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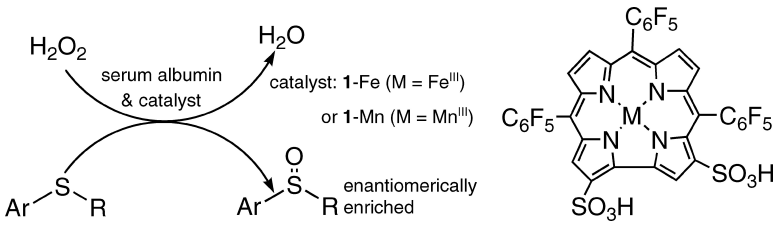

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Albumin-Conjugated Corrole Metal Complexes: Extremely Simple Yet Very Efficient Biomimetic Oxidation Systems

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Abstract: An extremely simple biomimetic oxidation system, consisting of mixing metal complexes of amphiphilic corroles with serum albumins, utilizes hydrogen peroxide for asymmetric sulfoxidation in up to 74% ee. The albumin-conjugated manganese corroles also display catalase-like activity, and mechanistic evidence points toward oxidant-coordinated manganese(III) as the prime reaction intermediate.

Introduction

The chemistry of corroles has remained quite undeveloped for decades, which may be appreciated by the very limited number of reported derivatives and lack of corrole-based applications.[1] Recent years have evidenced three major advances in the field: new synthetic routes for facile preparation of triarylcorroles,[2] efficient catalysis by the corresponding metal complexes,[3] and unique methodologies for preparation of amphiphilic corroles.[4] Regarding oxidation catalysis, manganese corroles have received a large amount of attention for three reasons: (a) the facile isolation of (oxo)manganese(V) corroles;[5,6a] (b) the low reactivity of the above and mechanistic puzzles regarding the identity of other oxygen-transferring intermediate;[5,7] (c) the large increase of catalytic activity upon halogen substitution of the β-pyrroles.[6] In parallel, the amphiphilic bis-sulfonated corrole **1** (Scheme 1) and its metal complexes were shown to spontaneously form tightly bound noncovalent conjugates with human serum albumin (HSA).[8] One particularly strong binding site was identified for the 1:1 conjugates, and the corresponding dissociation constants were found to be in the nanomolar range. These developments suggest that conjugation of metal complexes of corrole **1** with serum albumins might be useful for inducing asymmetric catalysis in a biomimetic fashion: the metal complex being responsible for catalysis and the protein for a chiral environment. This hypothesis was proven true: the albumin-conjugated iron and manganese complexes **1**−Fe and **1**−Mn catalyze the enantioselective oxidation of prochiral sulfides by hydrogen peroxide to sulfoxides, synthons of prime importance for asymmetric syntheses (Scheme 1).[9] Compared to related biomimetic systems,[10,11] this one has the advantage of relying on the most accessible and cheapest proteins and on extremely simple working procedures. An additional outcome of the investigations is concerned with the mechanism of action, primarily dealing with the identity of the oxygen-atom-transferring intermediate.

Experimental Section

Materials. Human serum albumin (essentially fatty acid free), pig serum albumin (essentially fatty acid free, essentially globulin free), sheep serum albumin (essentially fatty acid free), bovine serum albumin, and rabbit serum albumin (essentially fatty acid free) were purchased from Sigma. All the sulfides and H_2O_2 (30% in water) were obtained from Aldrich. The preparation of compound **1** and its manganese(III) complex **1**−Mn was described in previous publications.[4]

Preparation of **1**−Fe: One portion of $FeCl_2$ (30 mg, 23.7 mmol) was added at once to a pyridine solution (10 mL) of **1** (30 mg, 31.4 μmol), and the mixture was heated immediately to reflux for 5 min under argon, followed by evaporation of the solvent. The product was purified by two subsequent silica gel columns (the eluent was methanol for the first column and ethanol/CH_2Cl_2 1:1 for the second column), affording 31 mg (30.7 μmol, 98% yield) of the iron(III) complex of **1**. ^{19}F NMR (CD_3OD): δ = −106.2 (brs, *ortho*-F), −115.4

