

## Enhanced ternary 1:2 host–guest complexation of amino- $\gamma$ -cyclodextrins with 2-anthracenecarboxylic acid

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**Abstract** The complexation behavior of 6-amino-6-deoxy- $\gamma$ -cyclodextrin (CD), 6<sup>A</sup>,6<sup>X</sup>-diamino-6<sup>A</sup>,6<sup>X</sup>-deoxy- $\gamma$ -CDs and 3<sup>A</sup>-amino-3<sup>A</sup>-deoxy-*altro*- $\gamma$ -CD with 2-anthracenecarboxylic acid (AC) was studied by NMR, UV–vis and circular dichroism spectroscopy. These modified  $\gamma$ -CD derivatives were found to form stable 1:2 host–guest ternary complexes with AC in aqueous solution. Compared with native  $\gamma$ -CD, the primary-face-aminated  $\gamma$ -CDs exhibited remarkably enhanced overall association constants as a result of the additional electrostatic interactions between the oppositely charged host and guest. In contrast, the ternary complex formation of the secondary-face-aminated  $\gamma$ -CD with AC was hindered.

**Keywords** Amino- $\gamma$ -cyclodextrin · Anthracenecarboxylic acid · Host–guest complex · Electrostatic interaction

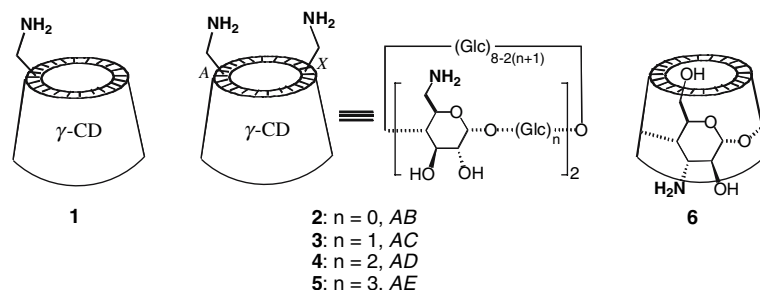
### Introduction

One of the most fascinating properties of native and synthetic hosts having a large binding site is

the unique ability to accommodate two or more individual molecules in their confined spaces with highly organized arrangements. The reaction kinetics and selectivity, and the photophysical and electrochemical properties of included guests can be significantly modified through the formation of multicomponent complexes [1–4]. Naturally occurring cyclodextrins (CDs) are bucket-shaped cyclic oligosaccharides composed of typically 6–8 (1–4)- $\alpha$ -linked D-glucopyranose units (which correspond to  $\alpha$ -,  $\beta$ - and  $\gamma$ -CDs, respectively). It is well known that the large cavity of  $\gamma$ -CD is suited for accommodating two guest molecules of appropriate size and shape [5]. This unique property of  $\gamma$ -CD has been applied to promote excimer fluorescence [6, 7], room-temperature phosphorescence [8, 9], as well as the reactivity and selectivity of thermal and photochemical reactions between the co-included reactants [10–23]. However, the driving force for native CDs to bind organic guests is primarily the hydrophobic and van der Waals interactions, which are often not sufficient for strong and selective complexation. To efficiently improve the binding affinity and manipulate the arrangement of guest molecules inside the CD cavity, multiple sites and modes of interaction are indispensable. In this work, we investigated the effect of electrostatic interactions on the complexation of  $\gamma$ -CD with 2-anthracenecarboxylic acid (AC) by using the primary- or secondary-face mono- and diaminated  $\gamma$ -CDs **1–6** as hosts, and confirmed a significant improvement of the ternary complexation particularly with the primary-face-diaminated  $\gamma$ -CDs.

