A highly reactive functional model for catechol 1,2-dioxygenase: reactivity studies of iron(iii) catecholate complexes of bis[(2-pyridyl)methyl][(1-methylimidazol-2-yl)methyl]amine

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The system consisting of an iron(III) salt and bis[(2-pyridyl)-methyl][(1-methylimidazol-2-yl)methyl]amine (bpia) in methanol reacts with various catechols with insertion of dioxygen; in the case of 3,5-di-*tert*-butylcatechol the efficient catalytic activity of the system is shown.

Intradiol dioxygenases are non-haem iron enzymes and take part in biological mechanisms for metabolising aromatic compounds.[1] The enzymes catalyse the intradiol cleavage of catechols to *cis,cis*-muconic acids. Spectroscopic investigations indicate that the active site iron remains in the iron(iii) oxidation state during the whole catalytic cycle. A variety of studies have tried to understand the mechanism in its enzymatic and model chemistry aspects and a number of functional models have been synthesised with various ligand systems.[2–4] Especially tetradentate ligands (L) have shown a great ability to influence the physical properties of the metal complexes and therefore the dioxygenase activity as the ligand sets are varied. Que and coworkers have found a correlation between the Lewis acidity of the iron centre in a series of iron(iii) complexes of tripodal ligands, the product yield, and the reactivity.[2] According to these investigations a substrate activation rather than oxygen activation mechanism has been proposed. In this mechanism the substrate loses both of its protons upon coordination to the iron centre followed by partial oxidation of the catecholate due to ligand-to-metal charge transfer, resulting in a substrate with semiquinone character. The attack of O_2 on the activated substrate yields a transient alkylperoxy radical which combines with the equally short-lived iron(ii) centre to generate an alkylperoxoiron(iii) species. The peroxy adduct decomposes by a Criegee-type rearrangement to muconic anhydride. In most cases 3,5-di-*tert*-butylcatechol (dbc) has been used as a substrate in functional investigations, but little work has been devoted to the oxygenation of other catechols.[3]

We have prepared iron(iii) catecholate complexes *in situ* under an argon atmosphere with bis[(2-pyridyl)methyl][(1-methylimidazol-2-yl)methyl]amine (bpia)[5] as a tetradentate ligand and a series of catechols (dbc, 4-mc, 4-bc, cat, tcc).† Their UV–VIS spectra in methanol solution are dominated by two moderately intense absorption bands. These bands are assigned as catcholate-to-Fe^{III} charge-transfer transitions similar to those observed in the spectra of other iron catecholate complexes with tripodal ligands,[6] suggesting that a complex of the form $[Fe(bpia)(catecholate)]^+$ has been prepared. The positions of the lower energy band are dependent on the nature of the catecholate, with the LMCT bands observed to shift to lower energies by varying the substituents on the catecholate from electron-withdrawing to -donating (Table 1). The complexes have been isolated, and with tetrachlorocatecholate (tcc) as substrate we have obtained crystals to solve the structure of $[Fe(bpia)(tcc)]ClO_4$.[7] The crystal structure exhibits an asymmetrical chelated tetrachlorocatecholate ligand (Fig. 1). The Fe–O bond *trans* to the aliphatic N [Fe–O(1) 1.919(3) Å] is about 0.03 Å shorter than the corresponding bond *trans* to the heterocyclic N [Fe–O(2) 1.948(3) Å]. The difference in bond lengths is due to a *trans* effect where the catecholate oxygen with the shorter bond is in the *trans* position to the much weaker amine ligand.

All catecholate complexes of Table 1 react with dioxygen to yield products due to the oxidative cleavage of the catechol ring.‡ The immediate product appears to be the *cis,cis*-muconic anhydride, although only in the case of 3,5-di-*tert*-butylcatechol was this cleavage product isolated as 3,5-di-*tert*-butyl-1-oxacyclohepta-3,5-diene-2,7-dione. With 4-bc, 4-mc, and cat furanones derived from nucleophilic attack on one carbonyl of the anhydride, followed by cyclisation, were identified.

The kinetics of the reaction with dioxygen was followed by monitoring the disappearance of the lower energy charge-transfer band (Fig. 2). The reactions all exhibit pseudo-first-order kinetics under conditions where dioxygen is in excess after complex formation. The pseudo-first-order rate constants show a dependence on the nature of the substrate. The rates of the reactions increase in the order tcc $\ll$ cat < 4-bc $\approx$ 4-mc < dbc (Table 1). While $[Fe(bpia)(tcc)]^+$ is rather stable against dioxygen attack, the reaction rate of the $[Fe(bpia)(dbc)]^+$ complex with O_2 is rather high. This order of activity correlates with the energy of the lower energy LMCT band of the complexes: electron-donating substituents on the catechol result in a higher dioxygenase reactivity.

Accordingly the reactivity grows with increasing Lewis acidity of the iron centre within the series of [Fe(bpia)(catechol-

Table 1 Properties of the $[Fe(bpia)(catecholate)]^+$ complexes

Catechol	λ_{max}/nm	k^a/dm^3 mol^{-1} s^{-1}
dbc	558, 865	4.3
4-mc	515, 842	2.6
4-bc	519, 836	2.3
cat	510, 800	0.083
tcc	528, 729	$> 10^{-5}$

[a] Reactions run in methanol under air, 25 °C, $c = 5 \times 10^{-4}$ mol dm^{-3}, 2 equiv. of piperidine as base, $k = k_{obs}/[O_2]$.

