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Synthesis of per(5-N-carboxamide-5-dehydroxymethyl)-β-cyclodextrins and their selective recognition ability utilizing multiple hydrogen bonds

Takashi Nakamura, Sota Yonemura and Tatsuya Nabeshima

Natural receptor proteins achieve sophisticated molecular recognition by exerting multiple hydrogen bonds at their hydrophobic binding pockets, in which amide groups of the main chain often play an important role. Learning from the excellent examples of the biomacromolecules, a number of artificial molecular receptors possessing multiple amide functionalities have been reported. In particular, the accumulative use of amide groups as hydrogen bond donors is suitable for their employment as receptors for anions. The introduction of multiple functional groups onto a scaffold is required to configure a recognition site. Due to synthetic reasons, many receptors are designed to possess equivalent interaction units, which usually leads to a high symmetry in the molecular structure. One strategy aiming at specific recognition is the introduction of different functional groups. In the case of anion binding, receptors equipped with both hydrogen bond donor and acceptor units are reported. However, the differentiation of host structures by introducing different substituents often requires more synthetic steps. In this context, if a molecule with equivalent substituents exhibits a recognition mode in which each functional group plays distinctive roles, it will be a simple approach for artificial receptors to achieve precise functions reminiscent of biological systems.

Per(5-N-carboxamide-5-dehydroxymethyl)-β-cyclodextrin derivatives with seven equivalent amide groups directly attached to each pyranose ring were synthesized. The amide cyclodextrins show unique recognition properties toward hydrogen phosphonate anions. An X-ray crystallographic analysis revealed its recognition mode in which unsymmetrically arranged amide groups play distinctive roles both as a hydrogen bond donor and acceptor.

We now report the first synthesis of per(5-N-carboxamide-5-dehydroxymethyl)-β-cyclodextrins with multiple amide groups directly attached to each pyranose ring, and their unique recognition ability utilizing multiple hydrogen bonds. β-Cyclodextrin, a cyclic heptamer of glucose, is one of the most widely used host compounds. In many cases, the framework of the native and functionalized cyclodextrins is regarded as a circular conical cylinder. Toward more sophisticated applications, such as enzyme mimics, the introduction of one or more substituents at specific positions of the cyclodextrins has been investigated. However, the separation of numerous isomers with different numbers and positions of the substituents is often formidable. It is known that native cyclodextrins maintain their circular scaffold through intramolecular hydrogen bonds between hydroxy groups, and conversion of the hydroxy groups increases the degree of freedom of each glucose unit thus making the entire macrocycle flexible. By taking this mobility into account, we postulated that cyclodextrins possessing multiple equivalent amide groups can take a desymmetrized conformation as a snapshot, which can be utilized for unique molecular recognition.

The N-methylamide derivative 1a and N-p-tolylamide derivative 1b were synthesized by the condensation of the corresponding amines with per(5-carboxy-5-dehydroxymethyl)-β-cyclodextrin 2a (Scheme 1). Among the several tested conditions, the employment of N,N-dicyclohexylcarbodiimide (DCC) together with 1-hydroxy-7-azabenzotriazole (HOAt) was

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The N-methylamide derivative 1a and N-p-tolylamide derivative 1b were synthesized by the condensation of the corresponding amines with per(5-carboxy-5-dehydroxymethyl)-β-cyclodextrin 2a (Scheme 1). Among the several tested conditions, the employment of N,N-dicyclohexylcarbodiimide (DCC) together with 1-hydroxy-7-azabenzotriazole (HOAt) was
effective. A MALDI TOF mass spectrum of the reaction mixture to 
synthesize 1b demonstrated that all the seven carboxylic 
groups of 2 were efficiently converted to p-tolylamide groups 
(Fig. S5).

