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ORIGINAL ARTICLE

Binding properties of heptakis-(2,6-di-*O*-methyl)-*β*-cyclodextrin and mono-(3,6-anhydro)-*β*-cyclodextrin: a polarimetric study

Paolo Lo Meo · Francesca D'Anna · Serena Riela · Michelangelo Gruttadauria · Renato Noto

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Abstract The binding constants for the inclusion complexes formed between heptakis-(2,6-di-*O*-methyl)-*β*-cyclodextrin (**M*β*CD**) and mono-(3,6-anhydro)-*β*-cyclodextrin (**A*β*CD**) with a set of suitably selected organic guests, were measured by means of polarimetry. Measurements were carried out at various pH values in order to ensure the correct protonation state for ionizable guests. Experimental data suggest that the binding properties of **M*β*CD** may be rationalized considering the less polar and more hydrophobic character of the cavity, although similar variations in conformational/dynamic behaviour occur as for native ***β*CD**. On the other hand, **A*β*CD** shows some similarities with **α**CD, due to the significant distortion in the shape and reduction in size of the macro cycle, as confirmed also by simple computational models.

Keywords Supramolecular chemistry · Modified cyclodextrins · Inclusion complexes · *p*-Nitroaniline derivatives

Introduction

Cyclodextrins (**CD**s) owe their widespread interest and popularity to their ability in forming host–guest inclusion complexes with a large variety of suitably sized and structured organic molecules [1–3]. This allows their application in various research and technological fields, as accounted for by an immense literature[1] [4–11]. Nevertheless, the features of the microscopic interactions occurring in systems where **CD**s are involved as hosts, appear elusive in some aspects, and consequently some old interpretative paradigms have been progressively abandoned during the last years. It is now generally agreed that the thermodynamics of the binding process (both in terms of enthalpic and entropic variations) is the outcome of a fine balance between various factors, including solvation phenomena [12–15] and the occurrence of both non-specific (van der Waals, electrostatic) [16–18] and specific (CH···π [19] hydrogen bond [20]) interactions. Moreover, **CD**s are not anymore considered as rigid buckets, but rather as fairly flexible objects [21–30] able to fit themselves upon the guest structure, in such a way to achieve an adaptation/optimization of the different possible host–guest interactions ("*induced fit*" effect) [31]. Finally, dynamic co-inclusion of solvent molecules into the host–guest complex has been recently recognized as a factor able to affect to a significant extent its stability [32].

Up to date, systematic studies on the topic have mainly dealt with the effects that can be led back to the features of the guest structure. As a matter of fact, molecular properties of the guest, such as shape and steric bulk, hydrophobicity, polarity, hydrogen bond donor/acceptor ability, can be easily varied on a large range, as well as the presence of charged groups or chiral centres. By contrast, despite the availability [33] and the enormous amount of analytical and technological applications involving chemically modified **CD**s [4–11], a possible approach exploiting the modification in the properties of the host has been explored much less frequently. Nevertheless, this could

P. L. Meo (✉) · F. D'Anna · S. Riela · M. Gruttadauria · R. Noto
University of Palermo, Palermo, Italy
e-mail: paolomeo@unipa.it

[1] Papers and reviews published on the topic are virtually countless, and appear at the rithm of thousands every year! For a few significant reviews see for instance ref. [4–11].

undoubtedly provide a very interesting piece of information.

We have recently carried out a polarimetric investigation on the binding properties of mono-(6-amino)-(6-deoxy)-β-**CD** towards *p*-nitroaniline derivatives, in order to study the effects due to the possible presence of a charged group on the host [34]. Proceeding on the line of host modification, we have now pointed our attention on two further **CD**s, namely the heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin [35] (**MβCD**) and the mono-(3,6-anhydro)-β-cyclodextrin [36] (**AβCD**, Fig. 1). The methylation of fourteen hydroxyl groups on **MβCD** enhances the hydrophobic character of the host cavity and decreases its polarity and ability to act as hydrogen bond donor, maintaining the formal axial symmetry (C_7) of the macro cycle and keeping almost constant the inner size with respect to native **βCD**. On the other hand, the modification in **AβCD** of a single glucose unit implies its irreversible inversion from a $^4C_1$ to a $^1C_4$-type chair conformation and overall symmetry loss, possibly with significant distortion of the macro cycle. At the best of our knowledge, the binding properties of **MβCD** have been investigated on a few occasions [37–41], whereas **AβCD** has been hardly studied.