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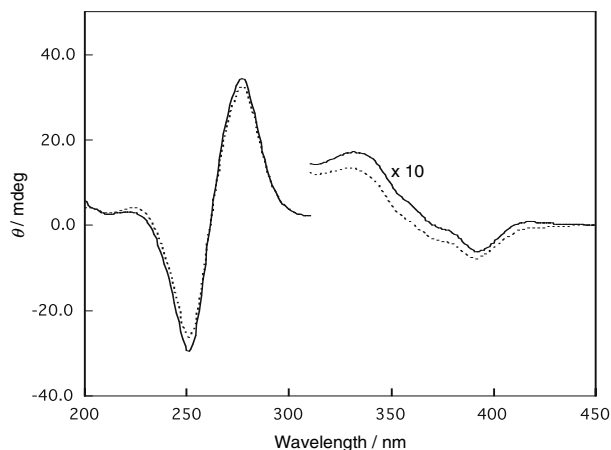


## Materials and methods

Native  $\gamma$ -CD and 2-anthracenecarboxylic acid (Tokyo Chemical Industry) were dried under vacuum before use. The modified hosts 6-amino-6-deoxy- $\gamma$ -CD **1**, 6<sup>A</sup>,6<sup>X</sup>-diamino-6<sup>A</sup>,6<sup>X</sup>-dideoxy- $\gamma$ -CDs **2–5** [16], and 3<sup>A</sup>-amino-3<sup>A</sup>-deoxy-altro- $\gamma$ -CD **6** [17] were prepared by the reduction of corresponding azides with triphenylphosphine in dried DMF. The <sup>1</sup>H-NMR spectra were recorded on a JEOL JNM-EX 400 spectrometer. UV–vis and circular dichroism spectra were obtained by using JASCO V560 and J-720WI spectrometers, respectively.

## Results and discussion

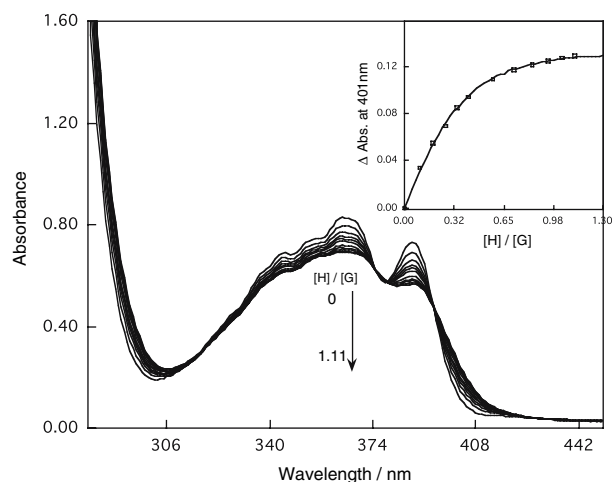
Native  $\gamma$ -CD has been demonstrated to form a stable 1:2 host–guest complex with AC in our previous study [13]. To elucidate the binding behavior of the synthesized amino- $\gamma$ -CDs with AC, the circular dichroism, NMR and UV–vis spectral examinations were performed in aqueous solution. As exemplified in Fig. 1, addition of an amino- $\gamma$ -CD to a solution of AC



**Fig. 1** Circular dichroism spectra of 0.8 mM AC in phosphate buffer solution at pH 7.0 in the presence of 2 mM **3** (dotted line) and **4** (solid line)

consistently led to a strong positive exciton coupling at the <sup>1</sup>B<sub>b</sub> band of AC, associated with a weaker negative exciton coupling at the <sup>1</sup>L<sub>a</sub> band. These bisignate Cotton effects, clearly arising from the intermolecular aromatic stacking of two ACs within a CD cavity, evidence that the size of  $\gamma$ -CD cavity is not greatly changed by the introduction of amino group(s) on the primary or secondary face. From the very strong positive exciton coupling, we deduce that the AC pairs exist mainly in a clockwise arrangement of the <sup>1</sup>B<sub>b</sub> transition moment in the cavity of amino- $\gamma$ -CDs [24].

