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Oxidation of 3,5-di-*tert*-butylcatechol and 2-aminophenol by molecular oxygen catalyzed by an organocatalyst†

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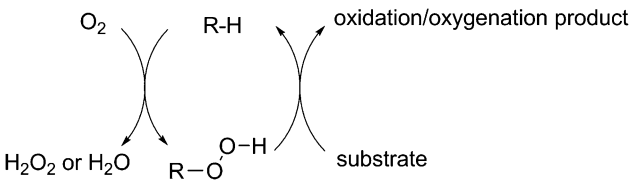
1,3,2-Oxazaphospholes are able to catalyze the oxidation of 3,5-di-*tert*-butylcatechol with $^3O_2$ to the corresponding *o*-quinone and 2-aminophenol to 2-aminophenoxazine-3-one in methanol. In both the cases, an overall third order reaction rate equation and a new type of biomimetic organocatalyst for oxidation reactions was found. A one electron transfer of the phenolate, which is formed through the deprotonation of the substrates by the catalyst, to dioxygen seems to be rate-determining step.

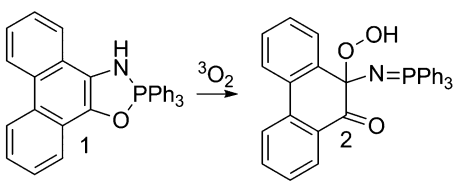
Oxidation reactions are widely applied in organic synthesis and in chemical industries. Triplet dioxygen would be an economically and environmentally[1] successful candidate as a primary oxidant; however, a spin restriction[2] and a thermodynamic[3] burden lower its reactivity and so its use in oxidation/oxygenation reactions is rather limited. Unfortunately, not just triplet dioxygen but also hydroperoxides (even H_2O_2) are sluggish oxidants[4] and they need activation either with the help of metalloenzymes (metal complexes)[5] or organic compounds. Much work has been carried out for the activation of $^3O_2$ or H_2O_2 by metal complexes, mainly copper,[6] iron,[7] and other metals.[8] Some organic co-factors and their mimics are also able to form hydroperoxides,[9] which oxidize various organic compounds. We were interested in finding organic compounds that react with $^3O_2$ to form hydroperoxides, which mimic organic co-factors, and these can oxidize several organic compounds either in a two or in a four electron oxidation, as shown in Scheme 1.

Recently, we found that 1,3,2-oxazaphospholes under ambient conditions pick up molecular oxygen and form hydroperoxides (eqn (1)), which can transfer oxygen to triphenylphosphine forming the oxide.[10] The peroxide formed was not stable at room temperature. Iodometric titration of the oxygenated solutions resulted in a peroxide content in the range of 10–30%.[11] This is similar



Scheme 1 General scheme for hydroperoxide formation and oxidation/oxygenation with O_2.

to flavin models, in which *N*,*N*,*N*-3,5,10-trialkylated flavins and their reaction with $^3O_2$ flavin hydroperoxides were observed.[12] Pterins[13] or even deprotonated uric acid[14] also form hydroperoxides with $^3O_2$. Former studies of the reaction of 2,3-dihydro-2,2,2-triphenylphenanthro[9,10-*d*]1,3,2λ^5-oxazaphosphole (**1**) with triplet dioxygen showed that methanol is the best-suited solvent. The reaction time for the oxygenation of the catalyst (**1**) was below 5 min and an unstable



(1)

hydroperoxide **2** (eqn (1)) was formed under ambient conditions.[10]

As a continuation of our work on the study of the models of organic cofactors in oxidation reactions, we studied the reactions of some phenolic compounds, namely, 3,5-di-*tert*-butylcatechol (**3a**) and *o*-aminophenol (**3b**), which are isoelectronic, with triplet dioxygen catalyzed by 2,3-dihydro-2,2,2-triphenylphenantro [9,10-*d*]1,3,2-λ^5-oxazaphosphole (**1**). Much work has been done until now on the oxidation of 3,5-di-*tert*-butylcatechol[15] just to gain insight into the possible mechanism of the intra- and extradiol cleavage of catechol dioxygenases. A fair number of model oxidations of *o*-aminophenol[16] have also been carried out as a model reaction for 2-aminophenoxazine-3-one synthase. The former enzyme contains two copper ions in its active site,[17]

