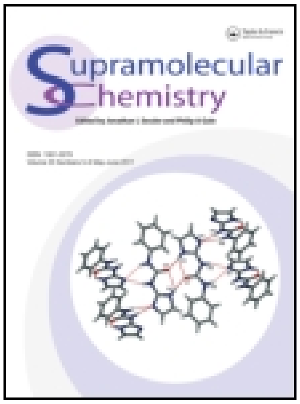

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Microwave-assisted synthesis of novel cyclodextrin–cucurbituril complexes

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Dedicated to the memory of Prof. Giorgio Modena

Microwave irradiation was successfully used in order to obtain stable supramolecular aggregates between cyclodextrins and cucurbiturils, without the participation of any long-chain common 'molecular thread' guest. These aggregates were characterised by means of various different techniques, namely NMR, thermogravimetry, polarimetry and ESI-MS. Cross-analysis of experimental data allowed us to obtain insights on the stoichiometries of the composites and their thermal stabilities. The possible structures of the composites are briefly discussed, as well as the actual nature of their intrinsic stability.

Keywords: cyclodextrins; cucurbiturils; microwave irradiation

1. Introduction

Cucurbiturils (Cuc[*n*]s, Figure 1(a)) constitute a family of cavitands, which have been receiving increasing attention during the last years as supramolecular hosts (*1*). These macrocyclic glycoluryl oligomers have been known since the beginning of the last century (*2*). For long time, the easy availability of the six-membered term (Cuc[6]) only, as well as its unsatisfactory solubility (enhanced in strongly acidic media (*3*)), made them unattractive for investigations. However, due to the relatively recent assessment of reliable synthetic routes, different-sized members of the family (from Cuc[5] up to Cuc[10]) have been obtained (*4*), and studies on the topic have undergone an outburst.

The behaviour of Cuc[*n*]s as hosts has been frequently compared to that of cyclodextrins (CDs, Figure 1(b)). The homologous terms (in relation to the number of subunits) of these two classes of compounds possess hydrophobic cavities that are rather similar in size (*5*, *6*). However, their features, modes of interactions and, consequently, binding affinities for a given guest are strikingly different. The bucket-shaped CDs show a fair flexibility (*7*) and its hydrophobic cavity possesses a significant electric dipole moment (*8*); so the stability of the inclusion complex is indeed the result of a balance between various factors (*9*). The Cuc[*n*]s are much less flexible, and the two carbonyl-fringed 'portals' possess a negative electrostatic potential (*6*), which favours the occurrence of strong interactions with alkali and alkali earth cations (*10–12*). Accordingly, Cuc[*n*]s exhibit remarkable binding abilities towards positively charged organic species (*11*, *13*). Both CDs and Cuc[*n*]s have been largely used as 'beads' for rotaxane systems (*12*, *14*, *15*). In view of their different and somewhat complementary features, a certain attention has been recently devoted to mixed CD/Cuc[*n*] systems (*16*, *17*), with the aim at obtaining structures where both macrocycles are connected by means of a common guest having the role of a 'thread'. In particular, the formation of Cuc[6]/dihexyl-ammonium/CDs (*18*, *19*) or Cuc[7]/-dialkyl-bipyridinium/αCD (*20*) ternary complexes has been studied from both the structural and the calorimetric point of view. In such systems, the role of the possible mutual interaction between the two host molecules on the overall stability of the aggregate appears somewhat ambiguous. In the former case, literature data indicate the occurrence of a favourable contribution to the stability due to the interactions between Cuc[6] and βCD, which result in a close spatial proximity between the secondary βCD rim and the Cuc[6] portal (*18*). No significant contribution seems to be present in the corresponding Cuc[6]/αCD system (*18*, *19*). On the other hand, in the latter case the Cuc[7]/αCD interactions seem to have even a slightly unfavourable effect (*20*), although a straightforward

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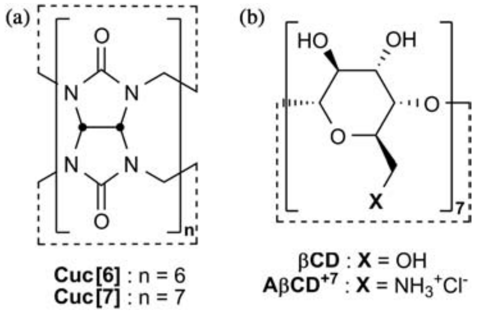

Figure 1. Structures of Cuc[*n*]s and CDs.

interpretation is difficult, because Cuc[7] can move along the threaded organic cation.

