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Compensation of steric demand by cation–π interactions, cobaltocenium cations as guests in tetraurea calix[4]arene dimers

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The affinities of ferrocene (2) and the cobaltocenium cation (3[+]), which have roughly the same size and differ in their charge, towards the inner cavity of the dimeric capsule formed by tetraurea calix[4]arene (1) were studied in $C_2D_4Cl_2$ solutions. While 3[+], which occupies more than 75% of the internal volume of the dimer, is readily encapsulated this is not the case for 2. This is probably due to cation–π interactions, which operate only between 3[+] and the aromatic rings of the calix[4]arene dimer. We found that the affinity of the cobaltocenium cation is higher than that of the tropylium cation (4[+]) and is only 2–3 times less than that of the tetraethylammoniun cation (5[+]). From the variable temperature ^{1}H NMR spectra of this capsule, the free energy of activation at 298 K ($\Delta G^{\ddagger}_{298K}$) for the reorientation of the hydrogen bonded belt between the two parts of the dimer could be determined by total line shape analysis for the aromatic protons of the calixarene. The value of 14.3 ± 0.2 kcal mol^{-1} for the dimeric capsules of $3^+PF_6^-$ is very similar to the free activation energy found for dimeric capsules of 1 with $4^+PF_6^-$ and $5^+PF_6^-$ in $C_2D_4Cl_2$. It becomes significantly lower, if PF_6^- is replaced by BF_4^-. We also found that ten times more DMSO is needed to disrupt the capsule 1·3[+]·1 than the corresponding 1·1 dimer containing benzene as guest. This demonstrates again the importance of the cation–π interactions for the stability of such hydrogen-bonded dimeric capsules.

Introduction

"Container molecules",[1] capable of encapsulating other molecules, have attracted much interest in recent years. Such capsules can be obtained in apolar solvents by dimerization of calix[4]arene derivatives[2] substituted by four urea groups at their "wider rim". These dimers as well as similar examples based on resorcinarenes, were characterized in the solid state and in solution by various spectroscopic techniques.[3–5]

Mostly steric effects were considered when discussing the relative affinity of various guests towards the inner cavity of the dimers and a packing coefficient of about 55% was suggested to be ideal in the absence of stronger and more specific interactions such as hydrogen bonding or cation–π interactions.[6a] However, cases in which this steric criterion for tetraurea calix[4]arene dimers is violated were also reported.[6b]

Cation–π interactions play an important role in various biological systems.[7] Recently, others and we have demonstrated the formation of dimeric capsules in which cation–π interactions are crucial.[6b,8] It was found that benzene and the slightly larger tropylium cation, which occupy around 40–50% of the inner volume of the capsule formed by tetraurea calix[4]arenes, differ in their affinity towards the dimer by at least 5 orders of magnitude. This difference was attributed to cation–π interactions.[8c] To verify whether cation–π interactions can compensate even larger steric demands, we decided to study the cobaltocenium cation (3[+]) and ferrocene (2) as potential guests, which differ in their charge but have analogous shape and size, corresponding to about 75–80% of the inner volume of the dimer 1·1 (Scheme 1). $C_2D_4Cl_2$ was used as solvent for all measurements.

Results and discussion

Fig. 1 shows the ^{1}H NMR spectra of 2, 3[+], 1·1 and the mixtures obtained by addition of these two guests to solutions of dimer
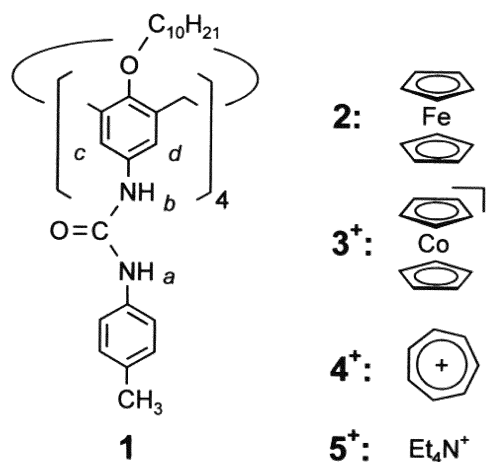