We succeeded in the single-crystal X-ray diffraction analysis of 
the carboxylic acid 2 (Fig. 1). As suggested in a previous study 
based on vapor-pressure osmometry, 2 forms a dimer upon 
intermolecular connection of the carboxy groups. Intriguingly, 
all the seven carboxy groups make tight hydrogen-bonded pairs 
with the counterpart of the other 2 (Fig. 1a,b), and the distances 
between the oxygens in the carboxy dimer are in the range of 
2.60–2.66 Å (Fig. 1c). Focusing on the macrocyclic framework, 
the shape of 2 in the dimer is close to a true circle. The distances 
between the carboxy carbons of the adjacent units are in the 
range of 3.94–4.05 Å (Fig. 1d). Their small variation is noticeable 
when compared to the unfunctionalized β-cyclodextrin; the 
distances between the carbons of the corresponding 
hydroxymethyl groups in its crystal are in the range of 4.41–4.82 
Å.\(^{10}\)

![Fig. 1 Structure of 2, determined by X-ray crystallography (an ellipsoid model, 50% probability, hydrogens are omitted). Side view (a) and top view (b). (c, d) Representative distances.](image)

The conversion of carboxy groups into amides drastically 
changes the macrocylic structure. A single crystal of the N-p- 
tolylamide derivative 1b suitable for an X-ray diffraction analysis 
was obtained by slow evaporation of a MeOH/H\(_2\)O solution. 1b 
has a characteristic twist in the macrocyclic framework, which 
comes from the steric repulsion between the seven p-tolyl 
groups and from the hydrogen bonds of the amides (Fig. 2a,b). 
In particular, one of the seven repeating units is largely tilted 
with p-tolyl groups directed outside. Focusing on the 
participation of the amide groups in the structural conformation, 
three intramolecular and one intermolecular amide-amide 
hydrogen bonds are observed in the crystal (Fig. 2c). In the 
cavity of 1b, five water molecules are found without disorder, 
and they form a hydrogen bond network with the amides and 
other functional groups. Elemental analysis of the isolated 
sample also matched with 1b·H\(_2\)O (see ESI).

![Fig. 2 Structure of 1b·SH\(_2\)O determined by X-ray crystallography. (a) Colouring by 
repeating unit (a space-filling model). (b) Top view (a stick model). Hydrogens 
except for amides are omitted. H\(_2\)O depicted as ellipsoids (50% probability). 
Hydrogen bonds are shown in magenta. (c) A hydrogen bond network between 
amide groups and water molecules inside the cavity. Colours of amide groups 
correspond to (a).](image)

Intriguingly, two conformational isomers of 1b are observed 
by NMR (Fig. 3). For one isomer, the NMR signals corresponding 
to one repeating unit are observed, suggesting its time-
averaged seven-fold symmetry. For the other isomer, seven 
sets of NMR signals are observed, suggesting that all seven 
repeating unit are in different environments on the NMR 
timescale. The \(^1\)H and \(^13\)C NMR signals for the two isomers 
have been successfully assigned by 2D NMR measurements (Fig. 3, 
Fig. S8–S14, Table S2 and S3). \(^1\)H–\(^1\)H ROESY revealed that the 
isomer with a lower symmetry has a conformation where one of 
the p-tolyl substituents is self-included in the cyclodextrin 
 cavity (1b\(_{\text{in}}\)).\(^{11}\) The \(^1\)H NMR signals of 1b\(_{\text{in}}\) in Fig. 3 are shown 
in a manner that assigns the p-tolyl group of the unit 1 (red) as the 
self-included one. Characteristic ROE correlations with \(i_1\) (2-
position of the p-tolylamide group) are observed for \(e_2, e_3,\) 
and \(e_4,\) and those with \(j_1\) (3-position of the p-tolylamide group) 
are observed for \(e_5, e_6,\) and \(e_7\) (Fig. 3b, Fig. S11). A \(^1\)H DOSY 
measurement shows similar diffusion constants (\(D = 6.5\times10^{-10}\) 
\(\text{m}^2\text{s}^{-1}\)) for the two isomers, thus supports that the isomer 
with a lower symmetry is a self-included monomer 1b\(_{\text{in}}\), not a 
doubly-threaded dimer\(^1\) (Fig. S14). The ratio between 1b\(_{\text{in}}\) and 
the other non-included isomer (1b\(_{\text{out}}\)) is dependent on the 
solvent (Table S1, 298 K). Among the investigated solvents, the 
ratio of 1b\(_{\text{in}}\) is relatively high in CD\(_3\)CN (1b\(_{\text{in}}\): 1b\(_{\text{out}}\) = 60 : 40) and 
acetone-\(d_6\) (1b\(_{\text{in}}\): 1b\(_{\text{out}}\) = 30 : 70). Meanwhile, the equilibrium 
shifted to 1b\(_{\text{out}}\) in solvents such as CDCl\(_3\) (1b\(_{\text{in}}\): 1b\(_{\text{out}}\) = 10 : 90) 
and DMSO-\(d_6\) (1b\(_{\text{in}}\): 1b\(_{\text{out}}\) = 10 : 90). At elevated temperatures 
(1,1,2,2-tetrachloroethane-\(d_2\), 373–393 K), the \(^1\)H NMR signals 
of 1b\(_{\text{in}}\) and 1b\(_{\text{out}}\) coalesced into one set of signals and are 
broadened, thus probably suggesting the interconversion of the 
cyclodextrin conformations (Fig. S6).
bind anions. This is explained by the rigidity of amide groups.