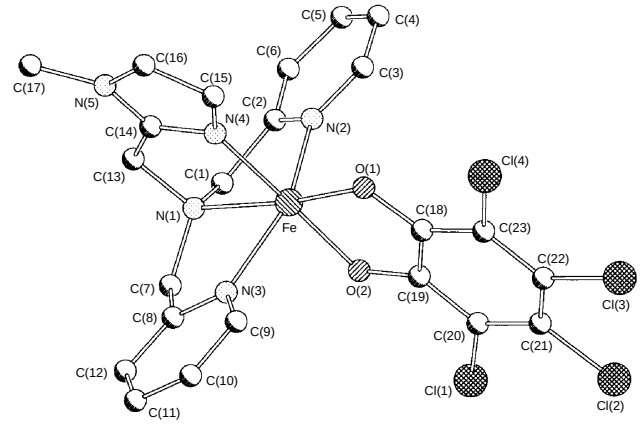

Fig. 1 Structure of $[Fe(bpia(tcc)]^+$

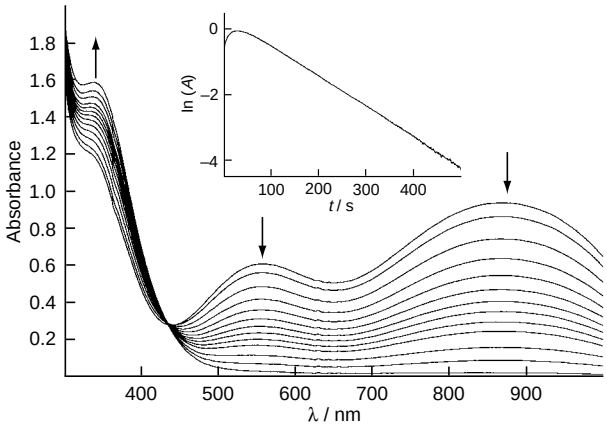

Fig. 2 Progress of the reaction of $[Fe(bpia)(dbc)]^+$ with air in methanol. Inset: plot of ln (*A*) *vs.* *t* at 25 °C.

ate)]$^+$ complexes. Our observation supports the substrate activation mechanism proposed by Que.[2]

The system consisting of $Fe(ClO_4)_3 \cdot 9H_2O$ and bpia in acetonitrile catalyses the oxidation of dbc to *cis,cis*-muconic anhydride rapidly and efficiently. In the presence of 10% of the catalyst 90% of the desired cleavage product is obtained. We have isolated 3,5-di-*tert*-butyl-*o*-benzoquinone (dbq) as a by-product in small amounts. By reducing the amount of the iron catalyst the yield of dbq increases, but even with 1% $[Fe(bpia)(MeCN)_2]^{3+}$ nearly 80% of the catechol reacts with dioxygen in 12 h to 3,5-di-*tert*-butyl-1-oxacyclohepta-3,5-diene-2,7-dione. With turnover numbers up to 80 this iron(iii) complex is the most effective catalyst for the oxidative cleavage of catechols reported yet.

Progress of the reaction can be followed by ^{1}H NMR spectroscopy (Fig. 3). The signals of the free substrate (δ 6.82, 1.36, 1.24) disappear along with the appearance of signals of the muconic anhydride (δ 6.57, 6.16, 1.25, 1.14) and of the by-product, 3,5-di-*tert*-butyl-*o*-benzoquinone (δ 7.01, 6.14, 1.23, 1.19). The width of the signals is due to the formation of the paramagnetic $[Fe(bpia)(dbc)]^+$ complex in solution during the reaction. At the end of the reaction the signals become sharp indicating a μ-oxo-bridged dinuclear iron(iii) complex with antiferromagnetic coupling in solution.

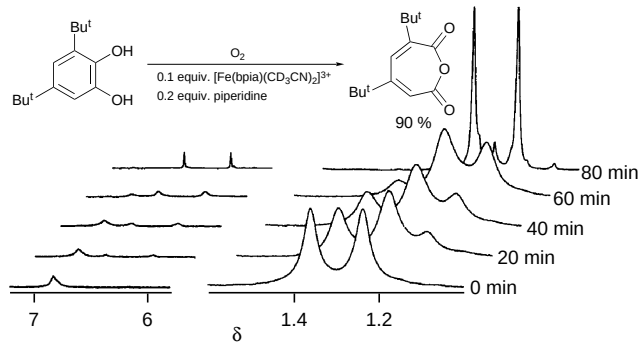

Fig. 3 Catalytic oxidation of 3,5-di-*tert*-butylcatechol monitored by ^{1}H NMR spectroscopy

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Footnotes

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† Abbreviations used: bpia = bis[(2-pyridyl)methyl][(1-methylimidazol-2-yl)methyl]amine, dbc = 3,5-di-*tert*-butylcatechol, 4-bc = 4-*tert*-butylcatechol, 4-mc = 4-methylcatechol, cat = catechol, tcc = tetrachlorocatechol; dbq = 3,5-di-*tert*-butyl-*o*-benzoquinone.

‡ The oxidation product of tetrachlorocatechol has not been isolated, due to the high stability of the $[Fe(bpia)(tcc)]^+$ complex.

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