JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Electrostatic Repulsion between Cucurbit[7]urils Can Be Overcome in [3]Pseudorotaxane without Adding Salts

M. Pessêgo,[†,‡] J. A. Moreira,[‡] A. M. Rosa da Costa,[‡] P. Corrochano,[§] F. J. Poblete,[§] and L. Garcia-Rio*[,†]

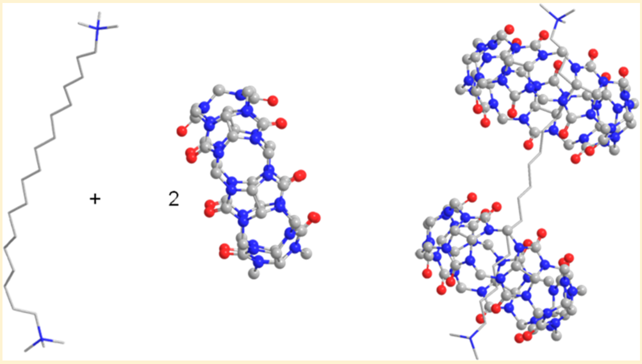
[†]Departamento de Química Física, Centro de Investigación en Química Biológica y Materiales Moleculares (CIQUS), Universidad de Santiago, 15782 Santiago, Spain

[‡]CIQA, Departamento de Química e Farmácia, Faculdade de Ciências e Tecnologia, Universidade do Algarve, Campus de Gambelas, 8005-139 Faro, Portugal

[§]Departamento de Química Física, Facultad de Ciencias y Tecnologías Químicas, Universidad de Castilla-La Mancha, Avda. Camilo José Cela s/n, 13071 Ciudad Real, Spain

Supporting Information

ABSTRACT: The host−guest chemistry between cucurbit[7]uril (CB7) and a series of bolaform (B*n*) surfactants with different chain lengths, *n* = 12−22, was the target of our study. [3]Pseudorotaxanes are formed when the alkyl chain of the bolaform has more than 14 carbon atoms. In these cases, two CB7 molecules can be accommodated between the two head groups of the bolaform without addition of electrolytes to the medium. In the case of a bolaform with 12 carbon atoms, the electrostatic repulsion between the carbonyl groups of the CB7 molecules avoids the threading of a second CB7 molecule yielding a mixed structure formed by a [2]pseudorotaxane and an external host−guest complex. The assembly behavior was investigated using NMR spectroscopy, isothermal titration calorimetry (ITC), and kinetic measurements.



■ INTRODUCTION

Cucurbit[*n*]urils (CB*n*, *n* = 5−8 and 10) are a family of macrocyclic host molecules composed of *n* glycoluril units linked by a pair of methylene groups with two identical carbonyl portals and a hydrophobic cavity.[1−4] The two carbonyl portals have a considerable negative charge density, which results in a high tendency of CB*n* to form host−guest complexes with cationic compounds.[5] Cucurbiturils have also been employed to construct polyrotaxanes and polypseudorotaxanes by differents aproaches.[6−15] The pseudorotaxanes may be formed by a "click" reaction between an alkyne and an azide in the inner cavity of cucurbituril. A second general procedure is to thread polymeric alkylammoniums or polyviologens with CB*n*. Combinations of heteromacrocyclices such as cyclodextrins (CDs) and CB*n* were used to construct polypseudorotaxanes. Liu[11,16,17] and Kim[18] studied the movement of CBs controlled by pH or by another macrocyclic molecule in polypseudorotaxanes containing CDs. Stoddart[19,20] and Du[21] have reported works on supramolecular nanovalves prepared by CB-catalyzed pseudorotaxanes, which could be activated under a range of pH stimuli and competitive binding.

In a recent study, we have showed that CB7 has a strong ability to complex alkyltrimethylammonium cations forming 1:1 complexes.[22] In the presence of an excess of CB7 2:1 complexes have been reported, where a mixed internal and external complex has been proposed (Scheme 1).[22a]

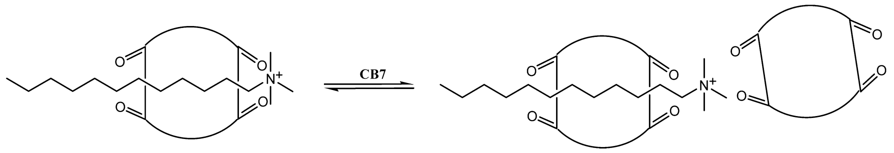
Macartney et al.[23−25] developed an extensive investigation on the host−guest interactions between CB7 and dicationic guests containing different head groups and various aliphatic and aromatic linkers. They found the formation of 1:1 ([2]-pseudorotaxane, Scheme 2a) and 2:1 host−guest complexes (Scheme 2b) between dicationic guests and CB7. Our previous results indicate that binding constants for internal alkyltrimethylammonium complexes are 10^2 times larger than for the external complexes.[22a] Consequently, the formation of [3]-pseudorotaxanes should be expected in the case of dicationic guests (Scheme 2c).

However, the formation of [2]pseudorotaxane plus an external complex instead of a [3]pseudorotaxane can be explained by the electrostatic repulsion between the negatively charged CB7 portals that hinders the formation of [3]pseudorotaxane structures. Traditionally, this problem has been solved by providing the medium with a high salt content, where cations dispose between the CB7 portals screening their electrostatic repulsions and allowing their approach.[8,9]

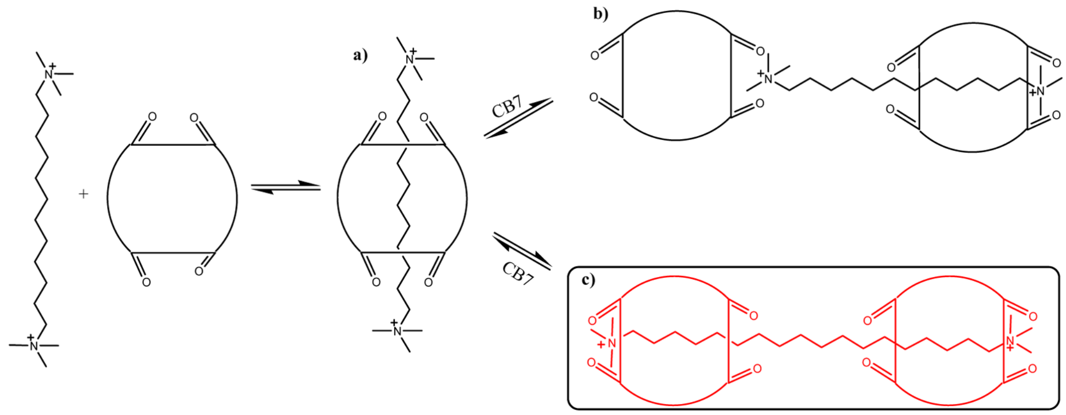
The aim of our study is to achieve the formation of [3]pseudorotaxane-type structures without addition of electrolytes to the medium. Our approach is based on the use of bolaform surfactants (dicationic guests) with cationic head

Received: February 7, 2013
Published: March 20, 2013

Scheme 1



Scheme 2



groups separated by an alkyl spacer. An increase in the alkyl spacer between the cationic head groups also increases the distance between the CB7 and, consequently, decreases the intensity of the repulsive forces, which facilitates the formation of the [3]pseudorotaxane. In this study, we show that when bolaform surfactants (B*n*) with $n \geq 14$ are used [3]-pseudorotaxanes form, with both hosts sharing the alkyl spacer, without electrolyte addition to the medium.

