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Binding properties of mono-(6-deoxy-6-amino)-β-cyclodextrin towards *p*-nitroaniline derivatives: a polarimetric study

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

Dipartimento di Chimica Organica 'E. Paternò', Università degli Studi di Palermo, V.le delle Scienze, Parco d'Orleans II, pad. 17, 90128 Palermo, Italy

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ABSTRACT

Polarimetry was used in order to investigate the formation of supramolecular complexes between mono-6-amino-β-cyclodextrin and various *p*-nitroaniline derivatives at two different pH values. Comparison with the behaviour of native β-cyclodextrin gave us the opportunity to consider the effect exerted by the presence of charged groups, having different solvation requirements, on the binding equilibrium. Data offer some support to the hypothesis of 'dynamic co-inclusion' of solvent molecules within the host–guest complex.

1. Introduction

Among the different factors, which affect the energetics of supramolecular binding equilibria involving cyclodextrins (**CD**s) as hosts,[1–6] the most important ones have been traditionally identified with solvation effects. According to the classical Tabushi's scheme,[2] the role of 'driving force' for the inclusion process has been usually attributed to the transfer of the guest from the aqueous pool into the more 'friendly' (hydrophobic) environment provided by the **CD**, together with the concomitant release of 'high energy' water molecules from the host cavity into the solvent pool.[2,5,7] These processes overall constitute the so-called 'environmental' (***e***) counterpart of the binding equilibrium, whereas the 'net' host–guest interaction constitutes the 'nominal' (***n***) counterpart (Scheme 1, where *h*, *g* and *i* are the mean number of solvation water molecules for the host, the guest and the complex, respectively).[5]

Smidtchen recently showed,[8] for the complexation of camphor with native **CD**s, that a large amount of the inclusion enthalpies and entropies (up to 80%) can actually be ascribed to the 'environmental' process (this is likely to be true anytime the inclusion of highly hydrophobic guests is concerned). Solvation effects have also been claimed to play a major role in determining ΔC_p trends.[9,10]

$$\mathbf{CD}_{aq} + \mathbf{G}_{aq} \rightleftharpoons [\mathbf{CD}\cdot\mathbf{G}]_{aq} \quad (\boldsymbol{n})$$
$$h\ H_2O_{\mathbf{CD}} + g\ H_2O_{\mathbf{G}} \rightleftharpoons i\ H_2O_{[\mathbf{CD}\cdot\mathbf{G}]} + (h+g-i)H_2O_{aq} \quad (\boldsymbol{e})$$
$$[\mathbf{CD}\cdot h H_2O] + [\mathbf{G}\cdot g H_2O] \rightleftharpoons [\mathbf{CD}\cdot\mathbf{G}\cdot i H_2O] + (h+g-i)H_2O$$

Scheme 1.

Attempts have even been made in order to rigorously lead back the well-known enthalpy–entropy isoequilibrium compensation effect[4,11] uniquely to the 'environmental' process.[5,12,13] However, it has been unquestionably shown that 'nominal' host–guest interactions also play a key role. Indeed, the occurrence of significant interactions, both aspecific (van der Waals, dipolar/electrostatic) and specific (hydrogen bond, CH···π[14]) largely affect the thermodynamics of the binding process (and the possible enthalpy–entropy compensation[4]) and the conformational behaviour of the host ('induced fit' effect[15]). In fact, no obvious hierarchy among all the different factors can be predicted a priori.

We recently carried out[16] a polarimetric study on the interaction between some suitably selected *p*-nitroaniline derivatives **1–8** (Fig. 1) and native **βCD** in mixed water–methanol solvent systems. We found that increasing amounts of methanol, in general, decrease both the binding constants *K* and the differential molar optical rotations $\Delta\Theta$. Thus, the organic co-solvent affects not only the thermodynamics of binding, but also the conformational dynamics of the complex and the time-averaged tilt of the guest inside the host cavity (as specifically accounted for by $\Delta\Theta$ values and relevant variations). Such effects were correlated with the thermochemical parameters previously determined for the same processes in aqueous buffers.[4] A thorough analysis of these correlations suggested to us that the role played by the solvent system is not restricted to the mere 'net' solvation of the species involved. Data trends, indeed, can be suitably explained, by accepting that the inclusion complex has enough room to host some solvent molecules, which can be in turn rapidly exchanged with the bulk in a 'dynamic co-inclusion' process. With this perspective, it is clear that a strict distinction between a 'nominal' and an 'environmental' counterpart of the process becomes somehow artificial, and probably constitutes a conceptual paradigm, which should undergo a deep critical revision in the future.

