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Evidence of a self-inclusion phenomenon for a new class of mono-substituted alkylammonium-β-cyclodextrins

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A new class of mono-substituted *N*-alkyl-*N*,*N*-dimethylammonium-β-cyclodextrins has been synthesized in a three step procedure from the native β-cyclodextrin. The structural analysis of these compounds undertaken by combined use of 1D and 2D NMR spectra indicate that the two methyl groups bound on the nitrogen are magnetically inequivalent due to a self-inclusion phenomenon of the alkyl chain inside the CD cavity. A variable-temperature ^{1}H NMR study showed that these mono-substituted CD derivatives formed temperature-independent intramolecular complexes with their own alkylammonium substituent. The strength of the interaction between the alkyl moiety and the cyclodextrin cavity has been evaluated by a competitive method using an adamantane derivative. Finally, surface tension measurements demonstrated the surface active character of these compounds and confirmed their self-inclusion ability.

Introduction

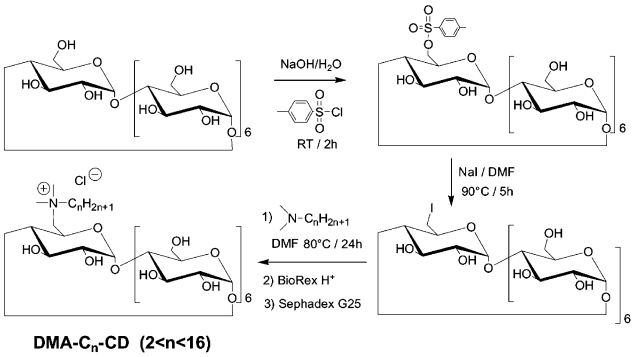
The great variety of available modified cyclodextrins (CD) and their ability to recognise a wide range of lipophilic guest molecules has made them useful tools in supramolecular chemistry.[1] Actually, thanks to their toroidal shape and strong binding affinity for hydrophobic drugs, CDs constitute potential carriers for transport through biological barriers.[2] In particular, it is thought that amphiphilic β-CD derivatives interact with biological membranes due to their lipophilic character and many modified cyclodextrins have been synthesized for that purpose.[3] Concurrently, studies have also shown that cationic entities may be anchored into membranes due to the electronic attraction force between the positive charge of these species and the negative charge of the lipid bilayer of the membrane.[4]

In order to take benefits from both cationic and lipophilic properties, we have recently focused our attention on modified CDs containing an ammonium salt and a long-alkyl chain. We describe here a straightforward three step synthesis of *N*-alkyl-*N*,*N*-dimethylammonium cyclodextrins (DMA–C_n–CD, with *n* the number of carbons on the alkyl chain). This new family of mono-substituted β-CDs is constituted of a β-cyclodextrin on which a quaternary ammonium group is grafted on its primary face so that the wider opening of the CD (secondary face) remains accessible for organic guest species. A detailed NMR analysis has been carried out to determine the conformation of the ammonium moiety with respect to the CD. In addition, their behaviour in water was examined as a function of their concentration and the length of the alkyl chain.

Results and discussion

Synthesis

Starting from the native β-CD, mono-tosylated[5] and mono-iodide[6] β-CDs were successively obtained according to procedures already described in the literature (Scheme 1). The mono-iodide β-CD then reacted on a ternary *N*-alkyl-*N*,*N*-dimethylamine whose linear alkyl moiety contained from 2 to 16 carbons (even number) to give the expected *N*-alkyl-*N*,*N*-dimethylammonium cyclodextrins in an average yield of 40%.



Scheme 1 Three step synthesis of DMA–C_n–CDs.

It is noteworthy that, contrary to amphiphilic CDs described in the literature whose use in large quantities proved inconvenient because of their poor solubility in water,[7] the DMA–C_n–CDs of this study showed great solubility in water (>60 mM).

