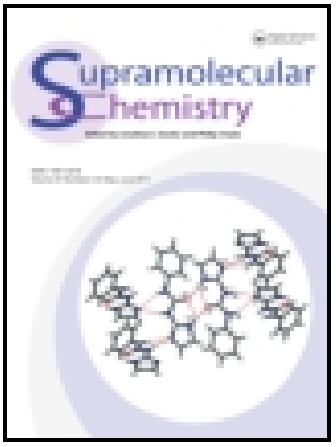

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Binding abilities of new cyclodextrin–cucurbituril supramolecular hosts

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Various combined techniques (UV–vis spectrophotometry, isothermal titration calorimetry, thermogravimetry, ESI-MS mass spectrometry, polarimetry and ^{1}H NMR spectroscopy) were used in order to study the interaction between a new combined supramolecular host, namely a bow-tie-structured cyclodextrin–cucurbituril association solely held by non-covalent interactions, and a suitably selected guest, namely the *N*-(*p*-nitrophenyl)-1,8-diaminooctane hydrochloride. In particular, the use of different techniques highlighted the peculiar features of the possible host–guest supramolecular interactions under different concentration conditions.

Keywords: cyclodextrins; cucurbiturils; supramolecular co-polymers

Introduction

Investigation of inclusion complexes (cavitates) has taken into consideration up-to-date various classes of supramolecular hosts, such as Viologens (**VG**s) (*1*), crown ethers (**CE**s) (*2*), cyclodextrins (**CD**s) (*3*), calixarenes (**CA**s) (*4*), cucurbiturils (**CUC**s) (*5*) and so on, which show different and somehow complementary binding abilities towards different classes of guests. Therefore, several efforts have been recently addressed towards the synthesis and investigation of systems combining the structural motifs of the aforementioned host classes, in order to combine their binding abilities as well. For instance, **CA**s have been decorated with polyether chains in order to achieve effective ion recognition (*6*), whereas donor ligand sites have been easily linked to both **CA**s (*7*) and **CD**s (*8*). Polyamine pendants have been attached to both the **CD** and **CUC** scaffolds to afford systems able in performing polynucleotide cell transfection (*9*). A click chemistry approach has also been occasionally exploited to synthesise joint **CA–CD** ligands (*10*). Noticeably, in all the aforementioned examples, covalent bond formation is required in order to hold together the different parts of the system; however, the latter one is not a necessary requirement.

By means of MW irradiation techniques, we recently succeeded in preparing some interesting new **CD–CUC** mixed hosts (*11*), joined by means of solely supramolecular interactions. In particular, by simply reacting the *heptakis*-(6-amino)-(6-deoxy)-β-cyclodextrin hydrochloride (**AβCD**$^{+7}$) with both cucurbit[6]uryl (**CUC[6]**) and cucurbit[7]uryl (**CUC[7]**), we were able to isolate two stable aggregates **1** and **2** (Figure 1) having a 2:1 stoichiometry, and presumably a bow-tie-like structure. The stability of these combined species may be ascribed to the occurrence of strong electrostatic interactions between the cationic primary **CD** rim and the negatively polarised **CUC** rims.

Aggregates **1** and **2** were satisfactorily characterised by means of NMR, ESI-MS and TGA combined techniques. Owing to the purely supramolecular nature of these composites, an investigation of their possible behaviour towards model guests seemed particularly intriguing. As a matter of fact, it has been believed for a long time that the presence of a suitable threading guest would have been a necessary requirement in order to held **CUC** and **CD** molecules together (*12*). Therefore, we were interested in verifying what influence a guest molecule could exert on our combined hosts. Although **CD**s and **CUC**s possess similarly sized cavities (the number of monomer units being equal), their features and properties are significantly different. In particular, **CUC**s have a quite rigid structure interacting well with cationic species in general, such as alkaline or alkylammonium ions (*13*). By contrast, due to their fair flexibility, which allows them to optimise time by time different types of microscopic interactions (*14*), **CD**s show a much more articulated behaviour (*15*). Hydrophobic polarised molecules such as *p*-nitroaniline derivatives (*16*), for instance, constitute an excellent class of guests for **CD**s, the study of which has allowed to gain a deep understanding of the microscopic features of these cyclic oligosaccharides. Therefore, in the present study, we attempted to test the binding properties of our new mixed hosts **1** and **2** by using a

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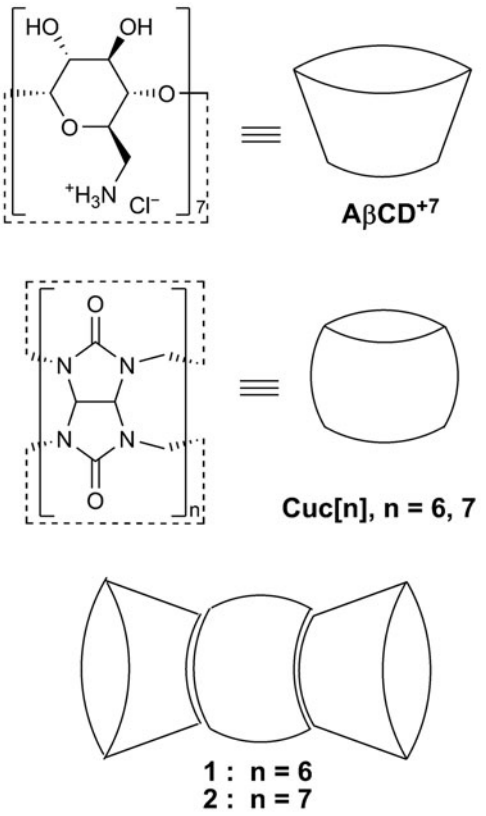

Figure 1. Structures of the hosts **1**–**2**.

suitable guest joining structural motifs apt to an effective interaction with **CD**s and **CUC**s as well. In particular, we chose the *N*-(*p*-nitrophenyl)-1,8-diaminooctane hydrochloride **3** as a suitable probe guest (Figure 2). This molecule, indeed, is both a long-chain alkylammonium cation and a *p*-nitroaniline derivative; therefore, we could reasonably expect it would fulfil our requirements on either moiety. We jointly studied the interaction of this probe guest by means of different techniques, namely UV–vis, NMR, polarimetry, ESI-MS, ITC and TGA, both in the solid state and in solution at different concentration conditions.