* Corresponding authors. Tel.: +39 091 596919; fax: +39 091 596825 (P.L.M. and R.N.).
E-mail addresses: paolomeo@unipa.it (P. Lo Meo), rnoto@unipa.it (R. Noto).

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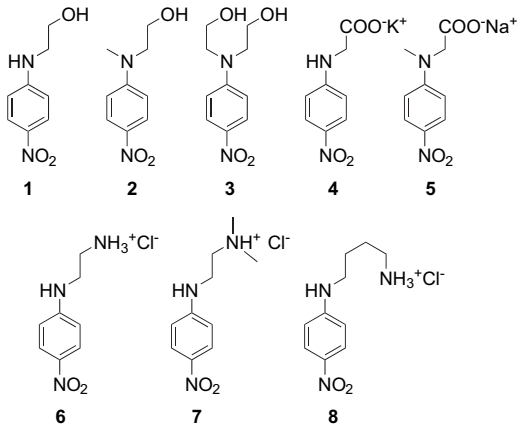

Figure 1. *p*-Nitroaniline derivatives **1**–**8**.

The occurrence of particularly unfavourable desolvation for the host cavity has been claimed in order to explain the worse binding properties of charged **CD** derivatives with respect to the corresponding neutral ones.[17] For instance, native **βCD** itself shows lower binding affinities in basic than in neutral or slightly acidic media,[3] owing to the partial deprotonation of the secondary hydroxyl groups on the largest **CD** rim occurring at high (>11) pH values.[7] Mono- and poly-amino derivatives of **CD**s have been also investigated in various occasions.[3,10,17–21] These hosts undergo a decrease of binding affinities towards hydrophobic guests in acidic media, i.e., when they are found in their protonated cationic forms (by the way, amino-**CD**s as free bases at high pH are usually worse ligands than the corresponding native **CD** in neutral media,[3,18] for the same reason mentioned above). Nevertheless, the same hosts show better binding properties towards anionic guests in their cationic forms.[21] As a matter of fact, in the latter case effective coulomb interactions occur between the oppositely charged groups of the host and the guest, respectively, affecting the direction of penetration of the guest into the cavity (as accounted for by NMR evidence).

On the grounds of these considerations, we decided to investigate by means of polarimetry the behaviour of mono-(6-deoxy-6-amino)-β-cyclodextrin (**AmβCD**, Fig. 2) towards *p*-nitroaniline derivatives **1**–**8** at two different pH values, namely 6.0 and 11.0, in order to get further information about the role played by solvation effects on binding equilibria.

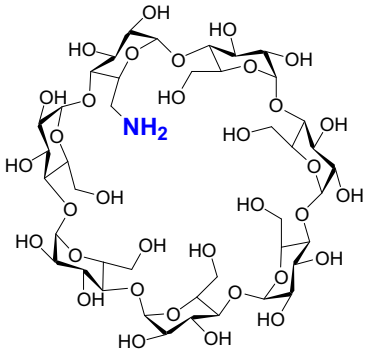

Figure 2. Structure of **AmβCD**.

2. Results and discussion

According to its pK_{BH+} value[17] (Table 1), the amino group of **AmβCD** is fully protonated at pH 6.0, whereas it is present in its free base form at pH 11.0. Therefore, this guest is cationic at the former pH value, but partly anionic (due to possible partial ionization of the secondary –OH groups) at the latter one. Guests **1**–**3** possess non-ionizable ancillary chains. On the other hand, according to the relevant pK_a values,[4] the amino acid derivatives **4** and **5** are completely ionized at both pH 6.0 and 11.0. The diamine derivatives **6**–**8** are found at pH 6.0 in their cationic (protonated) form. At pH 11.0 derivatives **6** and **7** are present almost completely as free bases, whereas **8** is still in its cationic form in significant amount (ca. 13%). However, on the grounds of the results found in our previous work,[4] at a first approximation level we may assume that the occurrence of partial protonation has a reasonably negligible importance. Data collected in this work are suitably compared with the corresponding data already available for **βCD**.[16] So, it is worth stressing that in the present investigation we had the opportunity to compare the behaviour of differently charged (cationic, neutral, partly anionic) hosts with differently charged guests.