The Job's plot of the UV–vis spectral changes, obtained at the total host plus guest concentration of 1 mM, also indicates that the 1:2 host–guest complex is the major species in the concentration range employed, as the maximum is found at the AC mole fraction of 0.67. Absorption spectral titrations were performed to quantitatively evaluate the ternary complexation by adding amino- $\gamma$ -CD to a buffered AC solution. As can be seen from Fig. 2, a gradual bathochromic shift of the <sup>1</sup>L<sub>a</sub> transition was observed upon incremental addition of **4**. From the spectral changes, the association constants for the stepwise formation of 1:1 and 1:2 host–guest



**Fig. 2** UV–vis spectra of AC (0.8 mM) at various concentrations of **4** (0–0.89 mM), and the nonlinear least-squares analysis (inset) for the calculation of 1:1 ( $K_1$ ) and 1:2 ( $K_2$ ) association constants

**Table 1** Association constants for 1:1 and 1:2 complexation of  $\gamma$ -CDs with AC<sup>a</sup>

Host	Association constant			Ref.
	$K_1/\text{M}^{-1}$	$K_2/\text{M}^{-1}$	$K_1K_2/10^6 \text{M}^{-2}$	
$\gamma$ -CD	161 ( $\equiv 1$ ) <sup>b</sup>	38500 ( $\equiv 1$ ) <sup>b</sup>	6.2 ( $\equiv 1$ ) <sup>b</sup>	c
<b>1</b>	943 (5.9) <sup>b</sup>	12030 (0.31) <sup>b</sup>	11.3 (1.8) <sup>b</sup>	d
<b>2</b>	1702 (10.6) <sup>b</sup>	17830 (0.46) <sup>b</sup>	30.3 (4.9) <sup>b</sup>	d
<b>3</b>	1415 (8.8) <sup>b</sup>	10330 (0.27) <sup>b</sup>	14.6 (2.4) <sup>b</sup>	d
<b>4</b>	1204 (7.5) <sup>b</sup>	10760 (0.28) <sup>b</sup>	13.0 (2.1) <sup>b</sup>	d
<b>5</b>	1650 (10.2) <sup>b</sup>	31280 (0.81) <sup>b</sup>	51.6 (8.3) <sup>b</sup>	d
<b>6</b>	275 (1.7) <sup>b</sup>	12800 (0.33) <sup>b</sup>	3.5 (0.56) <sup>b</sup>	d

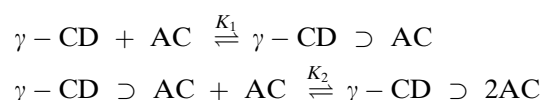
<sup>a</sup> The association constants measured in phosphate buffer solution at 25°C

<sup>b</sup> Relative to the values for native  $\gamma$ -CD

<sup>c</sup> Reference 13

<sup>d</sup> This work

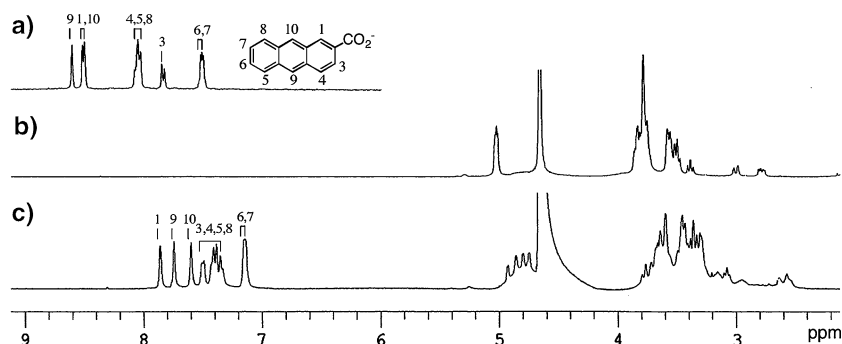
complexes ( $K_1$  and  $K_2$ ) were evaluated by the nonlinear least-squares analysis to give data shown in Table 1.



