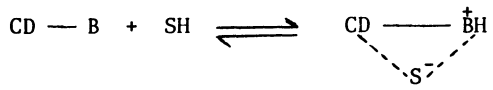
CHEMISTRY LETTERS, pp. 845 - 848, 1984.

ACID-BASE INTERACTION IN THE COMPLEXATION WITH A NICOTINOYL FUNCTIONALIZED CYCLODEXTRIN

Zafrir GOREN, Phyllis DAN, and Itamar WILLNER*
Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

Association of p-nitrothiphenol to a nicotinoyl functionalized α-cyclodextrin, is 5-fold enhanced as compared with its binding to nonfunctionalized α-cyclodextrin. This enhancement is attributed to an acid-base interaction operative in the association process.

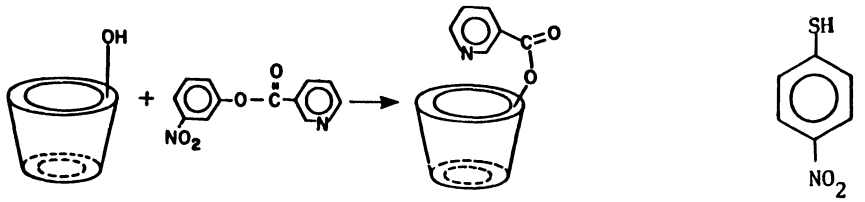
Cyclodextrins (cycloamyloses) have been extensively used as artificial receptoric enzyme models due to their ability to bind neutral and charged organic substrates.[1,2] Association of organic guest molecules with the hydrophobic cavity of cyclodextrins (CD) is usually characterized by moderate binding constants as compared with natural enzymes. The strong association of substrates with enzymes is attributed to the participation of remote functional groups of the protein backbone in their anchoring to the receptor sites. Several approaches to the enhancement of substrate-binding with cyclodextrins by means of functional modifications such as organometallic modified CD's[3,4] and "double" recognition CD-receptors[1] have been reported. Here, we wish to report the preparation of 3-α-CD-nicotinoate, (1). This modification of α-CD includes functionalization with a basic nicotinoyl moiety, and the association of an acidic substrate with its hydrophobic cavity is enhanced as compared with pure α-CD due to the substrate-anchoring by means of electrostatic acid-base interaction (Eq. 1).



(1)

Functionalization of α-CD with the nicotinoyl group followed Bender's observation that the secondary OH-groups of CD are rapidly acylated by m-nitrophenol esters.[5] Treatment of α-CD (1.00 g, 1.02 mmol) with 3-m-nitrophenyl nicotinoate, (2),(0.25 g, 1.04 mmol) in 25 ml of water-DMF (1:3 v/v) at 90 °C for 24 h gave,

after gel chromatography (Sephadex G-10), 3-α-CD-nicotinoate, (1), (37%, mp 235°C). ^{1}H NMR (in D_2O, TMS in capillary): 9.06 (1H, singlet, H_2-nicotinoyl), 8.76 and 8.25 (each corresponding to 1H, doublets, H_4- and H_5-nicotinoyl, respectively), 7.52 (1H, double doublet, H_5-nicotinoyl), 5.50 (12H, doublet, secondary α-CD protons), and 2.49-3.8 (12H,multiplet, primary α-CD protons). The population ratio of the nicotinoyl protons vs. the secondary α-CD secondary protons is 1:3. This implies monofunctionalization of α-CD with the nicotinoyl group.[6)]



2 1 3

The association of p-nitrothiophenol,(3),with the functionalized α-CD,(1),has been followed spectroscopically in water (Fig. 1). Two isosbestic points were clearly observed suggesting a 1:1 complex of 3 with the modified α-CD receptor, (1). From the Benesi-Hildebrand plot (Eq. 2 and Fig. 2) (where $[S]^\circ$ and $[R]^\circ$ are the initial concentrations of the substrate and the receptor; ΔOD is the change in absorbance upon addition of the receptor; Δε is the difference in molar extinction coefficient between the bound and free substrate), the association constant of 3 with 1 was determined to be K_{ass} = 1700 mol dm^{-3}. This binding constant was compared with those for association of p-nitrothiophenol, (3), with α-CD in the presence and absence of an equimolar amount of ethyl nicotinoate (with respect to α-CD) (Table 1). In all of these complexation studies two isosbestic points were observed upon addition of the receptor, implying the formation of 1:1 substrate-recep-

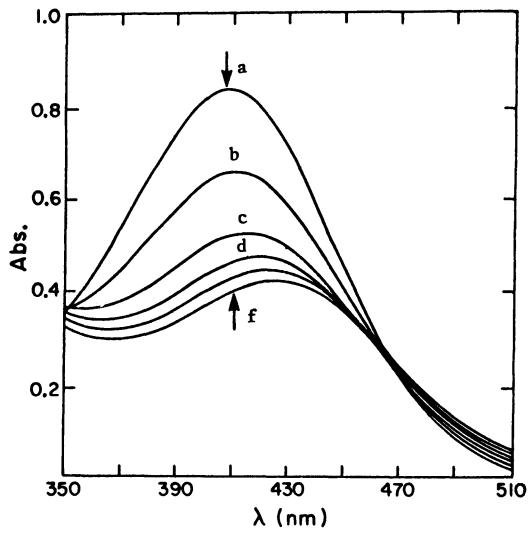


Fig. 1. Absorption spectra of 3, 1.12×10^{-2} mol dm^{-3} a) without 1, b) [1]=3.3×10^{-4} mol dm^{-3}, c) [1]=9.4×10^{-4} mol dm^{-3}, d) [1]=1.6×10^{-3} mol dm^{-3}, e) [1]= 2.2×10^{-3} mol dm^{-3}, f) [1]=2.84×10^{-3} mol dm^{-3}.

