Chinese Chemical Letters Vol. 13, No. 10, pp 1005 – 1006, 2002 1005
http://www.imm.ac.cn/journal/ccl.html

Binding Affinity of Novel Cyclodextrin Dimers to Ethyl Orange

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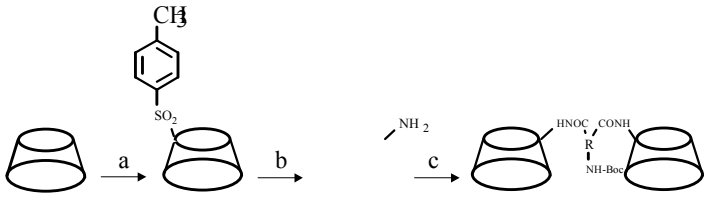
Abstract: The interaction between ethyl orange (Eto, guest) and β-cyclodextrin dimers (**1a**~**d**, host) bridged with 2-*t*-butoxycarbonyl(Boc)-amino diacid was investigated. A remarkable synergic complexation of two cavities in host molecule was observed.

Keywords: β-Cyclodextrin. inclusion compound. amino acid.

Cyclodextrins (CDs) have attracted increasing attention of many chemists since their striking characteristics of specific binding and inclusion[1~3]. Very recently, we reported the interaction between small peptide derivatives and some CD dimers labeled with isothiocyanate fluorescein by fluorescence polarization method[4]. In order to further realize the inclusion behavior of a double CD to large organic substrates and evaluate the structure effect of bridging components in host during host-guest binding, we synthesized the novel CD-amino diacid (Amda) conjugates, Boc-Glu(NH-β-CD)$_2$ **1a**, Boc-Asp(NH-β-CD)$_2$ **1b**, Boc-Acbd(NH-β-CD)$_2$ **1c** and Boc-Acpd(NH-β-CD)$_2$ **1d** as host molecules (**Figure 1**, Glu、Asp、Acbd and Acpd are the abbreviation of glutamic acid、aspartic acid、1-amino-cyclobutanecis-1,3-dicarboxylic acid and 1*R*, 3*R*-1-amino-cyclopentane-*cis*-1,3-dicarboxylic acid respectively), and examined their bonding affinity to ethyl orange by absorption spectra.

Figure 1 The synthesis of Boc-Amda(NH-β-CD)$_2$ **1**



1

1a R = >CH_2CH_2CH-

1b R = >CH_2CH_2CH-

1c R =

1d R =

Reagents and conditions: a. 6 equiv. *t*-methylbenzenesulfonyl chloride, ice water of 0.4 molL^{-1} NaOH, 1 h, yield, 27%; b. 11 equiv. NaN_3, H_2O (50 mL), 80°C, 5 h, yield, 56%; c. 0.5 equiv. Boc-Amda, 1.4 equiv. *N*-hydroxy-perrolidine-2, 5-dione, 1.2 equiv. diisopropylcarbodiimide, DMF (15.4 mL), CH_2Cl_2 (0.4 mL), 93 h, 25°C, yield, 41%.

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Boc-Amda was prepared from amino diacid and 3 equiv. triethylamine in water (6 mL) by treatment with 1 equiv. 2-*t*-butoxycarbonyloxyimino-2-phenylacetonitrile in 6 mL 1,4-dioxane at room temperature for 4 h. The yield is moderate (*ca*. 60% from amino acid). The β-CD dimers, Boc-Amda(NH-β-CD)$_2$ 1, was obtained according to the route outlined as above.

Mono-6-NH_2-6-deoxy-β-CD was used as the starting material for β-CD dimer. The crude product after washing thoroughly with saturated brine was purified by column chromatography to give pure **1**. It was dried to constant weight and stored over P_2O_5 under vacuum. TLC (water-ethyl acetate-isopropanol, 3:4:5) showed a single spot (**Table 1**).

In order to survey the binding ability, ethyl orange was employed as a guest. The host-guest binding was monitored by absorption spectra around 471 nm in phosphate buffer (pH 7.40) at 25°C. With increase the host concentration, the peak of absorption spectra shifted from 475 nm to 461 nm and a strong increase in absorption was observed. The association ratios were determined to be 1:1 by Job's treatment[5] of the difference spectra. The Benesi-Hilderbrand plot[6] gave a straight line in the concentration range of **1** from 4.50×10^{-5} to 2.00×10^{-4} mol L^{-1} at a concentration of 1.00×10^{-5} mol L^{-1} of ethyl orange. The binding constants for the complexation of ethyl orange by **1a**~**d** was presented in **Table 1**.

Table 1 The characterization of hosts and the binding constants of host-guest

Host	Yield (%)	R_f	Anal. Calcd for **1**·2H_2O (Found)			Binding Affinity to Eto
			C	H	N	K_b / $mol^{-1}L$
1a	27	0.72	44.89(44.65)	6.32(5.77)	1.67(1.82)	$(4.20\pm0.45)\times10^4$
1b	39	0.80	44.66(44.52)	6.33(6.05)	1.68(1.84)	$(6.61\pm0.38)\times10^4$
1c	41	0.69	45.15(45.01)	6.34(6.23)	1.66(1.44)	$(1.50\pm0.20)\times10^5$
1d	34	0.63	45.37(45.19)	6.38(5.65)	1.65(1.79)	$(2.30\pm0.25)\times10^5$

The values of K_b are significantly greater with a double β-CD (>4.20×10^4 $mol^{-1}L$) as a host compared to β-CD (6.55×10^2 $mol^{-1}L$) or to a capped β-CD such as Boc-alanine(NH-β-CD) (1.22×10^3 $mol^{-1}L$). This leads to a conclusion that two neighboring CD cavities of a dimer may act effective cooperation during host-guest recognition if there is a suitable fit between the double CD and guest components.

It had been found in comparison between the bonding constants of Eto with two hosts, Boc-Acbd(NH-β-CD)$_2$ (1.50×10^5 $mol^{-1}L$) and Acbd(NH-β-CD)$_2$ (2.06×10^5 $mol^{-1}L$) that the large Boc group in host molecule did not perform an act of obvious interference during host-guest interaction. As shown in the **Table** the structure of the bridge between the CD dimers did not seem play very important role in the binding constant of the host and guest complexation.

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Received 17 January, 2002