NMR structural analysis

First, to get information about the position of the ammonium moiety towards the CD cavity, 2D T-ROESY experiments have been performed. These experiments were preferred to classical 2D ROESY as it was shown that this sequence provides reliable dipolar cross-peaks with a minimal contribution of scalar transfer.[8] As an example, the region of the 2D T-ROESY contour maps concerning the interactions through space between the protons of the C_4 and C_{12} aliphatic chains and the inner protons of the cavity is shown in Fig. 1.

Intense cross-peaks were detected from DMA–C_4–CD to DMA–C_{16}–CD between the inner protons of the cavity (H-3 and H-5) and the alkyl region which confirmed the inclusion between the CD and the alkyl chain. The contacts detected for the DMA–C_4–CD derivative were informative of the depth of the inclusion: indeed, the intensity of the correlation between the methyl and the CD was much more important than those of the methylenes, suggesting that an alkyl chain length of four carbons constitutes a minimum for a recognition process to occur. By contrast, no contact was observed for DMA–C_2–CD which clearly showed

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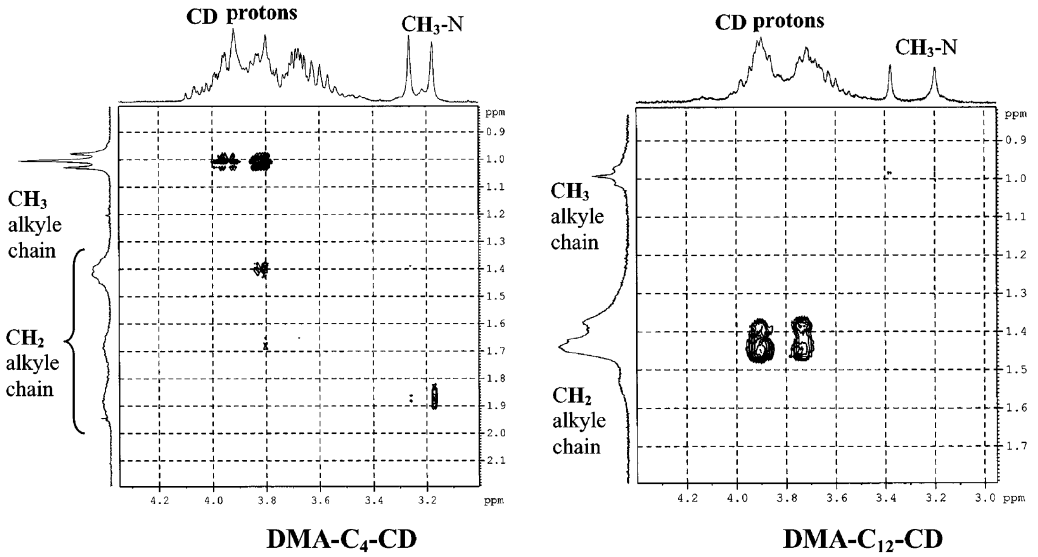


Fig. 1 2D T-ROESY data (300 ms mixing time) at 298 K in D_2O of DMA–C_4–CD (10 mM) and DMA–C_{12}–CD (10 mM).

that the ethyl group did not penetrate the β-CD cavity and was closely located in the outer layer of the CD.

Nevertheless, the question of intra- or inter-inclusion was not elucidated at this stage of the study. Thus, we then tried to get more information about whether the alkyl arm was included in the cavity of the CD on which it is grafted or in the cavity of another DMA–C_n–CD. It is then customary to assess the accurate position of the substituent with regard to the cavity of the CD by investigating the effect of the dilution of the compound in water on the ^{1}H NMR chemical shifts.[7a,9] Thus, to evaluate the influence of the alkyl chain length as a function of the concentration, three DMA–C_n–CD derivatives were chosen: DMA–C_4–CD, DMA–C_{10}–CD and DMA–C_{14}–CD. Their concentrations were varied from 10^{-4} to 10^{-2} M at 25 °C. Whatever the concentration or length of the alkyl chain, no difference in the chemical shifts was detected on the ^{1}H NMR spectra, neither in the CD pattern nor in the alkyl region. Given the low concentrations throughout the study, we favour the view that the obtained ^{1}H NMR spectra are relative to intramolecular inclusion processes. Moreover, the high hydrophobicity of long alkyl chains is not a favourable argument for their spreading in water and their inclusion in another DMA–C_n–CD cavity. Nevertheless, the hypothesis of an intermolecular recognition could not be definitely excluded, especially at high concentrations of DMA–C_n–CDs, since the corresponding spectrum could be very similar to the previous one. When increasing the concentrations, the system favours equilibrium between intra- and intermolecular complexes.

