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HbA/H_2O_2: an efficient biomimetic catalytic system for the oxidation of sulfides to sulfoxides☆

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Abstract—Human hemoglobin (HbA) catalyzed chemo-selective oxidation of sulfides to sulfoxides has been reported using hydrogen peroxide as an oxidant in a phosphate buffer. This biomimetic catalytic procedure was found to be simple, environmentally friendly, selective, and high yielding. Purified human oxyhemoglobin (HbA_0), crude human oxyhemoglobin, and ferryl oxyhemoglobin were used for sulfoxidation. HbA_0 and ferryl oxyhemoglobin (Fe^{+4}=O) efficiently catalyze the sulfoxidation reaction without over oxidation to the sulfone.

Sulfoxidation reactions have significant importance in organic chemistry, medicinal chemistry, and drug metabolism.[1] Organic sulfoxides are extensively used as anti-ulcer[2] (omeprazole, proton pump inhibitor), antibacterial,[3] antifungal,[4] antiatherosclerotic,[5] antihypertensive,[6] anthelmintic[7] and cardiotonic agents,[8] psychotropics,[9] vasodilators[10] and as CNS/CVZ[11] stimulants (Fig. 1).

In addition to this, sulfoxides are also valuable synthons used in synthetic organic reactions for carbon–carbon bond formation,[12] as chiral auxiliaries,[13] in Diels–Alder reactions[14] and for metal centered catalysis.[15]

There are several methods reported in the literature for sulfoxidation using reagents such as TEMPO-linked metalloporphyrins,[16] hypervalent iodine compounds,[17] $H_2O_2/ZrCl_4$,[18] transition-metal (Ti, Mo, Fe, V, W, Re, Ru)/H_2O_2[19] and halogens/H_2O_2.[20] Unfortunately many of these processes suffer from the use of toxic and expensive oxidizing systems, complicated and resource-wasting workup procedures, employment of chlorinated solvents, and the occurrence of side reactions. The use of halogen-mediated systems, for example, led to the generation of halogen-substituted sulfides or sulfonic or sulfinic acids as byproducts. Another major problem is over-oxidation to the sulfone. Therefore, there is still a need for an efficient, inexpensive, selective, and environmentally friendly catalyst for sulfoxidation. Biocatalysts such as peroxidases[21] and myoglobin[22] are used for selective sulfoxidation reactions, but their low operational stability with hydrogen peroxide limits their application. Human hemoglobin is an iron porphyrin metalloprotein, which acts as an oxygen carrier in biological systems.

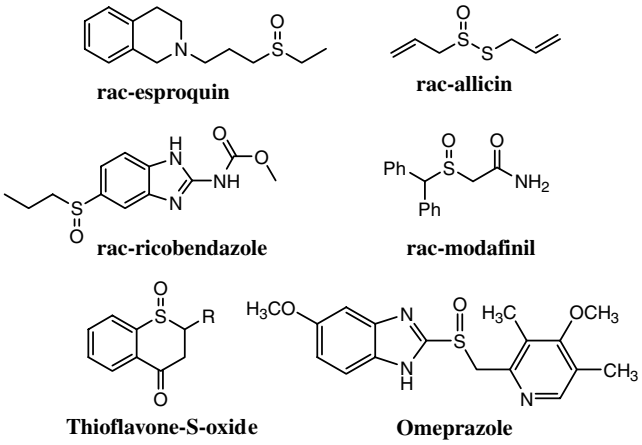

Figure 1. Structures of organic sulfoxides used as drug candidates.

Herein we report the biocatalytic activity of human hemoglobin (HbA) and H_2O_2 for sulfoxidation. We

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preferred hydrogen peroxide as the oxidant over other available oxidizing agents since it is cheap, operationally safe, environmentally friendly, and produces only water as a byproduct, which reduces purification requirements.[23]

The commercially available human hemoglobin (HbA) contains approximately 80% of the methemoglobin (Met Hb). Methemoglobin (Met Hb) is an oxygen carrying protein hemoglobin having Fe^{3+} in the heme group and is unable to transfer oxygen. Therefore, our initial strategy was the conversion of methemoglobin into oxyhemoglobin, which can efficiently transfer oxygen. Hence, we converted commercial human hemoglobin into oxyhemoglobin by treatment with dithionite in a phosphate buffer and subsequently eluted it through a Sephadex G-25 column to obtain the purified form of oxyhemoglobin (HbA_0).[24] The percentage of oxy-Hb of the total HbA can be determined from the absorbance (A) at 540 nm and at 576 nm. This equation is based on reported molar absorptivities of oxy-Hb and met-Hb.[24]

