Catalytic Mechanism for the Biomimetic Oxidation of Benzoin by *p*-Benzoquinone in the Presence of $\{Fe_4S_4\}$ Complexes with Bulky Arenethiolate or Cysteine-containing Tripeptide Ligands

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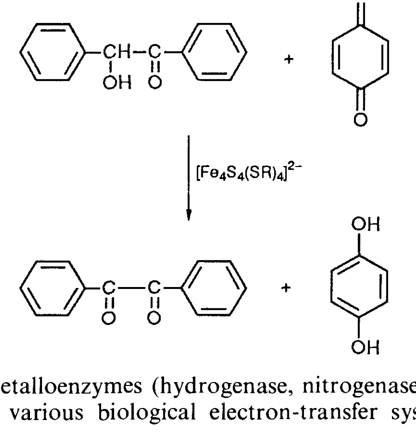
Catalytic oxidation of benzoin to benzil by *p*-benzoquinone in the presence of $[PPh_4]_2[Fe_4S_4(tipbt)_4]$ (tipbt = 2,4,6-triisopropylbenzenethiolate) obeys first-order kinetics in the concentrations of benzoin and the catalyst. The observed rate constant was found to depend on the bulkiness of the thiolate or the peptide ligand of $[Fe_4S_4(SR)_4]^{2-}$. A complex with a bulky peptide, $[Fe_4S_4(Z\text{-CysS-Pro-Val-OMe})_4]^{2-}$ (Z = benzyloxycarbonyl, CysS = S-deprotonated cysteinate), had an activity five times higher than that of $[Fe_4S_4(Z\text{-CysS-Pro-Gly-OMe})_4]^{2-}$. *para*-Substitution of benzoin indicated a trend in the oxidation rate: 4-Cl > H, 4-OMe. It is proposed that the methine hydrogen of benzoin is released as a proton in the rate-determining step. This is supported by the isotope effect (k_H/k_D 2.5:1) on the oxidation rate of α-C-deuteriated benzoin. An increase in the relative permittivity of the solvent results in an increase in the rate constant, indicating a polar transition state.

The $\{Fe_4S_4\}$ proteins (ferredoxins) play many important roles in biological systems, mainly in electron-transport and enzymatic redox reactions. For example, high-potential iron–sulphur proteins transport electrons using the 2−/1− redox cycle of the active site with a $[Fe_4S_4(SR)_4]^{n-}$ moiety.[1] Many studies of the catalytic activity of $\{Fe_4S_4\}$ model complexes utilizing the redox couple of $[Fe_4S_4(SR)_4]^{3-/2-}$ in synthetic model complexes have been reported[2–10] but only a few on $[Fe_4S_4(SR)_4]^{2-/1-}$ because this redox couple is thermodynamically unstable or air-sensitive. In a previous report[11] we have described the catalytic oxidation of benzoin and shown a correlation between the catalytic activity and the stability of the 2−/1− redox couple using a $\{Fe_4S_4\}$ complex with bulky arenethiolate ligands, *e.g.* 2,4,6-triisopropylbenzenethiolate. The stoichiometric and catalytic air oxidation of benzoin in the presence of $Ni(O_2CMe)_2$,[12] OsO_4,[13] $[MoO_2(CysS\text{-}OMe)_2]$ (CysS-OMe = S-deprotonated methyl cysteinate) and $[MoO_2(S_2CNEt_2)_2]$[14] has been reported. The mechanisms of oxidations catalysed by $\{Fe_4S_4\}$ complexes are of interest because these clusters are also known to act as effective electron-transfer mediators. In this paper, we present a mechanism for oxidation (1) which involves the transport of two electrons and two protons during the catalysis.