Table 1
Summary of $pK_{a/BH+}$ values

	$pK_{a/BH+}$		$pK_{a/BH+}$
AmβCD	8.42[a]	**6**	9.02[b]
4	3.52[b]	**7**	8.43[b]
5	3.54[b]	**8**	10.19[b]

[a] From Ref. 22.
[b] From Ref. 4.

The complete polarimetric data are collected in Table 2. It is worth mentioning that in a previous work[16] the interaction of native **βCD** with the diamine derivatives **6**–**8** had been investigated by polarimetry only at pH 6.0 (i.e., with the guests in their cationic form), whereas spectrophotometric investigations[4] had been carried out at both pH values. Thus, for the aims of this work, we had first to investigate by polarimetry also the inclusion of these guests in native **βCD** at pH 11.0. Unfortunately, however, guest **6** at pH 11.0 was not soluble enough to allow a reliable polarimetric determination of its inclusion constant.

Table 2
Polarimetric data

Host	pH	Guest	K (M^{-1})	$\Delta\Theta$ (deg dm^{-1} M^{-1})	R^{∞}_{Θ}
βCD	6.0	**1**[a]	603±14	74.6±0.8	40.5±0.6
		2[a]	1065±60	79.6±0.9	43.3±0.7
		3[a]	500±30	88.9±0.6	48.3±0.6
		4[a]	324±22	59.8±1.3	32.5±0.8
		5[a]	371±27	87.7±1.5	47.7±1.0
		6[a]	301±30	55.9±1.2	30.4±0.7
		7[a]	638±56	67.5±0.7	36.7±0.6
		8[a]	1040±40	80.0±1.0	43.5±0.7
	11.0	**7**[b]	1120±60	82.1±0.7	44.6±0.6
		8[b]	1270±90	85.3±1.1	46.4±0.8
AmβCD	6.0	**1**[b]	415±20	64.1±1.6	39.3±1.1
		2[b]	585±60	66.3±1.8	40.7±1.2
		3[b]	540±30	63.1±1.5	38.7±1.0
		4[b]	465±30	61.4±0.8	37.7±0.7
		5[b]	755±40	62.0±0.6	38.0±0.6
		6[b]	167±13	55.2±1.4	33.9±1.0
		7[b]	480±30	51.2±0.7	31.4±0.6
		8[b]	645±35	64.5±0.7	39.6±0.6
	11.0	**1**[b]	620±40	59.9±1.8	37.0±1.2
		2[b]	1020±60	71.1±1.5	43.9±1.1
		3[b]	1190±80	74.1±1.0	45.7±0.8
		4[b]	350±20	64.9±1.0	40.1±0.8
		5[b]	475±30	63.3±0.9	39.1±0.7
		7[b]	1240±70	67.3±0.7	40.7±0.7
		8[b]	1350±80	68.3±0.8	44.1±0.7

[a] From Ref. 16.
[b] This work.

It must be first noticed that the molar optical rotation (Θ_0) of free **AmβCD** at both pH values (164±2 deg dm^{-1} M^{-1} at pH 6.0; 163±2 deg dm^{-1} M^{-1} at pH 11.0) is significantly different than the one of native **βCD**[16,22] (184±2 deg dm^{-1} M^{-1}). This is clearly a consequence of the chemical modification of a glucose unit, which could affect Θ_0 because of both the different optical activity of the modified glucose and the possible effect of such a modification on the overall conformational dynamics of the host. These contributions might be approximately evaluated comparing the optical activity of suitable model molecules. In particular, specific optical rotation of methyl-α-glucoside **9** and of its 6-amino hydrochloride derivative **10** (Fig. 3) is available in literature.[23] Thus, on the grounds of data reported, we may estimate that the first contribution is almost negligible (ca. 2.1 deg dm^{-1} M^{-1}), at least for the protonated form of **AmβCD**.[24] Anyway, in order to carry out more correct comparisons among the different hosts, we calculated and reported in Table 1 also the values ($R^{\%}_{\Theta}$) of the ratios, normalized to 100, between the different $\Delta\Theta$ values and the molar optical rotation for the relevant hosts.

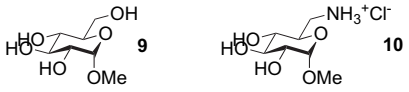

Figure 3. Model methyl-α-glucosides **9** and **10**.