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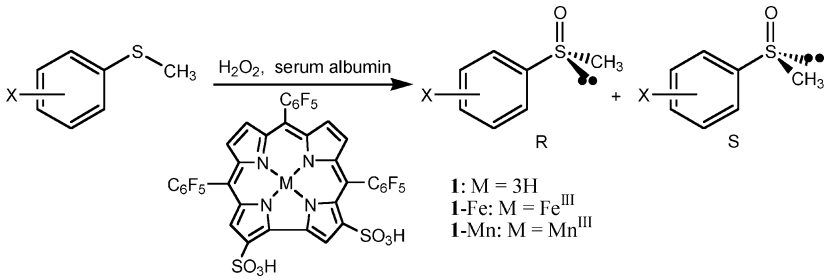
Scheme 1. Albumin-Conjugated Corrole Metal Complexes as Catalysts for Asymmetric Sulfoxidation



(brs, *ortho*-F), −116.5 (brs, *ortho*-F), −149.8 (s, *para*-F), −150.5 (s, *para*-F), −154.5 (s, *para*-F), −156.2 (s, *meta*-F), −157.2 (s, *meta*-F), −160.2 (s, *meta*-F). UV−vis (buffer solution, pH 7.00) λ_{max} ($\epsilon(M^{-1}$ $cm^{-1})$) = 404 (34 000), 552 (12 000), 738 (2300). MS (electrospray): *m*/*z* 503.5 $[(M - 2H)/2]^-$.

Analysis of Reaction Products. All the sulfoxides, except of 2-fluorophenyl sulfoxide, were analyzed by a Merck Hitachi HPLC on a Daicel chiral column OD (0.46ϕ cm × 25 cm). The enantiomeric sulfoxides from ethylphenylsulfide, *p*-tolylsulfide, 4-fluorothioanisole, 3-bromothioanisole, and 3-chlorothioanisole were eluted with 90% hexane and 10% isopropyl alcohol with retention times of 20 and 25, 22 and 25, 24 and 26, 26 and 28, and 26.8 and 27.5 min, respectively. Methyl phenyl sulfoxide was eluted with 80% hexane and 20% isopropyl alcohol with retention times of 16 and 19 min. The enantiomeric sulfoxides from 4-bromothioanisole and 2-chlorothioanisole were eluted with 98% hexane and 2% isopropyl alcohol with retention times of 78 and 83 and 47 and 51 min, respectively. The enantiomeric sulfoxides from 4-chlorothioanisole and 2-bromothioanisole were eluted with 95% hexane and 5% isopropyl alcohol with retention times of 40 and 43 and 33 and 37 min, respectively. The eluent was eluted at a flow rate of 0.5 mL/min and monitored at 250 nm. For all the sulfoxides the *S* enantiomer always eluted from the column first.[12] Reaction yields were measured by comparing the peak area ratios of the HPLC chromatograms of unreacted sulfide and produced sulfoxide. The response factor for every pair of sulfide/sulfoxides was calculated by a standard curve that was constructed from the peak area ratios of the HPLC chromatograms of mixtures of sulfide/sulfoxide obtained after analogous workup by ^{1}H NMR.

2-Fluorophenyl methyl sulfoxide was resolved by HP-54890 GC with a J&W chiral cyclodex-B capillary column and FID detector, linked to the HP Chem-Station (HP-3365). The GC retention times of the sulfoxides were 96 and 99 min under the following conditions: 100 °C at 7 psi. Nitrobenzene was used as an internal standard. On the basis of the relative retention times of other sulfoxides with known absolute configurations on the same GC column, the *R* isomer was assumed to be the faster eluting.

Biomimetic Sulfoxidation. Reactions were performed at 24 °C by subsequent feeding of the reaction vessel with sulfide, 1 mL of aqueous phosphate buffer solution pH 7.00 of albumin and catalyst, and hydrogen peroxide (3%) or iodosylbenzene. The ratios of oxidant: substrate:BSA:catalyst (0.2 mM) were 75:50:1.5:1 and 50:50:1:1 for the H_2O_2 and iodosylbenzene reactions, respectively. After 1.5 h the solution was extracted with CH_2Cl_2, and the extracts were concentrated under a steam of argon. The residue was taken up in the HPLC solvent and analyzed by HPLC. For the catalytic reaction with 2-flurorothioanisole, nitrobenzene was added as an internal standard to the CH_2Cl_2 extract prior to GC analysis.

