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# Thermodynamics of Formation of Host−Guest Supramolecular Polymers

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***Abstract:*** The interactions between three $\beta$-cyclodextrin hosts (having 1−3 binding sites) and two adamantyl guests (having 1−2 binding sites) have been studied by ITC, ROESY, static and dynamic light scattering (SLS and DLS), and AFM and TEM techniques. The enthalpy and free energy values (determined from ITC experiments) evidence that the single interaction between one binding site of the guest and one binding site of the host is independent of the number of binding sites of the interacting species. The average values are $\Delta H^\circ = -26.6 \pm 2.3$ kJ mol$^{-1}$ and $\Delta G^\circ = -30.4 \pm 3.2$ kJ mol$^{-1}$, indicating that the process is mainly enthalpy driven. In all cases, the experimental molar ratio (from ITC experiments) agrees with the expected one from the number of binding sites of both the host and guest. The formation of polymer-like entities was demonstrated by SLS, DLS, AFM, and TEM measurements. The structure of polymers is linear when both the host and the guest are ditopic entities and dendritic (or Cayley tree type) when the host and the guest have three and two binding sites, respectively.

## Introduction

A supramolecular polymer can be defined as a system based on the association of many unimers through noncovalent interactions.[1,2] Supramolecular polymers can be based on hydrogen bonding, discotic molecules, metal coordination bonding, or host−guest interactions.[3] Among the last ones, crown ethers[4,5] and cyclodextrins are the most common host unimer units.

During the past few years, descriptions of different supramolecular polymers involving cyclodextrin derivatives have been published, some of them during the preparation of this manuscript.[6] These polymers can be classified as four main types:

(i) Supramolecular polymers formed from interlocked unimers. The repetitive unimer carries complementary units, i.e., host and guest sites. Examples of this type of polymers have been published.[7−18]

(ii) Supramolecular polymers formed from two complementary monomers having a minimum of two interacting sites. Linear supramolecular polymers are expected when both monomers are ditopic entities.[19−28] In these cases, the formation

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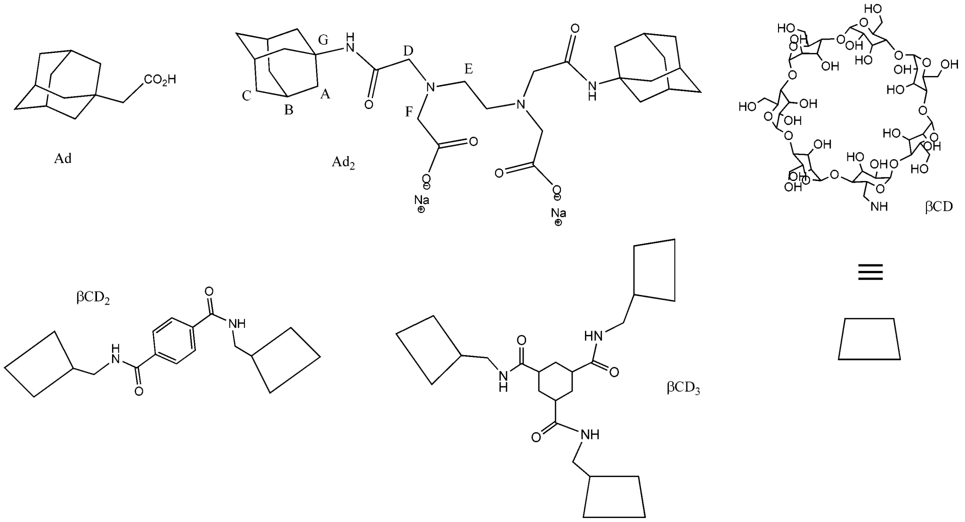

***Figure 1.*** Structures of the polymer precursors studied here.

of chelate complexes[29−33] has to be avoided. Otherwise, the formation of the chelate complex will compete with the formation of the supramolecular polymer. The reasons why one situation can be preferred to the other one are not clear, mainly due to a lack of thermodynamic measurements related to the formation of supramolecular polymers. On the other hand, if one of these monomers is a tritopic derivative, hyperbranched (dendritic or Cayley tree type) structures can be formed. As far as we know, only one supramolecular polymer formed by cyclodextrins with that hyperbranched structure has been published.[34]

(iii) Polytopic hosts and polytopic guests have been used to form other macromolecular assemblies.[35,36] High viscosity enhancements are observed, being maximum for a composition in which the stoichiometry is 1:1 cyclodextrin residue/adamantyl residue.[37] In some cases, phase separation can also take place.