Results and discussion

UV–vis spectrophotometry

We first studied the interaction between species **1**, **2** and **3** by performing UV–vis spectrophotometric titrations.

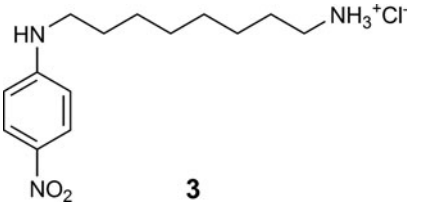

Figure 2. Structure of the guest **3**.

We operated at a fixed guest concentration, namely 1.3×10^{-5} M, and host concentrations ranging up to 1.2×10^{-3} M. A phosphate buffer at pH 6.0 ($I = 0.01$ M) was used as the solvent. The UV–vis spectra show a significant bathochromic shift due to host–guest interaction, although no apparent isosbestic point can be found.

A plot of the absorbances recorded at 417 nm, corresponding to the maximum wavelength for the solution at the largest host concentration (Figure 3), shows a typical curvilinear trend. However, regression analysis showed that experimental data cannot be satisfactorily fitted according to the usual 1:1 host–guest complex formation model. By contrast, we found out that the following expression seems suitable:

$$A_i - A_0 = \frac{c_G \times \Delta\varepsilon \times \beta_2 \times |H|}{1 + \beta_2 |H|},$$

accounting for the formation of a 1:2 complex, where A_i and A_0 are the absorbances of the *i*th sample and of the sample without host, respectively, c_G is the analytical concentration of the guest, $\Delta\varepsilon$ is the differential molar extinction coefficient at the operational wavelength, β_2 is the global equilibrium constant for the formation of the 1:2 complex and $|H|$ is the equilibrium concentration of the free host in the sample. This finding can be easily explained admitting that a single guest molecule is able to interact with two different host units at the same time (Figure 4).

The first one is likely to include the *p*-nitroaniline moiety with the nitro group directed towards the primary ring of the **CD**. This is the usual way by which *p*-nitroaniline derivatives are included into the **CD** cavity, due to the very favourable electrostatic interaction between the dipole momenta possessed by the cavity and the aromatic moiety of the guest, respectively (*16*). For guest **3**, indeed, such an arrangement leaves the long hydrophobic octyl chain protruding outwards and is ready to interact with a second host unit. We can reason that the octyl chain is long enough to penetrate quite deeply into the host, allowing the hydrophilic tail ammonium group to reach the negatively polarised **CUC** rim. Regression analysis of UV titration data allows us to estimate β_2 values for the [**1**·**3**·**1**] and [**2**·**3**·**2**] complexes as large as $(1.4 \pm 0.2) \times 10^6\ M^{-2}$ and $(4 \pm 1) \times 10^6\ M^{-2}$, respectively.

Isothermal titration calorimetry

Direct determination of enthalpy changes in solution through isothermal titration calorimetry (ITC) is a very powerful tool to investigate the energetics of supramolecular processes, and their modelling provides the equilibrium constant, the stoichiometry and the enthalpy change for the process as well. However, in order to perform ITC determinations, different operational concentration conditions were suitably required with respect

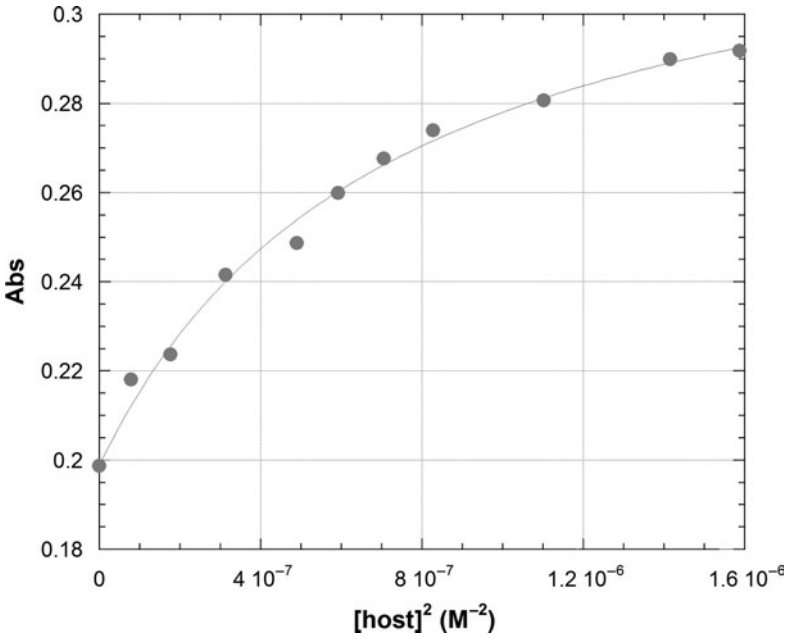

Figure 3. Plot of the absorbances at 417 nm for guest **3** (1.3×10^{-5} M) in the presence of host **1** (up to 1.25×10^{-3} M).