Four different reactions were performed for examining the effects of starting with either manganese(III) or (oxo)manganese(V) corrole (**1**−Mn and **1**−Mn^V(O), respectively) conjugated BSA on the asymmetric oxidation of thioanisole. The catalytic reactions that started with Mn(III) as catalyst and H_2O_2 or iodosylbenzene as oxidant were performed as follows: subsequent addition of substrate (11 μL as a 10% v/v solution in CH_3CN) and oxidant (15 μL of 3% H_2O_2 or 2.2 mg of PhIO) to a 1 mL aqueous solution (phosphate buffer, pH 7.00) of BSA (0.3 mM) and **1**−Mn (0.2 mM) at 24 °C. The reaction was stirred for 1.5 h prior to the regular workup. For the catalytic reaction that started with Mn^V(O) as catalyst, the subsequent addition of substrate and oxidant was performed only after the BSA/**1**−Mn solution was treated by a small amount of iodosylbenzene and filtrated after full development of the red-brown color due to **1**−Mn^V(O) (90 s). The electronic spectrum of the solution of **1**−Mn and BSA was recorded at three times: before formation of **1**−Mn^V(O), immediately after the addition of substrate and oxidant to **1**−Mn^V(O), and at the end of the catalytic reaction. This revealed that 7% catalyst decomposition occurred at the second stage (formation of **1**−Mn^V(O) in the absence of substrate), while no more catalyst was bleached after addition of H_2O_2, i.e., 0% catalyst decomposition after both substrate and H_2O_2 were added.

Quantitation of the Amount of Catalyst Bleaching. The amount of catalyst bleaching was appreciated by comparing the electronic spectra before and after catalytic reactions. For **1**−Mn, 0.1 mL from the catalytic reaction mixture (before adding the oxidant) was diluted into 1.9 mL of phosphate buffer solution (pH 7.0), and the electronic spectrum was measured with particular emphasis on the optical densities at λ = 418, 492, and 618 nm. The same procedure was repeated at the end of the catalytic reactions. At every wavelength the final absorbance was reduced from the initial one and the result was divided by the initial absorption. The average of the three results at the three wavelengths provided the percentage of **1**−Mn bleaching. The same procedure was performed for **1**−Fe, with emphasis on λ = 418, 558, and 622 nm.

Catalytic Oxidation with Larger Concentrations of Thioanisole and H_2O_2. A 1 mL amount of an aqueous phosphate buffer solution (pH 7.00) that contained 0.3 mM BSA and 0.2 mM **1**−Mn was added to a vessel that contained 11 μL of thioanisole (100 mM). A 15 μL amount of 30% H_2O_2 (150 mM) was added, and the reaction was stirred for 1.5 h. The solution was extracted with CH_2Cl_2, and the extracts were concentrated under a stream of argon. The residue was taken up in the HPLC solvent and analyzed by HPLC, which revealed a 30% yield (150 catalytic turnovers) and 46% ee (*S*) of methyl phenyl sulfoxide. Seventeen percent of the catalyst was bleached. When an identical catalytic reaction was performed but with a reaction time of 15 h, 97% yield with 29% ee (*S*) of methyl phenyl sulfoxide were obtained and 50% of the catalyst was bleached.

Catalytic Disproportionation of H_2O_2. The catalase-like activities of **1**−Fe/BSA and **1**−Mn/BSA were assessed by volumetric determination of the amount of O_2 released upon addition of H_2O_2. The reaction mixture contained pH 7.00 phosphate buffer, 0.3 mM BSA, and 0.2 mM **1**−Fe or **1**−Mn in a total volume of 4 mL. The reaction was started by addition of 0.3 mL of H_2O_2 (30%), i.e., an initial concentration of 743 mM. The amount of O_2 that was released within 1.5 h, at 1 atm and 24 °C, was 4 (11% yield) and 3.7 mL (10% yield) for **1**−Fe/BSA

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Table 1. Effects of Catalyst, Albumin Source, and Substrate on Asymmetric Oxidation of Aryl Methyl Sulfides (R = Phenyl Substituent in Column 1) and Ethylphenylsulfide (PhSEt)[a] (Yields of ≥90% and Enantiomeric Excesses (ee) of ≥60% Are Emphasized)