(1)

Many metalloenzymes (hydrogenase, nitrogenase, *etc.*) participate in various biological electron-transfer systems. The electron transfer is considered to be coupled to the transport of protons or other ionic species[15,16] One oxidant used as a biological redox partner to ubiquinone, vitamin K_3, *etc.* which are the carriers of electrons and protons in biological membranes is *p*-benzoquinone. In many biological cases, iron–sulphur proteins and ubiquinone are the redox partners.[17–19]

Oxidation of benzoin catalysed by the unique combination of ferredoxin model complexes and *p*-benzoquinone is a simple model of electron-and proton-transfer systems. Thus biomimetic characteristics of the present catalytic oxidation are apparent and such new functions of a series of $\{Fe_4S_4\}$ complexes are of interest especially from the mechanistic viewpoint.

Experimental

Materials.—All operations and measurements were carried out under argon. Dimethylformamide (dmf), acetonitrile, tetrahydrofuran (thf), 1,2-dimethoxyethane (dme), and dichloromethane were purified by distillation. 4,4′-Dimethoxybenzoin and benzoin were purchased from Nakarai Chemical Co. 4,4′-Dichlorobenzoin[20] and α-C-deuteriated benzoin[21] were synthesised by literature methods. The $\{Fe_4S_4\}$ complexes having 2-methylpropane-2-thiolato and arenethiolate ligands were also prepared according to the literature.[22]

Preparation of $[PPh_4]_2[Fe_4S_4(tipbt)_4]$ **1**.—This complex was prepared by the modified method reported in a previous paper.[22] To a stirred solution of sodium 2,4,6-triisopropylbenzenethiolate Na(tipbt) (3.4 g, 13.2 mmol) in methanol (10 cm^3) was added a solution of anhydrous iron(III) chloride (0.71 g, 4.4 mmol) in methanol. The solution rapidly became red-purple. A solution of sodium methoxide (0.24 g, 4.4 mmol) and sodium hydrogensulphide (0.25 g, 4.4 mmol) in methanol was immediately added. The colour became reddish brown. This solution was stirred for 20 h at room temperature. After filtration the filtrate was added to a solution of tetraphenylphosphonium chloride (1.24 g, 3.3 mmol) in methanol (10 cm^3) with stirring, whereupon black microcrystals formed. This material was collected on a glass filter, washed with methanol (5 cm^3) twice, and dried *in vacuo*. The crude material was dissolved in acetonitrile (20 cm^3) and filtered. The solvent was removed to

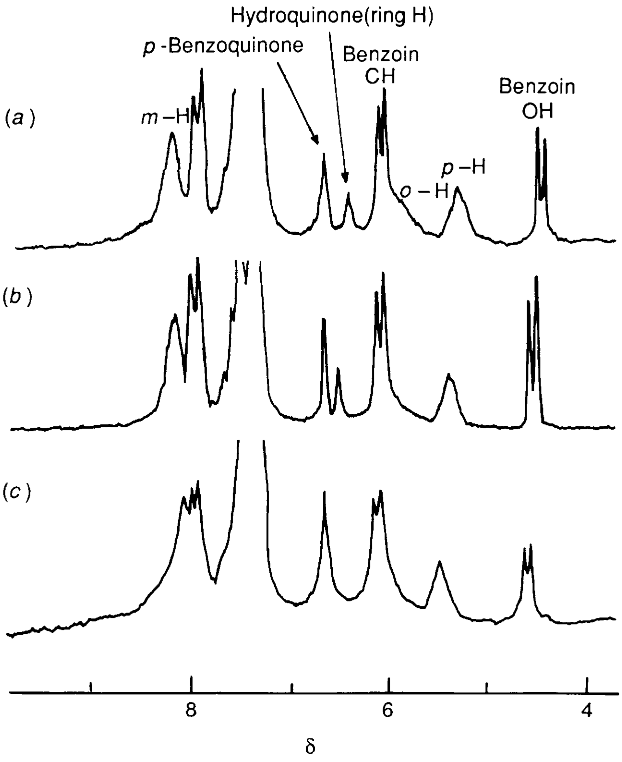


Fig. 1 Proton NMR spectra of the reaction mixture of $[Fe_4S_4(SPh)_4]^{2-}$, *p*-benzoquinone and benzoin (1:2:4) in CD_3CN at (*a*) +20, (*b*) 0 and (*c*) −20 °C

half volume. Addition of methanol and cooling to 0 °C afforded 1.1 g (51%) of black crystals (Found: C, 65.30; H, 6.80. Calc. for $C_{108}H_{132}Fe_4P_2S_8$: C, 65.80; H, 6.75%), m.p. 168–170 °C (decomp.).