Scheme 1

1·1. Obviously, the ^{1}H NMR spectra of the mixtures of ferrocene and dimer 1·1, shown in Figs. 1C and 1D, are a mere superposition of the spectra of their components (see Figs. 1A and 1B) even when ferrocene is added in large excess. The same result was found for the addition of ruthenocene, also a non-charged metallocene, to the solution of 1·1 (data not shown). Figs. 1E and 1F show the ^{1}H-NMR spectra of cobaltocenium hexafluorophosphate and the 1·1 dimer and Figs. 1G and 1H show the spectra of a 1 : 1 mixture of these components immediately and 60 hours after the mixing, respectively. Additional signals are observed immediately after mixing equimolar amounts of $3^+PF_6^-$ and dimer 1·1. While one set of signals corresponds to the dimer with encapsulated solvent molecules, the second set of signals should be attributed to a capsule containing a cobaltocenium cation as its guest (1·3[+]·1). After two days the signals of the solvent containing dimer disappeared

Table 1 Diffusion coefficients ($\times 10^{-5}$ in $cm^2\ s^{-1}$) of **2**, **3$^+$**, and the dimer **1·1** in $C_2D_4Cl_2$ solutions at room temperature

System	D of "free" **2/3$^+$**	D of encapsulated **3$^+$**	D of **1·1** containing $C_2D_4Cl_2$		D of **1·1** containing **3$^+$**	
2	1.18 ± 0.01 (4.06 ppm)	—	—	—	—	—
Mixture of **2** and **1·1** (1 : 1)	1.20 ± 0.02 (4.06 ppm)	—	0.24 ± 0.01 (5.81 ppm)	0.24 ± 0.01 (9.28 ppm)	—	—
3$^+$	0.75 ± 0.01 (5.61 ppm)	—	—	—	—	—
Mixture of **3$^+$** and **1·1** (1 : 1)	—	0.23 ± 0.02 (2.72 ppm)	0.22 ± 0.01 (4.15 ppm)	0.23 ± 0.01 (2.19 ppm)	0.23 ± 0.01 (9.04 ppm)	0.23 ± 0.01 (6.67 ppm)
Mixture of **3$^+$** and **1·1** (20 : 1)	0.73 ± 0.01 (5.61 ppm)	0.25 ± 0.01 (2.72 ppm)	—	—	0.24 ± 0.01 (9.04 ppm)	0.24 ± 0.01 (6.67 ppm)
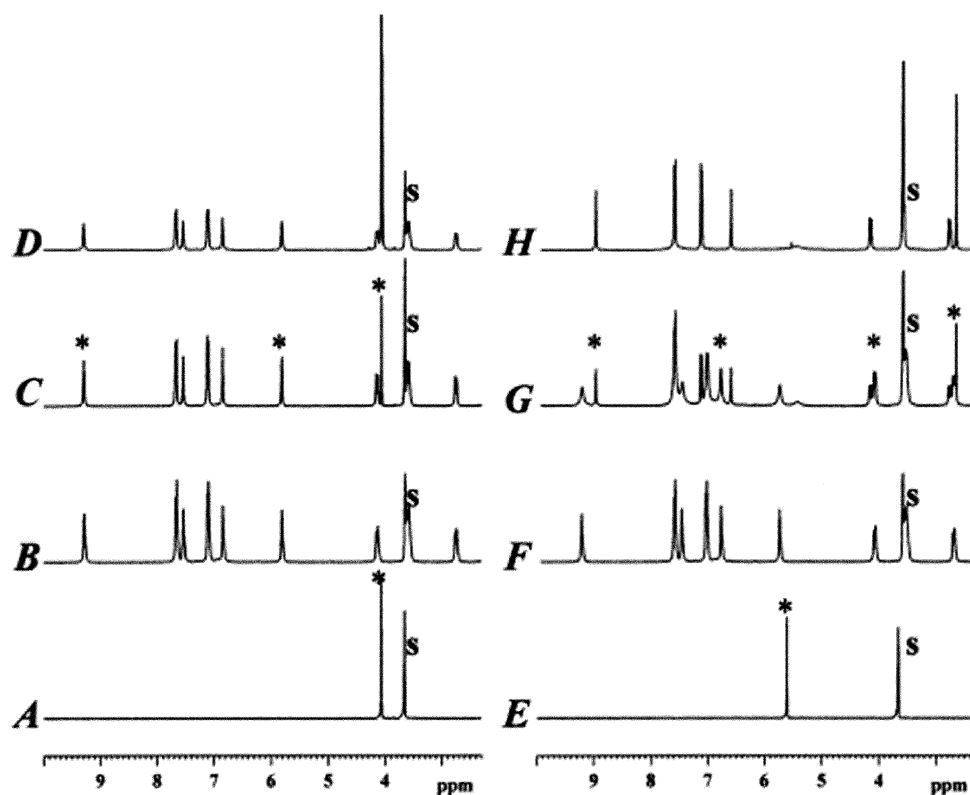
Fig. 1 Sections of ^{1}H NMR spectra (400 MHz, $C_2D_4Cl_2$, room temperature) of: (A) ferrocene; (B) **1·1**; (C) mixture of ferrocene and **1·1** (1 : 1); (D) mixture of ferrocene and **1·1** (10 : 1) measured 48 h after preparing the sample; (E) cobaltocenium hexafluorophosphate; (F) **1·1**; (G) mixture of cobaltocenium hexafluorophosphate and **1·1** (1 : 1) immediately and (H) 60 h after preparing the sample. Signals for which the diffusion coefficients are given in Table 1 are labelled with *.