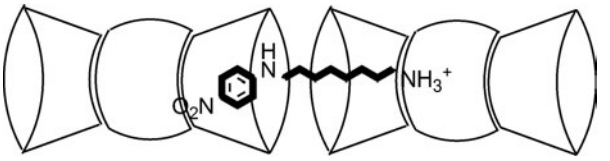

Figure 4. Possible structure of the 2:1 host–guest complex.

to UV–vis measurements. In particular, we chose to operate at a fixed starting guest concentration as large as 8×10^{-5} M and a varying host concentration ranging up to 1.4×10^{-4} M (the same buffer as for the UV–vis measurements was used as the solvent). The trends of the heat of injection corrected for the dilution effects (Q_i) as a function of the host:guest ratio ($R_{H:G}$) of **2** are shown in Figure 5. Noticeably, we tried to study under the same condition the possible interaction of guest **3** with **Am$_7$βCD** or **CUC**[7] alone for useful comparison (possible interaction with **CUC**[6] could not be studied owing to its unsatisfactory solubility); however, inspection of data trends ruled out the occurrence of any inclusion complex in the latter cases. Experimental data could be subjected to regression analysis according to a model providing the formation of a 1:1 stoichiometry complex (relevant data are collected in Table 1, see Experimental section for mathematical details). This remarkable difference with respect to UV–vis results may be easily explained considering the different concentration conditions. As a matter of fact, during ITC determinations, the host concentration is never so much larger than the one of the

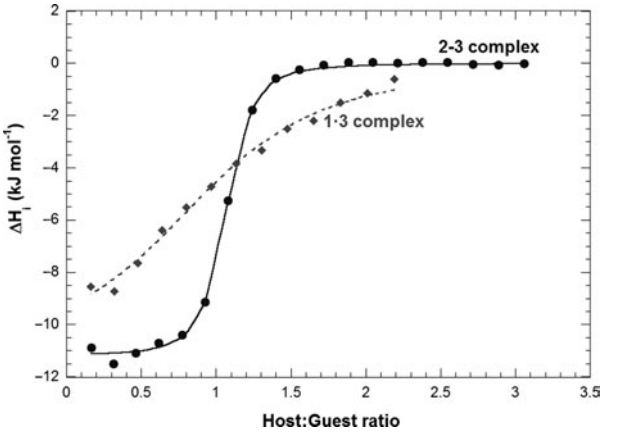

Figure 5. ITC titration curves for the **1**–**3** and the **2**–**3** complexes.

guest to allow the formation of a 1:2 complex in significant amounts.

For the 1:1 complexes with **1** and **2**, indeed, ITC data allow to estimate inclusion constants K_1 as large as $(5.6 \pm 0.5) \times 10^4\,M^{-1}$ and $(1.9 \pm 0.2) \times 10^5\,M^{-1}$, respectively. The very large and negative ΔG° values highlight the stability of complexes formed with both the composite hosts. It is worth noting that the K_1 values found are much larger than those observed for the two-step sequential binding of the dihexylammonium cation with one unit of **CUC[6]** and one unit of native **βCD** (*17*). The inclusion process is both enthalpy and entropy driven, as accounted for by the negative ΔH° values and positive

Table 1. Thermodynamics of inclusion complexes formation.

Host	K_{CPX} (M^{-1})	ΔG°_{CPX} (kJ mol^{-1})	ΔH°_{CPX} (kJ mol^{-1})	$T\Delta S^{\circ}_{CPX}$ (kJ mol^{-1})
1	$(5.6 \pm 0.5) \times 10^4$	-27.1 ± 0.2	-11.2 ± 0.7	15.9 ± 0.9
2	$(1.9 \pm 0.2) \times 10^5$	-30.1 ± 0.3	-13.13 ± 0.09	17.0 ± 0.4

$T\Delta S^{\circ}$ values found. Entropy variations, in particular, seem particularly intriguing because values found are higher than most of the ones available in the literature for the inclusion in free βCD. These variations manly reflect two phenomena occurring upon the complex formation, namely: (i) the structure loss of both the water molecules surrounding the free guest and those inside the host cavity (affording a positive contribution, due to the gain in translational mobility), and (ii) the loss of translational and conformational degrees of freedom for both the host and guest (affording a negative contribution). However, in our case, the latter term may be reasonably expected to be smaller than those for a hypothetical sequential two-step binding of cyclodextrin and cucurbituril with a given guest. Moreover, considering that the inclusion of *p*-nitroaniline derivatives in **βCD** is known to be subjected to an enthalpy–entropy compensation effect (*16*), it is very interesting to notice that the $T\Delta S^{\circ}$ values found here are much more positive than the ones that could be predicted on the grounds of literature reports (*3*). Finally, it is also interesting to consider that the differences in the thermochemical parameters for the two complexes may reflect the intrinsical structural differences between the free hosts. Indeed, the better size match between the **CD** and **CUC** subunits of **2** (both heptamers) makes it intrinsically a bit more rigid than **1**. As a consequence, inclusion into the latter host affords a slightly less favourable entropy gain upon inclusion.

Synthesis of solid **1–3** *complex and thermogravimetric analysis*

In order to get further insights about the composition and thermal stability of our complexes, we performed a thermogravimetric (TGA) analysis on a solid sample of a complex between host **1** and guest **3**, which was prepared by means of a combined US–MW irradiation technique described elsewhere. Noticeably, its elemental analysis (see Experimental section) gives results that are compatible with a formal 1:1 host:guest stoichiometry. The differential thermogravimetric (DTG) curves relevant to the free host **1** (a) and guest **3** (b), the obtained complex (c) and the 1:1 mol/mol physical mixture (d) between the reactants **1** and **3** are shown in superimposition in Figure 6. According to literature reports, thermogravimetric analysis curves on both the composite hosts **1** and **2** present two degradation steps at 238 and 459°C due to the **AβCD**$^{+7}$ and the **CUC** components, respectively. On the other hand, even the degradation of guest **3** shows a two-step process, with two peaks at ca. 270 and 470°C. The measured mass losses at each step are 54.2 and 33.1 wt%, respectively. Given that the nitro-aromatic moiety represents the 57.5 wt% of the molecule, and considered that the thermal stability of this moiety can be reasonably expected to be lower than the aliphatic one, we can infer that the thermal degradation of **3** implies at a first instance the aromatic ring, whereas the aliphatic portion is volatilised at higher temperature.