A preliminary comparison of the binding constant (K) values for **AmβCD** and **βCD**, respectively, is illustrated in Figure 4. As we mentioned previously, **AmβCD** at pH 11.0 could have been expected a slightly worse ligand as compared to native **βCD**. Interestingly, our data disappoint this prediction; as a matter of fact, K values found in the former case are comparable or even larger than in the latter one. With the exclusion of guest **3**, showing a much higher affinity for **AmβCD** than for **βCD**, data define a fair linear correlation ($K_{\mathbf{AmβCD},11}$=(44±66)+(1.01±0.08)$K_{\mathbf{βCD}}$; n=6, r=0.989). This result can be explained assuming that a possible hydrophilic ancillary chain on the guest structure is able to interact effectively with the secondary **CD** rim, even on the occurrence of a large solvation request due to partial deprotonation. On the other hand, in agreement with literature reports,[3,4,18] binding properties of **AmβCD** towards neutral (**1**–**3**) and cationic (**6**–**8**) guests decrease significantly on passing to pH 6.0. As a matter of fact, $K_{\mathbf{AmβCD},11}/K_{\mathbf{AmβCD},6}$ ratios ranging from 1.5 (for **1**) up to 2.6 (for **7**) can be found. At the same time, anionic guests **4** and **5** are better included at pH 6.0. Similar considerations can be drawn on comparing the behaviour of **AmβCD** with **βCD** at pH 6.0. Also in this case, guest **3** behaves in an anomalous way, showing comparable K values with the two hosts, and therefore a K value in **AmβCD** higher than reasonably expected.[25]

Analysis of $\Delta\Theta$ (Fig. 5) and $R^{\%}_{\Theta}$ values is quite intriguing. In general, data for **AmβCD** at each pH value span over a narrower range than for native **βCD**. Considering in particular data at pH 6.0, if we restrict our attention to neutral and anionic guests **1**–**5** only, $\Delta\Theta$ varies just within 5 units (61.4∼66.3 deg dm^{-1} M^{-1}). On going to cationic guests, we found that **8** falls in the same range too, whereas lower values are shown by **6** and **7**. Noticeably, the somehow distinct behaviour of cationic guests parallels the occurrence[16] of distinct $\partial\Delta\Theta/\partial\chi_{MeOH}$ trends observed for the inclusion into **βCD** in mixed water–methanol solvent systems. The occurrence of such a narrow range for $\Delta\Theta$ seems to indicate that the presence of a cationic group on the primary host rim exerts a sort of levelling effect on the conformational dynamics of the complex. This may be attributed to the occurrence of a quite strong electrostatic interaction between the host ammonium group and the negatively polarized nitro group of the guest. It is worth remembering, indeed, that *p*-nitroaniline derivatives are normally

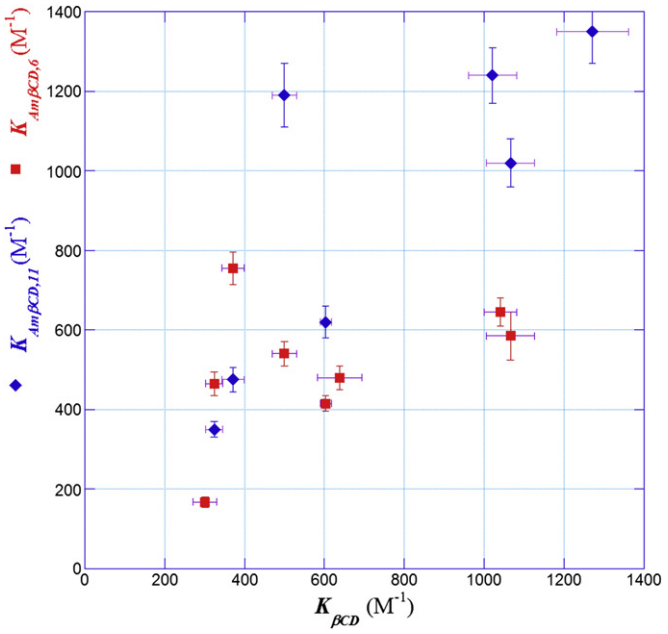

Figure 4.

included into the **βCD** cavity with the nitro group directed towards the primary host rim.[26] This, in turn, suggests that specific effects on entropy variations could be particularly involved. Some preliminary data actually indicate that, at least for guests **1** and **2**, protonation of the host **AmβCD** causes inclusion entropies to become significantly more negative.[27]

