Dual Effect of Cyclodextrins on Catechol Autoxidation

Alexey V. Eliseev*,† and Anatoly K. Yatsimirskii‡

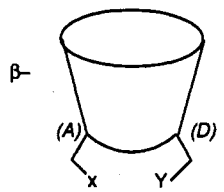
Department of Chemistry, Moscow State University, 119899, Moscow, Russia

Received August 19, 1993

Cyclodextrins, easily available natural host compounds, are nowadays becoming increasingly popular for encapsulation of drugs and bioactive substances.[1] Besides increased solubility this is supposed to protect the guest molecules from external agents, mainly dioxygen. Such applications imply that a molecule hidden inside the cyclodextrin cavity is less inclined to undergo transformations than a free one. However, numerous examples of cyclodextrin catalysis[2] show that formation of inclusion compounds might cause acceleration of an unexpected reaction. Here we report on an example of *both* of these cyclodextrin effects on autoxidation of compounds of similar structure.

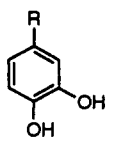
Amino cyclodextrins (CD's) have recently been demonstrated to be effective structure-sensitive receptors for anionic guests such as nucleotides[3] and catecholates,[4] forming electrostatically stabilized complexes with association constants up to 10^6 M^{-1}. Aromatic 1,2-diols in deprotonated form are known to undergo facile oxidation by molecular oxygen.[5] We have studied the effect of β-CD and 6-amino substituted β-CD's **1** on autoxidation of a number of catechol carboxylic acids **2** at pH 10.0 where the most stable complexes were formed.[4]

Formula (1)



X	Y	
CH_3NH	OH	(a)
CH_3NH	CH_3NH	(b)
$(CH_3)_3N^+$	OH	(c)
$(CH_3)_3N^+$	$(CH_3)_3N^+$	(d)

Formula (2)



R =		
	CH=CHCOOH	(a)
	COOH	(b)
	CH_2CH_2COOH	(c)
	CH_2COOH	(d)
	CH(OH)COOH	(e)
	$CH_2CH(NH_2)COOH$	(f)

Spectrophotometric study of the autoxidation reaction rates showed that β-CD had nearly no influence on oxidation of any of the catechols (Figure 1) owing to very weak binding.[4] Complexation with **1** did lead to the expected inhibitory effect for compounds **2a** (Figure 1a) and **2b** (Table 1). However, oxidation of other catechols was *catalyzed* by amino-CD (Table 1). That was even more surprising given the structural similarity, for instance, of compounds **2a** and **2c** for which the effect was opposite (Figure 1).

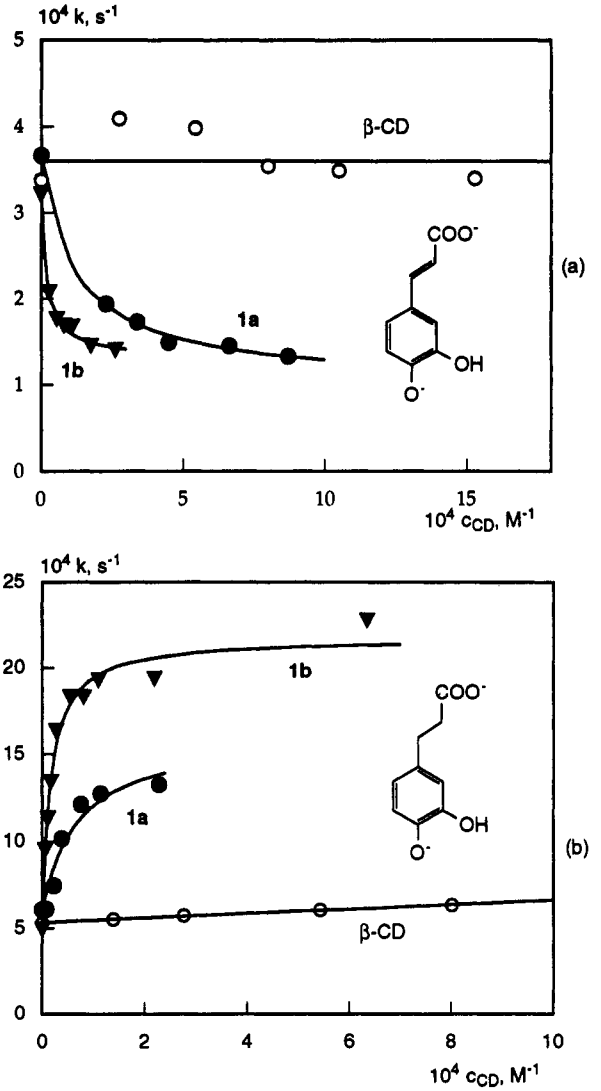


Figure 1. Cyclodextrin effects on the observed pseudo-first order reaction rate constants of autoxidation of **2a** (a) and **2c** (b).