Considering now the inclusion complex formed by **3** with host **1** (**AβCD**$^{+7}$**/CUC[6]**), the relevant differential thermogram shows first a sharp peak at 232°C, which can be related to the degradation of the **AβCD**$^{+7}$. Then a shallow, hardly visible degradation appears at ca. 445°C, followed by a much sharper and more apparent one centred at 531°C. Noticeably, the latter peak corresponds to the degradation of pure **CUC[6]**, whereas the degradation at 445°C can be confidently attributed to the alkyl chain moiety of the guest, due to the little relevant mass loss. Therefore, this peculiar trend can be explained as follows: the strong interaction between the nitro-arene moiety of the guest and the **CD** cavity first causes the almost simultaneous thermal degradation of both, with an unexpected mutual destabilising effect; then the complete degradation of the guest occurs. However, these processes cause the liberation of the **CUC** component of the host, which at this point shows its typical degradation as it would have been free. Finally, it is worth noting that the thermogram relevant to the simple physical mixture of **1** and **3** at the stoichiometric 1:1 molar ratio results in the mere superimposition of the thermograms relevant to single components.

ESI-MS analysis

Electrospray ionisation mass spectrometry (ESI-MS) has gained an increasingly important role in the investigation of host–guest complexes and non-covalent systems in general (*18*) because this technique allows to transfer non-covalent complexes into the gas phase without loss of interactions. Indeed, in a previous study, we were able to successfully assess the stoichiometry of our hosts **1** and **2** by the ESI-MS analysis (*11*). Spectra of water solution containing the preformed solid-state complexes at a 1.0×10^{-3} M concentration were recorded in a positive mode

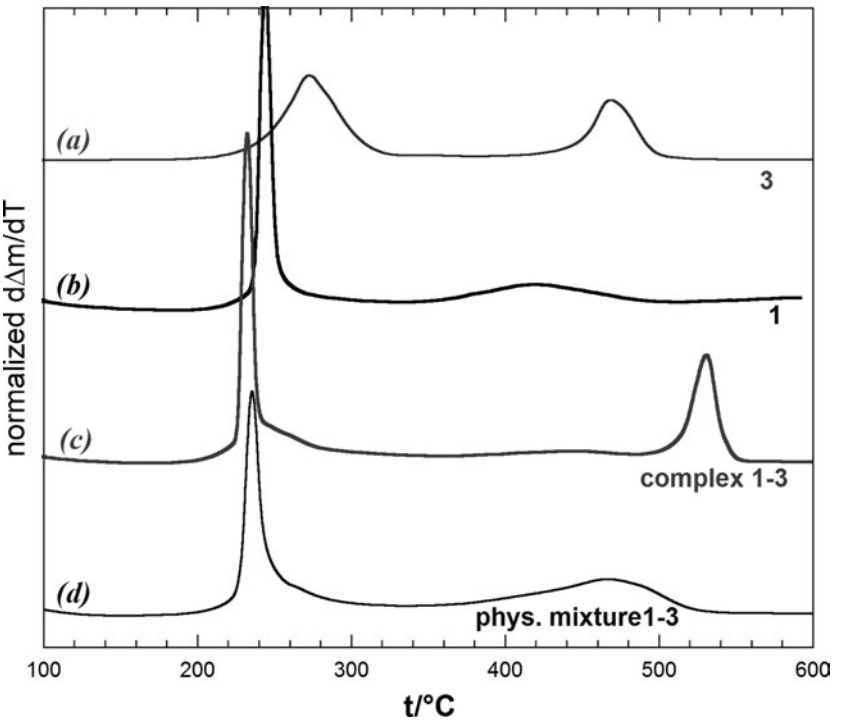

Figure 6. Thermograms for the **1**–**3** complex, its components and the relevant physical mixture.

(Figure 7(a) and (b), instrumental settings are reported in the caption, see Experimental section for details).

In the spectrum of the **1**·**3** complex (Figure 7(a)), a triple-charge ion at 1185.7 *m*/*z* ([2**AβCD**·**CUC[6]**·**3**·2H_2O·3H]$^{3+}$) clearly accounts for the formation of the desired complex species. On the other hand, the spectrum of **2**·**3** (Figure 7(b), spectrum recorded in the presence of a small amount of formic acid) shows the expected double-charge ion at 1860.6 *m*/*z* ([2**AβCD**·**CUC[7]**·**3**·2H_2O·2H]$^{2+}$), together with a very remarkable double-charge signal at 1982.7 *m*/*z*, which can be assigned to a species with a [2**AβCD**·**CUC**[7]·2(**3**)·H_2O·2H]$^{2+}$ composition (further assignments are reported in the caption). The latter finding is particularly interesting because it accounts for the possibility that a single host unit interacts at the same time with two guest molecules by exploiting the cavities of both the **AβCD** subunits. This, in turn, suggests the possibility that the solid material might be actually constituted by a sort of supramolecular polymer (see later).

Polarimetry and NMR

Further evidence about the interaction in solution between hosts **1** and **2** and the guest **3** were achieved by polarimetric and NMR measurements. It has been recently shown that the formation of inclusion complexes with **CD**s can be positively evidenced and studied by means of simple polarimetry, exploiting the fact that the optical activity of oligosaccharides is affected by their conformational dynamism (*19*), which is significantly modified on the occurrence of supramolecular interactions. On the other hand, NMR has been by long a technique of choice for the study of supramolecular interactions. In order to perform polarimetric and NMR experiments, we had to further modify the concentration conditions as compared with UV–vis or calorimetry. In particular, for polarimetry, we operated at a fixed host concentration as large as 1.4×10^{-3} M and a guest concentration ranging up to 2.3×10^{-4} M, whereas for NMR we fixed the concentration of the host at 1.0×10^{-3} M and ranged the concentration of the guest up to 3.0×10^{-4} M. Unfortunately, it was not possible to increase further the concentration of the guest because of the formation of suspended aggregates, eventually resulting in the formation of a precipitate, which hampered reliable polarimetric measurements.