To allow a better understanding of the inclusion process, an in-depth NMR analysis was necessary. A partial assignment of the resonances of the ^{1}H spectra with D_2O as the solvent gave us more details on the geometry of the ammonium moiety with respect to the CD cavity. A total assignment of the 1D spectrum was limited due to the extreme spectral overcrowding in the CD region, giving very broad and shouldered peaks.

Interestingly, a splitting into two of the resonance of some protons of the alkyl moieties has been detected for DMA–C_n–CDs with $n \geq 4$. As an example, the partial ^{1}H NMR spectra of DMA–C_2–CD and DMA–C_{12}–CD are displayed in Fig. 2.

The methyl groups appeared as only one singlet for DMA–C_2–CD and as two singlets for DMA–C_n–CD ($n \geq 4$). This magnetic inequivalence has also been detected for the protons in the β-position to the nitrogen for DMA–C_4–CD. The same splittings into two were observed on the ^{13}C{^{1}H} NMR spectra and HMQC experiments confirmed the assignments made through ^{1}H homonuclear NMR, especially the presence of

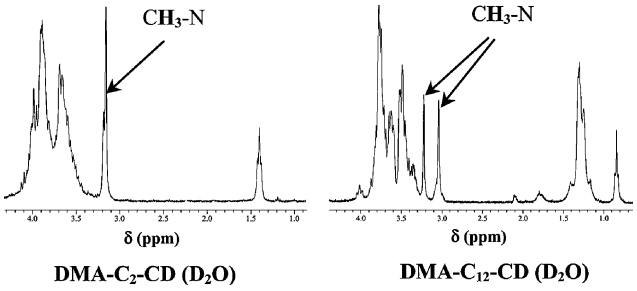


Fig. 2 Partial ^{1}H NMR spectra of DMA–C_2–CD and DMA–C_{12}–CD (10 mM) at 298 K in D_2O.

two magnetically different methyl groups. At first sight, the magnetic inequivalence between these methyl groups indicates that the motion of the ammonium residue is restrained, at least according to the NMR timescale, as soon as the alkyl chain lengthens. The ethyl group of the DMA–C_2–CD is too small to hinder the rotation of the ammonium around the bond linking the nitrogen to the primary carbon C-6 of the substituted glucoside unit in a consistent way. Therefore, the two methyl groups are magnetically equivalent in that case. On the other hand, the presence of longer alkyl chains (>C_4) may influence the respective orientation of the methyl groups or protons of the alkyl chain and their relative motion due to the self-inclusion process. Consequently, the geometry of the molecule might be modified to such an extent that the methyl groups bound to the nitrogen might be magnetically inequivalent.[7] For comparison, the ^{1}H NMR spectrum of the non-covalent complex β-CD–*N*-hexadecyl-*N*,*N*,*N*-trimethylammonium chloride (1 : 1 mixture) has been performed and exhibited for the host and guest signals a non-perturbed symmetry. Actually, in that case, the three methyl groups bound to the nitrogen were magnetically equivalent since only one resonance was detected at 3.14 ppm. Another proof of the structural inequivalence of the two methyls of DMA–C_n–CD in water was given by ^{1}H NMR spectra in DMSO-d_6 which is a well known dissociating solvent.[7a,10] As an example, the ^{1}H NMR spectra of DMA–C_4–CD obtained in D_2O and DMSO-d_6 are displayed in Fig. 3.

In that case, only one resonance was detected for both methyl groups indicating that the alkyl chain is not confined in the cavity but is able to spread in the solvent. The protons of the alkyl chain in the β-position to the nitrogen were also indicative of a non-included substituent since the two resonances observed in D_2O were merged in a single broad peak in DMSO-d_6.