From the present state-of-the-art, it emerges that the use of a molecular threading is apparently a necessary condition in order to connect CDs to Cuc[*n*]s. It is worth noting that quite low binding constants ($<40\,M^{-1}$) for the formation of 1:1 complexes between native CDs and Cuc[5], decamethyl-Cuc[5] or Cuc[6] have been found (*21*). In certain cases, it has been shown that the presence of an alkylamino group chemically bound to the CD scaffold is able to favour an effective mutual interaction (*17*). Amino- and poliamino-CDs can be easily synthesised (*22*, *23*) and their binding properties have been studied in some occasions (*24*, *25*). Thus, such derivatives, in their conjugate-acid cationic forms, appear as ideal candidates in order to verify the possible occurrence of interactions with Cuc[*n*]s. Moreover, operating in solution is not the only route to achieve the goal. Stable host–guest composites with CDs can be obtained and isolated in the solid state not only by precipitation of the complex formed in solution, but also by different methodologies. In particular, microwave (MW) irradiation of some suitable host–guest mixtures has been successfully accomplished (*26*).

A challenging task is to verify whether it is possible to design and prepare stable CD/Cuc[*n*] composites with no molecular thread, by exploiting 'non-conventional' procedures. In the present paper, we describe the preparation and the isolation in the solid state of different composites made up of native βCD or *heptakis*-(6-amino)-(6-deoxy)-βCD hydrochloride (AβCD^{+7}) with Cuc[6] or Cuc[7]. These composites were successfully obtained by means of a modified MW irradiation protocol (*26*). Indeed, MW irradiation is particularly appealing as an effective time- and solvent-serving technique, which is able to overcome possible problems deriving from unsatisfactory solubility of the reagents (which, in particular, might critically affect the behaviour of βCD or Cuc[6]). Our materials were studied and characterised by means of several complementary techniques, namely NMR, thermogravimetric (TG) analysis, polarimetry and ESI-MS.

2. Results and discussion

2.1 Synthesis and NMR analysis

In a typical synthetic procedure, 40 μmoles of the proper CD (i.e. 56.18 mg of AβCD^{+7} or 45.40 mg of βCD) and 20 μmoles of the proper Cuc[*n*] (i.e. 26.26 mg of Cuc[6]$\cdot 12H_2O$ or 23.24 mg of Cuc[7]) were suspended in 500 μl of a 1:1 v/v water–ethanol mixture. The system was irradiated for 10 min at such a power level to keep the temperature at 80°C. Then, the different systems underwent a slightly different work-up as follows. (i) The AβCD^{+7}/Cuc[7] system was completely solubilised upon the addition of 1 ml of water. The clear solution was then evaporated *in vacuo*, and the residue was washed several times with small aliquots of ethanol, leaving back a pale yellow solid (product A); quantitative yield. (ii) The βCD/Cuc[7] system was completely solubilised upon the addition of 2.5 ml of water. Then the clear solution was similarly evaporated *in vacuo* and the residue was washed with ethanol, leaving back a white solid residue (product B); quantitative yield. (iii) By adding 1 ml of water to the AβCD^{+7}/Cuc[6] system, a suspension was obtained from which a precipitate (product C1) was separated; yield 12.01 mg (see later). The liquid phase was then evaporated *in vacuo* to give a further solid residue (product C2); yield 64.00 mg (see later). (iv) By adding 2.5 ml of water to the βCD/Cuc[6] system, a suspension was obtained from which a precipitate (product D1) was separated; yield 31.98 mg (see later). The liquid phase was then evaporated *in vacuo* to give a further solid residue (product D2); yield 32.12 mg (see later). Finally, all the products were dried overnight in a desiccator *in vacuo* at 60°C before any further analysis. It is worth noting that the two pristine CDs and Cuc[7] alone are soluble in the aforementioned operation conditions, whereas Cuc[6] is not.

The different products obtained were first characterised by means of ^{1}H NMR spectrometry. Analysis of the spectra, recorded in D_2O (products A and B) or in D_2O/CF_3COOD 1:1 v/v (products C1, C2, D1 and D2), showed the presence of the signals expected for both the reagents. Thus, we used signal integration in order to establish the apparent stoichiometries of our products. In particular, A and B appeared as mixtures with a 2:1 CD/Cuc[7] mole ratio. By contrast, product C1 was found to be a 1:1 AβCD^{+7}/Cuc[6] mixture, whereas C2 appeared as 2:1 AβCD^{+7}/Cuc[6] mixture. Even more interestingly, D1 showed a 1:2 βCD/Cuc[6] mole ratio, whereas D2 was pure βCD. Based on the intrinsic solubility of the reagents, one may state that the isolation of the products C1 and D1 as precipitates just from the reaction mixtures is very intriguing, because it straightforwardly indicates that Cuc[6] is able to induce the coprecipitation of the otherwise soluble CD. On the other hand, the isolation of C2 evidences the positive ability of AβCD^{+7} to enhance the solubility of Cuc[6]. In all these