Polarimetric measurements evidenced (Figure 8) a regular decrease in the optical activity of the solution on increasing the amount of guest present. Once again, the observed behaviour undoubtedly accounts for the occurrence of a true supramolecular interaction. However, data could not allow even a rough estimation of the binding constant, because the analytical concentration of the guest never exceeds the one of the host. The observed decrease in the optical activity is an intriguing finding. As a matter of fact, the interaction between *p*-nitroaniline derivatives and **CD**s usually results in an increase in the optical activity, whereas the opposite is observed with aliphatic

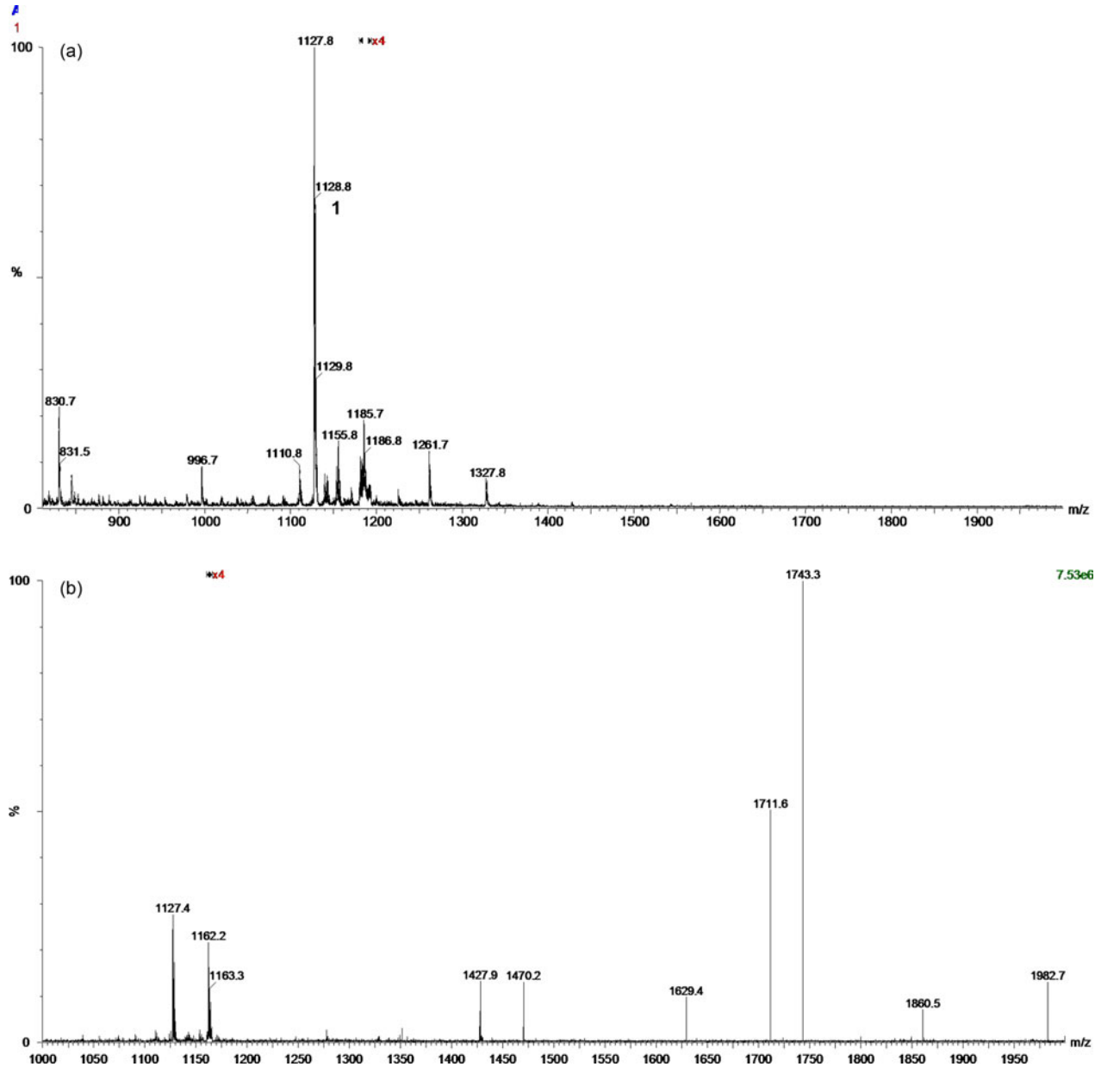

Figure 7. (Colour online) ESI-MS spectra of complexes **1**·**3** (a) and **2**·**3** (b). (a) Cone voltage 80 V, capillary voltage 3.2 kV, assignments (*m*/*z*): 996.7 [**CUC[6]**·H]$^+$, 1127.8 [**AβCD**·H]$^+$, 1185.7 [2**AβCD**·**CUC[6]**·**3** ·2H_2O·3H]$^{3+}$ and 1261.7 [**CUC[6]**·**3**·H]$^+$. (b) Cone voltage 60 V, capillary voltage 3.7 kV, assignments (*m*/*z*): 1127.4 [**AβCD**·H]$^+$, 1162.2 [**CUC[7]**·H]$^+$, 1427.9 [**CUC[7]**·**3**·H]$^+$, 1470.2 [**CUC[7]**·**3**·H_2O ·Na]$^+$, 1711.6 [2**AβCD**·**CUC[7]**·**3**·2H]$^{2+}$, 1743.3 [3**CUC[7]**·2H]$^+$, 1860.5 [2**AβCD**·**CUC[7]**·**3** ·2H_2O·2H]$^{2+}$ and 1982.7 [2**AβCD**·**CUC[7]**·2(**3**)·2H_2O·2H]$^{2+}$.

guests (*16c*, *19*). Therefore, our results indicate that the new mixed **CD**–**CUC** hosts have a peculiar polarimetric behaviour that is not comparable with the one of free **CD**s, probably as a consequence of the fact that the **CD** moiety of our new hosts is much more rigid as compared with the free **CD**s.