The reason for such ambiguous behavior should be sought in the different oxidation pathways of **2**. Scheme 1 displays the general route of oxidation of catechols with dioxygen.[5b-d] In the case of compound **2a**, whose autoxidation was inhibited by amino-CD's, clear *o*-quinoid absorption was built up in the UV trace of the reaction

† Current address: Department of Chemistry, Emory University, Atlanta, GA 30322.

‡ Current address: UNAM, Faculdad de Quimica, Dpto. Quimica Inorganica, Mexico D.F. CP 04510, Mexico.

(1) (a) Szejtli, J. *Cyclodextrins and their inclusion complexes*; Akad. Kiado: Budapest, 1982. (b) Szejtli, J. *Cyclodextrin Technology*; Kluwer Acad. Publ.: Dordrecht, Boston, 1988. (c) *New trends in Cyclodextrins and Derivatives;* Duchene, D., Ed.; Ed. de Sante, 1991.

(2) (a) Bender , M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978. (b) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66. (c) Breslow, R.; Anslyn, E.; Huang, D. L. *Tetrahedron* **1991**, *47*, 2365.

(3) Eliseev, A. V.; Schneider, H.-J. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1331.

(4) Yatsimirskii, A. K.; Eliseev, A. V. *J. Chem. Soc. Perkin Trans. 2* **1991**, 1769.

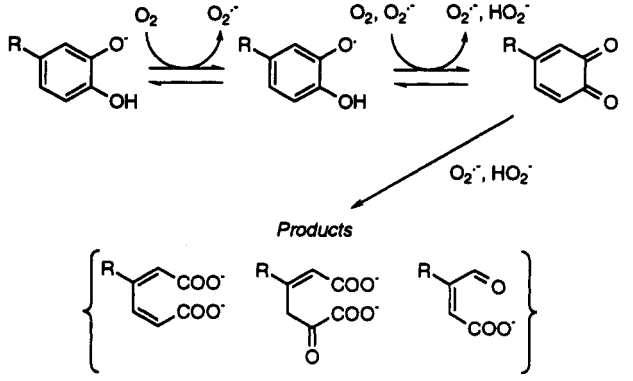
0022-3263/94/1959-0264$04.50/0

Table 1. Pseudo-First-Order Rate Constants of Autoxidation of Free Catechols (k_0) and Catechols Bound to a Cyclodextrin (k_c) at pH 10.0 and 25 °C

substrate	CD	10^4k_0, s^{-1}	10^4k_c, s^{-1}	k_c/k_0
2a	**1a**	3.40	1.1	0.31
2a	**1b**		1.4	0.40
2a	**1c**		0.6	0.2
2a	**1d**		0.2	0.07
2b	**1a**	–	–	0.33[a]
2c	**1a**	5.52	15	2.7
2c	**1b**		25	4.5
2d	**1a**	6.98	11	1.6
2d	**1b**		9.2	1.3
2e	**1a**	1.08	8.5	7.9
2e	**1b**		8.6	8.0
2f	**1b**	0.84	>2.5	>3[b]

[a] Ratio of the initial rates in presence and absence of **1a**. [b] Saturation was not reached due to low binding constant.

Scheme 1



[λ_{max} (ϵ) 287 (12800), 393 (1900 sh), 468 (600 sh)] with an isosbestic point at 291 nm which thus supported the previous conclusion that autoxidation of **2a** is terminated at the stage of the *o*-quinone.[6] The quinoid structure in this case should be stabilized by π-conjugation with carboxylate, which is likewise true for compound **2b**. The inhibitory effect of **1** would therefore be caused by steric protection of the complexed substrates from dioxygen. This is in line with the fact that inhibition increases with steric hindrance near the CD cavity in the series: **1a,b** < **1c** < **1d** (Table1).

Catalysis of autoxidation was observed for compounds **2c–f**. Here, in the absence of a conjugated structure, a more complete oxidation took place. Although the UV trace showed formation of quinoid intermediates, there were evidences of further degradation with ring opening. For example, oxidation of **2c** performed with pH control in unbuffered solution showed uptake of hydroxyl ions, as required by the stoichiometry of ring opening, unlike oxidation of **2a** where uptake of protons was observed. Likewise, ^{1}H NMR of the oxidation products of **2c** contained both pH-dependent olefinic and aldehyde signals [δ (360 MHz, D_2O) 6.6–6.9 (m), 8.32 (s) at pD 8.8; 5.6–5.8 (m), 8.07 (s) at pD 1.5.].