We took in consideration a set of selected model guests molecules **1**–**10** (Fig. 2), chosen in such a way to test the response of the hosts towards particular molecular properties and features of the guest. In particular, guests **1**–**3** have different size and hydrophobic character, whereas guests **4** and **5** allow to evaluate the effect of a sharp change in guest polarity. The inclusion of the bulky adamantane derivative **2** has already been studied extensively from both a structural and a thermodynamic point of view [42–44], due to its almost perfect fit into the **βCD** cavity. On the other hand, guests **6**–**10** are *p*-nitroaniline derivatives, the behaviour of which has been object of extensive investigations [15, 20, 32, 34]. These molecules possess a polarized fixed aromatic moiety (which penetrates into the cavity of native **βCD** with the nitro group always directed towards the primary host rim [45–47]), and a varying

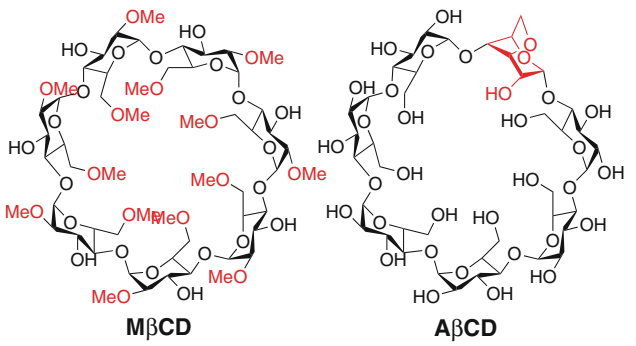

Fig. 1 Structures of the hosts

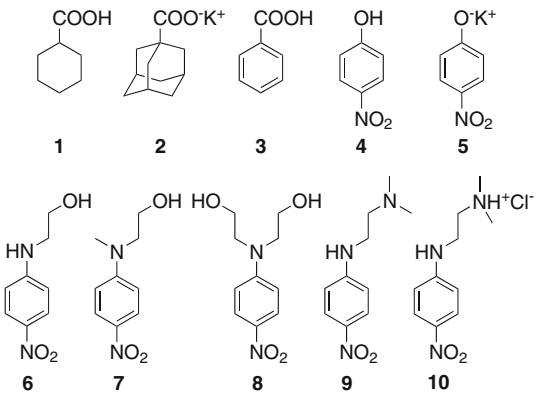

Fig. 2 Structures of the guests

ancillary chain of different hydrophobicity, hydrogen bond donor/acceptor ability and charge. The polarimetric technique has been proven to be a reliable and accurate investigation tool, able to provide with both thermodynamic and structural information [32, 34, 48, 49].

Results and discussion

Polarimetric behaviour of the free hosts

As a preliminary step, the molar optical rotations Θ_0 of the free (uncomplexed) **MβCD** and **AβCD** were measured in pure water. The two chemically modified hosts showed significantly different optical activities in comparison to native **βCD** (Table 1). It is well known that the optical properties of polysaccharides depend on the time-averaged dihedral angles assumed at the glycosidic linkages [50, 51]. As a consequence, differences between the native host and the modified ones have to arise from the combination of an *intrinsic* contribution due to the chemical modification *per se*, and a *conformational* contribution due to the differences induced by modifications on the overall conformational and dynamic behaviour of the macro cycle. The extent of these two contributions may be estimated on the grounds of the polarimetric behaviour of suitable model molecules. In particular, we considered the α-methyl glycosides of D-glucose **11** [52, 53], 2,6-di-*O*-methyl-D-glucose **12** [54] and 3,6-anhydro-D-glucose **13** [55] (Fig. 3). The specific optical activities of these compounds have been reported, thus the relevant molar optical rotations can be easily calculated.