Irrespective of the position and number of amino group(s) introduced to  $\gamma$ -CD, the 1:1 association constants ( $K_1$ ) are considerably enhanced by amination, although the degree of enhancement is much larger for the primary-face-diaminated  $\gamma$ -CDs **2–5** (7.5–10.6 times) than for the primary-face-monoaminated  $\gamma$ -CD **1** (5.9 times) and in particular the secondary-face-monoaminated monoalto- $\gamma$ -CD **6** (1.7 times). Obviously, the attractive electrostatic interactions between positively charged amino- $\gamma$ -CD and negatively charged AC are responsible for the stronger 1:1 binding exhibited by the amino- $\gamma$ -CDs. On the contrary, the  $K_2$  values of amino- $\gamma$ -CDs are moderately reduced by a factor of 0.3–0.8 with regard to that of native  $\gamma$ -CD. This result suggests that the spatial preorientation of the firstly-included AC molecule, defined by a combination of the hydrophobic and electrostatic interactions, is not suitable for immediately accommodating a

second AC molecule to the residual space. Thus, the inclusion of the second AC has to pay the enthalpic and entropic penalties arising from the reorganization of the whole complex structure upon the ternary complex formation, and the positional and rotational freedoms of ACs, pinned with the Coulombic force in the cavity of amino- $\gamma$ -CD, are expected to be considerably restricted. To prove this hypothesis, <sup>1</sup>H NMR spectra of the complexes of AC with amino- $\gamma$ -CDs were measured in D<sub>2</sub>O solution. As shown in Fig. 3, the complexation of **5** with AC leads to significant upfield shifts of AC protons, due to the mutual ring current effect of the co-included ACs. Upon inclusion of AC, the CD proton signals disperse over a wider range, and the originally superimposed H1 protons of **5** are clearly resolved into four kinds of anisotropic species. These results indicate that AC molecules are unable to freely rotate in the cavity of **5** due to the electrostatic interactions and hence display the non-equivalent shielding and deshielding effect on each glucose unit.

Comparison of the overall association constants  $K_1K_2$  reveals that, despite the appreciably smaller  $K_2$  values compared with that for native  $\gamma$ -CD, the introduction of amino group(s) on the primary rim of  $\gamma$ -CD



**Fig. 3** <sup>1</sup>H NMR spectra of (a) AC, (b) **5**, and (c) AC (3 mM) + **5** (2 mM) in D<sub>2</sub>O solution at pH 7.0

consistently improves the ternary complexation of AC with  $\gamma$ -CDs. Interestingly, the  $K_1K_2$  values for diamino- $\gamma$ -CDs are highly sensitive to the relative position of the two amino groups introduced. Intriguingly, A,B- and A,E-diaminated **2** and **5** exhibit the largest improvement in  $K_1K_2$  value of 4.9–8.3 folds, whilst A,C- and A,D-diaminated **3** and **4** show only moderate enhancement of 2.1–2.4 folds. Considering the fact that the significantly larger affinities for **2** and **5** originate mostly from the much preferred second AC complexation, we attribute this critical regioisomer-dependence of affinity to the different degree of face-to-face stacking between co-included ACs, which is governed by the inter-amino distance. Thus, each of the two amino groups at the closest A,B- and most remote A,E-positions attracts AC's carboxylic group to align two AC molecules in the cavity in *syn*- and *anti-head-to-head* fashion, respectively, leading to more efficient aromatic stacking between two ACs than the A,C- or A,D-diaminated **3** and **4**.

In sharp contrast to the much enhanced affinities observed for **1–5**, the altroside-bearing  $\gamma$ -CD **6** gave a  $K_1K_2$  value smaller than that for native  $\gamma$ -CD, despite the amino group introduced to the secondary rim. This exception is possibly due to its deformed and more flexible cavity [17], which suffers significant conformational changes with a larger entropic loss in the process to alter the shape for accommodating two ACs.

In conclusion, we studied the binding behavior of several amino- $\gamma$ -CDs with AC. As a result of the synergetic effect of hydrophobic and electrostatic interactions, the total association constants are significantly enhanced up to 8 times with amino- $\gamma$ -CDs modified on the primary face, whereas the altroside-bearing amino- $\gamma$ -CD **6** reduces the binding affinity of the parent  $\gamma$ -CD.

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