For that use, we used a well-established methodology to investigate host−guest complexes in aqueous solution: isothermal titration calorimetry (ITC) as well as diffusion-ordered NMR spectroscopy (DOSY) allowed us to obtain the equilibrium binding constants as well as the stoichiometry of the host−guest complexes. The analysis of the ^{1}H NMR chemical shifts of the guest as a function of host concentration can be used as an evidence of internal or external complexes. Moreover, we used a chemical probe in order to test the existence of internal or external complexes. In our previous work,[22a] the solvolysis of 4-methoxybenzenesulfonyl chloride (MBSC) proved to be a useful tool to distinguish between the formation of internal and external complexes.

■ RESULTS AND DISCUSSION

Isothermal Titration Calorimetry. The binding constants between CB7 and each B*n* were studied by calorimetric measurements. In the ITC experiments, the B*n* solutions were placed in the reaction cell and the CB7 solution was then added. As an example, the obtained results in the case of B18 are shown in Figure 1. The binding isotherm data were fitted to a model of "Two Sets of Sites".

The binding constants obtained between CB7 and B*n* for 1:1 and 2:1 complexes are shown in Table 1.

The binding constants reported in Table 1 show that in the formation of the 1:1 complex, the binding constants decrease as the alkyl chain of the surfactants increases, whereas the values for 2:1 complex increase with the alkyl chain. This behavior can be explained by electrostatic effects, which may play a crucial role in molecular recognition events in both aqueous and organic

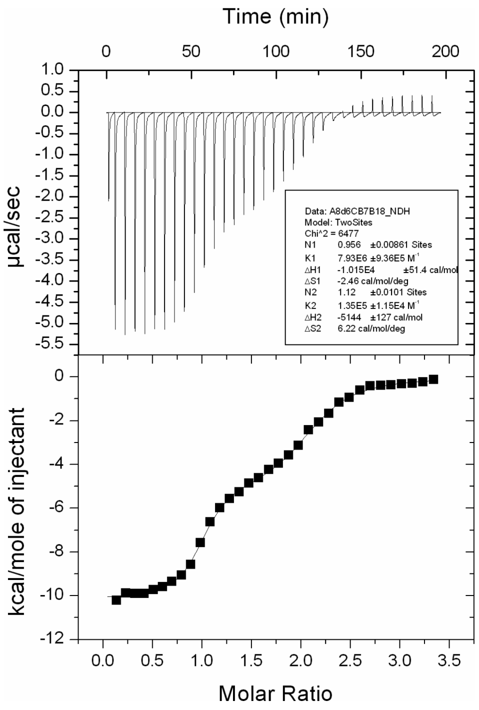


Figure 1. Titration of 1.459 mL of B18 (0.15 mM) with 266 μL of CB7 (2.5 mM) at 25 °C. Top: Calorimetric traces (heat flow against time). Botton: Integrated isotherms (obtained by integrating the peaks of the upper curve) vs molar ratio.

Table 1. Values of the Binding Constants for 1:1 and 2:1 Complexes of Bolaform Surfactants, Obtained by ITC

B*n*	$K_{1:1}$ (M^{-1})	$K_{2:1}$ (M^{-1})
B12	$(1.7 \pm 0.2) \times 10^7$	$(0.9 \pm 0.1) \times 10^4$
B14	$(2.9 \pm 0.7) \times 10^7$	$(3.5 \pm 0.5) \times 10^4$
B18	$(0.79 \pm 0.09) \times 10^7$	$(13.5 \pm 1) \times 10^4$
B20	$(0.27 \pm 0.07) \times 10^7$	$(29.9 \pm 3) \times 10^4$
B22	$(0.22 \pm 0.06) \times 10^7$	$(42.8 \pm 3) \times 10^4$

solutions.[26] The bolaform surfactants are dicationic compounds, so it is expected to obtain high values of binding constants in comparison with traditional surfactants. The magnitude of $K_{1:1}$ decreases as the alkyl chain increases, due to the increment on the distance between the head groups of the surfactant. In the 1:1 complex, CB7 moves along the hydrocarbon chain interacting with the head groups of the bolaform surfactant. As the alkyl chain length increases, the intensity of electrostatic interactions between the CB7 portals and the cationic head groups of surfactant decreases. On the other hand, the binding constant for the 2:1 host−guest complexes increases on increasing the alkyl chain length of the bolaform. This behavior can be explained on the basis of the electrostatic repulsions between the portals of both CB7. On increasing the alkyl chain length we also increase the distance between the two CB7 bonded to the bolaform and, consequently, decrease the intensity of the repulsive forces between the portal carbonyl groups of the different hosts.

Diffusion NMR Measurements. Figure 2 shows (as an example; see Supporting Information for B12, B14, B20, and B22 systems) the self-diffusion coefficients for B18 and CB7 as a function of molar ratio. The experimental data can be split into three different regions. As can be seen, as the concentration of CB7 increases, the self-diffusion coefficients of the bolaform show a significant decrease due to the formation of a 1:1 inclusion complex with the CB7 (Figure 2I), until a molar ratio of [CB7]/[B18] = 1. After this point (Figure 2 II), the diffusion does not reach a constant value. On the contrary, a continuous decrease is observed and this slope indicates the formation of a 2:1 complex until a molar ratio of [CB7]/[B18] = 2 is reached. After that initial decrease in the self-diffusion coefficients (Figure 2III), and in the presence of a large excess of CB7, the surfactant self-diffusion remains constant, since no more complexes are formed. On the other hand, a very small decrease in the self-diffusion coefficient of CB7 is observed in the region 2I. This behavior is due to the diffusion coefficient of the 1:1 host−guest complex being very close to that of uncomplexed CB7. On increasing the molar ratio [CB7]/[B18] (region 2II), the observed self-diffusion coefficient for CB7 decreases as a consequence of the formation of a 2:1 host−guest complex. An increase on the CB7 concentration after a molar ratio [CB7]/[B18] = 2 affords an increase in the concentration of uncomplexed CB7, and consequently, its observed self-diffusion coefficient increases (see region 2III).