Furthermore, it was found that water in the solvents shifted the equilibrium toward 1b_out (Table S1, 1b_out : 1b_in = 3 : 97 in CD3CN/D2O = 9/1 (v/v)). As shown in Fig. 2, 1b-5H2O in the crystal obtained from MeOH/H2O solution takes a conformation in which all seven p-tolyl groups are positioned outside, i.e., 1b_out. The water molecules are considered to stabilize the non-included conformer 1b_out via hydrogen bonds with the amides.

The amide cyclodextrins showed unique recognition properties of anions utilizing multiple hydrogen bonds inside the cavity. Table 1 summarizes the binding constants of various anions [M1+] of a series of hydrogen phosphonates (R-PO3H+) and hydrogen phosphates (R-PO2H+) in CDCl3 or DMSO-d6. A series of hydrogen phosphonates (R-PO3H+) and hydrogen phosphates (R-PO2H+) are encapsulated in the amide cyclodextrins in a 1:1 ratio, which was determined from the integral values of the encapsulated guest. In chloroform, the hydrogen phosphonate (PhPO3H+) and hydrogen methylphosphonate (MePO2H+) are bound the strongest with the p-tolylamide derivative 1b (log K = 4.5). In contrast, the amide cyclodextrin derivatives interact only weakly (log K ≤ 1–2) with the carboxylates (R-CO2−). As for the halides (Cl−, Br−, I−) and diphenyl phosphate (Ph(PO2)2), the binding constants were too low to be determined (Fig. S32, S43, S44 and S55). Thus, a remarkable selectivity toward hydrogen phosphonates is achieved. As the anion binding was not observed for per-O-methyl-β-cyclodextrin in this condition (Fig. S56), the recognition ability of 1a/1b can be attributed to the introduced amide groups. Comparing 1a and 1b, 1b tends to more strongly bind anions. This is explained by the rigidity of 1b derived from the steric restriction due to the multiple p-tolyl groups, which reduces the entropy loss upon guest binding.

The 1H NMR spectrum of the host-guest complex (n-Bu4N)[PhPO3H]·1b shows an amide proton signal at 10.03 ppm (downfield shift by 1.22 ppm compared to the guest-free 1b), which supports the hydrogen bonds with PhPO3H+ (Fig. S16). Furthermore, the signal of an acidic proton of the encapsulated PhPO3H+ is observed at 8.56 ppm. In fact, mixing a salt of the phosphonophosphate dianion (PhPO32−) with 1b also resulted in the inclusion as a hydrogen phosphonophosphate (PhPO3H+), which shows an interesting specificity toward the monoprotonated form (Fig. S41). The inclusion of PhPO3H+ was also confirmed by a ROESY measurement, in which the phenyl group showed ROE correlations with the introverted 3- and 5-protons of the pyranose rings and methoxy groups (c, e, and g, see Fig. S18).