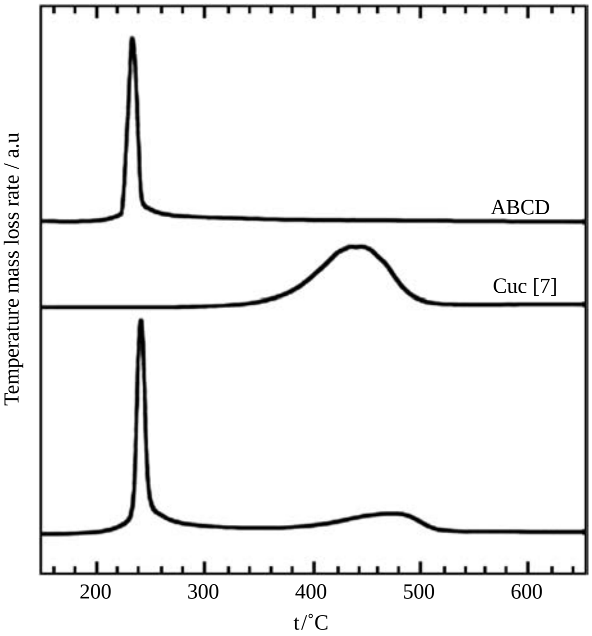

Figure 2. Thermal degradation rates for AβCD^{+7}, Cuc[7] and product A.

cases, significant interactions between CD and Cuc[*n*] take place, allowing the formation of stable aggregates. Interestingly, the recorded spectra showed negligible signal shift but a fair broadening with respect to pure components. This finding suggests that our materials are constituted by exclusion complexes. In other words, the interaction between the two macromolecules occurs in a rim-to-rim fashion, involving no mutual penetration (a similar situation, for instance, has been reported for the Cuc[6]/fullerene system (*27*)). Therefore, the 'probe' C—H groups do not actually experience any significant environmental change.

2.2 Thermogravimetry

TG and differential thermogravimetric (DTG) analysis of the obtained products provided further insights on their characteristics (Figure 2; the complete thermograms are collected in Supplementary Information). This technique has been frequently used in order to characterise inclusion complexes based on CDs or Cuc[*n*]s. (*28–30*) The results for our systems are collected in Table 1. Data for the pure reagents were also determined for a proper comparison. All the experiments were carried out at the constant heating rate of 10°C min^{-1}. In each case, a preliminary heating step at 120°C (for the duration of 10 min) was performed to register the possible loss of water in the samples.

The thermal decomposition of both βCD and AβCD^{+7} occurs in a single step, but at very different temperatures. It is worth noting that the decomposition temperature (t_d) of AβCD^{+7} is *ca.* 100°C lower than that of βCD. It may occur that the cationic ammonium groups decomposition starts at *ca.* 230°C likely allowing the formation of ammonia intermediates, which destabilise the CD structure. The presence of a quite large residual weight for both the CDs at the highest temperature indicates that part of the decomposed products is not volatile at temperatures higher than t_d under the experimental conditions. The Cuc[*n*]s exhibit degradation paths that are more complex than those of the CDs. In the DTG curves two degradation steps are clearly observed for Cuc[6], whereas a wide peak was registered for Cuc[7]. Similarly to the CDs, significant residual weights were measured. Both Cuc[*n*]s show t_d values considerably larger than those of the CDs, and therefore, one expects that the decomposition processes of their mixtures are satisfactorily well separated. Examples shown in Figure 2 confirm such an expectation.

All these observations provide convincing evidence that our materials are true supramolecular assemblies in

Table 1. Degradation temperature and complexes stoichiometry for CDs and Cuc[*n*]s in both the free and complexed states obtained from TGA data.

	t_d/°C	ML$_1$ (wt%)[a]	ML$_2$ (wt%)[b]	CD:Cuc[*n*]	n_w[c]
βCD	331.9	85.4	4.1		3[d]
AβCD^{+7}	232.6	61.5	10.1		8[d]
Cuc[6]	455.4; 527.6		80.0		4[d]
Cuc[7]	443.9		67.1		8[d]
A	240.6; 474.1	40.9	26.1	1.94	22[d] (24[e])
B	306.5; 452.1	53.5	23.0	2.12	20[d] (14[e])
C1	235.4; 452.1; 514.7	32.5	38.4	0.92	11[d] (12[e])
C2	237.8; 459.0	43.9	28.6	1.93	25[d] (20[e])
D1	326.5; 516.6	28.5	51.4	0.47	11[d] (11[e])

[a] ML from 150 to 400°C.
[b] ML from 400 to 800°C.
[c] Number of water molecules.
[d] Experimental value.
[e] Expected for the simple physical mixtures.

