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CATALYTIC PROPERTIES OF A Cu(II) COMPLEX WITH A MODIFIED CYCLODEXTRIN

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A 1:2 complex between Cu(II) and mono-(6-β-aminoethylamino-6-deoxy)-β-cyclodextrin significantly accelerates the oxidation of furoin at pH 10.5. The existence of two cyclodextrin cavities in the complex molecule may contribute to the remarkable rate acceleration.

Although the catalytic properties of cyclodextrin have been extensively studied as a simple model of enzymes such as chymotrypsin,$^{1,2)}$ penicillinase,$^{3)}$ and cholinesterase,$^{4)}$ the reactivity of the catalytically active hydroxyl groups of cyclodextrin is low at neutral pH's.$^{1)}$ Furthermore, the cylindrical cavity of cyclodextrin is open to solvent at both ends, so that most cyclodextrin-substrate inclusion complexes do not have the well-defined geometry required for great rate acceleration.$^{5)}$ An approach to overcome these problems is to prepare a cyclodextrin dimer,$^{6)}$ in which two cyclodextrin molecules are bound with each other by a catalytically active functional group. Such a cyclodextrin dimer would be bound at the two hydrophobic cavities to a compound which involves two hydrophobic residues in a molecule. When the compound has a reaction site in the middle of the hydrophobic residues, the site would be located in the vicinity of the catalytic site of the cyclodextrin dimer, and the reaction would be significantly facilitated. The present study deals with the catalytic properties of a 1:2 complex of Cu(II) with mono-(6-β-aminoethylamino-6-deoxy)-β-cyclodextrin (CDen).$^{7)}$ The complex involves two β-cyclodextrin cavities, between which a catalytically active Cu(II) ion is positioned.

The CDen was prepared by a modification of the procedure of Chao.$^{8)}$ Thus, β-cyclodextrin (CD) was tosylated with 0.5 equivalent of p-toluenesulfonyl chloride in dry pyridine for 2 days at 5°C. The resulting mono-6-p-toluenesulfonyl-β-cyclodextrin (CDts) was purified by recrystallization from water.$^{9)}$ The CDts was dissolved in 1,2-diaminoethane (en) and the solution was kept at 70°C for 1 hr under N_2. The product was purified by chromatography using a carboxymethyl cellulose column with 0.05 M ammonium bicarbonate as an eluant, and gave CDen in a 37% yield based on CDts. The pH titration of an aqueous CDen solution with NaOH gave a biphasic curve consistent with the monosubstitution of the CD hydroxyl groups by en. The pK_a values for the conjugate acids of CDen were 5.6 and 9.2, each of which is significantly smaller than the corresponding value for en (6.85 and 9.93 respectively [10]).

The addition of $CuSO_4$ to a CDen solution at pH 10.5 afforded a blue solution with the absorption maximum around 570 nm. The plot of the absorbance at 575 nm vs. [Cu(II)]/[CDen] (Fig. 1) gave an inflection point about [Cu(II)]/[CDen] = 0.5, indicating the formation of a 1:2 complex between Cu(II) and CDen. The solution became turbid when [Cu(II)]/[CDen] exceeded 0.7. The stepwise stability constants (K_1 and K_2) for 1:1 and 1:2 Cu(II)-CDen complexes were determined with the computerized least-squares treatment[11a] of the spectrophotometric data to be $10^{10.7}$ and $10^{3.7}$ M^{-1} respectively at pH 10.5 and 25°C. The K_1 value is comparable to that for a 1:1 Cu(II)-en complex ($10^{10.72}$ M^{-1} [11b]), whereas the K_2 value is much smaller than that for the corresponding en complex ($10^{9.31}$ M^{-1} [11b]). The coordination of a second CDen ligand to Cu(II) may be sterically unfavorable.

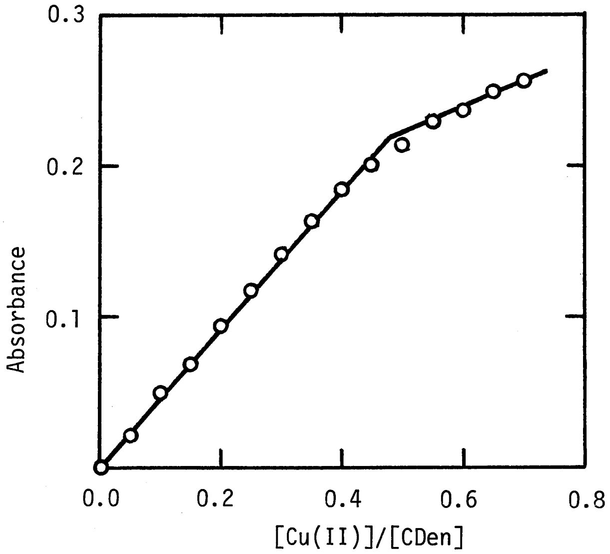


Fig. 1. Plot of the absorbance at 575 nm vs. [Cu(II)]/[CDen].
[CDen] = 5.0 mM
pH 10.5 (Borate buffer)
25°C