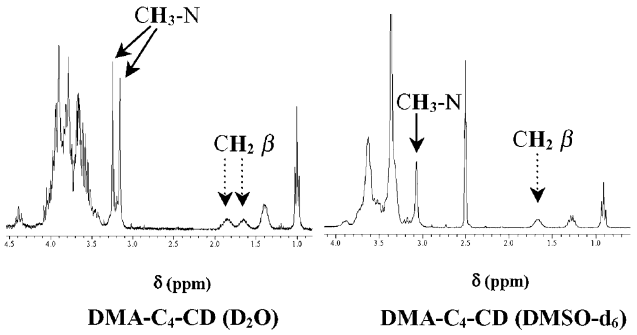
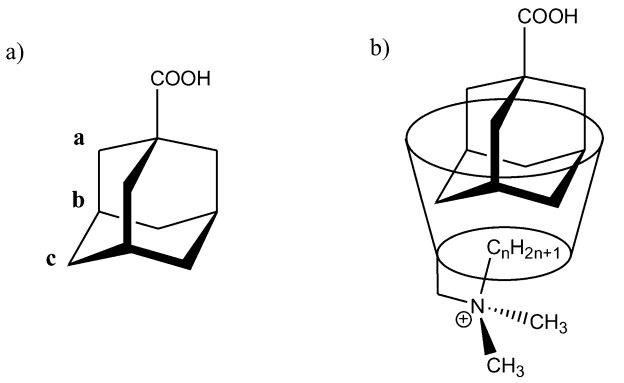


Fig. 3 Partial ^{1}H NMR spectra of DMA–C_4–CD (10 mM) in D_2O and DMSO-d_6 at 298 K.

In order to get further clarification on the dynamic of the system, the conformational change of DMA–C_n–CD derivatives, which may be induced by temperature variations, has been studied by a variable-temperature ^{1}H NMR experiment. The ^{1}H NMR spectrum of the alkyl or CD regions was virtually unaffected by temperature variations in the range 25–80 °C. Consequently, the self-inclusion of the alkyl arm in a CD cavity is not a function of the temperature certainly due to the high hydrophobic character of the former and its desire to stay closely coiled in the cavity. This led us to think that the association constant between the alkyl moiety and the CD is high.

Complexing properties with 1-adamantanecarboxylic acid

The determination of the association constant between the alkyl moiety and the CD on which it is grafted by classical methods proved inconvenient as the concentrations of the guest and the host could not be varied for evident reasons.[11] Therefore, we attempted to approach the value of the association constant between the alkyl chain and the CD on which it is grafted by a competitive method using 1-adamantanecarboxylic acid (Adac) as a guest (Scheme 2(a)).



Scheme 2 (a) 1-Adamantanecarboxylic acid (Adac); b) inclusion complex between DMA–C_n–CD ($n > 2$) and Adac.

Actually, adamantyl derivatives are well known to form stable inclusion complexes with many cyclodextrins ($10^4 < K_A < 10^5$ M^{-1}).[12] The inclusion of Adac in DMA–C_n–CDs has been evidenced by ^{1}H and T-ROESY NMR experiments. Actually, since H-3 and H-5 are located inside the cavity of the CD, they are sensitive to changes in the microenvironment upon inclusion. Competitive inclusion complexation of Adac is supported by several lines of evidence: (i) a 1 : 1 mixture of Adac and DMA–C_n–CD clearly showed downfield induced chemical shifts for some of the protons of the adamantyl moiety (0.2 ppm downfield for protons **b** (Scheme 2(a)). The shifts were smaller for the protons assumed to be exposed more to the solvent than to the cavity (protons **a**, Scheme 2(a)); (ii) chemical shifts were also detected on the $^{13}C\{^1H\}$ NMR spectrum, here again proving a through-space interaction; (iii) 2D T-ROESY NMR experiments clearly pointed out spin–spin interactions through space between the adamantyl part and the inner protons of the CD cavity (Fig. 4).