(iv) Finally, covalent polymers can enter the cavity of the cyclodextrin, forming polyrotaxanes.[38] These compounds are also known as molecular necklaces.[39,40]

Isodesmic models[2] predict that the degree of polymerization increases with increasing the association constant between the repeating units (Carothers equation). If a cyclodextrin is the host unit, then adamantyl residues appear as the most recommendable guests since the adamantyl moiety perfectly fits inside the $\beta$-cyclodextrin ($\beta$CD) cavity, resulting in high equilibrium constants.[12,41,42] However, because of the hydrophobic nature of the adamantyl residue, adamantyl compounds are poorly soluble in water (except those carrying charged groups), raising difficulties in the measurement of their properties in aqueous solution. Therefore, we have designed and obtained a new adamantyl dimer (Figure 1) by reacting two equivalents of 1-adamantanamine with one equivalent of a dianhydride bridge derived from ethylenediaminetetraacetic acid (EDTA). The reaction originates two amide linking groups and two carboxylic groups which facilitate the solubilities of both the guest and polymer. On the other hand, cyclodextrin dimers and trimers have been used as host unimers (Figure 1).

We report here the formation of polymer-like structures between these new guest and hosts. As reference, the complexation of the adamantyl acetic acid (sodium salt) with the three $\beta$CD derivatives was also studied. Different experimental techniques (isothermal titration calorimetry, ITC; rotating-frame Overhauser enhancement spectroscopy, ROESY; static and dynamic light-scattering , SLS and DLS, respectively, AFM and TEM) have been used to characterize the polymers.

## Experimental Section

**Materials.** Adamantyl acetic acid, Ad, (99%, Aldrich) and $\beta$CD (kindly supplied by Roquette) were used without further purification. For ITC experiments, stock solutions of reactants were prepared in bicarbonate buffer 15 mM ($pH = 10.0$). The syntheses of the precursors of the polymers are given as Supporting Information (SI).

**ITC Measurements.** The thermodynamic background for ITC is well-defined.[43] ITC allows the determination of enthalpy, entropy, and the equilibrium constant (or free energy) involved in complexation processes, in a single experiment. It also provides the molar guest:host ratio, i.e., the stoichiometry of the complex. Enthalpies of dilution of the hosts and guests were determined in separate experiments, being negligible. ITC experiments were carried out in a *MicroCalc Omega* titration calorimeter at $30.00 \pm 0.01$°C. Experimental titration curves

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***Table 1.*** Thermodynamic Parameters Deduced from ITC Experiments for the Different Host−Guest Systems Studied Here

| | $\beta$CD | $\beta$CD$_2$ | $\beta$CD$_3$ |
|---|---|---|---|
| Adamantyl Acetic Acid, Sodium Salt | | | |
| $n^b$ | 0.991 ± 0.001 (1) | 0.51 ± 0.08 (1/2) | 0.357 ± 0.002 (1/3) |
| $\Delta H^{\circ\, d}$/kJ mol$^{-1}$ | −26.8 ± 0.07 | −57.7 ± 0.4 | −71.8 ± 0.6 |
| $\Delta H^\circ$/kJ (host site mol)$^{-1}$ | −26.8 ± 0.07 | −28.9 ± 0.2 | −23.9 ± 0.2 |
| T$\Delta S^\circ$/kJ mol$^{-1}$ | 2.0 ± 0.1 | 2.2 ± 0.6$^c$ | 5.9 ± 0.3$^c$ |
| $\Delta G^\circ$/kJ mol$^{-1}$ | −28.90 ± 0.05 | −31.6 ± 0.5 | −31.5 ± 0.2 |
| $K_{eq}$ | (9.8 ± 0.2) × 10$^4$ | (2.9 ± 0.6) × 10$^5$ | (2.65 ± 0.19) × 10$^5$ |
| Ad$_2$ | | | |
| $n^b$ | 1.91 ± 0.01 (2/1) | 0.95 ± 0.01 (1/1) | 0.63 ± 0.01 (2/3) |
| $\Delta H^{\circ\, d}$/kJ mol$^{-1}$ | −26.0 ± 0.2 | −59.2 ± 0.7 | −73.3 ± 0.7 |
| $\Delta H^\circ$/kJ (host site mol)$^{-1}$ | −26.0 ± 0.2 | −29.6 ± 0.4 | −24.4 ± 0.2 |
| $T\Delta S^\circ$/kJ mol$^{-1}$ | 1.4 ± 0.2 | 2.3 ± 0.5$^c$ | 9.2 ± 0.3$^c$ |
| $\Delta G^\circ$/kJ mol$^{-1}$ | −24.6 ± 0.1 | −31.9 ± 0.2 | −33.6 ± 0.2 |
| $K_{eq}$ | (1.74 ± 0.08) × 10$^4$ | (3.18 ± 0.27) × 10$^5$ | (5.98 ± 0.42) × 10$^5$ |