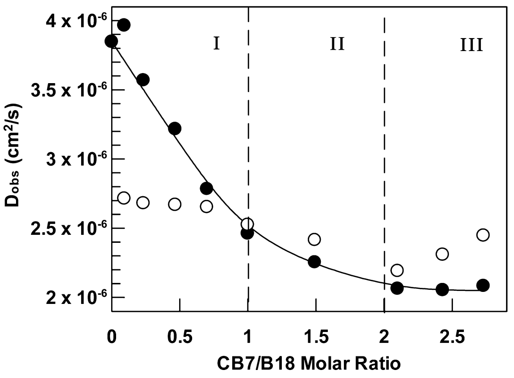


Figure 2. Self-diffusion coefficients of (●) B18 (1.3 mM) and (○) CB7 for varying CB7 concentration plotted as [CB7]/[B18] molar ratio. The solid line shows the fit to the model of self-diffusion coefficients for the 2:1 complex.

For the study of the experimental data in more detail and from a quantitative point of view, a model that takes into account the formation of two complexes, 1:1 and 2:1, allowed us to derive eq 1 to reproduce the experimental data (see the Supporting Information).

$$D_{\mathrm{Bn,obs}} = \frac{D_{\mathrm{Bn,f}} + K_{1:1}D_{\mathrm{CB7\text{-}Bn}}[\mathrm{CB7}] + K_{1:1}K_{2:1}D_{\mathrm{CB7_2\text{-}Bn}}[\mathrm{CB7}]^2}{1 + K_{1:1}[\mathrm{CB7}] + K_{1:1}K_{2:1}[\mathrm{CB7}]^2} \tag{1}$$

In order to fit the experimental results to eq 1, we used the values of the binding constants previously determined by calorimetric measurements. Global fits were performed on the assumption that 1:1 and 2:1 complexes are formed between CB7 and B*n*. The model of self-diffusion coefficients for 1:1 and 2:1 complexes can be used to obtain the values for the unknown variables $D_{\mathrm{Bn,f}}$ (self-diffusion coefficient for the uncomplexed bolaform), $D_{\mathrm{CB7\text{-}Bn}}$ (self-diffusion coefficient for the 1:1 host−guest complex) and $D_{\mathrm{(CB7)2\text{-}Bn}}$ (self-diffusion coefficient for the 2:1 host−guest complex). In the fitting procedure the values of $D_{\mathrm{Bn,f}}$, $K_{1:1}$ and $K_{2:1}$ were locked ($D_{\mathrm{Bn,f}}$ was independently obtained in the absence of CB7; $K_{1:1}$ and $K_{2:1}$ were taken from the ITC experiments (see Table 1). The results obtained are summarized in Table 2.

Table 2. Self-Diffusion Coefficients and Binding Constants for 1:1 and 2:1 Complexes of Bolaform Surfactants with CB7

B*n*	$D_{\mathrm{Bn,f}}$ (cm^2/s)	$D_{\mathrm{CB7\text{-}Bn}}$ (cm^2/s)	$D_{\mathrm{(CB7)_2\text{-}Bn}}$ (cm^2/s)
B12	$(4.79 \pm 0.08) \times 10^{-6}$	$(2.6 \pm 0.2) \times 10^{-6}$	$(2.4 \pm 0.2) \times 10^{-6}$
B14	$(4.5 \pm 0.1) \times 10^{-6}$	$(2.6 \pm 0.6) \times 10^{-6}$	$(2.1 \pm 0.3) \times 10^{-6}$
B18	$(3.9 \pm 0.7) \times 10^{-6}$	$(2.3 \pm 0.3) \times 10^{-6}$	$(2.1 \pm 0.2) \times 10^{-6}$
B20	$(3.90 \pm 0.08) \times 10^{-6}$	$(2.1 \pm 0.5) \times 10^{-6}$	$(1.9 \pm 0.2) \times 10^{-6}$
B22	$(3.3 \pm 0.1)\times 10^{-6}$	$(2.3 \pm 0.2) \times 10^{-6}$	$(1.7 \pm 0.3) \times 10^{-6}$

As can be seen, the self-diffusion coefficients decrease as the alkyl chain length of the bolaform increases, as well as when host−guest complexes with stoichiometries 1:1 and 2:1 are formed. These results are compatible with the increment of the molecular weight due to the formation of the host−guest complexes.

^{1}H NMR Measurements. In the ^{1}H NMR spectra of CB7 host−guest complexes, the complexation-induced chemical shift changes ($\Delta\delta = \delta_{\mathrm{bonded}} - \delta_{\mathrm{free}}$) in the proton resonances of the guest molecule are very informative about its average location with respect to the CB7 cavity. Upfield shifts ($\Delta\delta < 0$) are observed for protons located within the hydrophobic cavity, while the deshielding due to the polar carbonyl groups results in downfield shifts ($\Delta\delta > 0$) in the resonances of the guest protons in the proximity of the carbonyl oxygens.[1,3,4,27]

As can be seen in Figure 3 and in Figure S-3 (Supporting Information), the ^{1}H NMR spectra present alterations on gradually increasing CB7 concentration. The observed changes in the ^{1}H spectra of B*n* after addition of an excess of CB7 are in good agreement with the obtained results in DOSY and ITC experiments, pointing to the formation of a 1:1 and 2:1 complexes between CB7 and bolaform surfactants. Figure 3 show the ^{1}H chemical shift changes on the $^+N(CH_3)_3$ signals of B12 and B22 in the presence of increasing concentration of CB7.

In order to reproduce the experimental data, as in diffusion experiments, a mathematical model[28] based on a multiple

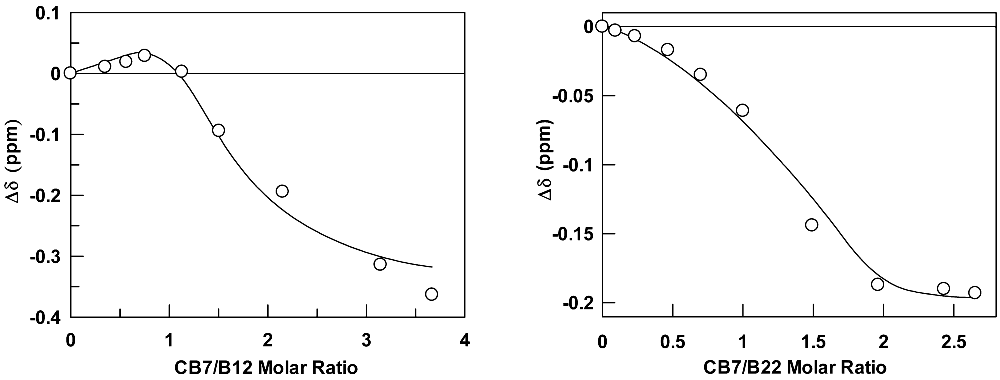


Figure 3. ^{1}H chemical shift changes on the signals of $^+N(CH_3)_3$ groups of B12 (left) and B22 (right) as a function of the [CB7]/[B*n*] molar ratio, at 25 °C; [B*n*] = 1.3 mM ($\Delta\delta = \delta_{\mathrm{bonded}} - \delta_{\mathrm{free}}$).