	catalyst = **1**–Fe: % yield, major enantiomer, % ee					catalyst = **1**–Mn: % yield, major enantiomer, % ee				
R	HSA	BSA	PSA	RSA	SSA	HSA	BSA	PSA	RSA	SSA
H	76, *S*, 10	87, *S*, 38	52, *S*, 13	29, *S*, 14	**91**, *S*, 20	69, *R*, 17	83, *S*, 52	60, *S*, 33	**90**, *S*, 55	**90**, *S*, 32
4-CH_3	30, *S*, 15	23, *S*, 22	66, *S*, 16	75, *R*, 7	60, *R*, 3	82, *R*, 6	73, *S*, 50	**94**, *S*, 20	48, *S*, 32	81, *S*, 16
2-F[b]	42, *S*, 7	67, *S*, 34	92, *S*, 33	76, *S*, 18	76, *S*, 25	39, *R*, 14	76, *S*, **68**	**98**, *S*, **65**	72, *S*, 52	27, *S*, 54
4-F	88, *S*, 7	86, *S*, 23	**95**, *S*, 24	**95**, *R*, 7	**93**, *R*, 7	74, *R*, 9	82, *S*, 50	**95**, *S*, 32	**90**, *S*, 26	**98**, *S*, 17
2-Cl	11, *R*, 2	42, *S*, 39	23, *S*, 25	12, *S*, 26	33, *S*, 41	38, *R*, 1	4, *S*, **70**	30, *S*, **60**	73, *S*, 59	40, *S*, **61**
3-Cl	40, *S*, 6	89, *S*, 26	5, *S*, 35	5, *S*, 17	61, *R*, 2	30, *R*, 4	2, *S*, 44	18, *S*, 19	27, *S*, **64**	52, *S*, 38
4-Cl	50, *S*, 11	50, *S*, 10	88, *S*, 16	75, *R*, 15	40, *S*, 6	27, *S*, 5	68, *S*, 51	35, *S*, 23	63, *S*, 23	74, *S*, 24
2-Br	<1, *S*, 12	17, *S*, 24	1, *S*, 27	7, *S*, 32	5, *S*, 26	1, *S*, 6	16, *S*, **74**	3, *S*, 59	24, *S*, 56	30, *S*, **60**
3-Br[c]	8, *R*, 2	25, *S*, 5	9, *S*, 27	6, *S*, 3	11, *R*, 11	6, *S*, 4	13, *S*, 32	38, *S*, 33	28, *S*, **61**	22, *S*, 10
4-Br[c]	61, *S*, 5	55, *S*, 2	65, *S*, 6	59, *R*, 2	36, *R*, 13	35, *S*, 5	23, *S*, 48	51, *S*, 29	29, *S*, 24	25, *S*, 13
PhSEt	34, *S*, 11	79, *S*, 17	86, *S*, 14	80, *S*, 16	69, *S*, 6	36, *R*, 1	**95**, *S*, 26	86, *S*, 26	**90**, *S*, 49	88, *S*, 29

[a] H_2O_2:sulfide:albumin:catalyst (0.2 mM) = 75:50:1.5:1; pH 7.0; T = 24 °C; reaction time = 1.5 h. % ee determined by "chiral" HPLC, and enantiomers (*R* vs *S*) identified by reference to published works.[12] [b] The identities of the enantiomers of 2-fluoro-thionanisole oxide were deduced from the BSA- and PSA-catalyzed reactions that provided an excess amount of the *S* enantiomer for all other substrates. [c] Identical to reaction conditions in a, but H_2O_2 was added in five portions (10 mM per hour).

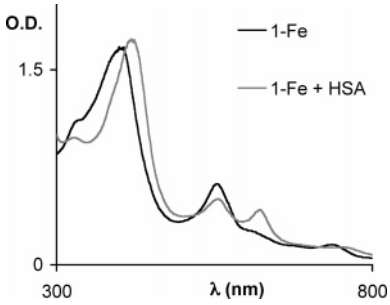


Figure 1. Electronic spectra of **1**−Fe (50 μM) in the absence and presence of HSA (50 μM).

and **1**−Mn/BSA, respectively. For **1**−Fe/BSA most of the O_2 was released within the first 20 min, and examination of the reaction mixture after 1.5 h revealed that the catalyst was completely bleached. For **1**−Mn/BSA the reaction was slower, and only 30% of the catalyst was bleached after 1.5 h.

Results and Discussion

One emphasis of the investigations was on simplicity, compared to other much more sophisticated enzyme-mimicking systems.[10,11] We already demonstrated the spontaneous and very strong association of corrole **1** and its manganese(III) complex **1**−Mn with HSA,[8] which is further exemplified by the pronounced changes in the electronic spectrum of **1**−Fe upon addition of 1 mol equiv of HSA (Figure 1). This allowed for the examination of these extremely simple noncovalent bioconjugates as catalysts for asymmetric oxidations.