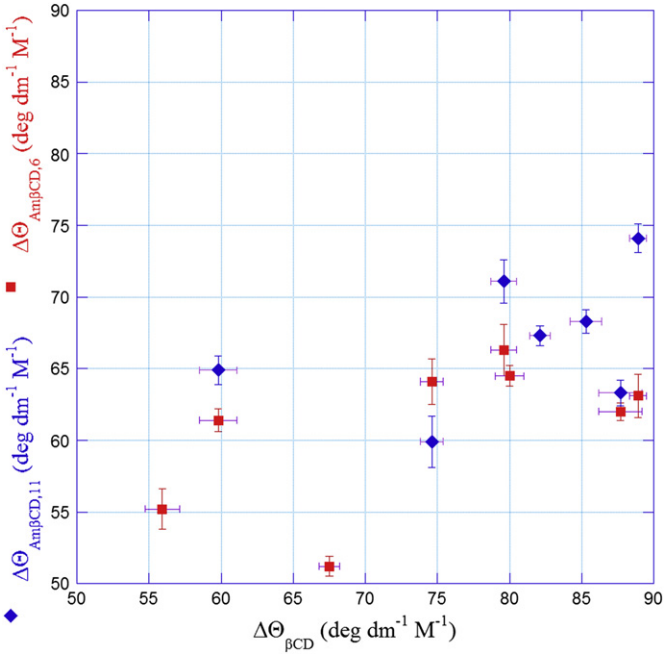

Figure 5.

The behaviour of guests **7** and **8** deserves further discussion. In agreement with previous UV–vis results,[4] **7** and **8** showed larger inclusion constants in native **βCD** at pH 11.0 than at pH 6.0 (of course, the same is observed with **AmβCD** too). Such a behaviour can be easily explained considering that the guest ancillary chain in its cationic form experiences a more difficult desolvation and a less effective interaction with the hydrophobic host cavity than its free

base neutral form. At the same time also $\Delta\Theta$ values decrease on passing from pH 11.0 to pH 6.0. It is important to notice that larger variations in both K and $\Delta\Theta$ values are recorded for the shortest chain guest **7** than for the longest one **8**. Keeping in mind that $\Delta\Theta$ accounts for the average tilt angle of the chromophore axis within the ideal host cavity,[16,22] data may be easily rationalized assuming that protonation of the ancillary chain induces it to protrude out of the cavity rim; this, in turn, forces almost mechanically the guest to assume a more tilted position (Fig. 6).

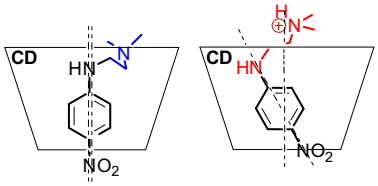

Figure 6.

The behaviour of the amino acid derivatives **4** and **5** is even more interesting. We already mentioned that these guests show larger affinities for a cationic host (**AmβCD** at pH 6.0) than for both a neutral or partly anionic one (**βCD** at pH 6.0 and **AmβCD** at pH 11.0, respectively). However, $\Delta\Theta$ values suggest that this behaviour cannot be attributed to the occurrence of a proximal coulomb interaction between the oppositely charged 'head' groups of the host–guest couple. As a matter of fact, such an interaction would compel the guest to revert its direction of penetration within the cavity. Thus, due to the consequent dipole interaction between the guest chromophore and the host cavity (which should now become energetically unfavourable), negative $\Delta\Theta$ values would have been expected, in striking contrast with the experimental results. In other words, the occurrence of positive $\Delta\Theta$ values in these cases too clearly indicates that inclusion of **4** and **5** still implies the penetration of the chromophore with the *p*-nitro group directed towards the primary **CD** rim, ruling out any near coulomb interaction between the oppositely charged groups.