the solid state. On the other hand, suitable physical mixtures of the solid reagents were also prepared for useful comparisons. We observed that all the TG and DTG curves are simply given by the combination of the curves for the pure components, ruling out the occurrence of any significant mutual interaction between the components not subjected to MW irradiation. Furthermore, it indicates that the thermal decomposition of the CD does not affect that of Cuc[*n*]. As concerns the obtained products irradiated by MW, the curves are similar in shape, but show remarkable variations in the t_d values. This finding well supports the idea that mutual components interaction induces the formation of an exclusion complex as expected on the basis of the macrocycles geometries and nature. In particular, the AβCD^{+7} in the A, C1 and C2 products presents t_d values larger than those of the pure component. Such a stabilising effect on the CD is a consequence of the effective interaction with the Cuc[*n*], which is strengthened in the order C1 < C2 < A. The largest effect is found for similar-sized molecules, having the same number of subunits. Oppositely, lower t_d values relative to the βCD decomposition are found for B and D1 products, evidencing a destabilising effect significantly larger in the former case. Once again, the strongest effect is observed for the CD having the same number of subunits as the Cuc[*n*]. However, for these two products the DTG peaks appear quite larger than those of pure βCD as the decomposition process is slowed down by the interaction with the Cuc[*n*]. The same result was observed for C1. This means that the AβCD^{+7}/AβCD^{+7} interactions appear less effective than the AβCD^{+7}/Cuc[*n*] interactions likely due to significant electrostatic forces (unfavourable if both species are positively charged). The opposite occurs if βCD is considered (*31*).

As concerns the second weight loss step, due to the decomposition of the Cuc[*n*]s, the t_d values for the MW-irradiated products are significantly different than those for the pure components; however, the variations are not easy to rationalise. For C2 and D1 products, the apparent decomposition pattern of Cuc[6] dramatically changes. The second decomposition step at 514.7°C is suppressed and only the first one at 452.1°C is observed. Indeed, for C1 the second step appears much less important. Therefore, one may conclude that the decomposition of Cuc[*n*] is strongly affected by the degraded CD residuals. This result is a proof that our products are supramolecular aggregates, where specific intermolecular interactions take place.

From the mass losses (MLs) observed in the TG curves, it is possible to calculate the amounts of each component in a given mixture (see Experimental section). Therefore, the stoichiometry of each product was calculated. For all the cases, the CD/Cuc[*n*] mole ratios were in excellent agreement with those obtained by ^{1}H NMR. Finally, water losses from TG measurements were analysed. Although quantitative results must be treated with caution, data seem to indicate that at least B and C2 products retain a significantly different number of water molecules (n_w) than that expected for the simple physical mixtures (Table 1). Of course, one cannot establish whether these water molecules are located inside or outside the macrocycles. However, this finding supports the idea that our products are true supramolecular systems. Moreover, the knowledge of n_w allowed us to calculate the correct formal molecular weights for the products, which in turn were used to reconsider the weight yields reported previously. In particular, it can be easily shown that the yields relative to Cuc[6] for products C1 and C2 are 23% and 75%, respectively; for product D1 it is 96%, with a recovery of unreacted βCD (product D2) as large as 68%.

2.3 Polarimetry, osmometry and ESI-MS

By means of polarimetry, osmometry and ESI-MS, complementary evidences were also obtained on the real existence of stable supramolecular aggregates in solution. In particular, polarimetry has been recently proven to be a versatile tool in order to study the binding properties of CDs. (*32*) As a matter of fact, their optical activities depend on the overall molecular dissymmetry, due to both the intrinsical chirality of the constituting glucose subunits and the istant-by-istant loss of the formal C_n axial symmetry allowed by its flexibility. Consequently, the occurrence of a supramolecular interaction causes a significant variation in the polarimetric response. The molar optical activities Θ_0 of the pure CDs and of our products are collected in Table 2. It is worth mentioning that measurements involving the two Cuc[7] complexes (A and B) and product C2 were performed in water–acetonitrile 1:1 v/v solution, whereas for the other Cuc[6] complexes (C1 and D1) a 1:1:2 v/v water–acetonitrile–trifluoroacetic acid (TFA) mixture was employed, according to the solubilities of the products. In the same table, we also reported the differential molar optical rotations $\Delta\Theta$ for our products, defined as the differences between the relevant Θ_0 values and the values for the corresponding free CDs.