[a] Temperature, 30.01°C; pH = 10.0 was kept constant by using a bicarbonate buffer (total concentration 0.15 mol dm$^{-3}$). [b] $n$: molar ratio of both components in the complex. The values in parentheses are theoretical values for the formation of complexes with all the binding sites of both guest and host occupied. [c] Values corresponding to the model of single one site−one site interaction, i.e., to the formation of hypothetical 1:1 complexes by using the estimated values of $\Delta H^\circ$ for such a complexation given in the text. [d] The units of the experimental enthalpy value are kJ mol$^{-1}$ of titrating species (i.e., the host species).

were analyzed with the *MCS Origin-ITC 5.0* program. Guests (in the calorimeter cell) were always titrated by hosts (in the syringe). Typical concentrations were 0.5−1 mM and 10 mM, respectively. The host solution was injected into the cell in injections of 10 $\mu$L, with a 3-min interval between injections.

**SLS and DLS Measurements.** The basic theories of static and dynamic light-scattering techniques are very well-known and can be found elsewhere (see also SI).[44,45] Light-scattering measurements were carried out in a Malvern 4700 apparatus and in a Brookhaven instrument constituted by a BI2030AT digital correlator with 136 channels and a BI200SM goniometer. The light sources were a Melles-Griot He−Ne laser operating at 632 nm (Malvern) and a Uniphase solid-state laser system model 4601 operating at 532 nm (Brookhaven). Dust was eliminated by filtering the samples with Nuclepore filters with a pore size of 0.2 $\mu$m. The samples were placed in the cell for at least 30 min prior to the measurement to allow for thermal equilibration. Their temperature was kept constant within 0.5 °C by a circulating water bath. To prevent mold growing, these experiments were carried out in the presence of sodium azide (10 mg mL$^{-1}$).

**NMR Measurements.** For NMR experiments $D_2O$ (99.90%) was supplied by SDS (France). Acidity was adjusted with KOD (Aldrich, 40% in $D_2O$). Samples were prepared directly in the NMR tubes. Spectra were recorded using a Bruker AMX-500 NMR spectrometer operating at 500 MHz for $^1$H and 125 MHz for $^{13}$C. TMS was used as external reference. $^{13}$C experiments were recorded on a Bruker AC-300 NMR spectrometer operating at 75 MHz and 293.1 K.

**AFM Measurements.** AFM was performed on a commercial Topometrix Explorer TMX-2000 SPM system. All measurements were conducted in contact mode at room temperature under ambient conditions to record topographic and lateral force (friction) images. Contact "V"-shaped cantilevers were used. The dimensions of the arm of the cantilever were: length, 200 $\mu$m; width, 18 $\mu$m; thickness, 0.6 $\mu$m. These cantilevers end with a pyramidal silicon nitride ($Si_3N_4$) tip with a radius <20 nm and force constant 0.032 N m$^{-1}$. The hardware linearized scanner (*Topometrix Explorer True Metrix*) has a travel of 10 $\mu$m in the $z$-direction and 100 $\mu$m in the $xy$-directions. The images obtained were processed by *TopoMetrix SPMLab*, version 4.0, software supplied with the microscope. Data were processed to remove background curvature using a three point leveling of the surface and a left shading of the image. All height measurements were obtained by the analysis of multiple AFM images with the Topometrix line measurement software option. Samples were placed on mirrorlike polished Si wafer pieces which were immobilized on metal sample holders by means of double-sided adhesive tape, and imaged with the AFM without any treatment. Most samples were imaged close to preparation date, but longer periods did not seem to affect the microscopic structure. The samples could be imaged for days without evident alteration of their macroscopic or microscopic appearance.

