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Supramolecular Oxidation of Anilines Using Hydrogen Peroxide as Stoichiometric Oxidant

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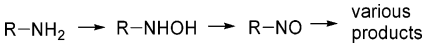
The mildness, selectivity, and rate of enzymatic catalysis greatly exceed those of ordinary chemical catalysis. Enzymes use binding and proximity effects to achieve astounding rate enhancements for specific reactions and substrates.[1] An important new area of organic chemistry is devoted to mimicking the supramolecular catalysis of enzymes,[2] which may lead to new insight into enzyme function, or unprecedented powerful and selective catalysts. Recently we and others reported that cyclodextrin ketones can catalyze epoxidation through intermediate dioxiranes formed in the presence of persulfates. While these reactions did provide enantioselectivity, they nevertheless required significant amount of catalyst, indicating that the supramolecular rate increase was not large.[3] We have now made the surprising finding that certain cyclodextrin ketones are powerful catalysts of amine oxidation in the presence of hydrogen peroxide as the stoichiometric oxidant. This oxidation follows Michaelis−Menten kinetics and depending on the substrate the oxidation rate is increased up to 1100 times.

The oxidation of amines has been performed with many different oxidants, but with respect to price and environmental friendliness hydrogen peroxide is infinitely to be preferred. This reagent has, however, a high activation energy, making catalysis necessary.[4] The reaction occurs as outlined in Scheme 1 with the primary products

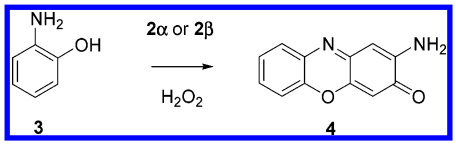
Scheme 1. Mechanism of Amine Oxidation



being hydroxylamine and nitroso derivative, and the later stages being inherently complex due to possible formation of dimerization products. Thus, not only nitro- but also azo- and azoxy- compounds are frequently observed, depending on case and conditions. Among the catalysts reported to work are ketones or ketone-derived dioxiranes.[5] Indeed a fluorinated ketone has been reported to promote amine oxidation with H_2O_2,[5a] which led us to investigate cyclodextrin ketones.

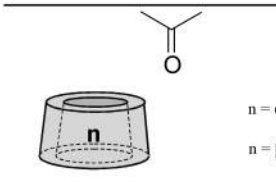
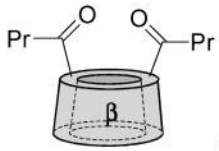
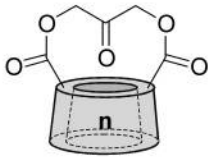
For the screening, the well-described oxidation of 2-aminophenol (**3**) into 2-aminophenoxazin-3-one (**4**) was employed (Scheme 2).[6]

Scheme 2. Oxidation of *o*-Aminophenol to 2-Aminophenoxazine-3-one



In the presence of hydrogen peroxide the reaction was monitored by determining the rate of the oxidation catalyzed by acetone and various cyclodextrin derivatives, and at pH 7.0 and 25 °C the catalyzed reaction is readily observed by following the formation of **4** by UV. While neither acetone nor diketone **1**[3c] promoted any catalysis, the ketones **2**α[3c] and **2**β[3c] were efficient catalysts (Table 1, Figure S1). The reaction rate increases with increasing amount

Table 1. Results and Kinetic Parameters for the Oxidation of 2-Aminophenol in the Presence of Various Potential Catalysts at 570 mM H_2O_2, pH 7.0 Phosphate Buffer and 25 °C[a]

Potential catalyst		K_M (mM)	k_{cat}/k_{uncat}	k_{cat} ($10^3 s^{-1}$)
		-	-	-
	n = α	-	-	-
	n = β	-	-	-
	**1**	-	-	-
	**2**α n = α	6.7±0.9	336	0.64±0.04
	2β n = β*	8.0±1.6	1068	1.35±0.14

[a] − indicates no catalysis. * indicates reaction conditions: pH 8.0, 72 mM H_2O_2. Pr = *n*-propyl.

of catalyst and follows Michaelis−Menten kinetics as seen from a Hanes plot (see Supporting Information, Figures S2 and S3). The enzyme kinetic constants were determined from least-squares nonlinear regression fitting to the V_{cat} vs S data giving the values shown in Table 1. As is seen the K_M for these reactions is 6−8 mM and k_{cat}/k_{uncat} up to 1068.

The artificial enzymes **2**α and **2**β also catalyzed oxidation of other aminobenzenes such as aniline, 4-methylaniline, 4-nitroaniline, and aminophenols. The products of these oxidations were mainly the nitro- compounds, but azo- and azoxybenzenes were in some cases also observed in GC/MS. The reactions of aminophenols were quantified using UV as explained above and gave the kinetic parameters shown in Figure 1 and Tables S1 and S2 (Supporting Information).