Preparation of Cysteine-containing Peptide Thiolate Complexes of the Fe_4S_4 *Core.*—The complexes were prepared by the ligand-exchange method between $[NEt_4]_2[Fe_4S_4(SBu^t)_4]$ and the corresponding peptide.[23] A solution of Cys-containing peptides, Z-Cys-Pro-Leu-OMe, Z-Cys-Pro-Val-OMe, and Z-Cys-Pro-Gly-OMe (Z = benzyloxycarbonyl), in dmf was added to a solution of $[NEt_4]_2[Fe_4S_4(SBu^t)_4]$ in dmf at room temperature. The solution was concentrated under reduced pressure to remove Bu^tSH and the solvent. Addition of diethyl ether resulted in formation of a black solid which was washed with ether several times. The purity of the $\{Fe_4S_4\}$ peptide complexes was determined as described by Gillum *et al.*[24]

Catalytic Oxidation of Benzoin.—A dmf solution of benzoin, α-C-deuteriated benzoin, 4,4′-dimethoxybenzoin, or 4,4′-dichlorobenzoin (10.6, 10.7, 17.4, 17.3 mg, 5.0×10^{-5} mol) was added to a dmf solution of compound **1** (0.39 mg, 2.0×10^{-7} mol). A dmf solution of an oxidant {*p*-benzoquinone, $[Fe(C_5H_5)_2]BF_4$, *etc.* (2 equivalents)} was added with stirring, and the total volume was 2.0 cm³. The solution was allowed to stand for a given period of time at the specified temperature. The oxidation of α-C-deuteriated benzoin was performed in the same way. Diethyl ether and water were added to collect benzil and unreacted benzoin in an ether layer. The conversion of benzoin and the yield of benzil were determined by HPLC with a μ-Bondpack C_{18} column (30 cm × 3.9 mm inner diameter). The standard deviation was obtained after several kinetic runs (at least three).

Physical Measurements.—Absorption spectra were obtained on a JASCO UVDEC-5A instrument, 90 MHz ^1H NMR spectra at −20 °C to +20 °C on a JEOL FX-90Q spectrometer. The NMR sample was prepared with exclusion of air using CD_3CN. For example, a mixture of $[NEt_4]_2[Fe_4S_4(SPh)_4]$ (16.3 mg, 1.6 mmol) and benzoin (13.2 mg, 6.2 mmol) in CD_3CN (0.5 cm³) was frozen at −78 °C. A CD_3CN solution of *p*-benzoquinone (3.35 mg, 3.1 mmol) was added at −78 °C for observation of any electron-transfer reaction by the NMR technique.

Results

Catalytic Oxidation of Benzoin.—The time courses of the oxidation of benzoin were investigated at the initial stage of the reaction catalysed by $[PPh_4]_2[Fe_4S_4(tipbt)_4]$ **1**. The molar ratio [$\{Fe_4S_4\}$ complex]:[benzoin]:[*p*-benzoquinone] = 1:50:100 was selected in order to minimize the interference of the proton dissociated from hydroquinone. A logarithmic plot of the yield of benzil against time was linear and thus the oxidation is first order in the concentration of benzoin. Since the oxidation proceeds under mild conditions, the cleavage of the C–C bond of benzoin does not occur. The observed rate constant is proportional to the catalyst concentration. The oxidation follows the rate equation (2).

$$-d[\text{benzoin}]/dt = k_{obs}[\text{benzoin}][\text{catalyst}] \qquad (2)$$

Compound **1** exhibits a turnover number of 73 ± 3 in 1 h at the ratio [$\{Fe_4S_4\}$ complex]:[benzoin]:[*p*-benzoquinone] = 1:250:500 in dmf. The one-electron oxidized catalytic species, $[Fe_4S_4(SR)_4]^-$, is unstable in dmf, but the decomposition of the catalyst was negligible until 40 min under these conditions, although accompanied by slight interference probably from the dissociated proton.