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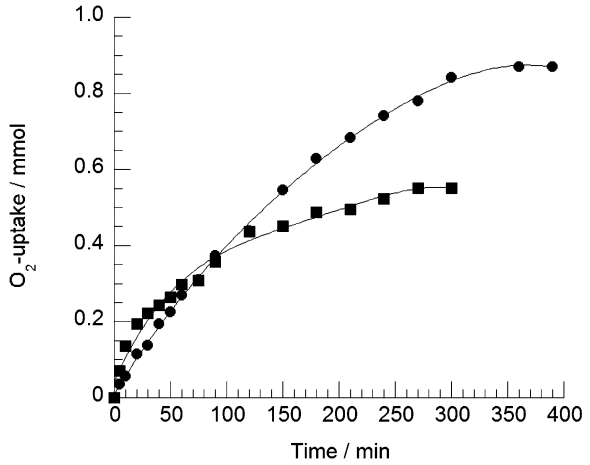


Fig. 1 Dioxygen-uptake of the oxidation of **3a** (●) and **3b** (■) catalyzed by **1**. [**3a**] = 8.9 × 10^{-2} M, [catalyst] = 8.9 × 10^{-3} M, V = 10 mL, T = 60 °C; [**3b**] = 8.9 × 10^{-2} M, [catalyst] = 8.9 × 10^{-3} M, V = 10 mL, T = 60 °C.

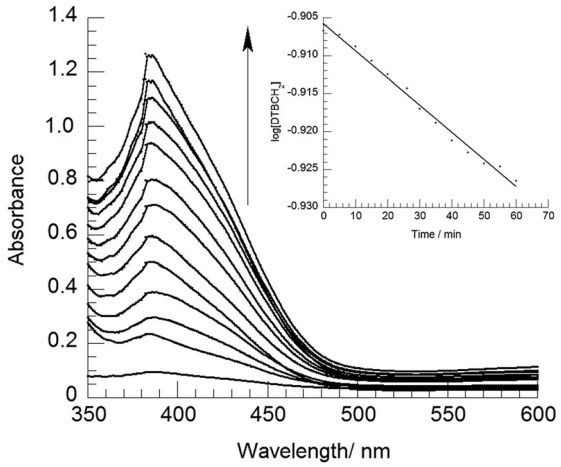
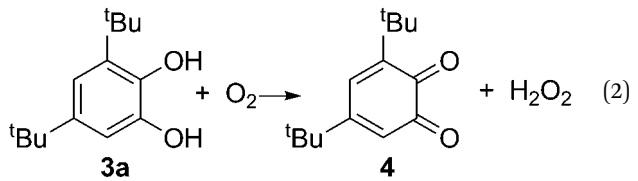
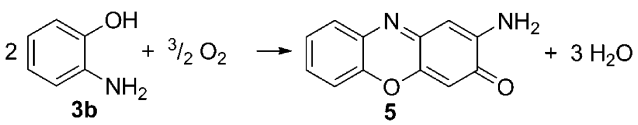


Fig. 2 Time dependence of the oxidation of **3a**. [3,5-di-*tert*-butylcatechol] = 12.5 × 10^{-2} M, [1,3,2-oxazaphosphole] = 12.5 × 10^{-4} M, [O_2] = 9.5 × 10^{-3} M, T = 298 K, 10 mL MeOH.

while 2-aminophenoxazine-3-one synthase is a multicopper enzyme catalyzed reaction.[18] Therefore, it was obvious that we tried 2,3-dihydro-2,2,2-triphenylphenanthro[9,10-*d*]1,3,2λ^5-oxazaphosphole (**1**) as a bioinspired catalyst for catechol oxidation and as a model reaction for the flavin co-factor in the case of 2-aminophenoxazine-3-one synthase. In the stoichiometric oxidations of 3,5-di-*tert*-butylcatechol H_2O_2 is formed (with the corresponding *o*-quinone) and from o-aminophenol H_2O (and 2-aminophenoxazine-3-one) (eqn (2) and (3)). This was evidenced by O_2-uptake experiments (Fig. 1) and iodometric titration of the solution.[11]



(2)

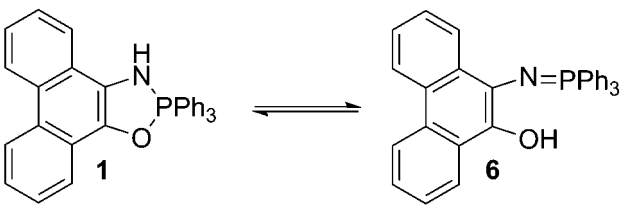


(3)