equilibrium taking into account the formation of 1:1 and 2:1 host–guest complexes was employed (eq 2).

$$\Delta\delta = \frac{\Delta\delta_{1:1}K_{1:1}[\mathrm{CB7}] + \Delta\delta_{2:1}K_{1:1}K_{2:1}[\mathrm{CB7}]^2}{1 + K_{1:1}[\mathrm{CB7}] + K_{1:1}K_{2:1}[\mathrm{CB7}]^2} \qquad (2)$$

Figure 3 shows the fit to eq 2 of the experimental $\Delta\delta$ on the $^+N(CH_3)_3$ signals of B12 and B22 vs CB7 concentration keeping constant the bolaform concentration. In the fitting procedure the binding constants $K_{1:1}$ and $K_{2:1}$ were locked and their values obtained from ITC experiments were used. A good fit between eq 2 (mathematical model based on a 1:1 and 2:1 host–guest complex, see the fitting parameters in Table S-1 Supporting Information) and the experimental points was obtained.

As can be seen from Figure 4, at CB7concentrations below the molar ratio [CB7]/[B*n*] = 1, for B12 a very small downfield shift is observed. This could be attributed to the rapid back and forth movement of CB7 due to strong ion-dipole interactions with both head groups of the bolaform as a consequence of their proximity to the carbonyl oxygens on its portals (Scheme 3 left). As the alkyl chain of the bolaform increases, the back and forth movement becomes slower. And being the CB7 mostly located on one of the head groups. Increasing the distance between the portal of CB7 and the other headgroup, results in a smaller effect on these protons (Scheme 3 right). The observed behavior for bolaform surfactants with long alkyl chain is comparable to that found in conventional surfactants, in which the protons of the headgroup show a gradually increase on the upfield shift as CB7 concentration increases.[22a]

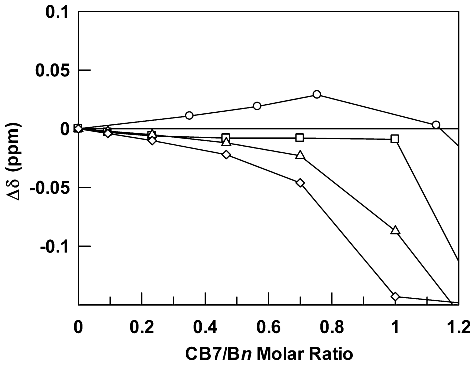


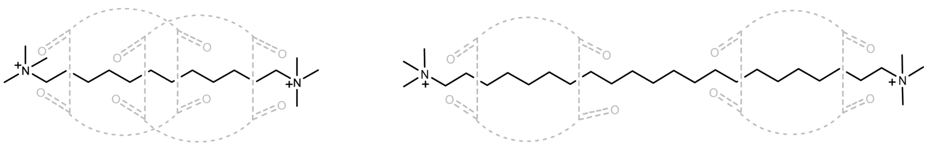
Figure 4. ^{1}H chemical shift changes on the signals of $^+N(CH_3)_3$ groups of B12 (○), B14 (□), B18 (△), and B20 (◊) as a function of molar ratio, [CB7]/[B*n*], at 25 °C; [B*n*] = 1.3 mM ($\Delta\delta = \delta_{\mathrm{bonded}} - \delta_{\mathrm{free}}$).

In the [2]pseudorotaxanes (Figure 5), the host residing over the central linker induces a large upfield shift ($\Delta\delta = \delta_{\mathrm{bonded}} - \delta_{\mathrm{free}} < 0$) on the methylene protons of the guest. The protons of the head groups show a very small upfield shift, which suggests that the $^+NMe_3$ groups are close to the portal. With the increase in the central chain of the guests, the host moves back and forth between both heads due to the ion dipole interactions with the trimethylammonium groups.

The addition of excess CB7, results in further changes on the chemical shifts of the guest protons (Figure 6). The magnitude and direction of the chemical shift changes suggest the conversion of 1:1 into 2:1 host–guest complexes, with the end groups inside the CB7 cavities (large upfield shifts). The magnitude of upfield shifts of the head groups protons decreases as the alkyl chain of bolaform surfactants increase. CB7-induced chemical shift changes ($\Delta\delta$) of B*n* (*n* = 12–22) for two differents molar ratios are summarized in Table 3.

The initial [2]pseudorotaxane formation results in a small upfield shift (B14, $\Delta\delta = -0.01$ ppm) on the protons of the head groups for all bolaform surfactants followed by a decrease on the magnitude of upfield shift on going from B14 ($\Delta\delta = -0.45$ ppm) to B22 ($\Delta\delta = -0.2$ ppm) in the presence of excess of CB7. The large upfield shift of the protons of the head groups suggests that these groups are placed in the CB7 cavity, while the small upfield shift observed for B*n* with $n \geq 20$ predicts that these protons are outside the cavity or near the carbonyl oxygens on the portal (Figure 6). At equimolar amounts, the central protons ($C_{n/2}$) of the chain experience an upfield shift that decreases on going from B12 ($\Delta\delta = -0.48$ ppm) to B22 ($\Delta\delta = -0.02$ ppm). In the presence of an excess of CB7, the upfield shift is gradually

Scheme 3. Dashed Lines Represent the CB7 Movement along the Alkyl Spacer of Bolaform Surfactant