Fig. 1 shows the ^1H NMR spectra of the stoichiometric reaction mixture in the presence of $[NEt_4]_2[Fe_4S_4(SPh)_4]$, *p*-benzoquinone and benzoin (1:2:4). The assignment of the signals for $[NEt_4]_2[Fe_4S_4(SPh)_4]$ in CD_3CN was carried out by reference to the literature.[25] The oxidation of benzoin does not occur at −20 °C as evidenced by the lack of a ^1H NMR signal due to hydroquinone. Over 0 °C a peak assignable to hydroquinone appears at δ 6.5. The peak intensity of hydroquinone was *ca.* 1/3 compared to the initial *p*-benzoquinone. Thus 1/3 of *p*-benzoquinone was converted into hydroquinone after 1 h at 20 °C.

A broad ^1H NMR signal at δ 5.4 due to H_p of the benzenethiolate ligand, which was contact-shifted by a slight paramagnetic character of $[Fe_4S_4(SPh)_4]^{2-}$, did not diminish for 30 min at 20 °C. The results indicate that the $\{Fe_4S_4\}$ core is mostly in the $[Fe_4S_4(SR)_4]^{2-}$ state during the stoichiometric reaction in $(CD_3)_2SO$ because the oxidized or reduced state of the $\{Fe_4S_4\}$ cluster should provide a more contact-shifted ^1H signal for H_p. The persistence of the peaks due to $[Fe_4S_4(SPh)_4]^{2-}$ indicates that the cluster remains intact during the catalytic cycles of the oxidation of benzoin. The retention of the effective catalytic cycle is mainly ascribed to the presence of the thermodynamically stable 2− species of the $\{Fe_4S_4\}$ cluster during the oxidation. The 3− or 1− state is known to be extremely unstable. This is coincident with the kinetic results of the catalytic oxidation.

Oxidation State.—Electronic absorption spectra of the reaction mixture were measured within 5 min of addition of *p*-benzoquinone. Since no change in the ligand-to-metal charge-transfer (l.m.c.t.) absorption maximum at 410 nm due to $[Fe_4S_4(tipbt)_4]^{2-}$ was observed after addition of benzoin to the solution, it is obvious that $[Fe_4S_4(tipbt)_4]^{2-}$ does not react with benzoin. When *p*-benzoquinone was added to the mixture in CH_2Cl_2 the l.m.c.t. maximum immediately changed from 410 to 450 nm. This is due to formation of $[Fe_4S_4(tipbt)_4]^-$, for which a l.m.c.t. maximum at 475 nm (ε 27 800 dm³ mol⁻¹ cm⁻¹ in CH_2Cl_2) has been reported.[26] The l.m.c.t. maximum at 450 nm indicates that $[Fe_4S_4(tipbt)_4]^-$ is preferred in CH_2Cl_2. On the contrary, the l.m.c.t. maximum in dmf was observed at 425 nm

Table 1 Rate constants k_{obs} at the initial stage of the oxidation of benzoin by *p*-benzoquinone in the presence of $\{Fe_4S_4\}$ complexes

Complex	k_{obs}/dm^3 mol^{-1} s^{-1}
None	0
$[Fe_4S_4(Z\text{-}CysS\text{-}Pro\text{-}Leu\text{-}OMe)_4]^{2-}$	5.0 ± 1.0
$[Fe_4S_4(Z\text{-}CysS\text{-}Pro\text{-}Val\text{-}OMe)_4]^{2-}$	6.8 ± 1.0
$[Fe_4S_4(Z\text{-}CysS\text{-}Pro\text{-}Gly\text{-}OMe)_4]^{2-}$	1.0 ± 1.0
$[Fe_4S_4(tipbt)_4]^{2-}$	5.4 ± 1.0
$[Fe_4S_4(tmbt)_4]^{2-}$ *	4.5 ± 1.0
$[Fe_4S_4(SPh)_4]^{2-}$	4.2 ± 1.0

Reaction conditions: 0.25 mol dm^{-3} benzoin, 0.5 mol dm^{-3} *p*-benzoquinone, 1.0 × 10^{-3} mol dm^{-3} complex; 3 h, 25 °C.
* tmbt = 2,4,6-Trimethylbenzenethiolate.