We may preliminarly note the occurrence of a significant solvent effect on the Θ_0 values of the free CDs, in particular for the native one (as large as 51 deg dm^{-1} M^{-}). This indicates that the different solvation requirements of the host cavity involve severe conformational changes for the overall macrocycle. Interestingly, the presence of TFA as an organic co-solvent causes a decrease in Θ_0 for the native βCD, in agreement with the behaviour observed for the inclusion of various other aliphatic guests of different steric bulks (*32*). Therefore, it is reasonable to assume that in the H_2O/TFA solvent mixture the water molecules usually present in the host cavity are almost completely displaced by TFA

Table 2. Polarimetric results.

	Solvent	Θ_0 (deg dm^{-1} M^{-1})[a]	$\Delta\Theta$ (deg dm^{-1} M^{-1})
βCD	H_2O	+183[b]	
	H_2O/TFA	+132	
AβCD^{+7}	H_2O	+102	
	H_2O/TFA	+129	
A	H_2O	+347	+143 (+72 per CD unit)
B	H_2O	+278	−88 (−44 per CD unit)
C1	H_2O/TFA	+15	−114
C2	H_2O	+287	+83 (+42 per CD unit)
D1	H_2O/TFA	+125	−7

[a] All data are given with *a* ± 10 deg dm^{-1} M^{-1} indetermination.
[b] From Ref. (*32*).

molecules. A different discussion should be carried out for AβCD^{+7}. It is noteworthy that the exhaustive replacement of the hydroxyl groups with the positively charged ammonium groups on the primary host rim cause a large decrease in the Θ_0 value (81 degthinsp;dm^{-1}M^{-1}) in aqueous solution. On the basis of the polarimetric behaviour of methyl-α-glucoside and methyl-(6-amino)-(6-deoxy)-α-glucoside (*24*), we should expect a fair increase (*ca.* 15 deg dm^{-1}M^{-1}) in Θ_0 as a consequence of chemical modification. Therefore, the obtained experimental value accounts for the occurrence of large intrinsic conformational modifications in comparison to native βCD. Indeed, the charged ammonium groups (having also large solvation requirements) experience a strong Coulomb repulsion, which forces the glycosidic linkages in such a way to enlarge the primary rim (*33*). On the other hand, the transfer of AβCD^{+7} from the pure aqueous system to the mixed solvent causes an increase in the Θ_0 value (27 deg dm^{-1}-M^{-1}). This finding, although opposite to the one observed for βCD, indeed accounts for the occurrence of further conformational effect upon transfer into a different solvent medium.

By examining our composites, it is very interesting to note that the interaction of AβCD^{+7} with both Cuc[*n*]s generates large variations of the molar optical activity per CD unit. These variations are positive for the 2:1 composites studied in pure water, namely A and C2, but negative for the 1:1 C1 studied in water/TFA mixture. The observed results account for the occurrence of a large conformational modification for the AβCD^{+7} when interacting with the Cuc[*n*], and therefore cannot be explained otherwise than with the existence of stable supramolecular assemblies also in solution. In particular, experimental data suggest that the AβCD^{+7} is forced to modify its overall conformation in such a way to make its primary rim narrower, and thus to optimise the possible interactions between the charged ammonium groups and the carbonyl-fringed Cuc[*n*] portals (see later). Interestingly, once again we noted that variations of opposite sign occur in the two different solvent systems. On the other hand, among the composites involving βCD, namely B and D1, the former one exhibits a negative $\Delta\Theta$ value, whereas D1 surprisingly exhibits only a negligible $\Delta\Theta$ value. However, the latter result is satisfactorily consistent with the idea of the formation of an exclusion complex as discussed previously. Thus, it should be concluded that, unlike AβCD^{+7}, the native βCD experiences only minor conformational changes when interacting with Cuc[6]. Furthermore, $\Delta\Theta$ values can be interestingly compared with those already found for true inclusion complexes (*32*). In particular, for the inclusion in βCD of adamantane derivatives (which are known to fit almost perfectly into the host cavity, thus inducing the severest conformational restrainments) typical negative $\Delta\Theta$ values as large as *ca.* −21 deg dm^{-1}M^{-1} are found, which are significantly smaller in absolute value than those for complexes B and C1. On the other hand, positive $\Delta\Theta$ values can be found whenever polar guests are included; in particular, values for *p*-nitroaniline derivatives are usually found in the range +50 to +90 deg dm^{-1}M^{-1}.

Osmometric experiments provided independent evidences on the actual stoichiometry of the obtained materials. Indeed, the aggregates stoichiometry determined from both ^{1}H NMR and TG experiments could not rule out the presence of larger or polymeric aggregates. Therefore, according to a reviewer's recommendation, we performed osmotic pressure measurements to determine the molar mass of the complexes in aqueous solution. The measurements were carried out for a limited number of samples, namely A and C2, which possess water solubility high enough for the instrument sensitivity. Unfortunately, the complexes B and D1 based on the native βCD could not be investigated owing to their unsatisfactory solubility in pure water.