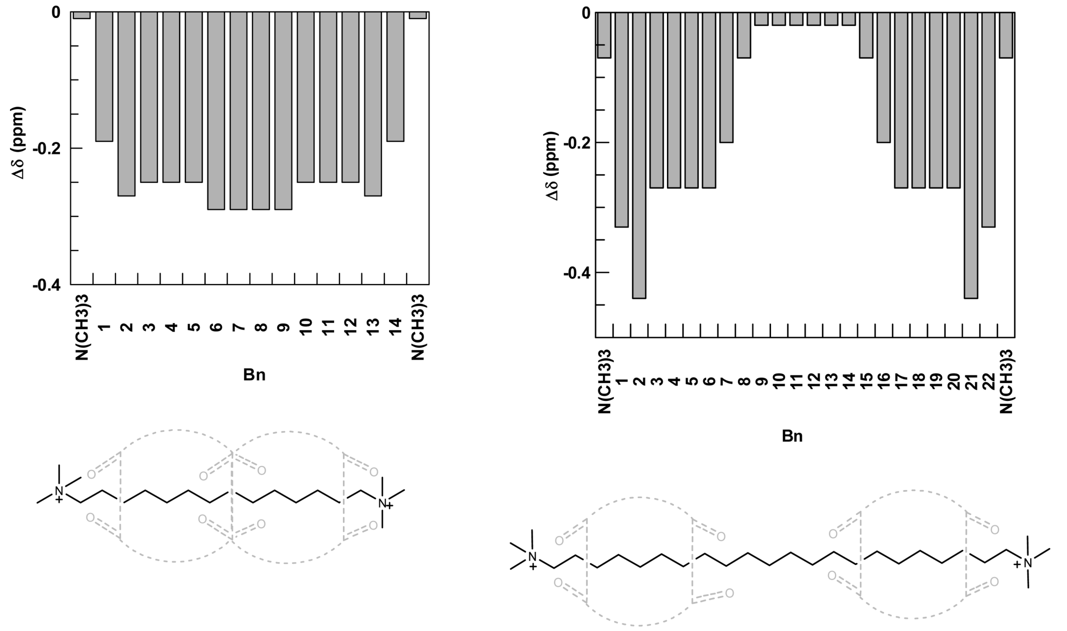


Figure 5. CB7-induced chemical shift changes ($\Delta\delta = \delta_{bonded} - \delta_{free}$, ppm) on the ^{1}H resonances of the protons of B*n* with *n* = 14 (left) and *n* = 22 (right) for a molar ratio [CB7]/[Bn] = 1; [B*n*] = 1.3 mM. Dashed lines represent the CB7 movement along the alkyl spacer of the bolaform surfactant.

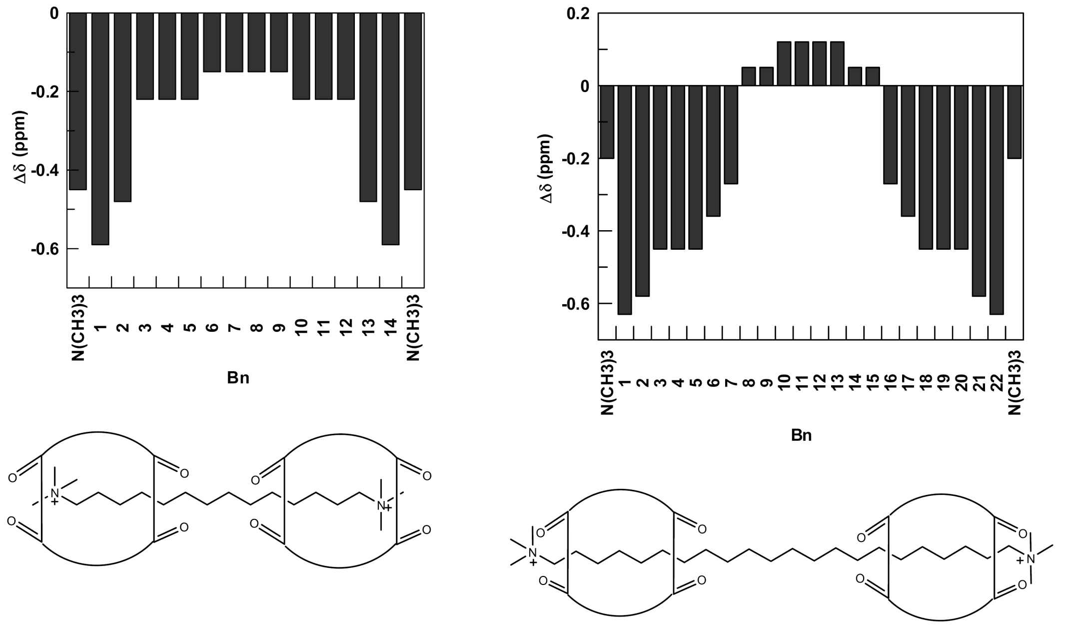


Figure 6. CB7-induced chemical shift changes ($\Delta\delta = \delta_{bonded} - \delta_{free}$, ppm) on the ^{1}H resonances of the protons of B*n* with *n* = 14 (left) and *n* = 22 (right) for a molar ratio [CB7]/[Bn] = 3; [B*n*] = 1.3 mM.

Table 3. CB7-Induced Chemical Shift Changes ($\Delta\delta = \delta_{bonded} - \delta_{free}$), ppm) on the ^{1}H Resonances of the Head Groups ($(^+NCH_3)_3$ and Methylene Protons (C_1 and $C_{n/2}$) for Molar Ratios 1 and 3

	molar ratio = 1, Δδ (ppm)			molar ratio = 3, Δδ (ppm)		
B*n*	$N^+(CH_3)_3$	C_1	$C_{n/2}$	$N^+(CH_3)_3$	C_1	$C_{n/2}$
12	−0.09	−0.25	−0.48	−0.35	−0.7	−0.14
14	−0.01	−0.19	−0.29	−0.45	−0.59	−0.15
18	−0.08	−0.32	−0.16	−0.36	−0.65	0.11
20	−0.04	−0.34	−0.01	−0.24	−0.63	0.15
22	−0.07	−0.33	−0.02	−0.2	−0.63	0.12

converted in downfield shift on going from B12 ($\Delta\delta = -0.14$ ppm) to B22 ($\Delta\delta = 0.12$ ppm), suggesting that the central portion of the guest is situated near the portal of CB7.

Contrary to the trend, B12 presents an upfield shift ($\Delta\delta = -0.35$ ppm) smaller than that observed for B14 ($\Delta\delta = -0.45$ ppm) in the presence of an excess of CB7. This fact could be explained on the basis that the structure of the 2:1 complex with B12 could be different from the one obtained with B14 (Figure 7 and Scheme 2b).

