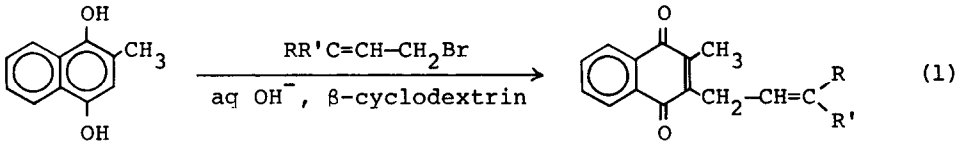
Tetrahedron Letters No. 24, pp 2083 - 2086, 1978. 0040-4039/78/0608-2083$02.00/0

CYCLODEXTRIN AS A LIGASE-OXIDASE MODEL. SPECIFIC ALLYLATION-OXIDATION OF HYDROQUINONE DERIVATIVES INCLUDED BY β-CYCLODEXTRIN

Iwao Tabushi,* Yasuhisa Kuroda, Kahee Fujita, and Hiromu Kawakubo
Department Synthetic Chemistry, Kyoto University,
Yoshida, Kyoto 606, Japan

(Received in Japan 13 March 1978; received in UK for publication 14 April 1978)

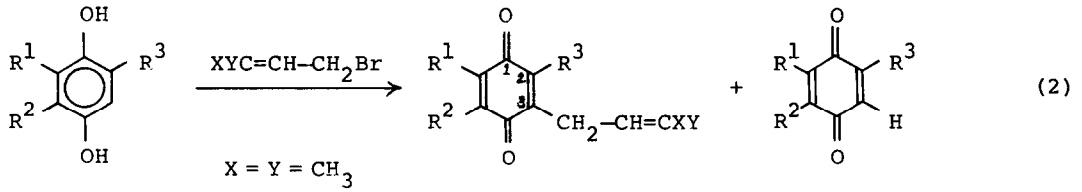
Several enzyme models for the catalysis of hydrolysis reactions have been constructed by appropriate functionalization of cyclodextrins.[1] Also, the cyclodextrins have been used to promote highly selective reactions, as demonstrated by p-chlorination[2] and regiospecific alkylation[3] followed by highly selective oxidation (eq. 1).[4] Examples of cyclodextrin-catalyzed reactions of synthetic utility, however, are still few in number, and the general applicability of this technique has not yet been convincingly demonstrated.



(1)

1 2 70—90 %

We wish to report that β-cyclodextrin very effectively catalyzes a variety of specific allylation-oxidation reactions of the type shown in eq. 2 to yield the α- and β-tocopherolquinone analogs and ubiquinone analogs listed in Table I.



(2)

3 4 (a-c) 5 (a-c)

a: $R_1 = R_2 = R_3 = CH_3$

b: $R_1 = H$, $R_2 = R_3 = CH_3$

c: $R_1 = R_2 = OCH_3$, $R_3 = CH_3$

Table I

Starting material	Yield of 4** (%)	Yield of 5** (%)	Yield of 4 based on the consumed starting material** (%)
3a	53 (7)	30 (41)	76 (12)
3b*	35 (18)	47 (49)	81 (35)
3c	39 (11)	45 (55)	71 (24)

*The diprenylated product was obtained in 10 % yield based on the consumed material in the presence of β-CD.

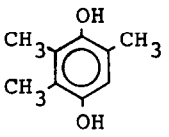
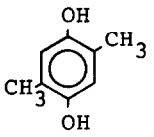
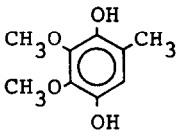
**The yields of products obtained in the absence of β-cyclodextrin are shown in parenthese.