The NMR study was carried out on the **1**·**3** complex only (i.e. using the host made up with **CUC[6]**). Spectra on increasing guest concentration are particularly interesting because the signals of the host and the guest fall in well-distinct regions. This allows to follow in detail the progressive modifications of the signals for the host. These, in general, experience an increasing upfield shift as the amount of added guest increases. The effect is particularly apparent for the H atoms of the **CUC** moiety and the H(1), H(2) and H(3) of the **AβCD** moieties. Data show a curvilinear trend comparable with the one shown by polarimetric or UV–vis results (Figure 9(a) and (b)).

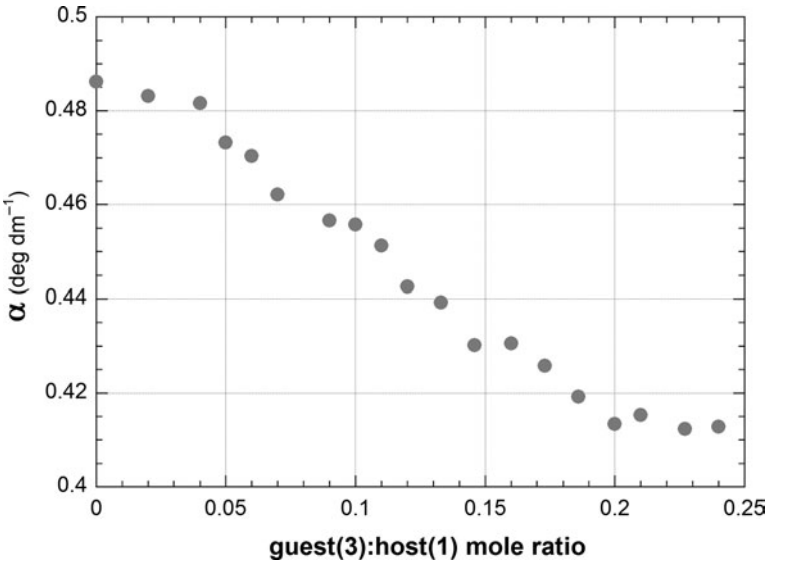

Figure 8. Polarimetric data for the **1**–**3** system at various host–guest mole ratios.

Unfortunately, the concentration of **3** was always too low to allow a reliable detection of similar shift effects for the signals of the guest.

These shifts once again account for the progressive formation of a host–guest complex. Even more interestingly, the presence of the guest splits into a more complex pattern for all the simple signals of the **CUC**, namely the two doublets at 4.15 and 5.60 ppm for the methylene exo- and endo-protons ($H_{exo\text{-met}}$ and $H_{endo\text{-met}}$) and the sharp singlet at 5.41 ppm for the glycoluryl protons (H_{gly}), respectively. Surprisingly, no comparable splitting is observed, however, for the signals of the **AβCD**s. Of course, the latter finding cannot be simply explained by the host–guest interaction, because an included guest molecule can in no way come in contact with the external **CUC** hydrogen atoms. Considering in particular the fate of the singlet at 5.41 ppm, we can observe that it is splitted into two signals having a nearly 3:1 intensity ratio on the addition of an amount of guest as large as 8% mol/mol. The intensity ratio becomes nearly 1:1 with an 18% mol/mol amount of guest, and 3:7 with a 30% mol/mol amount of guest. These results are interesting because they show that signal splitting has no quantitative correlation with the possible formation of 1:1 or 2:1 stoichiometry complexes in solution. However, it seems more likely that the intensity ratio consistently increases as the conditions are approached under which the formation of precipitates occurs. We can tentatively hypothesise that long supramolecular co-polymers are formed as the amount of guest increases. In other words, considering the aforementioned of 2:1 host–guest complexes, we may imagine that several host units are held in line by an equal number of guest molecules, each interacting at the same time with two hosts, by exploiting both its nitroaniline and alkylammonium moieties (Figure 10). This hypothesis is indeed supported by the results of elemental analysis mentioned previously. The supramolecular nature of the incipient precipitate formed as the guest concentration increases can be easily assessed by means of a very simple indirect test. As a matter of fact, by preparing a system formally 1.0×10^{-3} M in host and 3.5×10^{-4} M in guest, we verified that the cloudy pseudo-solution obtained turns clear in a few minutes upon addition of a small amount of potassium adamantanecarboxylate. The large adamantyl group, indeed, fits almost perfectly into the **βCD** cavity (*20*), and consequently adamantane derivatives in general form very stable complexes with **CD**s. Therefore, we can presume that the adamantate anion positively replaces the guest molecules, disrupting the supramolecular co-polymer.

Conclusions

The interaction between the new bow-tie-structured supramolecular mixed hosts **1** and **2** with the designed guest **3** was studied by means of various complementary techniques. Our results evidence how different behaviours and the formation of complexes with different stoichiometries (1:1 or 2:1) may take place, depending on the concentration ranges investigated. The stability constants for the relevant complexes are reported. In particular, ESI-MS and NMR evidence suggest that, in the solid state, a sort of supramolecular polymer is actually present. It is worth stressing here that we in the present study focused on a single suitably tailored guest, in order to assess advantages and drawbacks of different investigation techniques, as a function of the concentration ranges considered.