**TEM** Measurements. TEM images were obtained at room temperature in a JEOL JEM-1011, operated at 80 kV, equipped with a MegaView III camera. For the measurements, the samples were prepared by deposition of a drop of the solution onto carbon-coated copper grids.

## Results and Discussion

ITC experiments were carried out for measuring the thermodynamic parameters associated with the inclusion process, $\Delta H^\circ$, $K_{eq}$, $\Delta G^\circ$, $\Delta S^\circ$, and the molar ratio, $n$, of host and guest in the complex. The experimental titration curves were analyzed through the standard model of a single set of identical sites, according to which the total evolved heat in the solution cell, $Q$, (active cell volume $V_o$) is given by

$$Q = \frac{nM_t\Delta H^\circ V_o}{2}\left[1 + \frac{X_t}{nM_t} + \frac{1}{nK_{eq}M_t} - \sqrt{\left(1 + \frac{X_t}{nM_t} + \frac{1}{nK_{eq}M_t}\right)^2 - \frac{4X_t}{nM_t}}\right] \quad (1)$$

where $n$ is the number of identical sites, $X_t$ and $M_t$ are the total concentration of the guest and host, respectively, and $K_{eq}$ is the equilibrium constant given by $K_{eq} = \Theta/\{(1 - \Theta)[X]\}$, where $\Theta$ is the fractional saturation, related to the total concentration of complexed sites of the host by $n\Theta M_t$.

The value of $Q$ can be calculated for a given set of $n$, $K_{eq}$, and $\Delta H^\circ$ values at the end of every injection and can be compared with the experimental one, allowing the optimization of those parameters. The heat involved in the reaction is provided in kJ mol$^{-1}$ of injectant (in our case, mole of host). Representative titration experiments are given as Supporting Information. The average values for the thermodynamic parameters are given in Table 1.

The theoretical $n$ values for complexes formed between guests having one (Ad) or two binding sites (Ad$_2$) with hosts having

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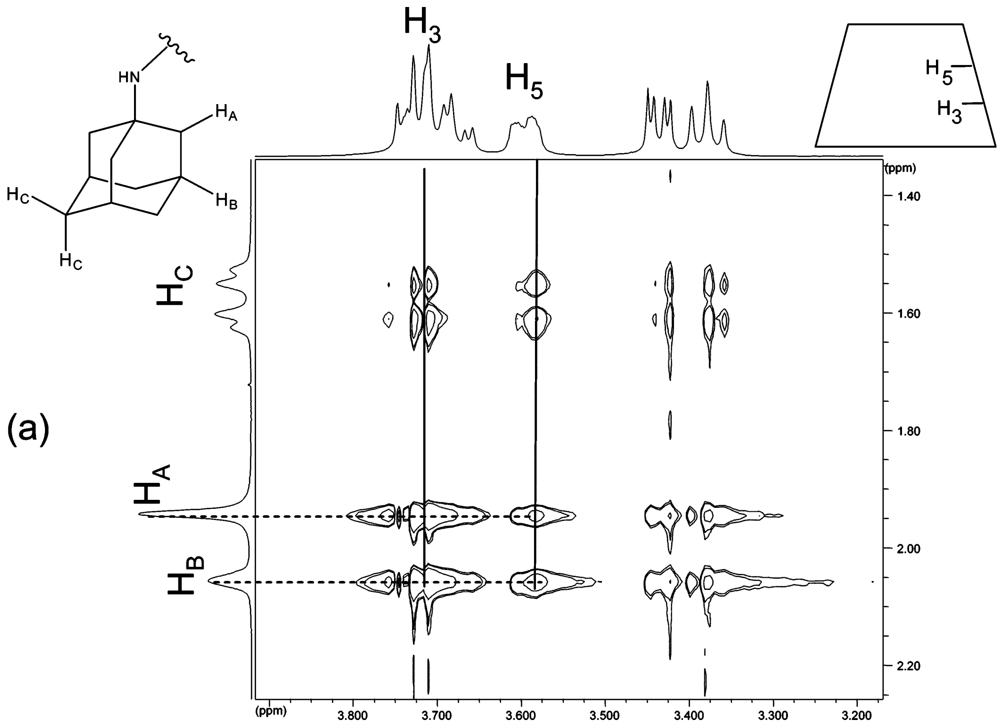