The catalytic properties of a 1:2 Cu(II)-CDen complex and the related compounds were examined with regard to the oxidation of furoin to furil in an alkaline solution at pH 10.5 and 25°C (Table 1). The reaction was followed by the change in absorbance at 330 nm. It was significantly accelerated by the addition of $Cu(II)(CDen)_2$ (Run 10), but only slightly by the addition of CD, en, $Cu(II)(en)_2$, or CDen (Runs 2-5). The rate effect of $Cu(II)(CDen)_2$ was decreased by the addition of cyclohexanol (Run 11), which is known to be a competitive inhibitor for a cyclodextrin catalyst.[1] The rate was not linearly increased with increasing $Cu(II)(CDen)_2$ concentration, but approximately followed the Michaelis-Menten kinetics (Runs 6, 7, 9, 10, and 12). These facts suggest that the reaction proceeds through an inclusion complex formation prior to the rate-

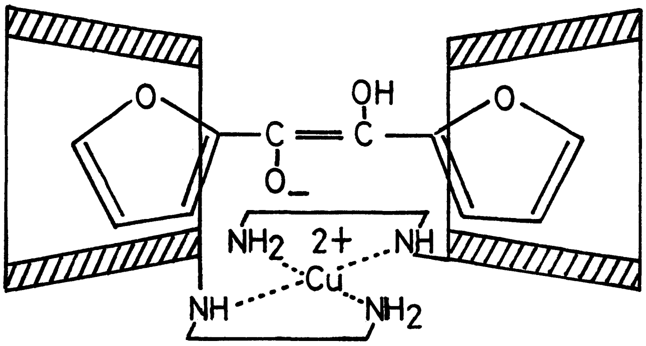
Table 1. Pseudo First-Order Rate Constants for the Oxidation of Furoin in the Absence and in the Presence of Additives at pH 10.5 and 25°C[a)]

Run No.	Additives	k_{obsd}, min^{-1}
1	None	0.0572
2	2.0 mM CD	0.0583
3	2.0 mM en	0.0793
4	1.0 mM Cu(II) + 2.0 mM en	0.0722
5	2.0 mM CDen	0.0651
6	0.25 mM Cu(II) + 0.5 mM CDen	0.148
7	0.50 mM Cu(II) + 1.0 mM CDen	0.259
8	1.0 mM Cu(II) + 1.0 mM CDen + 1.0 mM en	0.207
9	0.75 mM Cu(II) + 1.5 mM CDen	0.274
10	1.0 mM Cu(II) + 2.0 mM CDen	0.337
11	1.0 mM Cu(II) + 2.0 mM CDen + 20 mM Cyclohexanol	0.115
12	1.5 mM Cu(II) + 3.0 mM CDen	0.448

a) $NaHCO_3$-NaOH buffer; [furoin] = 0.025 mM; [O_2] = 0.30 mM.

determining step. On the assumption that a 1:1 complex is formed between $Cu(II)(CDen)_2$ and furoin, the dissociation constant (K_{diss}) of the inclusion complex and the rate constant (k_c) for the oxidation of the complexed furoin were evaluated by the Eadie plot[12)] to be 2.6×10^{-3} M and 1.1 min^{-1} respectively. The latter is ca. 20-fold larger than that for the uncatalyzed reaction.

The k_{obsd} value at 0.5 mM $Cu(II)(CDen)_2$ (Run 7) was appreciably decreased by the addition of 0.5 mM $Cu(II)(en)_2$ (Run 8), by which a complex of the type, Cu(II)(CDen)(en), may be formed to some extent. This fact suggests that the existence of two cyclodextrin cavities in a catalyst molecule is preferable for the rate acceleration to that of only one cavity in a molecule. It is possible that two cyclodextrin cavities of the $Cu(II)(CDen)_2$ complex fix a furoin molecule to locate the reaction site of furoin in the vicinity of the Cu(II) ion as illustrated below. The structure is possible to be constructed with the Corey-Pauling-Koltum molecular models. It has been suggested[13)] that the rate-determining step in the oxidation of acyloins is the enolization process. It is postulated in the present model that the enolate anion is electrostatically stabilized by the Cu(II) ion. However, there is another possibility that the enolate ion



coordinates to the Cu(II) ion. It is also possible that not only O_2 but also Cu(II) acts as an oxidant. A close mechanistic study is in progress.

References and Notes

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