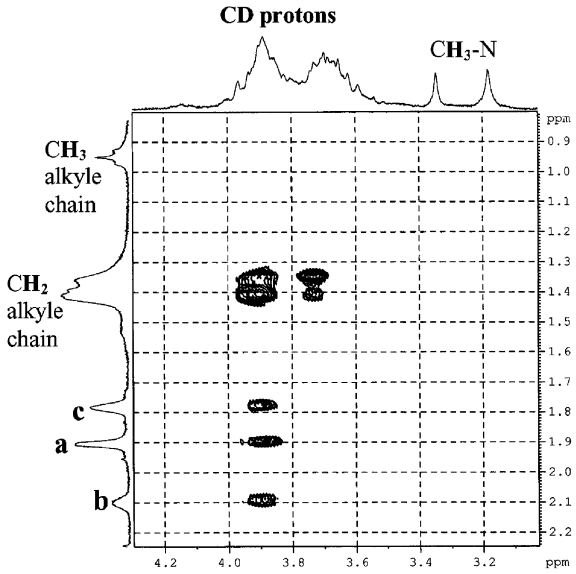


Fig. 4 2D T-ROESY data (300 ms mixing time) at 298 K in D_2O of a 1 : 1 mixture of DMA–C_{12}–CD (10 mM) and Adac (10 mM).

In fact, the DMA–C_n–CD intramolecular complex is only weakened on interaction of the cavity with Adac. As a matter of fact, Adac proved unable to completely extract the alkyl chain from the CD-cavity to form a binary inclusion complex since cross-peaks were always visible between the protons of the aliphatic chain and H-3 and H-5. Moreover, the two methyl groups still appeared magnetically inequivalent, proving that the ammonium moiety closely remains around the cavity. The adamantane group pushed out the alkyl chain from the CD cavity but the high hydrophobicity of the alkyl chain drives it to stay in the neighbourhood of the cavity, as if it covers the primary face of the CD (Scheme 2(b)).

The stoichiometry of the DMA–C_n–CD–Adac complexes ($n = 2$ and 4) has been established by the method of continuous variation (Job's method)[13], using various ratios of DMA–C_n–CD to Adac, while keeping the total moles of DMA–C_n–CD plus Adac constant. The Job diagrams for the protons of Adac showed a maximum at a guest/(host + guest) ratio of 0.5 indicating that there is one molecule of Adac for each molecule of DMA–C_n–CD. As a example, the Job plot of the DMA–C_4–CD–Adac couple is depicted in Fig. 5.

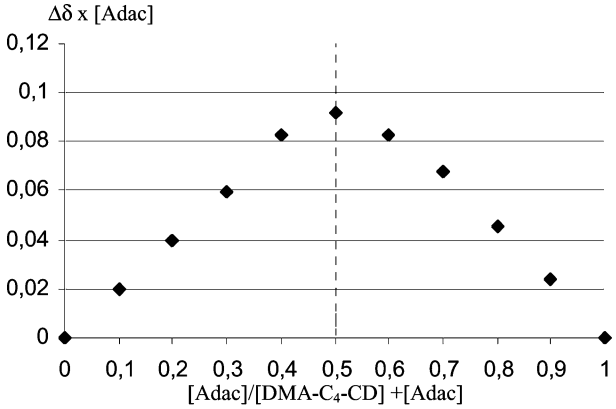


Fig. 5 Job plot upon mixing DMA–C_4–CD and Adac. The total concentration of the two components was 1 μM in D_2O, with mole fractions varying from 0 to 1.

A significant variation in the apparent association constant between Adac and the cavity could be measured when varying

Table 1 Association constants (K) of 1-adamantanecarboxylic acid (Adac) with the native β-CD and DMA–C_n–CDs ($n = 2$ and 4)

Host–guest complexes	β-CD–Adac	DMA–C_2–CD–Adac	DMA–C_4–CD–Adac
K/M^{-1}	42 000	39 000	16 100

the length of the alkyl chain. Indeed, ^{1}H NMR titration experiments have been performed with mixtures of DMA–C_n–CD and Adac. The concentration of Adac was kept constant (1 mM) and that of the modified cyclodextrin was varied from 0.3 to 3 mM. Association constants between those compounds could be deduced from a fitting programme[14] and are gathered in Table 1.