Kinetic studies of both the reactions resulted in an overall third order rate equation (eqn (4)) for **3a** and **3b** with k_{obs} values

$$\text{reaction rate} = k_{obs}\,[\text{catalyst}]\,[O_2]\,[\mathbf{3}] \qquad (4)$$

of 0.76 ± 0.11 and 0.62 ± 0.03 M^{-2} s^{-1}, respectively. The rates of the reaction were followed by UV-Vis spectroscopy at 400 nm (**3a**) (Fig. 2) and 434 nm (**3b**) (Fig. S1, ESI†). A typical time plot for the oxidation of **3a** and **3b** can be seen in Fig. 1. The dependence on the dioxygen concentration (Fig. S2 and S3, ESI†) on catalyst concentration (Fig. S4 and S5, ESI†), the log **3b** *vs.* time of **3b** oxidation (Fig. S6, ESI†) and on the initial concentrations on **3a** (Fig. S7, ESI†) and **3b** (Fig. S8, ESI†) plotted against the reaction rate gave straight lines, clearly showing that the both reactions follow an overall third order rate equation. The activation parameters for **3a** oxidation are $\Delta E^{\ddagger}$ = 34.03 ± 0.3 kJ mol^{-1}, $\Delta H^{\ddagger}$ = 31.47 ± 0.30 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −142.04 ± 0.55 J mol^{-1} K^{-1}, and for **3b** oxidation $\Delta E^{\ddagger}$ = 38.08 ± 0.41 kJ mol^{-1}, $\Delta H^{\ddagger}$ = 35.62 ± 0.40 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −129.58 ± 0.66 J mol^{-1} K^{-1} (Fig. S9 and S10, ESI†).

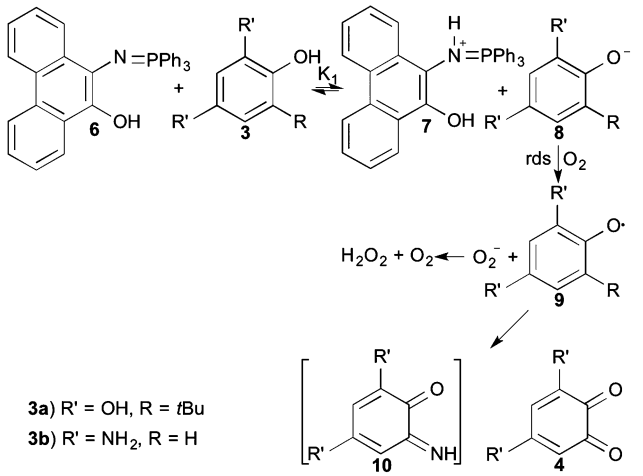


(5)

The KIE (kinetic isotope effect) data of 1.048 (**3a**) and 1.46 for **3b** oxidation (Fig. S11 and S12, ESI†) are very small and also suggest that protons are not involved in the rate-determining step. We know from earlier studies that there is an equilibrium between the ring form 1,3,2-oxazaphosphole (**1**) and the iminophosphorane tautomer (**6**) (eqn (5)). The equilibrium in solution shifted to the iminophosphorane tautomer (**6**). Studies have shown that the iminophosphorane tautomer (**6**) can be deprotonated by itself[19,20] or it is able to deprotonate the substrates **3a** and especially **3b** to the anion **8** and to the protonated iminophosphorane **7**.

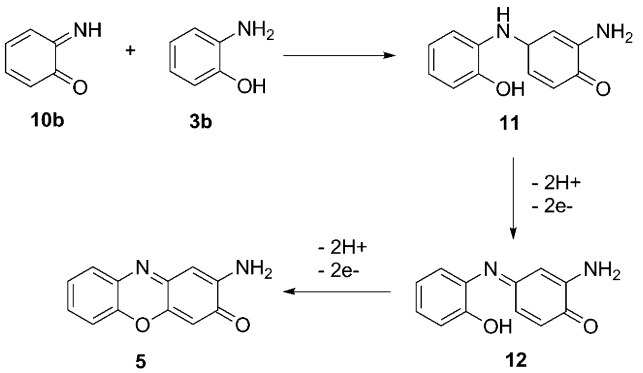
This proceeds probably *via* a charge transfer complex between **6** and **3** (Scheme 2). This reaction is a fast pre-equilibrium (K_1), which is largely shifted to the site of the starting components. This phenolate anion (**8**) then reacts in the rate-determining step with the **9** organic radical and superoxide anion. Phenolate anions are energy-rich molecules[21] and can give up one electron to the ground state dioxygen to form the phenoxyl radical **9** and superoxide anion.