and only the signals attributed to the dimeric capsule **1·3$^+$·1** remain. When a large excess of **3$^+$·PF$_6^-$** is added to the solution of the dimer, the cobaltocenium cation-containing capsule is observed nearly immediately.

Diffusion measurements[9] can be used and have been used to characterize supramolecular systems in solution.[10] Recently, we demonstrated that they are a useful tool for probing encapsulation and studying the structure of hydrogen-bonded capsules.[8c,10e,11] Support for the fact that the observed species is indeed the cobaltocenium cation-containing dimeric capsule **1·3$^+$·1** was obtained again by NMR diffusion measurements. They showed that both the set of signals attributed to the solvent-containing dimer and to the species bound to the cobaltocenium cation have the same diffusion coefficients within experimental error (Table 1). Moreover, the signal at 2.7 ppm, which is supposed to represent the encapsulated cobaltocenium cation because of its large up-field shift (~3 ppm),[3b,8c,10e] also has the same diffusion coefficient as the dimer, suggesting that the encapsulated cobaltocenium cation and the dimer diffuse as one supramolecular entity as expected.[8c,10e] The diffusion coefficient measured for this signal (($0.23 \pm 0.02) \times 10^{-5}$ $cm^2\ s^{-1}$) is also significantly lower than the diffusion coefficient

obtained for the signal at 5.6 ppm (($0.73 \pm 0.01) \times 10^{-5}$ $cm^2\ s^{-1}$), which represents the "free" cobaltocenium cation in a $C_2D_4Cl_2$ solution. On the other hand, the diffusion coefficients of the ferrocene peak in the absence and presence of dimer **1·1** were the same (Table 1) and much higher than that of the capsule **1·1**. These results are clearly reflected in Fig. 2 which shows the signal decay as a function of the gradient strength (G) used in the diffusion measurements, for one representative peak of **1·1** in a $C_2D_4Cl_2$ solution and the peaks of **2** and **3$^+$** in the presence of **1**. An additional support for the identification of the signal at 2.7 ppm as the encapsulated cobaltocenium cation is provided by a 2D-ROESY experiment. We found cross peaks between the signal at 2.7 ppm and the signal at 5.6 ppm (free **3$^+$**) and with the signals that represent the NH units of the dimer.

The complete assignment of the ^{1}H NMR spectra of the dimeric capsule was obtained by 2D-NMR experiments. Besides the ROESY experiment, which showed a correlation between the two NH protons mentioned above (*a* and *b*, see Scheme 1), the DQF-COSY ^{1}H NMR spectrum of this dimer at 248 K showed a clear correlation only between the two signals at 5.5 ppm and 7.6 ppm suggesting that they belong to the two aromatic protons *c* and *d* (Scheme 1). These two signals are
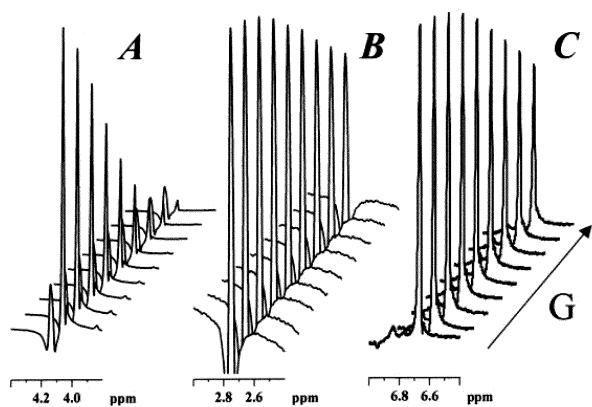
Fig. 2 ¹H NMR signal decay in a $C_2D_4Cl_2$ solution at 298 K as a function of the diffusion gradient strength (G) of: (A) ferrocene in the presence of **1**; (B) the encapsulated cobaltocenium cation; and (C) one representative peak of **1·3⁺·1**.