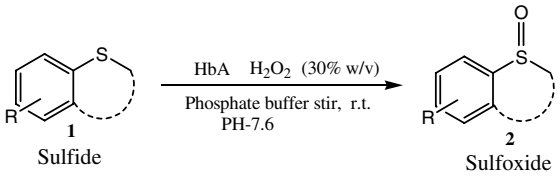
$$\%\ \text{oxy Hb} = \frac{70A_{540} - 117A_{576}}{169A_{576} - 236A_{540}} \times 100$$

We utilized this purified oxyhemoglobin for sulfoxidation (method I). Besides this we also tried two other methods for sulfoxidation (methods II and III). In Method II, oxyhemoglobin was generated in situ by the reaction of dithionite in a phosphate buffer (pH 7.6) from human hemoglobin (HbA) and this crude oxyhemoglobin was used for sulfoxidation without any purification. In method (III) human hemoglobin was reacted with hydrogen peroxide in a phosphate buffer (pH 7.6) and converted to [Met Hb–OOH] which finally yielded ferryl oxyhemoglobin and was used for sulfoxidation.[25] In our preliminary experiments, methyl phenyl sulfide was chosen as a model substrate and the reaction was studied using 30% aqueous hydrogen peroxide with a catalytic amount of purified oxy-Hb, in situ generated oxyhemoglobin and with ferryl oxyhemoglobin (Fig. 2). We observed that the purified oxyhemoglobin oxidizes methyl phenyl sulfide quite efficiently and yielded the corresponding sulfoxide in high yield, but this procedure needed extra purification. Therefore, we turned our attention to the in situ generated crude oxyhemoglobin via dithionite (method II), but this procedure required a longer time for the sulfoxidation reaction and also initiated other side reactions. Method III was found to be best as HbA with 30% of H_2O_2 in a slightly alkaline phosphate buffer (pH 7.6) gave a high yield of the sulfoxide within a short time. This procedure was also found to be clean and no further purification was required.

In order to check the feasibility of the HbA/H_2O_2 catalyzed system in an organic medium, we performed the sulfoxidation in methanol, acetonitrile, methanol, and DCM (3:1). However in organic medium, hemoglobin forms an emulsion and its work-up procedure was quite tedious. Thus an organic medium was not of choice for this catalytic enzymatic system. The HbA/H_2O_2 system worked quite efficiently in 15% acetonitrile in a phosphate buffer.

Encouraged by these results, we turned our attention to explore the generality and scope of the HbA/H_2O_2 catalyzed sulfoxidation using various sulfides (Scheme 1).

Using a similar protocol to that in method III, cyclic as well as acyclic sulfides formed sulfoxides in high yields (Table 1). No reaction could be detected when either hemoglobin or hydrogen peroxide was used alone. This procedure was also found to be chemoselective, other functional groups like CH_2, CO, CN and as olefin was unaffected.



Scheme 1.

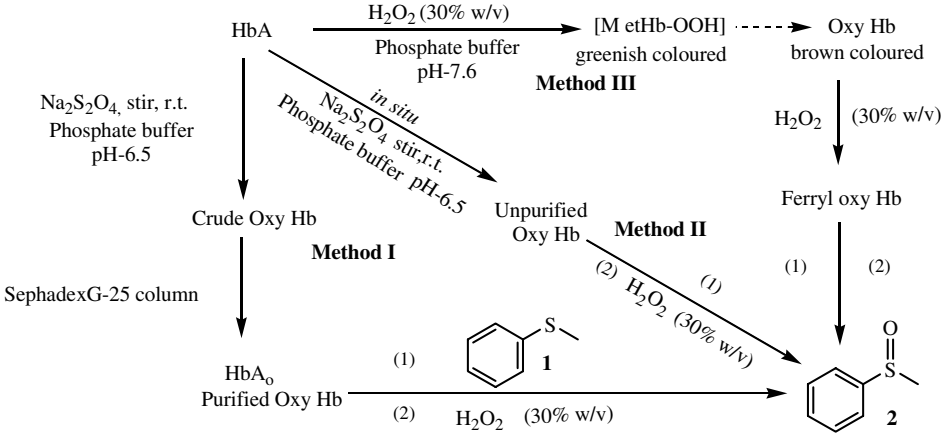
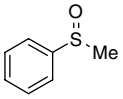
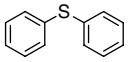
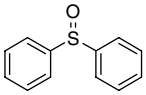
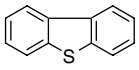
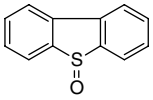
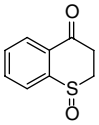
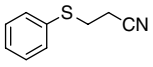
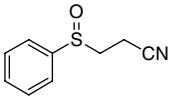
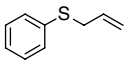
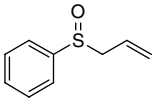
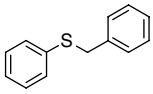
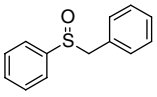


Figure 2. HbA/H_2O_2; a biomimetic catalytic procedure for sulfoxidation.