First, we determined the number average molar mass for the pristine CDs. By using the Pitzer Equation (*34*) in order to calculate the osmotic coefficient, a very good agreement is obtained between the theoretical and the experimental molar mass of AβCD^{+7}; of course for the non-ionic native CD the agreement is even better (Table 3). It is worth noting that these results rule out the occurrence of oligomeric aggregates, at least under the operational

Table 3. Osmolarity, calculated and theoretical molecular mass for CDs and some CDs:Cuc complexes.[a]

	CD:Cuc[*n*]	C_s	ϕ^b	*n*	M_n experimental	M_n theoretical
AβCD^{+7}		12.8	0.401	8	1152	1383
		18.1	0.359		1197	
		24.2	0.322		1138	
βCD		14.8	1	1	1143	1134
A	2:1	12.7	0.361	15	3482	3709
		26.9	0.264		3305	
C2	2:1	10.7	0.371	15	5134	3376
	4:2		0.191	29	5365	6752

[a] Units are: Cs, g kg^{-1}; Mn, g mol^{-1}.
[b] The osmotic coefficient was calculated from Pitzer equation or assumed unitary for the non-ionic solute.

conditions. Moreover, it is also important to stress that such a good agreement between expected and experimental results is important, because it provides a convincing (and necessary) validation of the method applied for. For the CDs:Cuc complexes, a strictly quantitative interpretation might be difficult due to the large number of ions generated upon dissociation (*n*) of each AβCD^{+7} in the complex and the electrostatic contribution to the osmotic coefficient (ϕ). Notwithstanding, for the complex A, based on the data in Table 3, one can state that a real 2:1 complex is present in solution. In the case of complex C2, data are consistent with the coexistence of 2:1 and 4:2 complexes.

Finally, the ESI-MS provides a soft ionisation technique suitable to identify the weak non-covalent interactions between host and guest molecules. This technique has been successfully and widely employed in order to evidence the interactions between CDs (*35–37*) or Cuc[*n*]s (*38*) and different organic species. In some cases, it has been used to obtain even a quantitative estimation of the binding constants. The ESI-MS provided evidence of the stability of the complexes even in conditions rather different with respect to the ones where they have been formed and are stable in solution (as an illustrative example, the spectrum of complex A is shown in Figure 3, whereas the complete set is reported in Supplementary Information).

Spectra of A, B and C2 compounds were obtained in water/acetonitrile 1:1 v/v mixture, whereas spectra of C1 and D1 compounds were obtained in water/acetonitrile/TFA 1:1:2 v/v mixture. Inspection of the spectra, in particular in the region of dicationic species, always reveals the occurrence of the signals proper for the expected complexes. The most significant peaks for each sample are summarised in Table 3. The fact that the signals relative to the complexes are quite weak in intensity is consistent with the hypothesis that only exclusion complexes are formed.

3. Conclusions and final remarks

The present work is, to the best of our knowledge, the first report on the formation and characterisation of stable CD/Cuc[*n*] supramolecular aggregates, obtained by means of MW irradiation, and without any common guest having the role of a 'molecular thread'. It is to be remarked that

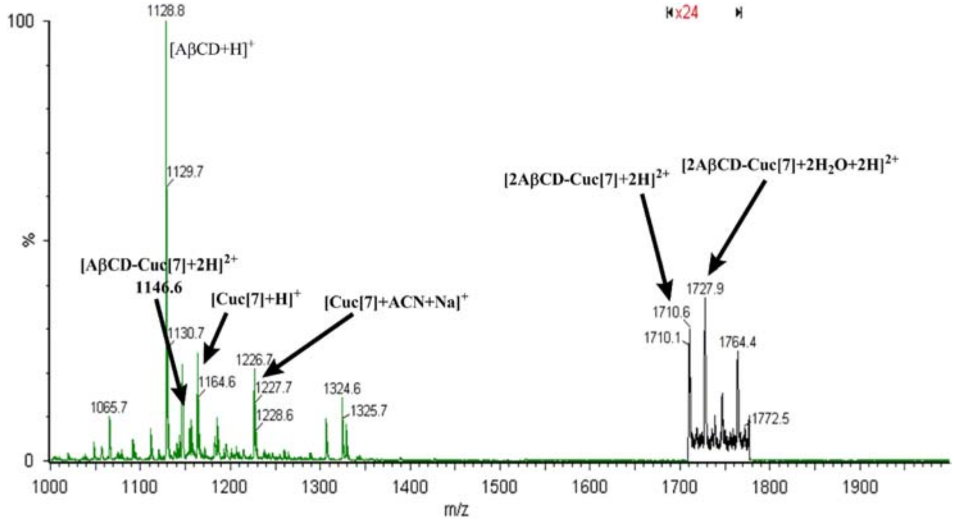

Figure 3. ESI-MS (*m/z* = 1000–2100) of complex A in solution.