broad over the temperature range of 298 K–338 K due to the hindered rotation of the belt of the urea groups in the cobalto-cenium cation capsule. Such a dynamic process has been recently documented in such cation-containing capsules.[8b,c] The energetic barrier for this process was determined, using total line shape analysis, to be $\Delta G^{\ddagger}_{298K} = 14.3 \pm 0.2$ kcal mol⁻¹. Similar energy barriers of 14.3 ± 0.2 kcal mol⁻¹ and 14.0 ± 0.2 kcal mol⁻¹ were found for the dimeric capsules with **4⁺PF₆⁻** [8c] and **5⁺PF₆⁻**,[8b] respectively. Interestingly, the barrier is lower for capsules with **4⁺BF₄⁻** and **5⁺BF₄⁻**, where only 12.6 ± 0.2 and 11.9 ± 0.2 kcal mol⁻¹, were found.

The volume of ferrocene or of the cobaltocenium cation is about 125 Å³ if it is considered as a "pentagonal antiprism". Since the volume of the groove cannot be filled, it seems more reasonable to consider a pentagonal column which would occupy a volume of 150 Å³. In spite of its larger size the affinity of the cobaltocenium cation **3⁺** towards the cavity of dimer **1·1** is even higher than that of the tropylium cation **4⁺** as seen in Fig. 3, since **3⁺** replaces **4⁺** if a 1 : 1 : 1 mixture is kept over a longer period.
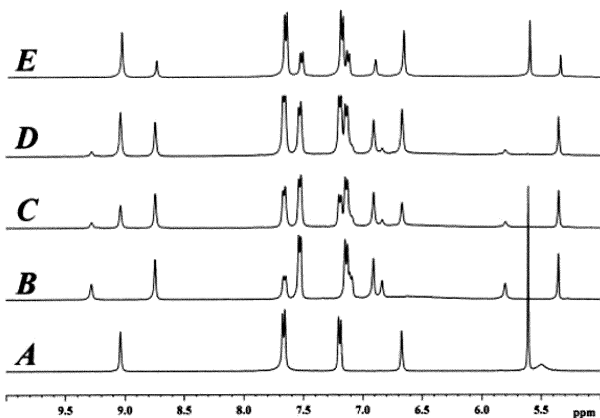

Fig. 3 Sections of the ¹H NMR spectra (400 MHz, $C_2D_4Cl_2$, room temperature) of: (A) mixture of **3⁺PF₆⁻** and **1·1** (1 : 1); (B) mixture of **4⁺BF₄⁻** and **1·1** (1 : 1); (C) mixture of **4⁺BF₄⁻** and **1·1** (sample B) and **3⁺PF₆⁻** (1 : 1 : 1) immediately after preparing the sample; (D) mixture C ~2 h after preparing the sample; and (E) mixture C ~2.5 weeks after preparing the sample.

Only the tetraethylammonium cation, which was the pre-ferred guest among various quaternary ammonium cations in mass-spectrometric studies,[6b] was found to have a slightly higher affinity than **3⁺** towards the cavity of the dimer. Fig. 4 shows sections of the ¹H NMR spectra of **1·3⁺·1** and **1·5⁺·1** as PF₆⁻ salts (Figs. 4A and 4B) and of the mixture shown in Fig. 4B immediately and 9 days after addition of one equivalent

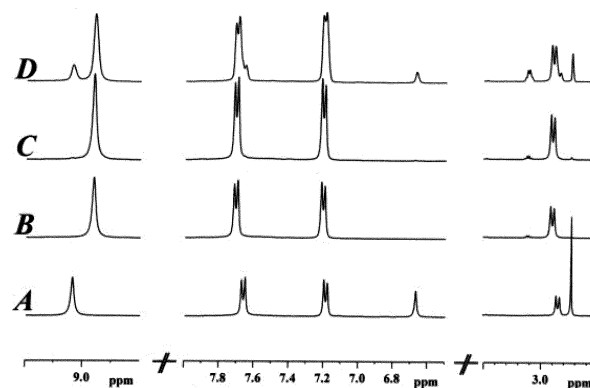**Fig. 4** Sections of the ¹H NMR spectra (400 MHz, $C_2D_4Cl_2$, room temperature) of the PF₆⁻ salts of: (A) **1·3⁺·1**; (B) **1·5⁺·1**; (C) mixture of **1·5⁺·1** and **3⁺** immediately after preparing the sample; and (D) 9 days after preparing the sample.

of **3⁺PF₆⁻** (Figs. 4C and 4D). Indeed, when the solution reaches equilibrium, the ratio of **1·5⁺·1** to **1·3⁺·1** in the $C_2D_4Cl_2$ solution is about 3 to 1.