As a rough estimate, CB7 can accommodate inside its cavity approximately seven carbon atoms of the aliphatic chain in an all-trans conformation. In an extended conformation, the B12 alkyl chain does not have enough length to fully fit within two host's

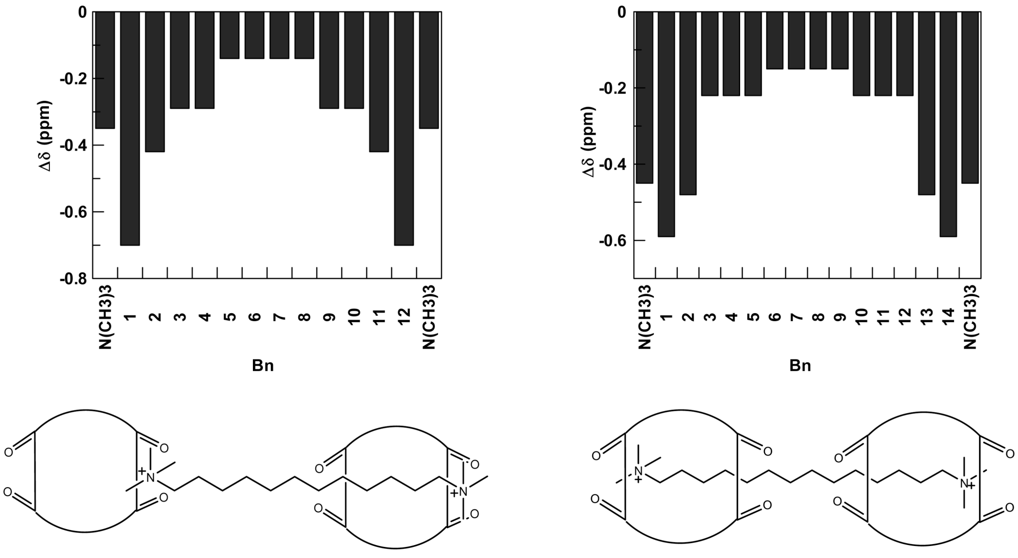


Figure 7. CB7-induced chemical shift changes ($\Delta\delta$, ppm) on the ^{1}H resonances of the protons of B*n* with $n = 12$ (left) and $n = 14$ (right) for a molar ratio [CB7]/[Bn] = 3; [Bn] = 1.3 mM.

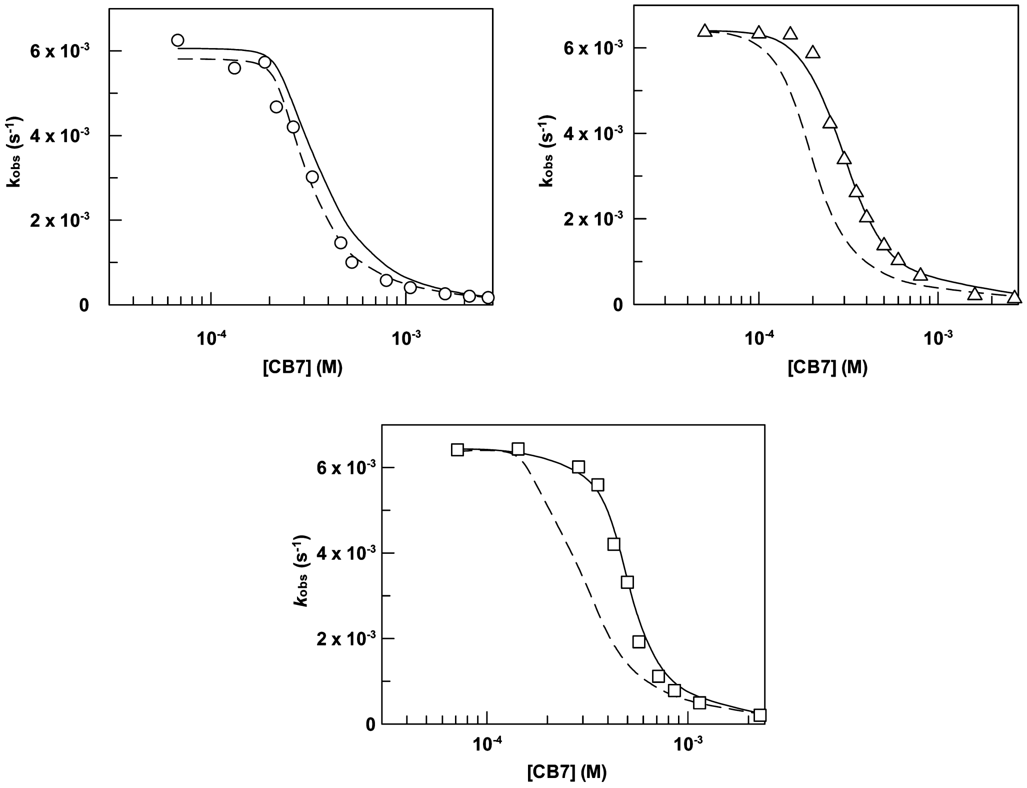


Figure 8. Influence of CB7 concentration on the observed rate constant for the solvolysis of MBSC in the presence of B12 (○), B14 (Δ), and B20 (□); [B*n*] = 0.21 mM; [MBSC] = 0.1 mM; $T = 25$ °C. Solid line: both host molecules include B*n* within their cavity. Dashed line: one host forms an internal and the other an external complex with B*n*.

cavities. However, the formation of a 2:1 host–guest complex is observed. In previous studies on host–guest interactions between CB7 and conventional alkyltrimethylammonium surfactants (C_nTA^+), we found the formation of a mixed internal and external complex with a 2:1 stoichiometry.[22a] From our point of view, the observed behavior in the case of B12 could suggest the possibility that in the formation of the 2:1 complex, one host form an inclusion complex with the bolaform surfactant and the other an external complex (Scheme 2b) in order to minimize the intensity of the repulsive forces between the carbonyl oxygens of both host molecules. However, additional experiments would be required to establish the possible structure of this 2:1 complex.

In summary, the obtained values for CB7-induced chemical shift changes for B*n* species suggest that in both 1:1 and 2:1 host–guest complexes the host molecules are situated over the central portion of the guest.

Kinetic Measurements. To study the mixed B*n* and CB7 systems, the hydrolysis of 4-methoxybenzenesulfonyl chloride (MBSC) was used as a chemical probe, since it shows high susceptibility to changes in the medium polarity. These systems were studied by carrying out experiments in which the bolaform surfactant concentration was kept constant and the CB7 concentration was varied. Considering that the solvolysis of MBSC takes place in two well-differentiated environments, water, k_w, and the CB7 cavity, k_{CB7}, eq 3 was derived (see the Supporting Information).

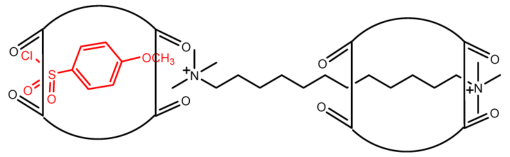
$$k_{obs} = \frac{k_w + k_{CB7}K_{CB7}[CB7]_f}{1 + K_{CB7}[CB7]_f} \tag{3}$$

As an example, results obtained for B12, B14, and B20 in the presence of CB7 are shown in Figure 8.

The experimental data were fitted to the model in which we assume that both CB7 host molecules include B*n* within their cavity (solid line) (Scheme 2c and Scheme S-3, Supporting Information). As can be seen from Figure 8, for B14 and B20 the model gave a good fit to the experimental data, while in the case of B12 it is evident that this model does not reproduce the experimental behavior.