On the assumption of effect additivity, one can reasonably expect that the difference in molar optical rotations between model molecules **12** and **11** (+6.5 deg dm^{-1} M^{-1}) accounts for the *intrinsic* contribution due to *O*-methylation at the positions 2 and 6 of a single glucose unit. Therefore, multiplying by seven this difference, we can get an estimation of the *intrinsic* contribution relevant

Table 1 Optical activities of model glycosides and free **CD**s

	11	12	13
Θ_0 (deg dm^{-1} M^{-1})	+30.6	+37.1	+3.7
Estim. *intrinsic* contrib.[a]	–	+6.5	−26.9
	*β*CD	M*β*CD	A*β*CD
Θ_0 (deg dm^{-1} M^{-1})	+184 ± 2[b]	+218 ± 3	+133 ± 2
Estim. *intrinsic* contrib.[a]	–	+45	−27
Estim. *conformational* contrib.[a]	–	−11	−24

[a] Same units as Θ_0, [b]from ref. [48, 49]

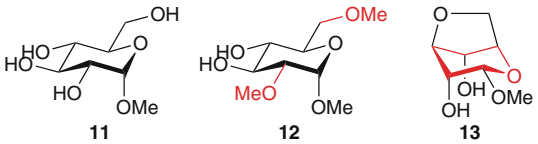

Fig. 3 Structures of glycosides **11–13**

to M*β*CD (ca. +45 deg dm^{-1} M^{-1}). On the other hand, this estimation is significantly larger than the actual difference in molar optical rotations between **M*β*CD** and native ***β*CD** (34 deg dm^{-1} M^{-1}). Thus, we can deduce the occurrence of a further contribution of −11 deg dm^{-1} M^{-1} due to changes in conformational dynamism. The same procedure applied to **A*β*CD** and model **13** leads us to calculate *intrinsic* and *conformational* contributions as large as −27 and −24 deg dm^{-1} M^{-1} respectively (the modification of one glucose unit only must be kept into account).

Polarimetric data pertaining complexation

The complete polarimetric results pertaining complexation equilibria, namely the values of the binding constants *K* and the differential molar optical rotations ΔΘ (*i.e.* the differences between the molar optical rotations of the inclusion complex and the free host), are summarized in Table 2, together with data relevant to native ***β*CD** for useful comparison.

Measurements were performed in aqueous buffers at various pH values, in order to ensure the correct protonation state for the ionizable guests (pH 6.0 was the reference value for non ionizable ones). On the grounds of our previous experience [17, 18] we could expect the occurrence of a small decrease in the host binding properties at the highest pH values, at least for neutral guests, due to incipient deprotonation of the hydroxyl groups of the glucose units. Of course, we had to keep into account this effect in an overall evaluation of experimental data. Nevertheless, it is worth stressing here that, for the aims of the present work, different pH values were needed in order to have different guests in solution. Everything considered, indeed, we reasoned that, at a first approximation level of analysis, the possible outcome of pH variations on the intrinsic binding properties of the hosts could be neglected with respect to the effect of changing the actual host!

It has been previously found that negative ΔΘ values occur [48, 49], in general, for the inclusion of aliphatic guests in native ***β*CD**, with absolute values increasing on increasing guest bulk. This behaviour, of course, is the combined outcome of the reduced conformational freedom and the micro-environmental effect consequent to the substitution of the inner solvent molecules by the guest. Aliphatic guests **1** and **2** qualitatively behave towards both **M*β*CD** and **A*β*CD** according to the previous statement. It is interesting to notice that the difference in ΔΘ values between guests **1** and **2** is nearly the same for native ***β*CD** and **M*β*CD**. This suggests that similar variations in guest bulk induce similar conformational/dynamic variations for

Table 2 Polarimetric data for complex formation

Guest	pH	*β*CD[a]		M*β*CD		A*β*CD	
		K (M^{-1})	ΔΘ (deg dm^{-1} M^{-1})	*K* (M^{-1})	ΔΘ (deg dm^{-1} M^{-1})	*K* (M^{-1})	ΔΘ (deg dm^{-1} M^{-1})
1	2.5	5200 ± 800	−8.2 ± 0.2	4200 ± 700	−19.0 ± 0.3	380 ± 100	−8.4 ± 1.5
2	9.2	12300 ± 2000	−21.9 ± 0.3	1700 ± 350	−34.2 ± 1.6	33 ± 2	−38.2 ± 1.3
3	2.5	950 ± 130	+9.8 ± 0.3	n.d.	0.0 ± 0.5	n.d.	+4.6 ± 0.5
4	2.5	740 ± 70	+13.5 ± 0.2	15 ± 3	−28 ± 3	240 ± 40	+9.9 ± 0.4
5	11.0	810 ± 20	+81.7 ± 0.2	630 ± 70	+58.0 ± 1.5	270 ± 20	+43.7 ± 1.1
6	6.0	600 ± 15	+74.6 ± 0.8	1560 ± 100	+47.8 ± 0.6	430 ± 30	+35.6 ± 0.9
7	6.0	1060 ± 60	+79.6 ± 0.9	6300 ± 600	+55.4 ± 0.5	1080 ± 150	+36.2 ± 1.0
8	6.0	500 ± 30	+88.9 ± 0.6	2900 ± 200	+59.7 ± 0.7	560 ± 40	+34.7 ± 0.7
9	11.0	1120 ± 60	+82.1 ± 0.7	3400 ± 200	+59.4 ± 0.5	650 ± 120	+37.3 ± 1.9
10	6.0	640 ± 60	+67.5 ± 0.7	1890 ± 140	+46.5 ± 0.5	143 ± 16	+41.9 ± 1.2