***Figure 2.*** ROESY for the system Ad$_2$:$\beta$CD.

one ($\beta$CD), two ($\beta$CD$_2$), or three ($\beta$CD$_3$) binding sites, are given in parentheses in Table 1. It can immediately be noticed the excellent agreement between the experimental values for $n$ and the expected ones. In particular, attention should be paid to the values corresponding to the reaction between hosts and guests with multiple binding sites as, for instance, the value between the cyclodextrin trimer and the adamantyl dimer. This is a first indication that large aggregates are formed between adamantane and $\beta$CD derivatives when both species have simultaneously multiple binding sites. The value of $n$ corresponds to the inflection point of the $Q$ vs molar ratio curves which are perfectly sigmoidal, allowing the accurate determination of $n$. This contrasts with observations of Zhang and Breslow[33] who, when titrating the $\beta$CD into two ditopic substrates, elicited two well-separated binding curves for the formation of a one-to-one and a two-to-one complexes. The experimental relative errors for $\Delta H°$ and $\Delta G°$ (or equivalently for $K_{eq}$) are low, since they do not exceed 0.9% and 1.5%, respectively.

Let us first consider the values for the reaction between the adamantyl monomer, Ad, and the $\beta$CD$_i$, ($i = 1-3$) series. The value of $-26.9$ kJ mol$^{-1}$ obtained for $\Delta H°$ for the Ad:$\beta$CD system is close to the average enthalpy value ($= -27.1 \pm 2.1$ kJ mol$^{-1}$) for the complexation of several adamantyl derivatives.[41,42] This comment is also valid for $\Delta G°$ (or $K_{eq}$). To analyze the remaining values of the series, it must be remembered that the units of $\Delta H°$ values given in Table 1 are kJ mol$^{-1}$ (of host injectant), i.e., it does not consider the number of binding sites of the host. In the absence of any cooperative (either positive or negative) effect, the enthalpy values for the second and third bindings should be equal to the one for the first binding. That is to say, the enthalpy for the complexation of two or three binding sites would be 2 and 3 times the value for one binding site. Values of $-29.4$ and $-25.6$ kJ mol$^{-1}$ binding site are obtained when the experimental values of $\Delta H°$ are multiplied by the experimental molar ratio $n$. Such values would correspond to hypothetical 1:1 complexes for the Ad:$\beta$CD$_2$ and Ad:$\beta$CD$_3$ systems, respectively. It must be noticed that these values favorably compare with the value for the actual 1:1 Ad:$\beta$CD complex (or the average enthalpy value commented on above).

The equilibrium constant, $K_{eq}$, or equivalently $\Delta G°$, corresponds to a single host−guest interaction irrespective of the number of binding sites of the host. When all the binding sites for the interacting species are identical, as in the case for the present series, it is expected that, within experimental error, $\Delta G°$ would be the same along the set, if progress of saturation of the binding sites is not considered. The three values (Table 1) are fully compatible with the $\Delta G°$ average value ($= -28 \pm 2$ kJ mol$^{-1}$) for the formation of 1:1 complexes between adamantyl derivatives and $\beta$CD.[41,42] Finally, it can be concluded that, for all these systems, the complexation is enthalpy driven with a small entropy contribution[33] ($\Delta H° < 0$ and $|\Delta H°| \gg |T\Delta S°|$) and since $\Delta H°$/binding site and $\Delta G°$ are close to each other, the calculated values for $\Delta S°$ are small and affected by relatively high experimental errors, a rather common fact for these systems.[46] The values for the equilibrium constants for the formation of complexes between adamantane derivatives and $\beta$CD systems are among the largest ones for the complexation of organic molecules by cyclodextrins. This is a consequence of the adamantyl residue fitting perfectly inside the $\beta$CD cavity.[42] The agreement between the measured thermodynamic quantities along the series suggests that the location of the adamantyl residue inside the cyclodextrin cavity is always the same, i.e., it is independent of the number of sites of the host and the guest. This has been confirmed by ROESY experiments. Figure 2 shows an example corresponding to the Ad$_2$:$\beta$CD system. Similar interactions between H3 and H5 cyclodextrin