tor complexes. The binding ability of the modified α-CD receptor is ca. 20-fold

$$\frac{[S]^{o}[R]^{o}}{\Delta OD} = \frac{1}{K_{ass}\,\Delta\varepsilon} + \frac{1}{\Delta\varepsilon}\,([S]^{o} + [R]^{o}) \qquad (2)$$

enhanced as compared with that of α-CD itself, and 5-fold enhanced as compared with α-CD in the presence of ethyl nicotinoate. This enhancement in binding the

Table 1. Association constants (K_{ass}) of 3 to 1 and non-functionalized α-CD

	1	α-CD	α-CD:3-ethylnicotinoate (molar ratio 1:1)
K_{ass} mol dm^{-3}	1700	70	300

substrate 3 is attributed to an acid-base interaction between the substrate and the nicotinoyl group (Fig. 3). This interaction results in an electrostatic anchoring of the substrate that is associated with the hydrophobic cavity of α-CD.

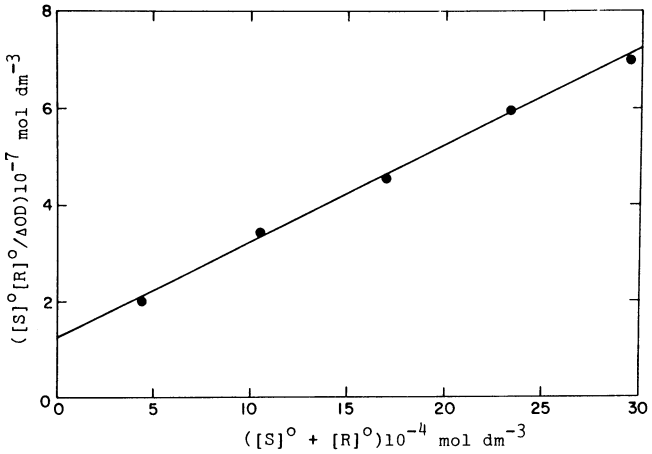


Fig. 2. Benesi-Hildebrand plot for the association of 1 with 3.

The ^{1}H-NMR analysis of the 3-α-CD-nicotinoate receptor, (1), after the complexation study reveals that ca. 70% of the modified receptor underwent hydrolysis to α-CD. This hydrolysis is probably catalyzed by the CD-bound thiophenolate anion, and is in accordance with the previous observation by Breslow indicating the lability of such groups.[4]

In conclusion, we have demonstrated the enhanced binding ability of α-CD towards the acidic substrate, (3), by means of the modification with the nicotinoyl moiety. The enhancement is attributed to the acid-base interaction between the functionalized receptor and the substrate, resulting in an effective anchoring of the guest molecule to the hydrophobic cavity of α-CD. The modified receptor, (1), offers a model system that mimics the functions of remote basic groups in proteins (such as imidazoles, indoles and amines) in anchoring substrates to natural enzymes.

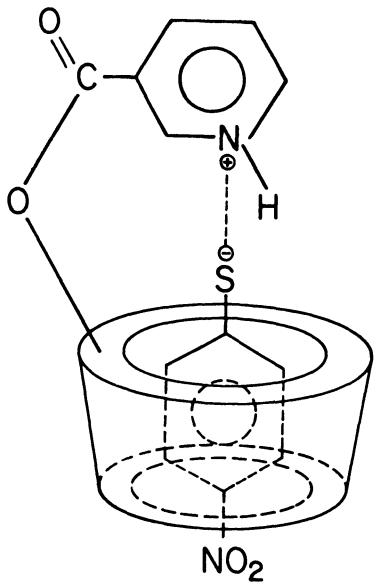


Fig. 3. Schematic representation for receptor-guest interaction of 1 with 3.

This study was partially supported by the E.D. Bergmann Fund (Jerusalem).

References

1) W. Saenger, Angew. Chem., Int. Ed. Engl. 19, 344 (1980); I. Tabushi, Acc. Chem. Res. 15, 66 (1982).

2) R. Breslow, Science, 218, 532 (1982).

3) I. Tabushi, Y. Kuroda, and A. Mochizuki, J. Am. Chem. Soc., 102, 1152 (1980); I. Tabushi, N. Shimizu, T. Sugimoto, M. Shiozuka, and K. Yamamura, ibid., 99, 7100, (1977).

4) R. Breslow, L.E. Overman, J. Am. Chem. Soc., 92, 1075 (1970).

5) R.L. van Etten, J.F. Sebastian, G.A. Cloes, and M.L. Bender, J. Am. Chem. Soc., 89, 3242, 3253 (1967).

6) Elementary analysis calculated for $C_{12}H_{63}NO_{31}$: C, 46.80; H, 5.89; H, 1.30. Found: C, 47.12; H, 6.01; N, 1.25.

7) R.J. Bergeron, J. Chem. Educ., 54, 204, (1977); H.A. Benesi and J.H. Hildebrand, J. Am. Chem. Soc., 71, 2703 (1949).

(Received February 20, 1984)