Firstly, the apparent association constant of the native β-CD–Adac couple has been measured to serve as a reference ($K_A = 42\,000\ M^{-1}$). Secondly, the similar value obtained for the association constant between Adac and DMA–C_2–CD ($K_A = 39\,000\ M^{-1}$) logically showed that the penetration of the adamantane part in the CD cavity by the secondary face was barely hindered by the non-included alkylammonium substituent grafted on the primary face. The determination of association constants between Adac and DMA–C_n–CD with a longer alkyl chain ($n > 4$) proved inconvenient because of the intramolecular inclusion process. One can reasonably think that the penetration of Adac was much more difficult with a lengthening of the aliphatic part and consequently the value of the apparent association constants decrease ($K_A < 16\,000\ M^{-1}$).

Finally, a variable-temperature ^{1}H NMR experiment has also been carried out with a 1 : 1 mixture of DMA–C_4–CD and Adac. This mixture was heated from 25 to 80 °C. Contrary to what was observed in the absence of an external guest, the ^{1}H NMR spectra obtained in the presence of Adac were slightly different when increasing the temperature. The induced chemical shifts at 60 and 80 °C were lower than those measured at 25 °C (0.20 and 0.18 ppm *vs.* 0.23 ppm respectively), suggesting that the association constant was lower at high temperature. This is consistent with the general trend for which the strength of the host–guest interactions decrease with the temperature.

Surface tension

Surface tension measurements have been carried out to evaluate the amphiphilic behaviour of these modified CDs. The results are gathered in Fig. 6. Due to the self-inclusion phenomenon, these compounds did not show similar curves to those of usual surfactants such as *N*-alkyl-*N*,*N*,*N*-trimethylammonium chloride.[15] In particular, no critical micellar concentration (CMC) could be defined and a lengthening of the alkyl chain did not lead to a decrease in the surface tension. Indeed, all DMA–C_n–CD derivatives showed similar behaviour since their surface tensions were all gathered in the same cluster. The surface active behaviour of these molecules was probably the result of a competition between an intra- or inter-inclusion phenomenon and a micellization process. Actually, when the alkyl chains were included in a CD cavity, the amphiphilic character was partially hidden which prevented any classical micelle aggregation from occurring.

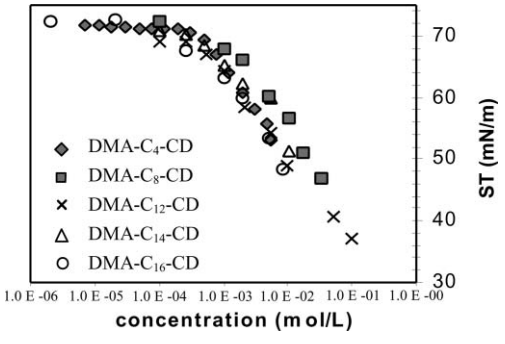


Fig. 6 Pendant drop surface tension curves of a DMA–C_n–CD series ($n = 4$, 8, 12, 14, 16).

Surface tension measurements have also been carried out in water with an increasing amount of a DMA–C_{12}–CD–Adac complex in a stoichiometric ratio. The obtained curve was superimposable on that of DMA–C_{12}–CD alone (Fig. 6). Therefore, the absence of CMC in that case clearly showed that the amphiphilic character of DMA–C_{12}–CD could not be restored upon addition of Adac. This corroborates the above NMR results according to which the alkyl chain and Adac coexist in the CD cavity.

Conclusion

As a conclusion, a direct route to a new and attractive class of amphiphilic alkylammonium β-CDs has been found. The compounds could be easily purified by a classical work-up and isolated in good yields (≈40%) from the last step of the synthesis whatever the length of the alkyl chain. A self-inclusion process was proved by surface tension measurements and a detailed NMR study. The use of Adac unambiguously demonstrated that an external guest may at least partially, if not totally, reduce the motion of the alkyl chain and confine it to the primary side of the CD cavity. As a consequence, the alkyl chain is supramolecularly trapped between a wall of water and a bulky guest as a spring jammed in a goblet with a heavy ball on it. A study is in progress to evaluate the behaviour of these compounds towards biological membranes.