Formation of quinoid intermediates in the case of **2c–f** proves the third step in Scheme 1 to be rate-limiting for extensive autoxidation. This step involves the attack of *o*-quinone by reduced *anionic* oxygen species which is likely to be accelerated when the substrate is bound to a *cationic* CD causing the overall reaction to be catalyzed by **1**.

Both the inhibitory and catalytic effects of amino-CD can be up to 10-fold. The above results show that the stabilization of guest molecules by complexation with CD is not a general phenomenon even in a series of related compounds. The nature of the rate-determining step must obviously be considered.

A part of this work was performed in the Universitaet des Saarlandes (Germany) and made possible due to the Alexander von Humboldt fellowship for A.V.E. We thank Prof. Dr. H.-J. Schneider for helpful discussion.

Experimental Section

Materials. Caffeic acid (**2a**) ("Reachim") was recrystallized from water. Other catechol derivatives were purchased from Aldrich and used without further purification.

6^A-Deoxy-6^A-(methylamino)-β-CyD (**1a**), 6^A,6^D-deoxy-6^A,6^D-bis(methylamino)-β-CyD (**1b**), 6^A-Deoxy-6^A-trimethylammonium-β-CyD chloride (**1c**), 6^A,6^D-deoxy-6^A,6^D-bis(trimethylammonium)-β-CyD dichloride (**1d**) were prepared through selective tosylation of β-CD,[7] followed by reactions with the respective amines and purification by ion-exchange chromatography.[7a,8] Analytical data. **1a**·HCl: ^{1}H NMR (400 MHz, D_2O) δ 4.83 (7H, br s), 3.3–3.6 (42H, m), 2.47 (3H, s). Anal. Calcd: C, 44.0; H, 6.40; N, 1.12. Found: C, 43.6; H, 6.33; N, 1.18. **1a**·2HCl: ^{1}H NMR δ 4.83 (7H, br s), 3.3–3.6 (42H, m,), 2.47 (6H, s). Anal. Calcd: C, 42.7; H, 6.47; N, 2.18. Found: C, 42.8; H, 6.37; N, 2.27. **1c**·$3H_2O$: ^{1}H NMR δ 4.83 (7H, br s), 3.3–3.6 (42H, m), 3.15 (9H, s). Anal. Calcd: C, 42.6; H, 6.79; N, 1.10. Found: C, 42.6; H, 6.63; N, 1.11. **1d**·$3H_2O$: ^{1}H NMR δ 4.83 (7H, br s), 3.3–3.6 (42H, m), 3.15 (18H, s). Anal. Calcd: C, 43.1; H, 6.55; N, 2.01. Found C, 42.8; H, 6.40; N, 2.08.

Kinetics. Catechol autoxidation was monitored by UV-visible spectroscopy in air-saturated Tris-HCl or glycine–NaOH buffers at pH 10.0 and 25 °C following the disappearance of the catecholate bands. In a typical run, concentrations (2.5–4) × 10^{-5} M of catechol and (0–10) × 10^{-4} M of CD were employed. Thus pseudo-first-order conditions with respect to dissolved oxygen (2.5 × 10^{-4} M[9]) were maintained. Kinetic analysis was carried out by integration methods and/or analysis of initial rates.

(5) (a) Grinstead, R. R. *Biochemistry* **1964**, *3*, 1308. (b) Nishinaga, A.; Itahara, T.; Matsuura, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1811. (c) Speier G.; Tyeklar, Z. *J. Chem. Soc. Perkin Trans. 2* **1981**, 1176. (d) Speier, G.; Tyeklar, Z. *J. Mol. Catal.* **1990**, *57*, L17. (e) Cox, D. D.; Que, L., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 8085 and refs therein.

(6) Nakano, H.; Tahara, S.; Iizuka, T.; Mizutani, J. *Agric. Biol. Chem.* **1987**, *51*, 549.

(7) (a) Matsui , Y.; Okimoto, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3030 (for **1a,c**). (b) Tabushi, I.; Yamamura, K.; Nabeshima, T. *J. Am. Chem. Soc.* **1984**, *106*, 5267 (for **1b,d**).

(8) Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762.

(9) Seidell, A. *Solubilities of inorganic and metal organic compounds*; 3rd ed.; D. van Nostrand Co., Inc.: New York, 1940; Vol. 1.