In our previous paper, we found evidence on the formation of a 2:1 complex between CB7 and conventional cationic surfactants (C_nTA^+) where both CB7 host molecules complex the trimethylammonium group of the surfactant. One of the CB7 molecules forms an inclusion complex that includes in its cavity the alkyl chain of the surfactant and the other host molecule, an external complex with an empty cavity.[22a] In order to explain the experimental behavior of B12, we assumed the possibility that in the 2:1 complex one of the hosts forms an inclusion complex and the other an external complex with an empty cavity, which could then form an inclusion complex with the chemical probe, MBSC, (Scheme 4 and Scheme S-4, Supporting Information).

Scheme 4



A model that takes into account such a structure (Scheme 4) for the 2:1 complex was used to reproduce the experimental results. The results obtained in the case of B12, fitted using this model (dashed line), are shown in Figure 8. It is clear that the model that predicts the formation of an external complex between CB7 and B12 provides better agreement with the experimental data.

In an effort to confirm the proposed structural model for the 2:1 complex formed between CB7 and B*n*, we carried out an independent experiment. The continuous variation method (Job plot) was used to determine the stoichiometry of the complexes. In order to construct the Job plot, we studied the solvolysis reaction of MBSC in the presence of different ratios of CB7 and B*n* in such a way that the total concentration of [CB7]+[B*n*] was kept constant at 2 mM and the molar ratio was varied between 0 and 1. Job plot experiments were fitted to the structural models for B*n* with $n = 12$ and $n \geq 14$, previously proposed. Once more, we confirmed that for the 2:1 complex with B12, the model in which it is predicted the formation of an internal and external complex reproduces the experimental results.

As can be seen from Figure 9, for B12 a maximum was identified in the Job plot for a 0.5 molar ratio of CB7, which indicates that a 1:1 host−guest complex is formed between them. The Job plot suggests the formation of a 1:1 complex because one of the host molecules forms an inclusion complex and the other an external complex, which could form an inclusion complex with MBSC. However, in the case of B20, the maximum was obtained for a 0.6 molar ratio of CB7, which suggests the formation of a 2:1 host−guest complex. In the case of B20, both host molecules form an inclusion complex and none of them can accommodate the MBSC molecule. In this way, MBSC (the chemical probe used in the Job plot) considers that the complex between CB7 and B12 has a pseudo-1:1 stoichiometry, since the second CB7 presents an empty cavity that can accommodate the MBSC.

In the Job plot, we should expect to see a triangular behavior; however the slopes become irregular due due to the difference in magnitude of the equilibrium constants: $K_{CB7} = (1.8 \pm 0.1) \times 10^4$ M^{-1}, while $K_{1:1} \approx 10^6$ M^{-1} and $K_{2:1} \approx 10^4$ M^{-1}. Considering the kinetic results and ^1H measurements for B12, we believe that in the 2:1 complex one host molecule forms an inclusion complex and the other an external complex with the bolaform surfactant (Scheme 2b). On the other hand, evidence was found that in the formation of 2:1 complexes for B*n* with $n \geq 14$ both host molecules form an inclusion complex with the dicationic surfactants.

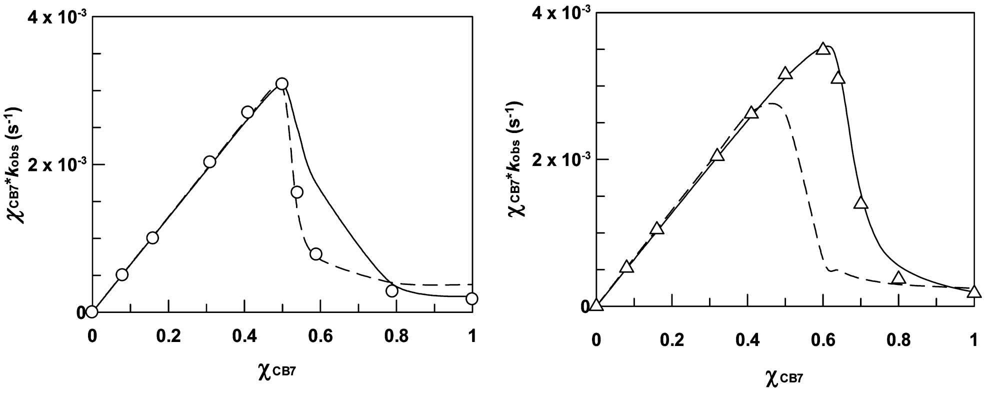


Figure 9. Job plots for B12 (○) and B20 (Δ). Solid line: both host molecules include B*n* within their cavity. Dashed line: one host form an internal and the other an external complex with B*n*.

Formation of polypseudorotaxanes using cyclodextrins is a well-reported procedure in the literature. The cyclodextrin assembly is due to hydrophobic interactions between the guest and the hosts and to the attractive interactions between cyclodextrins due to hydrogen bond stabilization of adjacent CDs.[29] However, in the case of cucurbiturils, the inclusion behavior is mainly controlled by electrostatic interactions. Considering this behavior for CB*n*, the formation of [2]-pseudorotaxanes is most favored than the [3]pseudorotaxanes with the bolaform surfactants, since in the system there is nothing that can minimize the electrostatic repulsions between the carbonyl groups of portals of each host molecule. To the best of our knowledge, this study shows for the first time evidence on the formation of [3]pseudorotaxanes with cucurbit[*n*]urils, without cationic groups to screen the electrostatic repulsions between the host molecules. An alkyl spacer with 14 carbon atoms appears to be sufficient to accommodate two CB7 host molecules, with the pseudorotaxane being stabilized by the electrostatic interactions between the carbonyl oxygens and the cationic head groups of the bolaform surfactant.

CONCLUSIONS

In this study the possibility of formation of [3]pseudorotaxane-type structures between CB7 and bolaform surfactants, without addition of electrolytes, was proved. Increasing the alkyl spacer of B*n*, the ion-dipole interactions between the CB7 and the cationic head groups of surfactant compensates the repulsive interaction between the portals of both CB7. When the separation of the cationic head groups is over 14 methylene groups, this condition is satisfied, and therefore [3]pseudorotaxanes are formed in these cases, with two CB7 molecules accommodated between the two head groups of the bolaform.

The results obtained in this study allow us to conclude that CB7 can form very stable 1:1 and 2:1 complexes with B*n*, with binding constants for both stoichiometries larger than those obtained with alkyltrimethylammonium surfactants. In the former, this is a consequence of the CB7 interaction with the two head groups of the bolaform surfactant instead of one in the conventional surfactants yielding a [2]pseudorotaxane. In the latter, two CB7 interact with two head groups, instead of sharing the same headgroup.

