = 2,2′-[(1,2-ethanediyl) bis(nitrilopropylidyen)]bisphenol). The study reports the catalytic properties of these five complexes in sulfoxidation reactions of aryl alkyl sulfides to the corresponding sulfoxides at ambient temperature in the presence or absence of SAs. The catalytic activity and enantioselectivity of the complexes were increased in the presence of SAs. Almost perfect chemical yield (up to 100%) was obtained in most cases and the sulfoxide was obtained in surprisingly high enantiopurity in certain cases (up to 94% *ee*). From environmental and economic viewpoints,[10] this process has the advantages of using the most accessible and cheapest proteins as chiral environment, water as the reaction solvent and extremely simple working procedures (Fig. 1).

2. Results and discussion

2.1. Description of the crystal structure

Complex 1. Single-crystal X-ray structural analysis shows that **1** crystallized in space groups of $I4_1/a$. Cu1 adopts a N_2O_2 distorted square-planar geometry (Fig. S1 (a)), surrounded by two imino-N atoms (Cu–N1 = Cu–N2 = 1.942(3) Å) and two phenolato-O atoms (Cu–O1 = 1.884(2), Cu–O2 = 1.873(2) Å).

Complexes 2 and 3. Complexes **2** and **3** crystallized in the space groups $P2_1$ and P-1 (Fig. S1 (b) and (c)). Mn1 adopts a N_2O_2Cl distorted tetragonal pyramid geometry, coordinated square-pyramidal by two imino-N atoms and two phenolato-O atoms from one Schiff base ligand, and the axial position is occupied by one chlorine atoms. **3** has a similar geometry to **2** except position is occupied by one oxygen atom.

Complex 4. Compound **4** crystallized in the non-centrosymmetric space group $P2_1/c$. Single-crystal X-ray crystallographic analysis of **4** reveals a binuclear Fe(III) cluster (Fig. S1 (d)). Bridged through two μ2-phenolato-O atoms with the Fe1···Fe1A separation of 2.8105(6) Å. Each crystallographically independent Fe(III) ion is coordinated by three phenolato-O atoms, two nitrogen atoms and one chlorine atom form a FeO_3N_2Cl octahedral coordination configuration. One μ_2-phenolato-O, one terminal-phenolato-O atom and two nitrogen atoms from the same ligand occupy the equatorial plane and another different ligand. Selected bond lengths and bond angles of complexes **1**–**4** were given in Table S1.

2.2. Binding of ML to serum albumin

UV–visible spectra of **ML** solutions (83 μm) were recorded in 50 mM PB buffer, pH 7.45, in the absence or presence of equimolar SAs (BSA, HSA, RSA, PSA, SSA) to examine the extremely simple noncovalent binding by comparing the spectrum of **ML** with **ML**-SAs.[43] It can be seen that SAs caused different degrees of band shift, accompanied by decreases in their intensity (Table S2 and Fig. S2). Fig. 2 shows the UV–visible spectra obtained in the typical case of complex **5**, in the absence and in the presence of BSA or RSA (1.0 equiv), respectively. The reaction of BSA with **5** resulted in a new, weak UV–visible absorption band at λ = 300 nm, while a 4 nm shift of the band at 250–254 nm was accompanied by a decrease of intensity, indicating that the **5** was indeed strongly anchored to the protein. In the case of RSA the effect was very small, which may indicate that binding was weaker.[42]

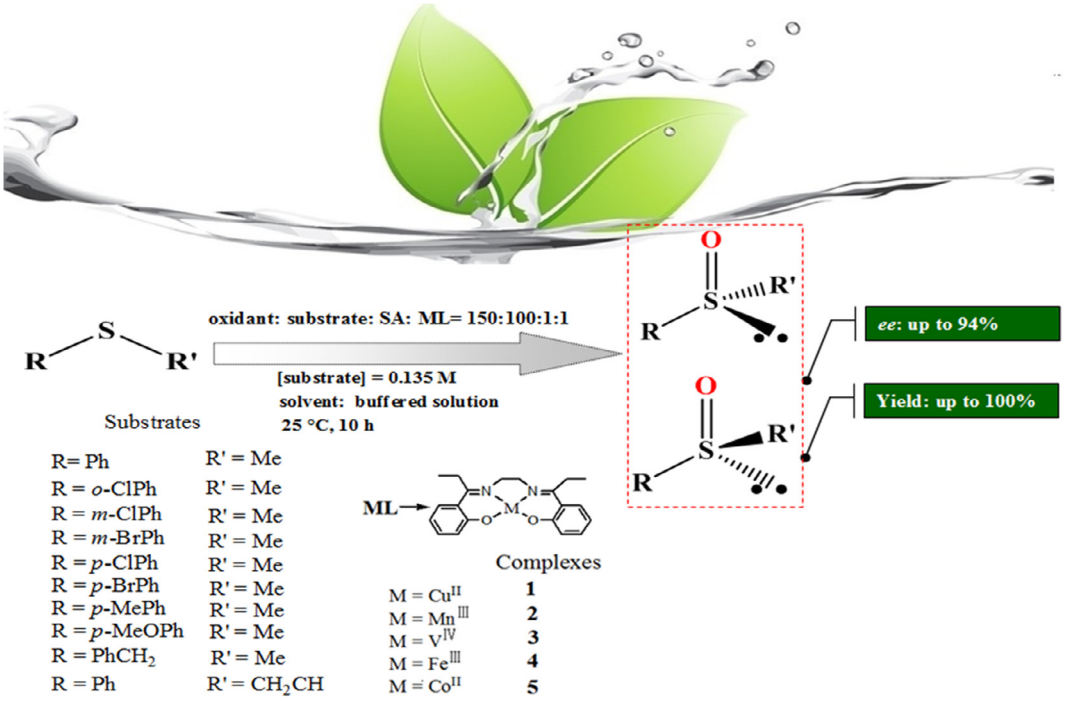

Fig. 1. Achiral Schiff base complexes as catalysts for asymmetric sulfoxidation in the presence of SAs.