A solution of 1.134 g (1.0 mmole) of β-cyclodextrin, 373 mg (2.5 mmole) of prenyl bromide and 76 mg (0.5 mmole) of trimethylhydroquinone in 35 ml of borate buffer (pH 10.4) and 15 ml of methanol was stirred at room temperature for 48 hr in the dark and under a stream of carefully deoxygenated nitrogen. The reaction mixture was then treated with 250 ml of water, 2 ml of concentrated HCl, 4 ml of cyclohexylamine and 20 g of crushed ice, and the solution was extracted with six portions of 50 ml of ether. The combined ether extract was washed with two portions of 20 ml of 1 N-HCl and dried over anhydrous sodium sulfate. Evaporation of the solvent and passage of the residue through a silica gel column yielded 58 mg (53 % based on starting material employed; 76 % based on starting material consumed) of 2,5,6-trimethyl-3-prenylbenzoquinone and 22 mg (30 % of the hydroquinone used) of trimethylbenzoquinone. When the same reaction was carried out in the absence of β-cyclodextrin the yield of desired material was only 7 % (12 % based on starting material consumed), and 41 % of trimethylbenzoquinone was produced.

The association constants for complex formation between β-cyclodextrin and the three hydroquinones listed in Table I were determined fluorometrically by

measuring the competitive binding of a fluorescent guest molecule, 1-anilino-8-naphthalenesulfonate.[5] The K_{assn} values, shown in Table II, are reasonably large,[6] indicating that under the conditions described above, a reasonable amount of the β-cyclodextrin is complexed with the hydroquinone.

Table II. Association constants of complex formation between β-cyclodextrin and hydroquinones*

			
K_{ass} (M^{-1})	33	36	40

*In pH 5.0 phosphate buffer, 25°C, in 30 % (v/v) CH_3OH–H_2O.

That β-cyclodextrin does, indeed, act as a catalyst for this process is indicated by its almost quantitative recovery. Its ability to act as a mimic for allylquinone synthetase is attributed to an accelerated and regiospecific C_3 allylation (ligase-type activity) followed by specific oxidation to quinones (oxidase-type activity). The ligase-like activity may be due to (a) enhanced nucleophilicity of the (partially) negatively charged carbon of the hydroquinone guest molecule and (b) prevention of C_2 allylation as a result of the steric protection afforded by the cyclodextrin cavity. The oxidase-like activity may be due to (a) the allowed oxidation of hydroquinone monoanions (or dianions) to the corresponding quinones by dioxygen via radical anion intermediates[7] and (b) the inhibition of oxidative fragmentation of the C_2–C_3 bond of the quinone as the result of its location deep in the cyclodextrin cavity; deep binding is postulated on the basis of the electronic and fluorescence spectra of complexes of cyclodextrin with substituted naphthohydroquinones or benzoquinones. These successful C-allylation on substituted hydroquinone anion, coupled with the earlier demonstration of similar allylation on naphthohydroquinone system, indicate that this process, using cyclodextrin as an enzyme model, is generally applicable as a useful synthetic procedure. A more detailed discussion of these data will be published in the near future.

REFERENCES AND NOTES

1. F. Cramer and G. Mackenson, Chem. Ber., 103, 2138 (1970); Y. Kitaura, and M. L. Bender, Bioorg. Chem., 4, 237 (1975); R. Breslow and L. E. Overman, J. Amer. Chem. Soc., 92, 1075 (1970).
2. R. Breslow and P. Cambell, Bioorg. Chem., 1, 140 (1971).
3. In the homogeneous condition, the desired C_3-allylation product was accompanied with considerable amounts of the O-allylation and the C_2-allylation products.
4. I. Tabushi, K. Fujita, and H. Kawakubo, J. Amer. Chem. Soc., 99, 6456 (1977).
5. I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata, and K. Fujita, J. Amer. Chem. Soc., 98, 7855 (1976).
6. Since very similar magnitudes of association constants were observed for undissociated and monoanionic hydroquinones by separate kinetic and/or thermodynamic measurements, determinations of equilibrium constants were carried out under the acidic condition in order to avoid any rapid oxidative degradation of the hydroquinones during the measurements.
7. In the case of 2-methylnaphthoquinone (vit. K model), the corresponding stable anion radical was detected by ESR spectroscopy.