Reactions were performed at 24 °C by subsequent feeding of the reaction vessel with substrate, an aqueous pH 7 buffer solution of albumin and catalyst, and hydrogen peroxide (3%).[13] The workup procedure was also very simple: washing with CH_2Cl_2 provides a colorless solution that contains only product and unreacted substrate, while the catalyst and protein remain in the aqueous phase. The other focus was on variability, as may be appreciated by the results obtained for 11 substrates and 5 different albumin sources (Table 1). Control reactions without catalyst (Table 2) were performed as well to rule out two possible interferences: (a) direct oxidation of the sulfides by H_2O_2 as an important route for the high yields; (b) significant contributions to the enantiomeric excesses (ee's) due to the existence of protein binding sites for either the substrates or the oxidant.[14]

Table 2. Effects of Albumin Source and Substrate on Asymmetric Oxidation of Aryl Methyl Sulfides (R = Phenyl Substituent in Column 1) and Ethylphenylsulfide (PhSEt) in the Absence of Metal Catalyst at the Same Reaction Conditions as In Table 1

	no catalyst: % yield, major enantiomer, % ee				
R	HSA	BSA	PSA	RSA	SSA
H	13, *R*, 2	5, *R*, 2	9, *S*, 3	6, *R*, 1	4, *S*, 1
4-CH_3	12, *R*, 4	10, *R*, 3	3, *R*, 21	2, *R*, 3	1, *R*, 1
2-F	18, *R*, 8	0, −, −	3, *S*, 1	2, *S*, 5	0, −, −
4-F	0, −, −	17, *R*, 1	1, *S*, 4	6, *S*, 1	10, *S*, 1
2-Cl	<1, −, 0	<1, −, 0	0, −, −	<1, −, 0	0, −, −
3-Cl	0, −, −	1, *S*, 5	0, −, −	2, *S*, 6	1, −, 0
4-Cl	0, −, −	2, −, 0	4, *R*, 4	0, −, −	<1, −, 0
2-Br	0, −, −	0, −, −	0, −, −	0, −, −	0, −, −
3-Br	0, −, −	0, −, −	6, *S*, 2	0, −, −	1, *R*, 5
4-Br	5, *R*, 24	0, −, −	9, *R*, 22	1, *R*, 10	8, *R*, 4
PhSEt	7, *R*, 1	27, *R*, 1	1, *S*, 7	4, *R*, <1	8, *S*, 9

The comparison between the results of Table 1 and the control reactions (Table 2, negligible yields and ee's) clearly demonstrates that catalysis is due to the metallocorrole and that the enantiomeric excesses reflect the chiral environment surrounding the albumin-conjugated catalyst. The albumin source had a highly significant effect on the ee's with the values for all substrates averaging 51.4%, 45.5%, 36.3%, 32.2%, and 6.5% for conjugates of **1**−Mn with BSA, RSA, PSA, SSA, and HSA, respectively (the corresponding numbers without taking PhSEt into account were 53.2%, 45.2%, 37.3%, 32.5%, and 7.1%). A similar effect was obtained for the conjugates of **1**−Fe with the same albumins, but the ee's were significantly lower: 21.8%, 14.3%, 21.5%, 14.5%, and 8.0% (22.3%, 14.1%, 22.2%, 15.4%, and 7.7% without taking PhSEt into account). BSA and PSA provided an excess of the *S* enantiomer for all substrates in conjugation with both catalysts, and the same holds for RSA and SSA conjugates with **1**−Mn, while significant variations in the identity of the major enantiomer were obtained in reactions catalyzed by conjugates of **1**−Fe with HSA, RSA, and SSA and the **1**−Mn/HSA system. Another reflection of the metal effect is that the identity of the major enantiomer obtained

(13) HSA, BSA, PSA, RSA, SSA: Human, bovine, pig, rabbit, and sheep serum albumin.

(14) For an example of catalyst-free asymmetric sulfoxidation due to a binding site for the oxidant, see: Colonna, S.; Banfi, S.; Annunziata, R. *J. Org. Chem.* **1986**, *51*, 891.