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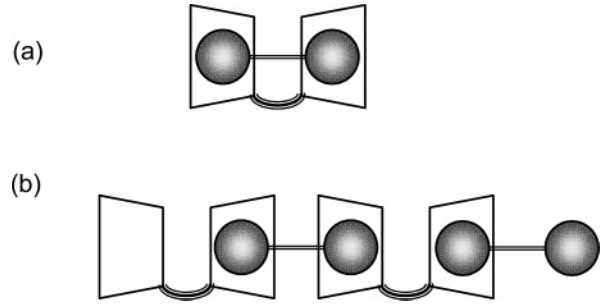

***Figure 3.*** Schematic representation of complexes formed by a ditopic guest and a ditopic cyclodextrin: (a) chelate complex; (b) linear supramolecular conglomerates (oligomers or polymers).

inner protons and those of the adamantyl residue are evident along the series (see SI).

Now the interpretation of the second set of values, that is for the adamantyl dimer, $Ad_2$, is straightforward. Remembering that the measured enthalpy does not consider the number of binding sites of the host (see above), to obtain $\Delta H°$ per host site, the experimental $\Delta H°$ values have to be divided by the number of sites of the host, resulting in the values given in Table 1. These values are very close to that corresponding to the complexation of the adamantyl acetic acid. Table 1 evidences that the differences are less than 1.5 kJ $mol^{-1}$, representing 3.4, 2.6, and 2.1% for the three hosts, respectively. Thus, all issues commented on above for $\Delta H°$, are also valid for this series. Such values have been used to calculate $\Delta S°$ by taking into consideration that the experimental $\Delta G°$ (or $K_{eq}$) values belong to a 1:1 host site−guest site reaction. It can be noticed that all $\Delta S°$ values are low and positive (a common fact when adamantyl carboxylic acids of different length chains are complexed by $\beta$CD), and there is no significant increase in $\Delta S°$ with the increase of the number of binding sites of the host. Again the concordance along the series is due to the fact that identical host−guest interactions are observed for all systems, corroborated by ROESY experiments (see SI).

As already noticed, when a ditopic guest is complexed by a cyclodextrin dimer, two different supramolecular entities can be formed (Figure 3). The first situation (Figure 3a), known as chelate binding, arises when the ditopic guest is complexed simultaneously by both cyclodextrin residues of the same dimer, forming a 1:1 complex. If a cooperative effect is present, a higher stability constant than that expected for the complexation by isolated cyclodextrins would be obtained. The chelate effect has been mainly studied by Breslow et al.[29,33,47] The second situation (Figure 3b) arises when a ditopic guest is complexed by two cyclodextrins belonging to two dimers, resulting in the formation of higher-order supramolecular entities (oligomer- or polymer-like) with an *n*:*n* stoichiometry.[19] In the absence of any cooperative effect, we might expect that $\Delta G°$ for a ditopic guest was 2 times the value for the monotopic binding interaction between a $\beta$CD unit and a monotopic guest. Unfortunately, even for chelate complexes, this is not always observed.[48] In the absence of any cooperative effect, both situations are indistinguishable from a thermodynamic point of view.

However, a first indication that chelate complexes are not formed is given by ROESY experiments. All systems evidence host proton−guest proton interactions identical to those observed for the simplest Ad:$\beta$CD system (see Supporting Information). This fact justifies the similarity of the thermodynamic results commented on above. These spectra do not show any cross-peak between H6 cyclodextrin protons and the guest, suggesting that the adamantyl residue enters into the $\beta$CD cavity by its secondary rim, ruling out the formation of the chelate complex.

However, the best way to distinguish both situations is to measure the size or the molecular weight of the complexes. Consequently, static and dynamic light-scattering experiments were carried out. First, the molecular weights of $\beta$-cyclodextrin derivatives were measured by SLS, thus checking the validity of the determination. The values obtained for the cyclodextrin dimer ($M_w = 2.3 \times 10^3$ g $mol^{-1}$) and trimer ($M_w = 4.4 \times 10^3$ g $mol^{-1}$) are well in agreement with molecular weights deduced from their formulas ($2.4 \times 10^3$ and $3.5 \times 10^3$, respectively). Analogously, hydrodynamic diameters (1.27 and 1.42 nm for dimer and trimer, respectively) were measured by DLS. The results are also in good agreement with the molecular size of these species (the height of one cyclodextrin cone is around 0.8 Å).[49]

Concerning the polymers, the light scattering results are reported in Figure 4. Even though we neglected the interparticle interaction, the results very clearly indicate that the $Ad_2$:$\beta CD_3$ polymer grows by increasing the concentration. A much lower growth is observed in the case of the $Ad_2$:$\beta CD_2$, in agreement with data reported for polymers with similar flexibility.[28] Anyway, a good correlation between the hydrodynamic radius and the molecular weight is observed.