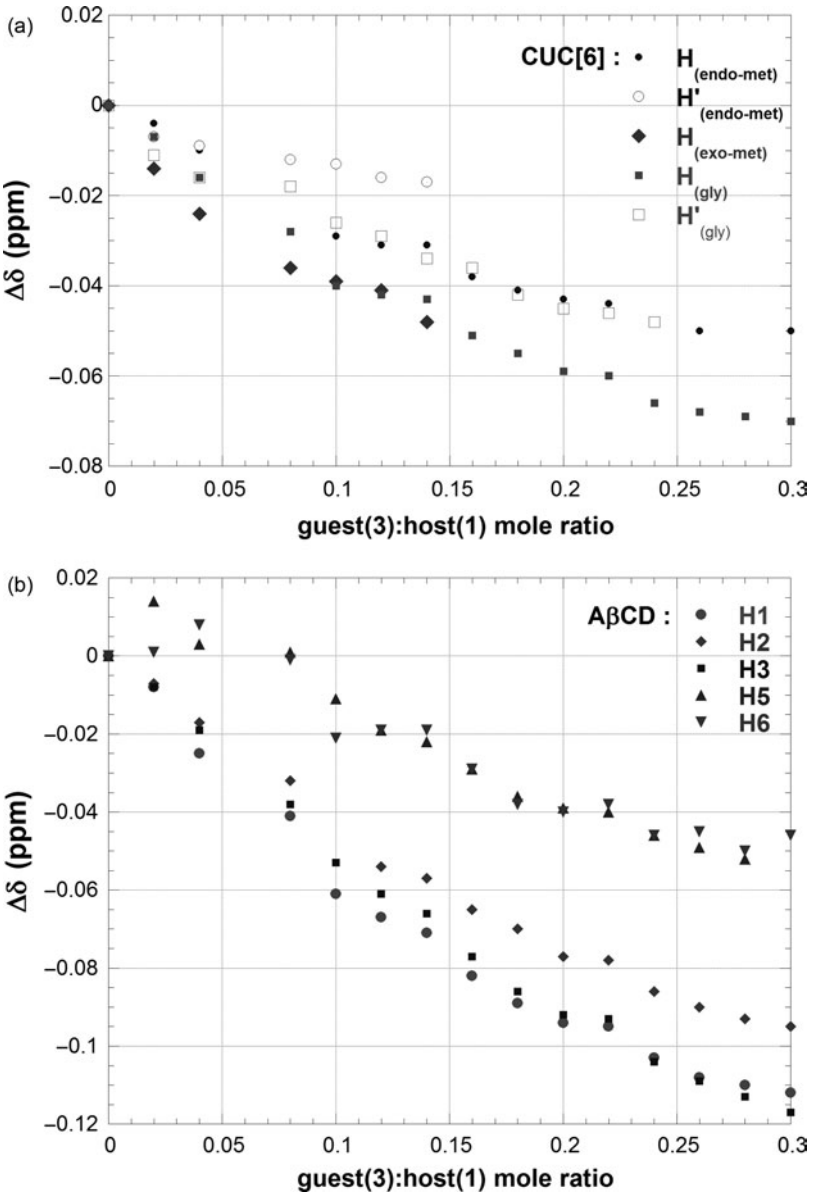

Figure 9. Variations in chemical shifts of the host protons for the **1**–**3** system at various host–guest mole ratios: (a) **CUC** signals; (b) **AβCD** signals.

Experimental

All the materials needed (Aldrich and Fluka) were used as purchased, with no preliminary purification. Hosts **1** and **2** were prepared and fully characterised (NMR and ESI-MS) according to previous reports (*11*). Guest **3** was prepared by an aromatic nucleophilic displacement reaction between *p*-fluoro-nitrobenzene and 1,8-diaminooctane, according to the procedure reported elsewhere for the preparation of other *p*-nitroaniline derivatives (*16*).

N-(p-Nitrophenyl)-1,8-diaminooctane hydrochloride 3

p-Fluoro-nitrobenzene (1.38 g 10 mmol) was dissolved in DMSO (10 mL), a 10-fold excess of 1,8-diamino-octane

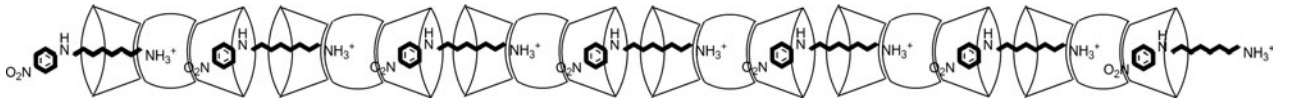

Figure 10. Possible depiction of the supramolecular polymeric structure of the host–guest complex in the solid state.

(14.42 g, 100 mmol) was added and the mixture was allowed to react at 60°C for 2 h. The reaction crude was poured in 200 mL of water, acidified with HCl up to pH 2 and extracted twice with CH_2Cl_2. The aqueous phase was rapidly filtered, NaOH 2 M was added to raise the pH value up to 12 and the cloudy solution was extracted with AcOEt. The organic extracts were dried on sodium sulphate and distilled *in vacuo*. The orange residue was dissolved in the minimum amount of methanol and a little excess of concentrated HCl was added, then a 10-fold volume of diethyl-ether was added to the mixture to allow the precipitation of the pure product. Yield 85%. Yellow powder, m.p. 140–141°C. IR (nujol) $\tilde{n}$ (cm^{-1}) 2680, 2605, 2574, 2515, 2442, 1604, 1535, 1303. NMR (D_2O): ^1H δ (ppm) 1.24 (br s, 8H, $-(CH_2-)$, 1.50–1.55 (m, 4H, $-CH_2-$), 2.86 (t, 2H, $J = 7.6$ Hz, $-CH_2-NHAr$), 3.15 (t, 2H, $J = 7.0$ Hz, $-CH_2-NH_3^+$), 6.62 and 7.99 (2d, 2H + 2H, $J = 9.4$ Hz, ArH); ^{13}C δ (ppm) 28.7, 29.2, 29.8, 29.9, 31.1, 31.4, 42.8, 46.3, 115.1, 130.4, 141.3, 158.7. Elem. Anal. for $C_{14}H_{24}ClN_3O_2$ calcd C 55.71%, H 8.02%, Cl 11.75%, N 13.92%; found C 55.68%, H 8.05%, Cl 11.73%, N 13.90%.