[a] From references [32, 34] and [48, 49]

the two symmetrical hosts, although larger absolute $\Delta\Theta$ values are indeed found with the second one. On the other hand, the observation of an abnormally large $\Delta\Theta$ value with **A*β*CD** for guest **2**, in comparison with **1,** easily suggests the occurrence of particularly severe conformational restrainments upon interaction of the bulky guest with the unsymmetrical host. It is noteworthy that the relevant K value is very low, resembling the one (53 M^{-1}) previously found for the inclusion of the same guest in native **α**CD [48, 49], which has a narrower cavity than ***β*CD**. Interestingly, both **1** and **2** shows lower binding constants with the modified hosts than with native ***β*CD**. This behaviour seems particularly surprising for **M*β*CD**, considering that the inclusion of aliphatic guests should be favoured on increasing the extent of hydrophobic interactions. In particular, the rather low K value for guest **2** suggests that the possible occurrence of hydrogen bond interactions between the anionic carboxylate group and the primary host rim, is an important factor in stabilizing the inclusion complex.

Unfortunately, we were not able to get any reliable estimation of the binding constant values for benzoic acid **3**, due to the occurrence of too small $\Delta\Theta$ absolute values. Nevertheless, this apparent failure is not devoid of information. In native ***β*CD**, indeed, **3** is characterized by a lower K value and an inversion in the sign of $\Delta\Theta$ as compared to its saturated analogue **1** [48, 49]. Now, it is noteworthy that the difference in $\Delta\Theta$ values between **1** and **3** is nearly the same for both ***β*CD** and **M*β*CD**. This finding provides further confirmation to the aforementioned idea that the two hosts experience similar modifications upon guest inclusion. Clearly, the same cannot be strictly true for **A*β*CD**, which lacks formal C_7 molecular symmetry. Therefore, a little smaller difference in $\Delta\Theta$ values is observed with this host.

As we mentioned above, comparison between *p*-nitrophenol **4** and its more polarized anion **5** (as potassium salt) provides with information regarding the dipolar character of the host cavity. As a matter of fact, K values for native ***β*CD** undergo only a very little increase on passing from **4** to **5** ($K_{\beta CD,5}/K_{\beta CD,4} \approx 1.1$, but the effect is almost unsignificant within the limits of experimental indeterminations), because of the simultaneous occurrence of contrasting factors. In comparison to **4**, indeed, the inclusion of **5** is disfavoured by (de)solvation effects, but also positively favoured by its stronger polar character and the consequent interaction between the dipole momenta of the cavity and the guest. At the same time, $\Delta\Theta$ values show a sharp increase (ca. 68 deg dm^{-1} M^{-1}), because of the increased dipolar interactions [48, 49]. Observed K values for these two guests in **A*β*CD** are lower than in ***β*CD**, but show a similar trend. At the same time, a smaller increase in $\Delta\Theta$ values (34 deg dm^{-1} M^{-1}) is observed. Both these results suggest that the **A*β*CD** cavity possesses a weaker dipolar character than ***β*CD**. On the other hand, the behaviour of **M*β*CD** appears anomalous, because guest **4** shows a strikingly low K value[2] and a negative $\Delta\Theta$ value. The latter finding suggests the possibility of an inversion in the sense of penetration of the guest into the cavity, i.e. with the nitro group directed towards the secondary rim. Such an inversion has been actually shown to occur, for instance, in **α**CD [56]. This possibility is clearly related to both the intrinsically weaker polar character of the cavity, and the lack of stabilizing hydrogen bond interactions between the nitro group and the primary rim (whereas hydrogen bonding may still occur at the secondary rim with the –OH(3) groups). As a consequence, this particular system cannot be properly compared with the other ones. However, once assumed (on the grounds of the previous discussion) that similar contributions for modifications in host dynamism should occur, the less polar character of the **M*β*CD** cavity compared to ***β*CD** is unambiguously accounted for by the lower $\Delta\Theta$ value observed for guest **5**. Accordingly, a lower K value is observed too.