The average degree of polymerization in supramolecular polymers is dependent on the concentration of the solution and the association constant.[2,3] Polymers with a high molecular weight can only be obtained when the repeating units have a high association constant. From the large equilibrium constants measured here, higher molecular weights than those determined from SLS should be measured. Thus, it seems that SLS data do not adequately represent the actual degree of polymerization. Sometimes the effect of impurities and stoichiometric imbalance on the degree of polymerization have been invoked to explain the cut of the polymer molecular weight.[3] For instance, for an extent of the reaction of 99.7%, corresponding to a equilibrium constant value of $10^5$ (Carothers equation), the simplest isodesmic model predicts that an impurity of 1% cuts the molecular weight in quarter. However, that level of impurities does not influence ITC mesurements.

The actual dimensions of linear and branched polymers were better determined from AFM measurements. Panels a and b of Figure 5 correspond to $Ad_2$:$\beta CD_2$ and $Ad_2$:$\beta CD_3$ systems, respectively. They show that the structures of the polymers are the expected ones, i.e., supramolecular linear polymers for the first one and supramolecular Cayley tree polymers for the second one.

The bright lines in Figure 5a evidence a regular organization of the elongated polymer in parallel arrays which extend to hundreds of nanometers. The tendency to form parallel arrays is similar to that of the columns observed in the crystal[12] formed by the self-assembly of mono-6-deoxy-6-adamantylamide−$\beta$-cyclodextrin which are stacked on parallel. Such a structure is

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(48) Wilson, D.; Perlson, L.; Breslow, R. *Bioorg. Med. Chem.* **2003**, *11*, 2649.
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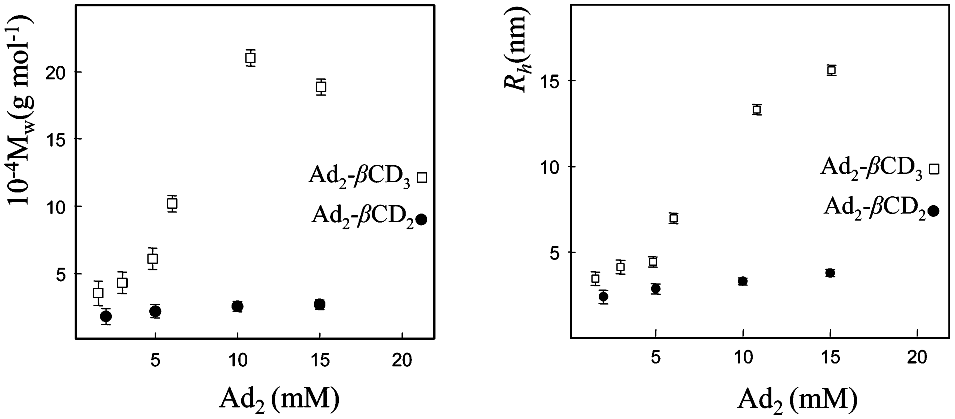

***Figure 4.*** Apparent molecular weights (a) and hydrodynamic radii (b) of the supramolecular polymers as a function of the Ad$_2$ concentration.