Table 3. Effects of Oxidant on Asymmetric Oxidation of Selected Aryl Methyl Sulfides under Catalysis by the 1-Mn/BSA-Conjugate[a]

oxidant	substrate	% yield	% ee	catalyst bleaching	color changes
H_2O_2	thioanisole	83	52; *S*	0%	no[b]
PhIO		92	32; *S*	20%	yes[c]
H_2O_2	2-chloro-thioanisole	4	70; *S*	0%	no[b]
PhIO		24	42; *S*	30%	yes[c]
H_2O_2	2-bromo-thioanisole	16	74; *S*	0%	no[b]
PhIO		28	45; *S*	30%	yes[c]

[a] All reactions were performed at pH 7.0, 24 °C, for 1.5 h. The ratios of oxidant:substrate:BSA:catalyst (0.2 mM) were 75:50:1.5:1 and 50:50:1:1 for the H_2O_2 and iodosylbenzene reactions, respectively. [b] The color of the reaction mixture remained green (due to **1**−Mn) during catalysis, and very few bubbles of gas (oxygen) were released during the reaction. [c] The color of the reaction mixture turned from green to brown-red upon addition of the oxidant, signaling the formation of **1**−Mn^V(O), and returned to green after 20, 30, and 40 min for thioanisole, 2-chlorothioanisole, and 2-bromothioanisole, respectively.

with the same albumin conjugated to either **1**−Fe or **1**−Mn was frequently opposite: for four, five, and seven of the substrates with RSA, SSA, and HSA, respectively. The last variations are concerned with the organic substrates. The ee's obtained for methylphenylsulfide were either similar or superior to ethylphenylsulfide, and the effect of *para*-aryl substitution in the methylarylsulfides was similar for the similar in size methyl and chloro substituents. However, regardless of the albumin source and the catalyst, the highest ee's in each combination (except of HSA) were obtained for meta and/or ortho substitution. This suggests that the substrate's effect is mostly of steric rather than electronic origin.

Throughout the series of substrates and albumins the results obtained with **1**−Mn were superior to those with **1**−Fe regarding all three important subjects: enantioselectivity, chemical yield, and stability of the catalyst. The first two aspects may be easily deduced from Table 1 (note numbers in bold): nine cases of ≥90% yield with **1**−Mn as catalyst vs only four with **1**−Fe as catalyst; nine cases of ≥60% ee with **1**−Mn conjugates vs null with albumin-conjugated **1**−Fe (the largest ee under **1**−Fe catalysis was 41% for 2-chloro-thioanisole/SSA). The least obvious benefit of the **1**−Mn-catalyzed reactions is the stability of the system, reflected in the absence of catalyst bleaching and/or protein oxidation even when less reactive substrates (such a the 2-halogeno-thioanisoles) were employed. To elucidate the origin of this intriguing and unique phenomenon, which is not shared by the related porphyrin-based systems whose main drawback is catalyst bleaching,[15] the sulfoxidation of three substrates was performed with iodosylbenzene (PhIO), the most commonly used oxidant in metal-catalyzed oxidations.[15,16]

The results shown in Table 3 revealed that reactions performed with PhIO provide larger chemical yields but smaller ee's than those with H_2O_2. The comparison also revealed pronounced differences with regard to catalyst bleaching: none for H_2O_2 with any of the substrates and more for PhIO oxidation of the 2-halogeno-substituted than for the more reactive nonsubstituted thioanisole.[17] An important clue for the uniqueness of H_2O_2 is that bubbles due to the formation of molecular oxygen were clearly seen. Although not fully quantified, the extent of O_2 formation was more significant in the low-yielding reactions.

Table 4. Effects of Starting with Either Manganese(III) or (Oxo)manganese(V) Corrole (1−Mn and 1−Mn^V(O), respectively) Conjugated BSA on Asymmetric Oxidation of Thioanisole

oxidant	catalyst	% yield	% ee	% catalyst bleaching
H_2O_2 (15 mM)	**1**−Mn	83	52; *S*	0
H_2O_2 (15 mM)	**1**−Mn^V(O)	76	44; *S*	7 (0)[a]
PhIO (10 mM)	**1**−Mn	92	32; *S*	20
PhIO (10 mM)	**1**−Mn^V(O)	81	17; *S*	22

[a] The 7% bleaching occurred during the preparation of **1**−Mn^V(O), i.e., prior to addition of substrate and H_2O_2.