Interaction of *p*-nitroaniline derivatives **6–10** with native ***β*CD** has been shown to be affected both by the dipolar interaction between the host cavity and the aromatic moiety, and by the occurrence of effective van der Waals and hydrogen bond interactions with the ancillary chain[3] [15, 20]. Furthermore, it has been shown that $\Delta\Theta$ values for this class of guests depend on the time-averaged dot product between the dipole momenta of the host cavity and the guest chromophore [32, 34, 48, 49]. Consequently, $\Delta\Theta$ can be correlated with the time-averaged tilt angle of the guest aromatic moiety with respect to the ideal cavity axis. Significantly larger K values are observed with **M*β*CD** than with ***β*CD**. Considered the previous findings, we may conclude that the occurrence of weaker dipolar interactions between the **M*β*CD** cavity and the polarized aromatic moiety of these guests, is largely compensated by very effective interactions with the guest ancillary chain. As a matter of fact, the largest increases in K values can be observed for the two bis-*N*-substituted guests **7** and **8** ($K_{M\beta CD}/K_{\beta CD} \approx 6$) having the most lipophilic ancillary chains. On the other hand, we observed that $\Delta\Theta$ values with **M*β*CD** are lower than with native ***β*CD**, but show

[2] The K value for **4** found by us is much lower than the one previously measured calorimetrically by Bertrand (380 M^{-1}, see ref. 16), but at a different pH value.

[3] Noticeably, guests **4–10** constitute on the whole a representative set of nitrobenzene derivatives. One would expect data could be subjected to some sort of LFER (such as Hammett or Taft) correlation analysis. However, these systems are so strictly affected by the occurrence of specific (hydrogen bond, for instance) interactions that this approach is matter-of-factly unsuitable. In particular, on considering *p*-nitroanilines **6–10**, we have to assume that possible variations of electronic effects for the aromatic moiety are almost negligible.

similar qualitative trends. With both hosts, indeed, $\Delta\Theta$ values regularly increase along the series **6** < **7** < **8**; moreover, **9** shows a larger $\Delta\Theta$ value than its conjugated acid form **10**. The latter finding, in particular, was explained in a previous work [34] considering that the protonation of the guest tail amino group forces it out of the host cavity, resulting in an almost mechanical tilt effect for the included aromatic moiety. Indeed, it is worth stressing that, despite the aforementioned effect of pH on the intrinsic binding properties of the host, both ***β*CD** and **M*β*CD** include the neutral guest **9** at pH 11.0 much more efficiently than its cationic conjugate acid **10** at pH 6.0.

On passing to **A*β*CD**, we may easily notice that the bis-*N*-substituted guests **7** and **8** show similar binding constant values as in native ***β*CD**. However, significantly lower *K* values are found for the more hydrophilic guests **6** and **9** and, in particular, for the cationic guest **10**. Even more interestingly, the four neutral derivatives **6–9** show nearly the same $\Delta\Theta$ value, whereas cationic **10** shows just a little larger $\Delta\Theta$ value than **9**. The latter findings indicate that the inclusion in the narrower and less symmetric **A*β*CD** cavity involves similar conformational restrainments for all the guests considered. Therefore, such results suggest that any possible interaction between the guest ancillary chain and the host cavity occurs only to a very limited extent. Clearly, this behaviour is different from the one shown by both ***β*CD** and **M*β*CD**, resembling once again the behaviour shown by **α**CD** [20, 48, 49]. It is important to point out that the solvation requirements of the ancillary chain clearly play an unfavourable role on the binding equilibrium. By analogy with the behaviour of **α**CD** [20], the latter observation might be rationalized assuming that the peculiar distorted shape of the **A*β*CD** secondary rim is able to exert some unexpected structuring effect on the solvation shell of the host, in such a way to constitute an "expanded hydrophobic sphere" upon the **CD** cavity. As a matter of fact, the interaction of the ancillary chain of *p*-nitroaniline derivatives with the "expanded hydrophobic sphere" has been recognized as a factor able to positively affect the stability of the host–guest complex with **α**CD** [3, 15, 20].