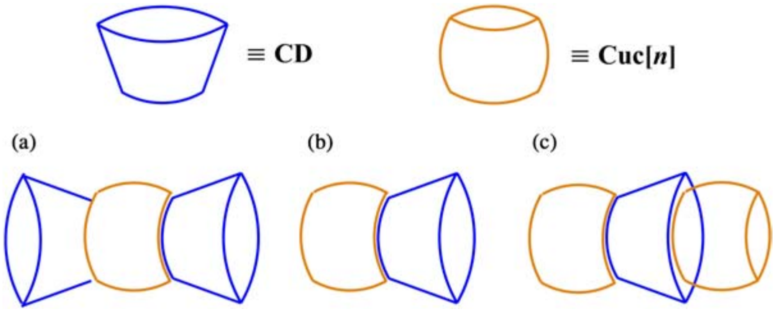

Figure 4. Possible structures of the complexes.

the latter aspect undoubtedly introduces an element of novelty in the field of current supramolecular chemistry. Cross-analysis of the results obtained by means of different complementary techniques (NMR, TG, polarimetry, osmometry and ESI-MS), on both the complexes and the corresponding physical mixtures, straightforwardly evidenced that supramolecular aggregates are formed, and actually exist both in the solid state and in the solution. Therefore, these materials may be viewed as a new potential class of interesting supramolecular hosts conjugating the typical features of both Cuc[*n*]s and CDs.

Of course, two questions remain open. The first one concerns the structure of the aggregates. On the basis of the well-known affinity of Cuc[*n*]s towards organic cations, it appears rather reasonable to assume that the interaction with AβCD^{+7} may involve its cationic primary rim. In particular, the 2:1 complexes (A and C2) likely form a nice bow–tie structure (Figure 4(a))[1], whereas a sort of half-bow–tie shape might be reasonably supposed for the 1:1 complex C1 (Figure 4(b)). As concerns the structure of complexes involving native βCD, for the 1:2 complex with Cuc[6] a sandwich-type one seems reasonable (Figure 4(c)). Of course, this means that both the secondary and the primary βCD rims are interacting with Cuc[6]. On the other hand, we have no hint about the actual modes of interaction in the 2:1 complex B.

The stoichiometries of the products themselves are interesting, and deserve some further consideration. As a matter of fact, it is highly significant that the reaction between both the CDs and the similar-sized Cuc[7] seems to specifically lead to a 2:1 aggregate, whereas the same does not take place when this apparent size-complementarity requisite is not met. On the other hand, the fact that the product D1 has its own stoichiometry, which does not match the initial βCD:Cuc[6] ratio, indicates also in this case the occurrence of a specificity in the interaction between the two reactants. The same is not strictly valid for AβCD^{+7}/Cuc[6], leading to the formation of two products (namely C1 and C2) having different stoichiometries.

The latter considerations lead us to the second question, i.e. the nature of the stability shown by our complexes. We previously mentioned the fact that a possible 1:1 βCD/Cuc[6] complex had been found to have a 'low' thermodynamic stability (*21*). However, the 1:2 complex D1 appeared perfectly stable in solution, as well as the 2:1 complex B with Cuc[7]. Indeed, it must be kept into account that we are dealing in our cases with complexes having different stoichiometries, obtained and studied under conditions that are not strictly comparable. On the other hand, we have already remarked that the interaction between AβCD^{+7} is likely to be essentially electrostatic in nature. Moreover, the kinetic aspect of the problem is worth to be explored. Our results suggest that both the formation and the dissociation of the complexes might have an unexpectedly large activation energy barrier. In this sense, it is important to stress the importance of MW irradiation in order to obtain our products. As a matter of fact, compared to 'classical' heating, MWs offer the advantage to reduce the reaction times and the use of solvents, providing an interesting economy-friendly methodology.

4. Experimental

4.1 Materials

All the reagents and solvents needed were used as purchased without further purification. Native βCD was dried before use in a desiccator *in vacuo* over P_2O_5 at 60°C for 24 h and kept in the same apparatus. The AβCD^{+7} was synthesised according to the procedure reported in the literature (*23*).