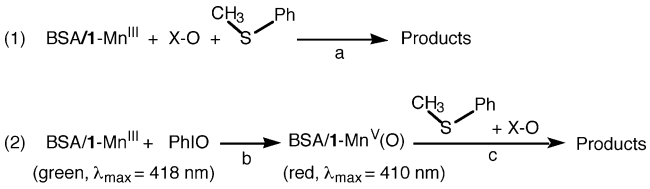
One obvious difference between PhIO and H_2O_2 is that only the latter can play a dual role, oxidant and reducible substrate. The formation of O_2 indicates that H_2O_2 is oxidized in the presence of less reactive substrates, thus preventing catalyst bleaching and protein oxidation by the reactive intermediate. This route does not exist when PhIO is the oxidant, hence the more extensive catalyst bleaching with less reactive sulfides. On the other hand, larger chemical yields of sulfoxides are obtained with PhIO vs H_2O_2 as oxidants due to competition of H_2O_2 with the sulfides for the same reactive intermediates. These conclusions were substantiated by treating two **1**−Mn/BSA solutions by concentrated (30%) H_2O_2 in the presence and absence of substrate. Examination of the reaction products after 1.5 h revealed a 30% yield (150 catalytic turnovers) of thioanisole oxide (46% ee of the *S* enantiomer) with 17% catalyst bleaching in the former case, while a 10% yield production of O_2 with 30% catalyst bleaching was obtained in latter reaction. **1**−Fe also affected the disproportionation of H_2O_2 (11% yield of O_2) but was completely bleached quite fast.

Another difference (Table 3, last column) between the oxidants is that the color of reaction mixtures turned from green to red upon addition of PhIO and returned to green only toward the end of the reactions, while no color changes were noticed with H_2O_2 as oxidant. As the colors of manganese(III) and (oxo)manganese(V) corroles are green and red, respectively,[5,6] the above results indicate the presence and absence of substantial amounts of (oxo)manganese(V) corrole in reactions performed with PhIO and H_2O_2, respectively. This and the very different ee's (Table 3, fourth column) clearly indicate that different reactive intermediates are responsible for oxygen-atom transfer to the sulfides in the two systems. It is also consistent with examinations in protein-free systems that uncovered the very low reactivity of (oxo)manganese(V) corroles and suggested that oxygen-atom transfer could take place from either its precursor or its successor (oxidant-coordinated manganese(III) and (oxo)-manganese(V) corroles, respectively).[3,5,7,18]

To address the mechanistic issues a comparison was made between reactions performed as shown in eqs 1 and 2 (results are shown in Table 4). The normal reaction conditions (eq 1) consisted of subsequent addition of substrate and oxidant to BSA/**1**−Mn solutions, while in those described by eq 2 thioanisole and the full amount of oxidant were only added after the reaction mixture was first transformed to BSA/**1**−Mn(O) by a small amount of PhIO (signaled by a color change from

(15) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.
(16) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189.
(17) Similar results were obtained for **1**−Fe, but the differences were smaller: 87% yield, 38% ee, and 15% bleaching vs 98% yield, 16% ee, and 40% bleaching for oxidation of thioanisole by H_2O_2 and PhIO, respectively.
(18) For similar proposals in porphyrin chemistry, see: Nam, W.; Jin, S. W.; Lim, M. H.; Ryu, J. Y.; Kim, C. *Inorg. Chem.* **2002**, *41*, 3647.

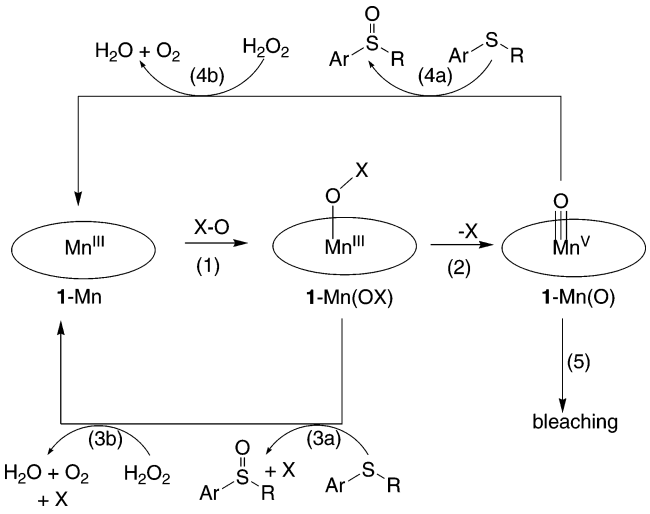
green to red-brown). The responses to the latter modification were quite different for the two oxidants. The color remained red until full consumption of the oxidant, and the ee decreased from 32% to 17% when PhIO was the final oxidant. In contrast, addition of H_2O_2 to the BSA/**1**−Mn(O) solution induced an immediate color change back to that of **1**−Mn, and the ee only decreased from 52% to 44%. Importantly, no fast reaction took place when thioanisole was added to the BSA/**1**−Mn(O) solution. Together with the earlier described results, these observations provide strong evidence for the reaction mechanisms shown in Scheme 2.



a: normal reaction conditions, X-O = PhIO or H_2O_2.
b: -PhI, filtration of any unreacted PhIO.
c: X-O = PhIO or H_2O_2.