Further support for the high affinity of the cobaltocenium cation towards the dimer is reflected in the relative stability of the **1·3⁺·1** capsule. Although we previously found that only 4 molecules of DMSO per monomer (one DMSO molecule per urea unit) are required to disrupt the benzene encapsulating dimer,[10e] in the case of **1·3⁺·1**, 12–13 DMSO molecules per urea unit are required in order to decompose the dimer into two monomers. In addition, if a limited amount of DMSO is added to a solution of **1·3⁺·1** and **1·4⁺·1** in $C_2D_4Cl_2$ then the dimers containing the tropylium cation are disrupted while the dimers containing cobaltocenium remain intact.

In conclusion, the data presented here provide an additional example for the importance of cation–π interactions for the encapsulation of charged guests by hydrogen-bonded tetraurea calix[4]arene dimers and for the stability of the formed inclu-sion complex. Apparently, such interactions are strong enough in the present system to compensate for the steric demands, which prevent a guest with a similar size as ferrocene or cobaltocene from encapsulating. It should be noted, however, that cation–π interactions cannot compensate for the stronger steric demands of a bis(pentamethylcyclopentadienyl)cobalto-cenium cation, which was not encapsulated in **1·1**. Since cobalto-cene is not encapsulated in the dimer, we can speculate that reducing the encapsulated cobaltocenium cation would eject it from the dimer. Oxidation of the cobaltocenium cation may result in the encapsulation of the obtained product into the dimer. Therefore, this system may be regarded as a potential "molecular switch". Such a process was recently reported for the hexameric capsule of resorcinarene.[12]

Experimental

Materials

All deuterated solvents were supplied by Aldrich (USA) and used as is. The tetraurea calix[4]arene derivative **1** was prepared according to the procedure published in reference 3c.

¹H-NMR of 1·3⁺·1 PF₆⁻ (400 MHz, 298 K, C₂D₄Cl₂)

$\delta = 9.04$ (s, 8H), 7.67 (d, $J = 7.4$ Hz, 16H), 7.6 (broad, 8H), 7.20 (d, $J = 7.4$ Hz, 16H), 6.67 (s, 8H), 5.5 (broad, 8H), 4.23 (d, $J = 12$ Hz, 8H), 3.65 (m, 16H), 2.84 (d, $J = 12$ Hz, 8H), 2.72 (s, 10H), 2.21 (s, 24H), 1.84 (m, 16H), 1.24 (m, 112H), 0.83 (t, $J = 6.2$ Hz, 24H).

¹H-NMR of 1·3⁺·1 PF₆⁻ (400 MHz, 258 K, C₂D₄Cl₂)

$\delta = 9.09$ (s, 8H), 7.64 (d, $J = 7.4$ Hz, 16H), 7.63 (s, 8H), 7.18 (d, $J = 7.4$ Hz, 16H), 6.70 (s, 8H), 5.45 (s, 8H), 4.16 (d, $J = 12$ Hz,

8H), 3.58 (m, 16H), 2.81 (d, $J = 12$ Hz, 8H), 2.63 (s, 10H), 2.18 (s, 24H), 1.82 (m, 16H), 1.19 (m, 112H), 0.80 (t, $J = 6.2$ Hz, 24H).

NMR measurements

NMR spectra were recorded on 400 MHz Avance Bruker NMR spectrometers (Karlshruhe, Germany). The deuterated solvents were used as internal locks and internal references (^{1}H NMR: $C_2D_4Cl_2$ 3.65 ppm; ^{13}C NMR: $C_2D_4Cl_2$ 51.7 ppm). Diffusion experiments were carried out on the 400 MHz NMR spectrometer equipped with a Great 1/10 pulse gradient unit capable of producing a Z-gradient of about 50 G cm^{-1}. All ^{1}H diffusion measurements were performed with a pulsed gradient spin echo (PGSE) pulse sequence [9] with a pulse gradient duration of 2 ms and a pulsed gradient separation of 62 ms. The pulsed gradients were incremented from 0 to 40.2 G cm^{-1} in ten steps. The diffusion experiments were performed at least three times and only data for which the correlation coefficient was higher than 0.999 were included.

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