Table 2 Aromatic *p*-substituent effect in the catalytic oxidation of benzoin or its derivatives by benzoquinone in the presence of $[Fe_4S_4(tipbt)_4]^{2-}$

p Substituent	k_{obs}/dm^{-3} mol^{-1} s^{-1}
4-MeO	7.9 ± 0.8
H	8.9 ± 1.0
4-Cl	19.3 ± 1.6

Reaction conditions: 0.25 mol dm^{-3} substrate, 0.5 mol dm^{-3} *p*-benzoquinone, 1.0 × 10^{-3} mol dm^{-3} complex in dmf; 1 h; 15 °C.

Table 3 Catalytic oxidation of benzoin by various oxidants in the presence of $[Fe_4S_4(tipbt)_4]^{2-}$

Oxidant	Turnover
p-Benzoquinone	73 ± 3
$[Fe(C_5H_5)_2]BF_4$	3 ± 0.5
Pyridine *N*-oxide	4 ± 0.4
Air	14 ± 0.8

Reaction conditions: 0.25 mol dm^{-3} benzoin, 0.5 mol dm^{-3} *p*-benzoquinone, 1.0 mol dm^{-3} $[Fe(C_5H_5)_2]BF_4$ and 0.5 mol dm^{-3} pyridine *N*-oxide.

under the same conditions. The content (over 80%) of $[Fe_4S_4(tipbt)_4]^{2-}$ was estimated from the absorption maximum observed under the catalytic oxidation conditions on the basis of the maxima of both the reduced and oxidized states. The oxidized cluster $[Fe_4S_4(SR)_4]^-$ is found to be converted into $[Fe_4S_4(SR)_4]^{2-}$ or $[Fe_4S_4(SR)_4]^{3-}$ smoothly in dmf by oxidation of benzoin. Thus, $[Fe_4S_4(SR)_4]^-$ exhibits a higher reactivity in dmf than in CH_2Cl_2.

The rate constants k_{obs} at the initial stage of the oxidation of benzoin in the presence of various $\{Fe_4S_4\}$ model complexes are shown in Table 1. The activity of the catalytic oxidation depends on the bulkiness of the side-chain alkyl groups of the cysteine-containing peptide ligands and of the *o*,*p*-substituted groups of the benzenethiolate ligands. The amino acid residues next to the Pro residue in the complexes, *e.g.* $[Fe_4S_4(Z\text{-}CysS\text{-}Pro\text{-}X\text{-}OMe)_4]^{2-}$ have a large influence on the catalytic activity. In the case of Val and Leu residues, the k_{obs} values were five times higher than that in the Gly case. This trend is essentially the same as obtained for $\{Fe_4S_4\}$ complexes having *o*,*p*-substituted benzenethiolate ligands. We have studied[27] the relation between stability of the 2−/1− redox cycle and bulkiness of the thiolato ligands in $[Fe_4S_4(SR)_4]^{2-}$ complexes, and found that increasing bulkiness stabilized the redox cycle. The catalytic activity shows good correspondence with the stability of the 2−/1− redox cycle.

p-*Substituent Effect.*—The yields of the catalytic oxidation of 4,4′-dichlorobenzoin, benzoin and 4,4′-dimethoxybenzoin in the presence of $\{Fe_4S_4\}$ complexes are listed in Table 2. An electron-withdrawing substituent, *e.g.* *p*-Cl, accelerates the oxidation significantly. The observed reactivity of the *p*-substituted benzoins conforms to the order, Cl > H, OMe.