According to Scheme 2 addition of oxidant X−O to **1**−Mn first affords the oxidant-coordinated **1**−Mn(OX) (step 1), which may either release X to afford **1**−Mn(O) (step 2) or react with sulfide (step 3a) to produce sulfoxide and regenerate **1**−Mn. The results with preformed **1**−Mn(O) [*immediately* reduced to **1**−Mn by H_2O_2 (producing O_2) and not by substrate or PhIO] clearly demonstrate its low reactivity toward sulfides (step 4a) and its large reactivity toward H_2O_2 (step 4b). As sulfoxides are nevertheless formed in high yields in the reactions with H_2O_2 as oxidant, the presence of another intermediate that is much less discriminatory than **1**−Mn(O) for oxidation of H_2O_2 relative to sulfide is clearly required. The most reasonable candidate is **1**−Mn(OX): its enantioselectivity with regard to sulfide oxidation (step 3a) may safely be expected to be different than that of **1**−Mn(O) (step 4a), and it should further depend on the identity of OX being PhIO or H_2O_2. The other differences between results obtained with PhIO and H_2O_2 may also be explained similarly. Sulfoxides are almost exclusively produced by route 3a when X−O = H_2O_2, since route 4a is depressed by the large efficiency of route 4b (oxidation of H_2O_2). As route 4b does not exist when X−O = PhIO (**1**−Mn(O) does not decompose PhIO efficiently), sulfoxides may be obtained via both routes 3a and 4a with this oxidant. This hypothesis also explains the much larger extent of catalyst bleaching with PhIO (route 5 of Scheme 2) than with H_2O_2 and that it is especially pronounced for low-reactivity substrates. The larger the amount of **1**−Mn(O) that is formed via step 2, because of either the absence of H_2O_2 (routes 3b and 4b not being available) or the low reactivity of the sulfide (routes 3a and 4a not being efficient), the more catalyst bleaching is observed. In fact, when **1**−Mn/BSA mixtures were treated with either PhIO or 3% H_2O_2 in the absence of substrate, complete bleaching and complete survival of the catalyst were obtained, respectively.[19]

Scheme 2. Plausible Reaction Sequences and Plausible Intermediates in the Catalytic Oxidation of Thioanisoles by Either PhIO or Hydrogen Peroxide[a]



[a] Note that according to MO theory the manganese(V) ion and oxygen atom in **1**−Mn(O) are connected via a triple bond.[3]

Conclusions

We demonstrated the efficiency of an extremely simple biomimetic oxidation system that consists of mixing metal complexes of amphiphilic corroles with serum albumins and utilizes hydrogen peroxide for asymmetric sulfoxidation of sulfides. The albumin-conjugated manganese corroles act exactly as the various heme enzymes which all display catalase-like activity when treated by hydrogen peroxide in the absence of more oxidizable substrates.[20] Mechanistic investigations revealed the importance of the hydrogen-peroxide-coordinated manganese(III) corrole as the prime intermediate for efficient and enantioselective oxygen-atom transfer. One issue that remains to be investigated is if the metal or the corrole is responsible for the larger reactivity of (corrole)Mn−O−X than (corrole)-Mn(O). In hemes and synthetic iron porphyrins $[(\text{porphyrin})\text{Fe(O)}]^+$ is significantly more reactive than (porphyrin)Fe−OX,[21] but both the reactivity and enantioselectivety of oxidant-coordinated (porphyrin)Ru(O) are larger than of (porphyrin)-Ru(O)_2,[22] while the very large emphasis on isolation of the extremely reactive $[(\text{porphyrin})\text{Mn(O)}]^+$ might have had a shading effect on the search for other reactive intermediates of possible importance.[23]

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(19) Similar results were obtained in protein-free solutions, but the lifetime of nonconjugated **1**−Mn(O) (seen only with PhIO as oxidant) was significantly shorter than that of **1**−Mn(O)/BSA.
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