Preparation of the 1–3 *complex*

The solid sample was obtained as follows: 112.85 mg of **Am$_7$βCD** (81.6 μmol), 48.78 mg of **CUC[6]** (48.8 μmol) and 12.16 mg of **3** (40.3 μmol) were suspended in 1 mL of a 1:1 v/v water methanol mixture. The suspension was first subjected to ultrasound irradiation (200 W) at room temperature for 4 min; the sample was subsequently irradiated in an MW apparatus at 80°C for 10 min. Then, the system was cooled with a stream of N_2 at − 20°C, 2 mL of water were added and the product was filtered off. Yield 158.47 mg. Elem. Anal. for $C_{134}H_{228}Cl_{15}N_{41}O_{70}$ (i.e. for a formally 1:1 stoichiometry complex) calcd C 39.59%, H 5.65%, Cl 13.08%, N 14.13%; found C 39.55%, H 5.69%, Cl 13.07%, N 14.09%.

Preparation of the 2–3 *complex*

The solid sample was obtained by the same procedure as the previous one from 112.85 mg of **Am$_7$βCD** (81.6 μmol), 56.70 mg of **CUC[6]** (48.8 μmol) and 12.16 mg of **3** (40.3 μmol). Yield 166.15 mg. Elem. Anal. for $C_{134}H_{228}Cl_{15}N_{41}O_{70}$ (i.e. for a formally 1:1 stoichiometry complex) calcd C 39.74%, H 5.57%, Cl 12.57%, N 14.90%; found C 39.70%, H 5.60%, Cl 12.57%, N 14.89%.

Isothermal calorimetry

The ITC experiments were performed by using the ultrasensitive nano-ITC200 calorimeter (MicroCal). The amount of approximately 40 μL of host solution was injected into the thermally equilibrated ITC cell (200 μL) containing the guest solution. The calibration was done by NaCl dilution experiments. The quantitative data analysis was done according to the following equilibrium:

$$G + H \rightarrow \mathrm{CPX},$$

where G, H and CPX represent the guest, the host and the inclusion complex, respectively. The injection heat (Q_i) is given by

$$Q_i = Q_j - Q_{j-1} + (Q_j + Q_{j-1})V_a/2V_c,$$

where V_a is the volume of each addition, Q_j. and Q_{j-1} are the heat effect content before and after each injection. The third term at the right-hand side of the latter relationship is the correction for the displaced volume (*21*). The injection heat per moles of injectant (ΔH_i) can be written as $\Delta H_i = Q_i/(V_a[H]_S)$, $[H]_S$ being the host concentration in the syringe.

The equilibrium constant (K_{CPX}) and ΔH_{CPX} were determined through the best fit of the experimental titration curve by calculating ΔH_i at each addition, and therefore the host:guest mole ratio ($R_{H:G}$). To this aim, one can write

$$Q_j - \{\Delta H_{CPX}\chi_{CPX,j}\}V_c[H]_j,$$

where ΔH_{CPX} is the complex enthalpy of formation, $\chi_{CPX,j}$ is the fraction of complexed host, V_c is the cell volume and $[H]_j$ is the host concentration in the cell. It should be noted that $\chi_{CPX,j}$ depends on the concentrations in the cell and K_{CPX}. By suitably combining the previous relationships, the best fit of experimental data provides the values for K_{CPX} and ΔH_{CPX}.

Thermogravimetry

Thermogravimetric analyses were performed on a Q5000 IR apparatus (TA Instruments) under nitrogen flow. The weight of each sample was ca. 10 mg. The measurements were conducted by heating the sample from room temperature to 900°C with a rate of 10°C min^{-1}.

Mass spectrometry

ESI-MS spectra were acquired with a ZMD Micromass single quadrupole mass spectrometer. The samples were sprayed into the instrument with a Hamilton syringe driven by a Havard pump at 15 μL/min. The following parameters were kept rigorously constant in each series of solutions: desolvation temperature, 150°C; desolvation gas (N_2), 230 L/h; cone gas (skimmer), 50 L/h.

Supplemental data

Supplemental data for this article can be accessed at http://dx.doi.org/10.1080/10610278.2014.975704

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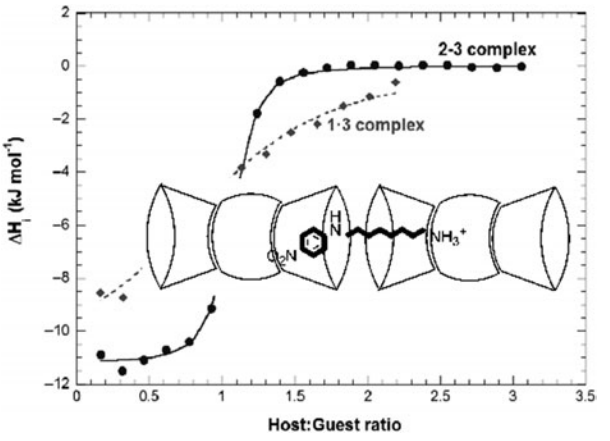

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Binding abilities of new cyclodextrin–cucurbituril supramolecular hosts