In more detail, we can also notice that $R^{\%}_{\Theta}$ for the glycine derivative **4** significantly increases on passing from **βCD** to **AmβCD** (both at pH 6.0). Therefore, the introduction of a cationic group on the host forces **4** into an averagely less tilted position within the cavity. By contrast, the *N*-methyl-glycine derivative **5** shows an opposite behaviour. On the grounds of our previous studies on the enthalpy–entropy compensation[4] for the inclusion of *p*-nitroaniline derivatives, we already knew that the possible occurrence of multiple hydrogen bonding with the host is an overall unfavourable feature, because of the rigidity of the inclusion complex and the consequent large negative entropy variations involved. Therefore, the increase of K value for guest **4** on changing the host suggests the overall occurrence of less effective hydrogen bonding and diminished complex rigidity. The hypothesis of dynamic co-inclusion of water molecules within the complex might provide a suitable rationale. As a matter of fact, the presence of a positively charged group on the host may attract some solvent molecules, which, in turn, may compete with the host cavity and rims for interaction with the negatively charged ancillary chain. In other words, we may hypothesize that the electrostatic interaction between the oppositely charged groups is somehow mediated by co-included water molecules. On the other hand, the inclusion of guest **5**, which can form at the most only one hydrogen bond, has been shown to be mainly controlled by non-specific interactions, so that enthalpy effects prevail. Therefore, we may assume that the same mechanism of interaction with co-included water, as hypothesized above, might strengthen cavity-chain hydrophobic interaction. This, in turn, both makes the complex more rigid (as accounted for by the lower $R^{\%}_{\Theta}$ value) and overall enhances the inclusion constant K value.

3. Conclusions

A comparative examination of the behaviour of cationic (**AmβCD** at pH 6.0), neutral (**βCD**, at pH 6.0) or partly anionic (**βCD** or **AmβCD** at pH 11.0) hosts towards differently charged *p*-nitroaniline derivatives **1**–**8** offered us the opportunity to reconsider some aspects of solvation effects involved in the binding process. In particular, our results indicate that possible occurrence of high solvation requirements for the host cavity (consequent to the presence of charged groups) is not necessarily an unfavourable factor in determining the energetics of the process. As a matter of fact, guests with a sufficiently hydrophilic ancillary chain are found to be quite effectively included at high pH values. Moreover, our results seem to provide interesting support to the idea of 'dynamic co-inclusion' of water molecules into the complex, which has recently been put forward.[16] This particular mechanism, indeed, is able to rationalize the features of the inclusion equilibria involving anionic derivatives **4** and **5**, for which proximal interaction between the oppositely charged head groups is ruled out by polarimetric evidence.

4. Experimental

4.1. Materials

All reagents, solvents (HPLC grade) and materials needed were used as purchased, without further purification. Guests **1**–**8** and **AmβCD** were prepared, purified and characterized as described elsewhere.[4,17] Cyclodextrins 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 were prepared according to literature reports and used within a few days, after checking the 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.

4.2. Polarimetric measurements

A general protocol for performing the polarimetric determination of binding constants has been described in our previous papers.[16,22] 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 buffer. Alternatively, in order to achieve a more reliable estimate of low ($\leq$200 M^{-1}) K values, in some cases we slightly modified the procedure, by directly dissolving weighted amounts of the proper guest into the buffered **CD** solution. Whatever the procedure chosen, polarimetric data were subjected to suitable fitting analysis as described elsewhere.[22]

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23. (a) Fischer, E. *Chem. Ber.* **1893**, *26*, 2400–2412; (b) Cramer, F.; Otterbach, H.; Springmann, H. *Chem. Ber.* **1959**, *92*, 384–391 From data reported we can easily calculate the molar optical rotations of **9** and **10** as 30.9 and 33.0 deg dm^{-1} M^{-1}, respectively.
24. Of course, evaluation of the intrinsic contribution due to chemical modification relies on the assumption that, at least to a first approximation, effects on optical activities are nearly additive. To the best of our knowledge, no data are available in order to get similar estimations for unprotonated **AmβCD** at pH 11.0. Nevertheless, it seems reasonable to admit that a different protonation state for the amino group should imply different effects on the overall conformational behaviour of the host. Further investigations on the point are needed.
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27. Lo Meo, P.; Noto, R. unpublished data. For the inclusion of **1** in **AmβCD** we found at pH 11.0: $\Delta H^{\circ}=-16.7\pm0.7$ kJ mol^{-1}, $T\Delta S^{\circ}=-1.7\pm0.7$ kJ mol^{-1}; at pH 6.0: $\Delta H^{\circ}=-16.8\pm0.5$ kJ mol^{-1}, $T\Delta S^{\circ}=-2.6\pm0.5$ kJ mol^{-1}. For the inclusion of **2** we found at pH 11.0: $\Delta H^{\circ}=-13.5\pm0.8$ kJ mol^{-1}, $T\Delta S^{\circ}=2.0\pm0.8$ kJ mol^{-1}; at pH 6.0: $\Delta H^{\circ}=-22.2\pm1.1$ kJ mol^{-1}, $T\Delta S^{\circ}=-7.2\pm1.1$ kJ mol^{-1}.