Experimental

General

Organic compounds were purchased from Sigma-Aldrich and Acros Organics in their highest purity and used without further purification. β-CD was a generous gift of Roquette Frères (France). The Bio-Rex 70 resin was purchased from Bio-Rad and the G-25 Sephadex resin from Sigma-Aldrich.

The surface tensions were measured by the pendant drop method using a DSA 10 Mk2 drop shape analysis system (Krüss GmbH Germany). The DMA–C_n–CD solutions were prepared by using double-distilled deionized water (Milli-Q, Millipore) as a solvent. All measurements were carried out at 20.0 ± 0.1 °C.

The ^{1}H and ^{13}C NMR spectra were recorded at 300.13 and 75.476 MHz respectively on a Bruker Avance DRX spectrometer. ^{1}H and $^{13}C\{^1H\}$ chemical shifts are given in ppm relative to the external reference sodium [D_4]3-(trimethylsilyl)propionate (98% atom D) in D_2O. The 2D T-ROESY experiments were run using the software supplied by Bruker. Mixing times for T-ROESY experiments were set at 300 ms. The data matrix for the T-ROESY was made of 512 free induction decays, 1 K points each, resulting from the co-addition of 32 scans. The real resolution was 1.5–6.0 Hz/point in F2 and F1 dimension, respectively. They were transformed in the non phase-sensitive mode after QSINE window processing.

Synthesis of DMA–C_n–CD

To a stirred solution of mono-iodo-β-CD (1 g, 0.8 mmol) in dry DMF (40 mL) was added *N*-alkyl-*N*,*N*-dimethylamine (16 mmol). The reaction mixture was stirred for 24 h at 80 °C. After removal of the solvent, the residue was washed under stirring in a mixture of acetone–chloroform. The insoluble powder was recovered by filtration. After dissolution in water,

the crude product was subjected to chromatography on a Bio-Rex® 70 ion-exchange column and eluted with a water to 0.1 M aqueous NaCl gradient. The appropriate fractions were partially evaporated and then desalted on a Sephadex G-25 column with water as an eluent. The CD-containing aliquots were then lyophilisized to give the expected *N*-alkyl-*N*,*N*-dimethylammonium-*β*-CD as a white powder in an average yield of 40%. The purity of each compound was checked by NMR, ES-MS and elemental analysis.

Selected spectral data for mono-6-(*N*,*N*-dimethylethylamino)-*β*-cyclodextrin hydrochloride (DMA–C_2–CD)

^{1}H NMR (300 MHz, D_2O) δ 5.41 (d, 1H, H-1 ammonium–glucose), 5.14–5.02 (m, 6H, H-1 *β*-CD), 4.49 (t, 1H, H-5 ammonium–glucose), 4.09–3.48 (m, 43H, H-2, H-3, H-4, H-5, H-6, H-6′ *β*-CD, H-2, H-3, H-4, H-6, H-6′ ammonium–glucose and $CH_2\alpha$), 3.16 (s, 6H, $N^+(CH_3)_2$), 1.41 (t, 3H, $CH_3\beta$). ^{13}C NMR (75 MHz, D_2O) δ 102.49–101.94 (C-1 *β*-CD), 100.74 (C-1 ammonium–glucose), 83.41–81.17 (C-4 *β*-CD), 79.64 (C-4 ammonium–glucose), 73.57–72.02 (C-2, C-3, C-5 *β*-CD and C-2, C-3 ammonium–glucose), 67.20 (C-5 ammonium–glucose), 62.17 ($CH_2\alpha$), 61.19–60.53 (C-6), 51.52 ($N^+(CH_3)_2$), 8.01 ($CH_3\beta$). ES-MS $(M–Cl)^+$ *m*/*z* calc 1190.4, found 1190.5. $C_{46}H_{80}O_{34}NCl$, $3H_2O$ %N = 1.09; %C = 43.14; %H = 6.77; found %N = 1.05; %C = 43.43; %H = 6.66.