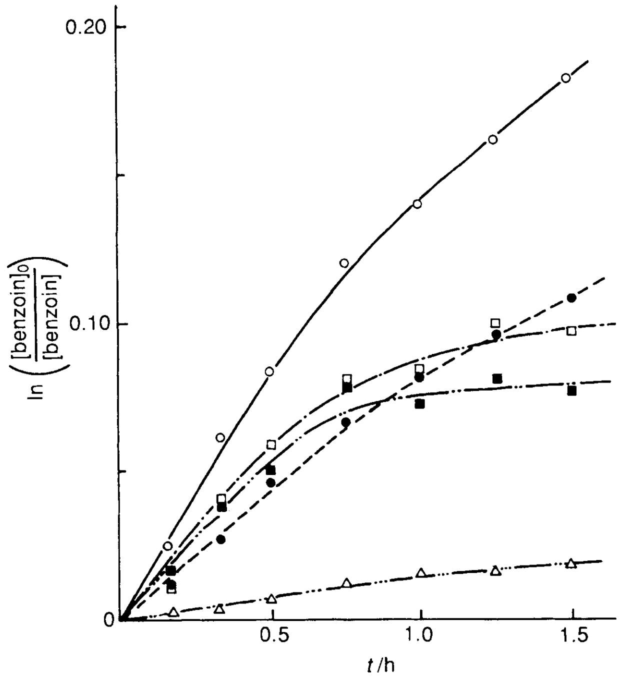


Fig. 2 Time conversion curves for the oxidation of benzoin in various solvents [(○) dmf, (□) thf, (■) dme, (●) acetonitrile and (△) CH_2Cl_2] in the presence of 1.0 × 10^{-3} mol dm^{-3} compound **1**; 0.25 mol dm^{-3} benzoin and 0.5 mol dm^{-3} *p*-benzoquinone at 15 °C

The appreciable influence of *p*-substituted groups indicates that the energy barrier to the rate-determining step depends on the facility of cleavage of the methine C–H bond of benzoin. It appears that proton release from the methine group of benzoin is involved in the catalytic oxidation cycle. The air oxidation of *p*-substituted benzoin has been investigated in the presence of various reactants $[Ni(O_2CMe)_2]$,[12] OsO_4,[13] *etc.*]. The trend in the oxidation rate with the *p*-substituent (Cl > H > Me) in the presence of $Ni(O_2CMe)_2$ is almost the same as that for $\{Fe_4S_4\}$ complexes. The proton seems to be transferred from benzoin in both reactants.

The kinetic deuterium effect was examined at the initial stage in the presence of compound **1** in dmf at 25 °C. The observed k_H/k_D ratio (2.5:1) indicates cleavage of the α-C–H bond in the rate-determining step.

Oxidants.—In order to investigate the function of *p*-benzoquinone as a proton acceptor, various oxidants were examined for the catalytic oxidation. The results are summarized in Table 3. Compound **1** exhibited the highest rate constant with *p*-benzoquinone which can accept two protons on conversion into hydroquinone as mentioned in connection with the ^{1}H NMR results. Dioxygen and pyridine *N*-oxide gave low rate constants owing to decomposition of the catalyst. The complex $[Fe(C_5H_5)_2]BF_4$ is able to oxidize $[Fe_4S_4(tipbt)_4]^{2-}$ to its 1− state,[26] but is not a suitable oxidant in such a catalytic system since $[Fe(C_5H_5)_2]^+$ only works as an electron acceptor, not as a proton acceptor. For the present catalytic system, as the proton concentration in an aprotic solvent increases, the apparent reaction rate decreases by protolytic decomposition of the catalyst. Therefore, proton acceptability is virtually a requirement for the oxidant in the present catalytic oxidation of benzoin.

Solvent Effect.—Fig. 2 shows the solvent effect on the catalytic oxidation of benzoin. The relative permittivity and protophilic property of the solvent significantly influence the oxidation. In a solvent of low permittivity (thf, ε_r = 7.3; dme, ε_r = 7.2; CH_2Cl_2, ε_r = 8.9) some precipitates formed in 10–30