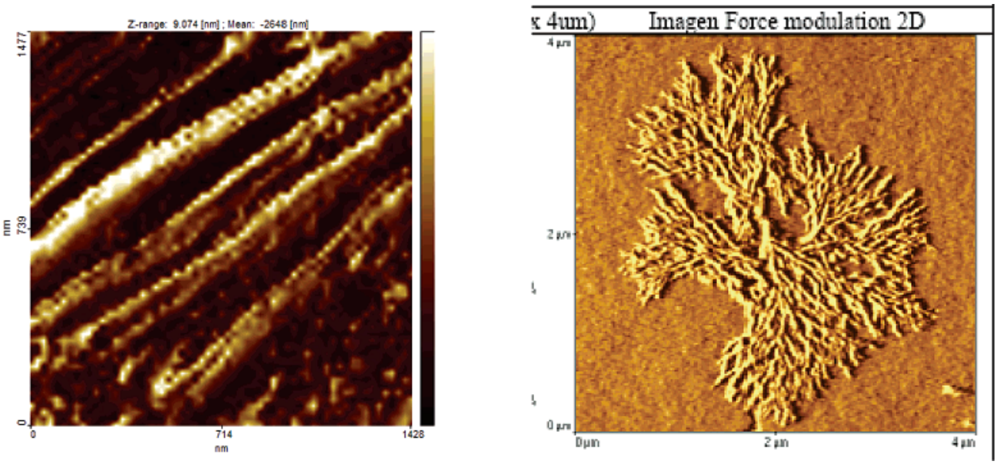

***Figure 5.*** AFM amplitude images of linear supramolecular polymer (bright particles) formed by the reaction between a dimer guest, Ad$_2$, and (a, left) a dimer host, $\beta$CD$_2$ an a trimer host $\beta$CD$_3$ (b, right).

stabilized by the formation of hydrogen bonds with water molecules which reside in the channels and act as bridges for the formation of hydrogen bonds between adjacent polymer columns.

In the literature, much less attention has been paid to the formation of dendrimer-like structures formed by cyclodextrin derivatives. As far as we know only our former dendrimer formed by sodium deoxycholate (as the ditopic guest) and a $\beta$CD trimer with an aromatic (1,3,5-benzene tricarbonyl) ring as bridge has been published.[34] The two topic sites of sodium deoxycholate are very close to each other, and some steric hindrance is expected when a polymer-like structure is being formed. The adamantyl dimer studied here has two advantages over sodium deoxycholate. First, the equilibrium constant for the formation of the inclusion complex is much higher for the adamantyl residue than it is for the steroid body of the bile salt. Second, the flexibility of its alkyl chain bridge allows any appropriate geometry which the polymer could adopt.

A close inspection of the dendrimer of Figure 5b suggests that it is in fact a mixture of dendrimers of smaller size. The measurement of the width of the branches and their height (see SI) shows a clear relationship between the height and the width of the branches. The minimum observed values (less than 40 nm) indicate that we are far from observing the Cayley tree at a molecular level and that these branches are composed by smaller ones which are superimposed on each other. The limitations of the AFM technique did not allow the detection of the Cayley tree at a molecular level. TEM images of Cayley trees can be seen at the SI section.

Finally, we have to remark that the adamantyl dimer is a powerful surfactant. Although Vashkevich et al.[50] have synthesized several adamantylammonium salts and studied their surface activity, this is the first adamantyl dimer for which such an activity is reported, probably because most of the published adamantyl dimer derivatives have a rather low solubility in water. However, its full characterization as a surfactant is far outside the scope of this paper, and further work is in progress. The surface tension−log(concentration) plot is linear until a concentration of 15 mM (reaching a $\gamma$ value of 49.3 mN m$^{-1}$ at 21.5 mM) which suggests that a continuous association process is taken place. The maximum concentration used for the ITC experiments, 0.5 mM, is low enough to prevent any influence on the measured heat derived from any de-aggregation process as a demicellization one.[51]

## Conclusions

From the experimental enthalpy and free energy values determined from ITC experiments, we have demonstrated that

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the single interaction between one binding site of the guest and one binding site of the host, is independent of the number of binding sites of each interacting species. The average values (from six systems studied here) are $\Delta H° = - 26.6 \pm 2.3$ kJ mol$^{-1}$ and $\Delta G° = - 30.4 \pm 3.2$ kJ mol$^{-1}$. Thus, the process is mainly enthalpy driven. The formation of polymer-like entities was demonstrated by static and dynamic light scattering experiments and by AFM and TEM measurements. AFM evidences that these polymer-like structures are linear for the $Ad_2$:$\beta CD_2$ system and Cayley tree type for the $Ad_2$:$\beta CD_3$ one.

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**Supporting Information Available:** Synthesis of polymer precursors of Figure 1; basic theories of static and dynamic light-scattering techniques; ITC calorimetric titration thermograms; ROESY spectrum for the monomer−monomer reaction used as reference; ROESY spectrum for the $Ad_2$:$\beta CD_2$ system; ROESY experiments for the $Ad_2$:$\beta CD_3$ system; AFM amplitude images of the linear supramolecular polymer; AFM image of a Cayley tree; measurement of width and height of the branches of the Cayley tree polymer (AFM image); TEM image of Cayley tree structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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