Table 1. HbA/H_2O_2 catalyzed biomimetic oxidation of sulfide to sulfoxide in phosphate buffer (PH 7.6)[a,b,c]

Entry	Sulfide (1)	Time (h)	Sulfoxide(2)[b]		Yields[c] (%)	Mp. (°C)/(lit mp.)[Ref]
1.		0.5		**2a**	96	30–35/ (30–30.5)[18,23]
2.		1.0		**2b**	92	(71–72)/(72–73)[23]
3.[a]		1.2		**2c**	90	204–205/ (205–207)[18,23]
4.		1.5		**2d**	88	96–100
5.		1.8		**2e**	73	Oil[17,20]
6.		1.5		**2f**	69	Oil
7.		1.2		**2g**	92	120–122/(122–124)[18]

Reaction conditions: Sulfide (1 mmol), HbA (0.5–0.7 mmol), H_2O_2 (30% w/v, 2 mmol) in phosphate buffer (pH 7.6, 3 mL), stirred at room temperature.

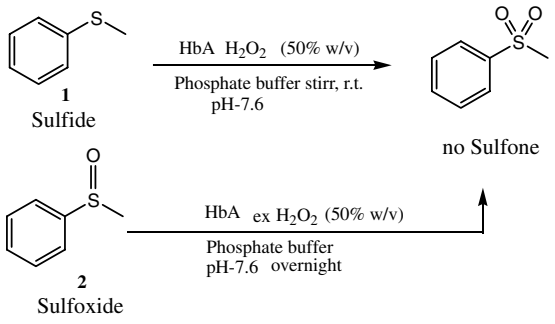
[a] 1 mL of 15% acetonitrile used as solvent.

[b] Products were characterized by ^1H NMR, ^{13}C NMR, IR, and MS spectroscopy.

[c] Isolated yield.

All the compounds reported in Table 1 were characterized by IR, ^1H, and ^{13}C NMR.[26,27]

Many reagents are available for the oxidation of sulfides but most cause over-oxidation to sulfones. Therefore, we examined reaction conditions such as time, temperature and the relative amount of oxidant that can cause over-oxidation to sulfones. For this purpose, we stirred the reaction overnight in the presence of HbA/H_2O_2 (50% w/v) in a phosphate buffer but we did not obtain any sulfone, even when using an excess of hydrogen peroxide (Scheme 2).



Scheme 2.

In conclusion, we have reported an efficient and versatile biomimetic procedure for the oxidation of sulfides to sulfoxides catalyzed by HbA/H_2O_2 in a 15% acetonitrile phosphate buffer system at room temperature. This methodology is efficient, simple, chemoselective, and high yielding.

Acknowledgment

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26. **Compound 2d:** White solid. Mp 96–100 °C. FAB-MS, *m/z*: 180, Anal. Calcd for $C_9H_8O_2S$ (180.2): C, 59.98; H, 4.47. Found: C, 59.92; H, 4.49, IR (KBr, cm^{-1}): 3072, 3028, 2985, 2942, 2909, 1698, 1589, 1447, 1338, 1294, 1185, 1054, 786, ^1H NMR ($CDCl_3$, 300 MHz): δ 2.90 (1H, m), 3.44 (3H, m), 7.67 (1H, t, $J = 7.4$ Hz), 7.70 (1H, t, $J = 7.4$ Hz), 7.91 (1H, d, $J = 7.6$ Hz), 8.10 (1H, d, $J = 7.6$ Hz), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 29.66, 45.96, 127.79, 128.12, 128.53, 131.43, 133.92, 144.94, 191.47.
27. **Compound 2f:** Oil. FAB-MS, *m/z*: 166, IR (KBr, cm^{-1}): 3094, 3072, 3028, 2990, 2963, 2920, 1643, 1491, 1431, 1403, 1092, 1000, 934, 757, 694, ^1H NMR ($CDCl_3$, 300 MHz): δ 3.40–3.62 (2H, m), 5.17–5.22 (1H, m), 5.30–5.33 (1H, m), 5.55–5.70 (1H m), 7.50–7.53 (3H, m), 7.57–7.63 (2H, m), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 60.23, 123.40, 123.83, 124.77, 128.57, 130.63, 142.35.