Table 1. Binding constants log K = [M1+] of anionic guests with 1a/1b (H NMR, 298 K).

<table>
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<tr>
<th>Entry</th>
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<td></td>
<td>(CDCl3)</td>
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<td>(DMSO-d6)</td>
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<td>2.6</td>
<td>1.8</td>
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<td>−</td>
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</tr>
<tr>
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<td>PhCH2PO2−</td>
<td>3.3</td>
<td>3.0</td>
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a n-Bu4N+ salts except for entry 7, in which a Et4N+ salt was used. b The binding constant is too low to be determined. c Bound as PhPO3H+.

The binding of PhPO3H+ is also strong in other solvents such as DMSO-d6 (log K = 4.5), CD3CN (log K > 5), and CD2Cl2 (log K = 5.0) (Fig. S19, S20 and S50). The PhPO3H+ was released from the cavity of 1b in an aqueous mixed solvent CD3CN/D2O = 9/1 (v/v), probably due to the interaction of water with amide groups (Fig. S57). For a series of other anions, 1b shows comparative or even higher binding constants in DMSO-d6 in comparison to those in CDCl3 (Table 1). The strong binding via hydrogen bonds in competing solvents such as DMSO-d6 is of significant note. The thermodynamic parameters for the binding of PhCH2PO3H+ (Table 1, entry 9) by 1b in CDCl3 and DMSO-d6 were evaluated by variable-temperature 1H NMR measurements (Fig. S58–S63): ΔH298 = −13 kJ mol−1 and ΔS298 = 16 J mol−1 K−1 in CDCl3; ΔH298 = −9.5 kJ mol−1 and ΔS298 = 37 J mol−1 K−1 in DMSO-d6. Thus, the entropy gain contributes to the strong binding in DMSO-d6. The molecular origin of this entropy change is elusive, but the release of DMSO solvent molecules from amide moieties upon anion binding probably plays an important role.13

An X-ray crystallographic analysis of (n-Bu4N)[PhPO3H]·1b revealed the detailed recognition mode (Fig. 4). PhPO3H+ is tightly bound in the cavity of 1b by multiple hydrogen bonds with amides. Seven amide groups play distinct roles in the recognition. The four amide groups work as a hydrogen bond donor to the three oxygen atoms of PhPO3H+. Meanwhile, one amide group behaves as a hydrogen bond acceptor to the acidic proton of PhPO3H+. Thus, the unsymmetrical arrangement of both the hydrogen donor/acceptor sites in the binding pocket was confirmed in the recognition of hydrogen phosphonates (R-PO3H+). The other two amides do not interact with
PhPO$_3$H$^+$ but get involved in the structure formation by intramolecular hydrogen bonds with the adjacent amides. The pattern of the hydrogen bonds of 1b-5H$_2$O (Fig. 2c) and that of (PhPO$_3$H$^+$)·1b (Fig. 4d) share a common feature. The difference is the two p-tolylamide groups shown in orange and yellow in both figures; they work as one hydrogen bond acceptor to the H$_2$O inside the cavity, but as two hydrogen bond donors to the PhPO$_3$H$^+$. Thus, the intramolecular hydrogen bonds of the seven amide groups have a preferable pattern irrespective of the including guest to some extent, which can explain its unique recognition toward hydrogen phosphonates that possess both hydrogen donating and accepting moieties.

In conclusion, novel cyclodextrin derivatives with seven amide groups were synthesized. The p-tolylamide derivative 1b showed selective binding of hydrogen phosphonates, and the ambivalent use of the equivalent amide groups as a both hydrogen bond donor and acceptor is demonstrated from the single-crystal X-ray measurement. The reported amide cyclodextrin derivatives would be promising for applications, such as sensors and carriers of phosphorylated molecules. Furthermore, desymmetrization of an apparently symmetric structure would bring a fresh view to the design strategy of artificial functional molecules.

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Conflicts of interest

There are no conflicts to declare.

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