Selected spectral data for mono-6-(*N*,*N*-dimethylbutylamino)-*β*-cyclodextrin hydrochloride (DMA–C_4–CD)

^{1}H NMR (300 MHz, D_2O) δ 5.41 (d, 1H, H-1 ammonium–glucose), 5.25–5.07 (m, 6H, H-1 *β*-CD), 4,39 (t, 1H, H-5 ammonium–glucose), 4.02–3.54 (m, 43H, H-2, H-3, H-4, H-5, H-6, H-6′ *β*-CD, H-2, H-3, H-4, H-6, H-6′ ammonium–glucose and $CH_2\alpha$), 3.25 (s, 3H, CH_3–N^+), 3.17 (s, 3H, $CH_3\beta$–N^+), 1.87–1.65 (m, 2H, $CH_2\beta$), 1.44–1.39 (m, 2H, $CH_2\gamma$), 1.01 (t, 3H, $CH_3\delta$). ^{13}C NMR (75 MHz, D_2O) δ 102.40–101.90 (C-1 *β*-CD), 100.20 (C-1 ammonium–glucose), 82.97–81.05 (C-4 *β*-CD), 79.18 (C-4 ammonium–glucose), 73.68–71.69 (C-2, C-3, C-5 *β*-CD and C-2, C-3 ammonium–glucose), 67.14 (C-5 ammonium–glucose), 63.66 (Cα), 61.54–60.13 (C-6), 54.18 and 53.25 ($N^+(CH_3)_2$), 24.73 ($CH_2\beta$), 19.55 ($CH_2\gamma$), 13.43 (CH_3). ES-MS $(M–Cl)^+$ *m*/*z* calc 1218.5, found 1218.9. $C_{48}H_{84}O_{34}NCl$, $2H_2O$ %N = 1.09; %C = 44.67; %H = 6.87; found %N = 1.06; %C = 44.69; %H = 7.06.

Compounds DMA–C_6–CD, DMA–C_8–CD, DMA–C_{10}–CD, DMA–C_{12}–CD, DMA–C_{14}–CD and DMA–C_{16}–CD gave similar NMR data to that of DMA–C_4–CD except for the signal at 1.50–1.00 ppm on the ^{1}H NMR spectrum whose integration depended on the number of methylene groups on the alkyl chain.

Calculation of association constants by ^{1}H NMR spectroscopy

The H_b proton of Adac was chosen for evaluating the apparent association constant. Assuming a 1 : 1 inclusion mechanism, the observed chemical shift of the H_b proton (δ_{OBS}) and the complex concentration [COMP] are described as follows:

$$\delta_{OBS} = \left(\delta_{Hb}\cdot[\mathrm{Adac}] + \delta_{Hbcomp}\cdot[\mathrm{comp}]\right)/[\mathrm{Adac}]_{tot}$$

$$[\mathrm{comp}] = \frac{1}{2}\left([\mathrm{CD}]_{tot} + [\mathrm{Adac}]_{tot} + \frac{1}{K}\right) - \frac{1}{2}\sqrt{\left([\mathrm{CD}]_{tot} + [\mathrm{Adac}]_{tot} + \frac{1}{K}\right)^2 - 4[\mathrm{CD}]_{tot}\cdot[\mathrm{Adac}]_{tot}} \quad (1)$$

where K and $[\ ]_{tot}$ stand for the association constant and total concentration, respectively.[14] For a given value of K, [COMP] is known and δ_{COMP} may be calculated from eqn. (1) for each $[CD]_{tot}$. Standard deviation over δ_{COMP} is minimized relative to K to obtain the 1 : 1 association constant. For DMA–C_n–CD with $n > 4$, an accurate standard deviation could not be properly determined because the concentration of the intramolecular CD–C_n complex is no more negligible than the concentration of the CD–Adac complex.

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