4.2 Instrumentation

MW-assisted syntheses were carried out with a CEM DISCOVER monomode system in closed vessel. NMR spectra were recorded with a Bruker 300 MHz spectrometer. TG experiments were performed with a TA Instruments Q5000 IR apparatus, under a nitrogen flow of 25 $cm^3 min^{-1}$ for the sample and 10 $cm^3 min^{-1}$ for the balance. Each sample (*ca.* 10 mg) was kept at 120°C to ensure the moisture evaporation and a heating rate of 10°C min^{-1} was successively applied up to 800°C. The curves of ML to temperature (TG) and the first-order differentiation curves of ML to temperature (DTG) were determined. The decomposition temperatures (t_d) were taken at the maximum of the peaks in the DTG curves. The ML from 150 to 400°C (ML_1) and from 400 to 800°C (ML_2) was determined. Note that ML_1 and ML_2 are related mainly to the CDs and Cuc[*n*]s degradation, respectively. The percentage of the CDs (C_{CD}, wt%) and Cuc[*n*]s (C_{cuc}, wt%) into the mixture was determined by means of the following equations, which take into account the incomplete degradation of the components in the investigated range.

$$C_{CD} = \frac{ML_1(\text{mix})}{ML_1(\text{CD})} \cdot 100, \quad (1)$$

$$C_{cuc} = \frac{ML_2(\text{mix}) - C_{CD}ML_2(\text{CD})}{ML_2(C_{cuc}[n])} \cdot 100. \quad (2)$$

Therefore, the stoichiometries of complexes (see Table 1) were calculated from the C_{CD} and C_{cuc} values combined with the macrocycles molar mass. Polarimetric measurements were performed with a JASCO P-1010 polarimeter. The osmotic measurements were carried out by means of a vapour pressure osmometer (Osmomat 070-SA; Gonotec GmbH Berlin, GERMANY), which enabled us to measure the molal decrease in the vapour pressure of water. The osmolarity (N_{osm}) was determined at 37.0°C and it depends on the molal concentration (m_s) of the solute according to the relationship: $N_{osm} = \phi\, n\, m_s$, where n is the total number of ions generated upon dissociation and ϕ is the osmotic coefficient which can be approximated to 1 for dilute non-ionic solute and it can be calculated for rather dilute electrolytes in water by means of the Pitzer Equation (*34*). As soon as the concentration in g kg^{-1} (C_s) of the solute is known, the number average molar mass (M_n) can be calculated as: $M_n = C_s\ \phi\ n/N_{osm}$. ESI-MS were acquired with a ZMD Micromass single quadrupole mass spectrometer operating at 4000 *m/z* (Table 4). A Hamilton syringe driven by a Harvard pump was used for direct injection of the sample into the instrument. To minimise the influence of variations in instrumental conditions on the reliability of mass spectra, the ESI-MS parameters (i.e. the pressure of the gas, the desolvation temperature, the capillary, cone voltages, etc.) were kept rigorously constant from run to run in each series of solutions. The spectra were recorded by using the following instrumental setting: positive ion mode; capillary voltage, 3.20 kV; cone voltage, 80 V; desolvation temperature, 150°C; desolvation gas (N_2), 230 l/h; cone gas (skimmer), 50 l/h. A change in the cone voltage from 20 to 150 V did not change significantly the absolute intensity of the peaks. Mass spectra were averaged over 40 scans in all cases.

Table 4. ESI-MS results.

Complex	*m/z*	Assignment
A	1146.6	$[\text{A}\beta\text{CD/Cuc[7]} + 2\text{H}]^{2+}$
	1710.6	$[2\text{A}\beta\text{CD/Cuc[7]} + 2\text{H}]^{2+}$
	1727.9	$[2\text{A}\beta\text{CD/Cuc[7]} + 2\text{H}_2\text{O} + 2\text{H}]^{2+}$
	2291.6	$[\text{A}\beta\text{CD/Cuc[7]} + \text{H}]^{+}$
B	1168.6	$[\beta\text{CD/Cuc[7]} + \text{K} + \text{H}]^{2+}$
	1739.2	$[2\beta\text{CD/Cuc[7]} + 2\text{Na}]^{2+}$
	1750.3	$[\beta\text{CD/2Cuc[7]} + \text{H}_2\text{O} + \text{Na} + \text{H}]^{2+}$
C1	1063.5	$[\text{A}\beta\text{CD/Cuc[6]} + 2\text{H}]^{2+}$
	2126.1	$[\text{A}\beta\text{CD/Cuc[6]} + \text{H}]^{+}$
C2	1063.6	$[\text{A}\beta\text{CD/Cuc[6]} + 2\text{H}]^{2+}$
	1627.4	$[2\text{A}\beta\text{CD/Cuc[6]} + 2\text{H}]^{2+}$
D1	1065.5	$[\beta\text{CD/Cuc[6]} + \text{K} + \text{H}]^{2+}$
	1584.3	$[\beta\text{CD/2Cuc[6]} + \text{K} + \text{H}]^{2+}$

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Note

1. Regarding product C2, considered that osmometric data suggests the simultaneous occurrence of both 2:1 and ‘dimeric’ 4:2 aggregates, the bow–tie model strictly applies to the former one only.

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