The color of the reaction mixture was red, which may be due to the relative persistent phenoxyl radical **9** or also to 3,5-di-*tert*-butylbenzoquinone (**4a**). It was interesting to observe that radical **9** does not react with triplet dioxygen in a radical reaction. However, it reacts with superoxide anion (added KO_2) and not with



Scheme 2 Proposed mechanism of the oxidation of **3a** and **3b** with dioxygen catalyzed by **1**.

molecular oxygen. If we start with the substrate 3,5-di-*tert*-butylcatechol (**3a**), the corresponding quinone **4** is formed together with hydrogen peroxide. The last one could be determined quantitatively by iodometry or O_2-compsumtion measurement (Fig. 1) and was found to be in the range of 85–90%. In the case of *o*-aminophenol (**3b**), imino-*o*-quinone (**4b**) and hydrogen peroxide is formed, which comes from **9b** and HO_2 disproportion.[22] The product of *o*-aminophenol oxidation formed imino-*o*-quinone **10b**, which is not stable. It reacts with the starting aminophenol (**3b**) to form the compound **11** in a 1,4-addition reaction. A compound similar to **11** was characterized by UV-Vis spectroscopy recently when the 5-methyl derivative of *o*-aminophenol was used.[23] This is then further oxidized to compound **12** and then to the end product **5** by O_2 or the H_2O_2 formed (eqn (6)). The yields of both products (**4** and **5**) are good and the reactions could have preparative significance.



(6)

The use of 2,3-dihydro-2,2,2-triphenylphenanthro[9,10-*d*]1,3,2λ^5-oxazaphosphole (**1**) as an organic catalyst in the oxidation of 3,5-di-*tert*-butylcatechol (**3a**) and *o*-aminophenol (**3b**) to the corresponding *o*-quinone (**4**) and 2-aminophenoxazine-3-one (**5**) by triplet dioxygen are preparatively useful reactions, and the kinetic measurements resulted in an overall third order rate equation. The single electron transfer from the deprotonated substrates **3a** and **3b** to the dioxygen, forming *O*-centered radicals (**9**) and superoxide anion occurred. These convert to **4** and **10** in fast reactions and also H_2O_2 is formed. **10b** further reacts with *o*-aminophenol and subsequent oxidation leads to 2-aminophenoxazine-3-one (**5**) (eqn (6)).

The compound 2,3-dihydro-2,2,2-triphenylphenanthro[9,10-*d*]-1,3,2λ^5-oxazaphosphole (**1**) is a new organic oxidation catalyst, which mimics biologically important organic cofactors. In these reactions, the formation of the hydroperoxide (**2**) does not play a role, the catalyst, as a strong base, deprotonates the substrates (**3a**, **3b**) forming energy-rich phenolates, which give an electron to molecular oxygen in the rate-determining step. These reactions represent a new type of dioxygen activation by phenolates, which lead to well defined end products in good yields.

Experimental

2-Aminophenol (24 mg, 0.223 mmol) or 3,5-di-*tert*-butylcatechol (49 mg, 0.223 mmol) and 2,3-dihydro-2,2,2-triphenylphenanthro-[9,10-*d*]1,3,2λ^5-oxazaphosphole (**1**) (104 mg, 0.223 mmol) were dissolved in 10 mL methanol in a Schlenk tube and stirred under dioxygen at 60 °C for 5 h. The solvent was distilled off, and the residue was treated with ether and recrystallized from benzene or isooctane. Yields: 2-aminophenoxazine-3-on: 87% and 51%, 3,5-di-*tert*-butylbenzoquinone: 85% and 53% (UV-Vis and preparative, identification see ESI,† Fig. S13–S18). Kinetics: into a Schlenk vessel, the substrates 3,5-di-*tert*-butylcatechol or *o*-aminophenol were weighed in under an argon atmosphere, wherein already 10 or 20 mL methanol as solvent was present. Thereafter, the catalyst, 1,3,2-oxazaphosphole, was added and argon was replaced by dioxygen. The temperature was adjusted with a water bath, the solution stirred with magnetic bar and samples were taken at regular intervals using a septum. In the samples, the formed amount of 3,5-di-*tert*-butylquinone and 2-aminophenoxazine-3-one were measured at 400 ($\log\varepsilon = 3.21$)[24] and 434 ($\log\varepsilon = 3.743$)[25] nm. The initial rates of the reactions were determined.

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