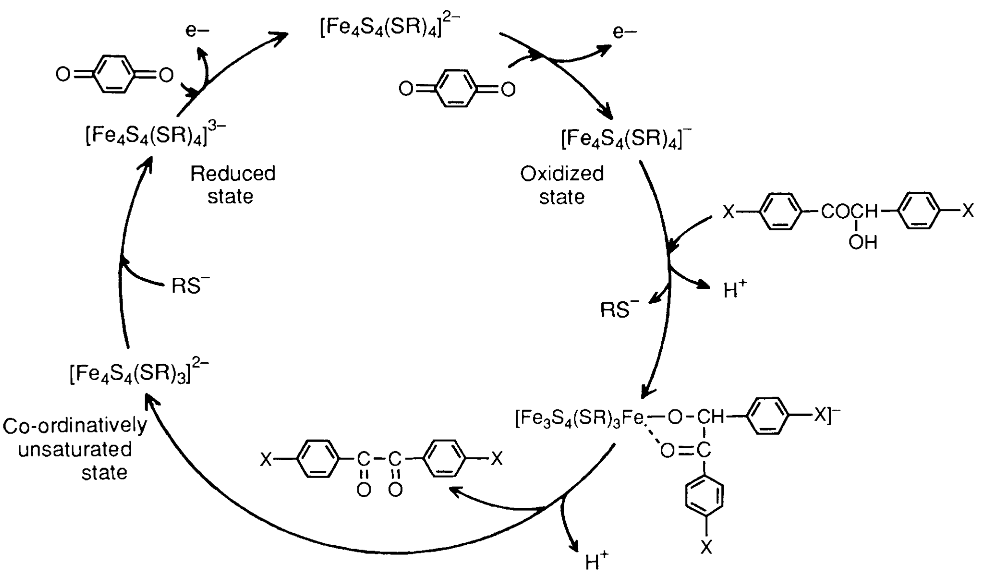


Fig. 3 Proposed catalytic cycle for the oxidation of benzoin by *p*-benzoquinone in the presence of $[Fe_4S_4(SR)_4]^{2-}$; X = Cl, H or OMe

min. However, precipitation did not occur within 3 h in dmf ($\varepsilon_r = 36.7$) or in acetonitrile ($\varepsilon_r = 37.5$). This indicates an ionic mechanism in the catalytic oxidation. In dmf and acetonitrile the formation of precipitates is negligible within 3 h at lower temperature (< 25 °C). The initial stage of the reaction seems to differ between the two solvents. This is explained on the basis of the protophilic property of the solvent. Dimethylformamide is more protophilic than acetonitrile, as the donor numbers of dmf and acetonitrile are 26.6 and 14.1,[28] respectively. As mentioned previously, the methine hydrogen of benzoin is considered to be released as a proton, not as a hydride, in the present oxidation. Proton transfer is thus more favourable in dmf than in acetonitrile.

At the initial stage of oxidation of benzoin the reaction rates depend not only on the permittivity of the solvent but also on its protophilic property. In support of this, compound **1** was found to have a high activity within 1 h in thf (donor number 20.0), only a negligible one in CH_2Cl_2 (donor number 0).

When 25–125 equivalents of hydroquinone based on the $\{Fe_4S_4\}$ complex were added at the initial stage of oxidation of benzoin the yield of benzil decreased by 10–30% during the first 30 min. The k_{obs} values decrease with excess of hydroquinone.

Discussion

A tentative mechanism for the oxidation of benzoin is shown in Fig. 3. The first step of the catalytic cycle involves one-electron oxidation of $[Fe_4S_4(SR)_4]^{2-}$ to $[Fe_4S_4(SR)_4]^{-}$ by *p*-benzoquinone, because no reaction was detected between compound **1** and benzoin on the basis of electronic absorption measurements in dmf. The co-ordination of substrate to metal has been considered in the cases of $Ni(O_2CMe)_2$[12] and OsO_4.[13] It was proposed that an alcoholic OH, ketyl O, or both could co-ordinate to metal ions. The formation of a Fe–O(C) bond in the $\{Fe_4S_4\}$ complexes was reported for some ligands (O_2CMe, PhO, *cis*-aconitase, *etc*.). The first oxygen-ligated tetramer $[Fe_4S_4(O_2CMe)_4]^{2-}$ was obtained by ligand-substitution reaction of $[Fe_4S_4(SPh)_4]^{2-}$ with excess of $(MeCO)_2O$.[29] The complex $[Fe_4S_4(O_2CMe)_4]^{2-}$ can be converted into $[Fe_4S_4(SPh)_4]^{2-}$ by addition of excess of PhS^-. This exchange has been found reversible without decomposition. Some other 'mixed'-ligand complexes, *e.g.* $[Fe_4S_4(SPh)_2(OC_6H_4Me\text{-}p)_2]^{2-}$, have been isolated by Kanatzidis *et al.*[30] Therefore, the ligand exchange of one of the co-ordinated thiolate ligands with benzoin is assumed to be involved in the second step as shown in Fig. 3. Benzoin cannot interact with the $\{Fe_4S_4\}$ complex because of the bulkiness of the ligand. The high activity of the complexes having bulky ligands indicates that the dissociative exchange process between benzoin and thiolate ligand is important during the catalytic oxidation without decomposition.