Most of these substrates are converted with a k_{cat}/k_{uncat} of 27−680. In general, the introduction of methyl groups into the aromatic nucleus decreased k_{cat}/k_{uncat}. Nevertheless, analogues of 2-aminophenol (**3**) are excellent substrates although to a lesser extent than **3** itself. The 4-methyl group is better accepted (analogue **8**) than a 3-methyl group (compound **10**), while a 5-methyl group (analogue **9**) reduces k_{cat}/k_{uncat} most.

Some experimentation with the conditions for the conversion of **3** to **4** in the presence of **2**β was made. Replacing H_2O_2 by *tert*-butyl hydroperoxide is possible, giving a k_{cat}/k_{uncat} of 107 and K_M of 1.7 mM at pH 7. Under these conditions a k_{cat}/k_{uncat} of 783 and K_M of 2.5 mM is obtained with H_2O_2, which means that *tert*-butyl

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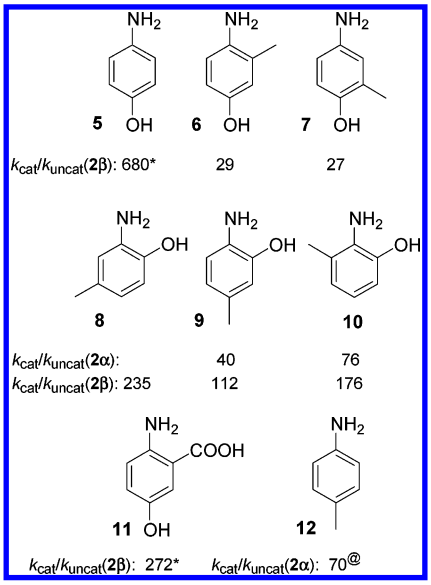

Figure 1. Kinetic constants for the oxidation of various substrates in the presence of **2**α or **2**β and 570 mM hydrogen peroxide (pH 7.0, 25 °C). All amines were oxidized to the corresponding nitro derivatives, except **12**, which was oxidized to azo- and azoxy- compounds. Details are found in Supporting Information, Table S1. * indicates reaction conditions: 36 mM H_2O_2, pH 8.0 @ at 60 °C.

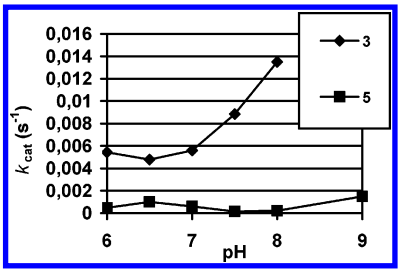

Figure 2. Plot of k_{cat} vs pH for oxidation of **3** and **5** catalyzed by **2**β. The T = 25 °C and $[H_2O_2]$ = 36 mM for **5** and 72 mM for **3**.

hydroperoxide is somewhat less efficient. With oxone as oxidant, no catalysis was observed. The pH dependency in the area where **2**β is stable was also investigated (Figure 2). The rate of oxidation of **3** increases somewhat at the higher pH, while the oxidation of **5** appears independent of pH. The rate of the catalyzed reaction depends little on the hydrogen peroxide concentration (Figure S4, Supporting Information) and works well in the entire $[H_2O_2]$ range from 5.7 to 570 mM.

Cyclodextrin **2**β does not catalyze epoxidation of styrene in the presence of H_2O_2, as it does in the presence of oxone.[5c] This is taken as evidence for dioxiranes not being intermediates in these amine oxidation reactions.

We therefore propose the mechanism in Figure 3. Hydrogen peroxide reacts with the ketone to form the hydroperoxide adduct. This adduct is the oxidizing species that is responsible for oxidizing

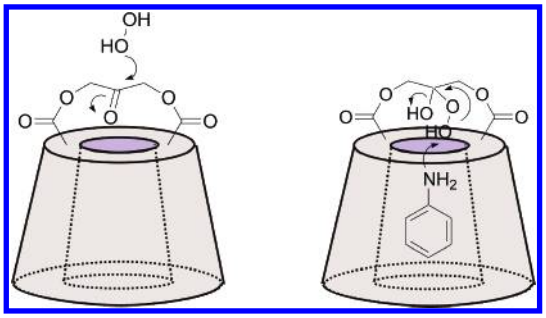

Figure 3. Proposed mechanism for the catalysis.

the amine bound in the cavity to the hydroxylamine. Oxidation of the hydroxylamine to the nitroso compound and further oxidations occur as shown in Scheme 1.

The catalysts **2**α and **2**β are remarkably good artificial enzymes for amine oxidation. These results are very encouraging both for extending the reaction to other oxidations and using **2**α or **2**β in selective synthesis.

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Supporting Information Available: Procedures for kinetic experiments, Hanes plots, etc. This material is available free of charge via the Internet at http://pubs.acs.org.

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