Finally, we decided to elaborate also some simple home-made computational model of **A*β*CD** (in the gas phase), in order to better rationalize its peculiar behaviour. A full-geometry optimized structure is shown in Fig. 4. Calculation predictions confirm the occurrence of a distorted, roughly elliptical shape, with inner diameters measuring *ca.* 3.6 and 7.6 Å respectively. It is worth noting that the modified glucose unit lies along the major diameter, with its axial –OH(2) group pointing towards the inner cavity. Consideration of this model clearly supports the idea that only the aromatic moiety of guests **6–10** actually penetrates into the host cavity in a tight, quite rigid way; consequently, this results in the occurrence of only minor variations in $\Delta\Theta$ values for these guests.

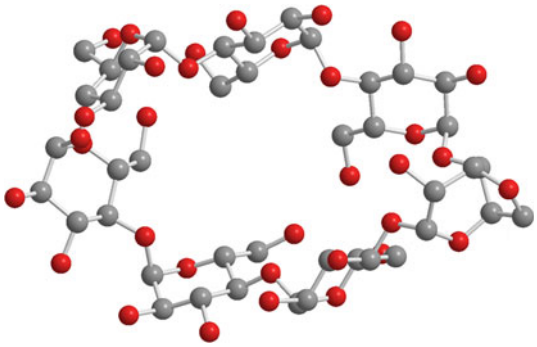

Fig. 4 Gas phase full-geometry optimized model of **A*β*CD** (H atoms are not shown for clarity)

Experimental

Materials

All reagents, solvents (HPLC grade) and materials needed were used as purchased, without further purification. **A*β*CD** [36] and guests **6–10** [15, 21–30, 45–47] were prepared, purified and characterized according to literature reports. **CD**s were dried before use *in vacuo* over P_2O_5 at 60 °C for at least 48 h, and stored in the same apparatus at 40 °C. Stock phosphate buffer solutions (at the suitable pH values) were prepared and used (as solvents for sample preparation) within a few days, after checking their actual pH value. Freshly double-distilled water was used for the preparation of the buffers, which were in turn used as solvents for the preparation of the measurement solutions.

Polarimetry

A general protocol for performing the polarimetric determination of binding constants has been described in our previous papers [48, 49]. The standard procedure provides the preparation of a set of sample solutions, by adding variable micro-amounts (up to 150 μL) of a concentrated guest solution (usually *ca.* 0.3 M) to fixed volumes (5 mL) of a standard solution (usually 2.0 mM) of the **CD** in the proper aqueous buffer. Alternatively, in order to get a more reliable estimate of low ($\leq$200 M^{-1}) *K* values, we modified the procedure by directly dissolving weighed amounts of the proper guest into the **CD** solution. Whatever the procedure chosen, polarimetric data were subjected to suitable fitting analysis as described elsewhere[4] [48, 49], by means of the proper equation derived analytically:

[4] A pictorial representation of a typical trend for experimental data can be found in ref. [48].

$$\vartheta_i = \frac{\vartheta_0 + \frac{\Delta\Theta}{2}\left(\mathrm{CD}_0 + G_0\frac{v_i}{V_0} + \frac{1+fv_i/V_0}{K} - \sqrt{\left(\mathrm{CD}_0 + G_0\frac{v_i}{V_0} + \frac{1+fv_i/V_0}{K}\right)^2 - 4\mathrm{CD}_0 G_0\frac{v_i}{V_0}}\right)}{1+fv_i/V_0}$$

The values of the differential molar optical rotations $\Delta\Theta$ for the inclusion of benzoic acid **3** in both **M*β*CD** and **A*β*CD** were directly estimated from the optical rotation of samples obtained by dissolving 20 mg of **3** in 5 mL of a 2 mM solution of the host.

Computational

Computational models (MM2) for **A*β*CD** were elaborated using a simulated annealing technique, by means of the CS Chem 3D^{TM} software package from CambridgeSoft Corporation. A "simulation pool" was first obtained, carrying out a molecular dynamics simulation run for 1000 ps at 300 K, in order to sample the conformational space of the system. A step interval of 1 fs was used, with a heating/cooling rate of 1 kcal ps^{-1} atom^{-1}. Frames were collected every 200 steps. Then, several frames were randomly sampled from the simulation runs, and allowed to "cool" slowly down to 0 K in a further dynamic run (a cooling rate of 0.025 kcal ps^{-1} atom^{-1} was used). In this way, a limited amount of true minima were obtained (Fig. 4 refers to the absolute minimum found).

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