As reported,[31] the bulkiness of thiolato ligands of $\{Fe_4S_4\}$ complexes contributes to stabilization of the 1− state which is more stable in a non-polar solvent than in a polar one. O'Sullivan and Millar[26] have reported that the stability trend CH_2Cl_2 > MeCN ≫ dmf. The observed rate constants for the catalytic oxidation of benzoin in these solvents exhibit the opposite order to that of the stability of the 1− state of the $\{Fe_4S_4\}$ cluster. The polar solvents presumably support an ionic intermediate or accelerate the ionic reactions.

Although we have assumed dissociative exchange between benzoin and thiolate ligand in the 1− state of the $\{Fe_4S_4\}$ cluster, it is also acceptable to consider an octahedral intermediate formed by co-ordination of benzoin to one tetrahedral iron ion at a corner of the cluster without dissociation of the thiolate ligand. Such an octahedral intermediate has been proposed for the active site of aconitase, which also involves a $\{Fe_4S_4\}$ cluster.[32] Further study will be required to understand the structure of these intermediates.

A large electronic effect of *p*-substituted benzoin was observed, the electron-withdrawing group accelerating the oxidation. The observed isotope effect ($k_H/k_D = 2.51$) using α-C-deuteriated benzoin indicates that the release of the methine proton is the rate-determining step. Therefore, the *p*-substituent effect indicates that the methine hydrogen is released from benzoin as a proton. In the air oxidation of benzoin in the presence of $Ni(O_2CMe)_2$ the same trend of *p*-substituent effect has been found with a large k_H/k_D value (7.5:1).[12] The k_H/k_D value of our system is in the 'unsymmetrical linear H-transfer' region (k_H/k_D = 2–5) which has been discussed in the Kwart's paper.[32] Therefore, the oxidation of benzoin in the presence of $\{Fe_4S_4\}$ complexes proceeds through a transition state involving this type of proton-transfer step. Dissociated protons should be transferred to the *p*-benzoquinone. However, dissociated protons from hydroquinone interfere in the oxidation of benzoin, since the k_{obs} values decreased.

The catalytic activity is highest in dmf, which has a larger donor number than that of water. The value of the Gibbs free energy of H^+ transfer from water to dmf is negative (−18 kJ mol^{-1}). The proton transfer in dmf is preferred to that in water or other organic solvents. These results support release of the methine proton in the catalytic benzoin oxidation.

In the oxidation of benzoin two electrons and two protons must be transferred from benzoin. These protons are transferred to the oxidant. Several efforts have been made to determine whether the alcohol oxidation involves a one-electron transfer in the rate-determining step. Oxidation of cyclobutanol with two-electron oxidants [*e.g.* peroxotungsten(VI) complexes] leads to cyclobutanone.[34,35] Although the $\{Fe_4S_4\}$ complex was not able to oxidize cyclobutanol, the oxidation of benzoin in the presence of $\{Fe_4S_4\}$ model complexes is suggested to involve the transfer of an electron and a proton separately. A similar separate transfer process has been discussed to be of utmost importance in the chemical processes inside biological membranes.

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Received 12*th September* 1990; *Paper* 0/04170J