In the case of a bolaform with 12 carbon atoms, the electrostatic repulsion between the carbonyl groups of the CB7 molecules avoids the threading of a second CB7 molecule yielding a mixed structure formed by a [2]pseudorotaxane and an external host−guest complex. As a result, both internal and external CB7 complexes are observed on the 2:1 host−guest complexes.

EXPERIMENTAL SECTION

Preparation of Compounds. Cucurbit[7]uril was synthesized as described in our previous paper.[22] The α,α′-bolaform (B*n*) surfactants with the general structure

$$\mathrm{Br^{-}Me_3\overset{+}{N}-\underset{n=12-22}{(CH_2)_n}-\overset{+}{N}Me_3Br^{-}}$$

were synthesized as follows. B12 was obtained from 1,12-dibromododecane (commercial available) as described in the literature.[30] The bolaform surfactants with $n > 12$ were synthesized from α-bromo carboxylic acids (8-bromooctanoic acid, 10-bromodecanoic acid, 11-bromoundecanoic acid and 12-bromododecanoic acid, commercial availables) via α,α′-dibromides. These were prepared by Kolbe's electrolysis of the α-bromo carboxylic acids in methanol[31] and converted to the corresponding bolaform surfactants following the same procedure used in the preparation of B12.[30]

ITC Experiments. ITC experiments were carried out on a VP-ITC instrument at 25 °C under stirring at 459 rpm. The ITC experiments were performed by placing each B*n* solution in the reaction cell and adding the CB7 solution by microsyringue.

NMR Experiments. The stock solutions were prepared in D_2O (99.9%). The B*n*-CB7 systems for NMR measurements were prepared by mixing the appropriate volumes of stock solutions of CB7 and B*n*. In all cases, the B*n* concentration (1.3 mM) was kept constant, below the critical micellar concentration (cmc), and the CB7 concentration was varied.

^1H NMR spectroscopy and diffusion-ordered NMR spectroscopy (DOSY) were carried out at 25 °C on a 400 MHz spectrometer. The DOSY spectra were acquired with the standard stimulated echo pulse using LED and bipolar gradient pulses.[32] Square-shaped pulsed gradients (G) of 2 ms duration were applied with the power level linearly incremented from 2.0 to 65.6 G/cm in 20 steps. To obtain reliable results for the diffusion coefficient, D, the diffusion time, Δ, of the experiments was optimized for each sample to a value between 50 and 90 ms. The raw data were processed using the commercially available software.

Kinetic Measurements. In this study we used the hydrolysis of MBSC as a chemical probe (commercial available). The reaction kinetics was monitored by UV−vis spectroscopy at 270 nm (the absorbance maximum of MBSC) in a spectrophotometer thermostatted at 25 °C. A solution of MBSC was prepared in acetonitrile. In all cases, the MBSC concentration was 1.0×10^{-4} M. B*n*-CB7 systems were prepared by mixing the appropriate volumes of aqueous stock solutions of CB7 and B*n*. The absorbance-time data for all kinetic experiments were fitted to a first-order integrated rate equation.

ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR measurements (^1H NMR spectra and DOSY), kinetic experiments, and binding models used to simulate the NMR and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: luis.garcia@usc.es.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the Ministerio de Economía y Competitividad (Project No. CTQ2011-22436) and Xunta de Galicia (PGIDIT10-PXIB209113PR and 2007/085) is acknowledged. M.P. acknowledges the Fundação para a Ciência e Tecnologia (FCT, Portugal) and POPH/FSE for a Ph.D. grant (Grant No. SFRH/BD/60911/2009).

REFERENCES

(1) Lagona, J.; Mukhopadhyay, P.; Chakrabati, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844−4870.

(2) Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **2000**, *122*, 540−541.

(3) Lee, J. W.; Samal, S.; Selvapalan, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621−630.

(4) Kim, K. *Chem. Soc. Rev.* **2002**, *31*, 96−107.

(5) For example, see: (a) Ong, W.; Gomez-Kaifer, M.; Kaifer, A. E. *Org. Lett.* **2002**, *4*, 1791−1794. (b) Choi, S.; Park, S. H.; Ziganshina, A. Y.; Ko, Y. H.; Lee, J. W.; Kim, K. *Chem. Commun.* **2003**, 2176−2177. (c) Moon, K.; Kaifer, A. E. *Org. Lett.* **2004**, *6*, 185−188. (d) Choudhury, S. D.; Mohanty, J.; Pal, H.; Bhasikuttan, A. C. *J. Am. Chem. Soc.* **2010**,

132, 1395−1401. (e) Gamal-Eldin, M. A.; Macartney, D. H. *Org. Biomol. Chem.* **2013**, *11*, 488−495. (f) Mohanty, J.; Thakur, N.; Choudhury, S. D.; Barooah, N.; Pal, H.; Bhasikuttan, A. C. *J. Phys. Chem. B* **2012**, *116*, 130−135.

(6) Tuncel, D.; Steinke, J. *Macromolecules* **2004**, *37*, 288−302.

(7) Tuncel, D.; Tiftik, H. B.; Salih, B. *J. Mater. Chem.* **2006**, *16*, 3291−3296.

(8) Tuncel, D.; Katterle, M. *Chem.—Eur. J.* **2008**, *14*, 4110−4116.

(9) Tuncel, D.; Ozsar, O.; Tiftik, H. B.; Salih, B. *Chem. Commun.* **2007**, 1369−1371.

(10) Liu, Y.; Shi, J.; Chen, Y.; Ke, C.-F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7293−7296.

(11) Liu, Y.; Ke, C.-F.; Zhang, H.-Y.; Wu, W.-J.; Shi, J. *J. Org. Chem.* **2007**, *72*, 280−283.

(12) Ke, C.-F.; Hou, S.; Zhang, H.-Y.; Liu, Y.; Yang, K.; Feng, X.-Z. *Chem. Commun.* **2007**, 3374−3376.

(13) Yin, J.; Chi, C.; Wu, J. *Chem.—Eur. J.* **2009**, *15*, 6050−6057.

(14) Samsam, S.; Leclercq, L.; Schmitzer, A. R. *J. Phys. Chem. B* **2009**, *113*, 9493−9498.

(15) Kaifer, A. E.; Li, W.; Silvi, S.; Sindelar, V. *Chem. Commun.* **2012**, *48*, 6693−6695.

(16) Ding, Z.-J.; Zhang, H.-Y.; Wang, L.-H.; Ding, F.; Liu, Y. *Org. Lett.* **2011**, *13*, 856−859.

(17) Liu, Y.; Li, X.-Y.; Zhang, H.-Y.; Li, C.-J.; Ding, F. *J. Org. Chem.* **2007**, *72*, 3640−3645.

(18) Ooya, T.; Inoue, D.; Choi, H. S.; Kobayashi, Y.; Loethen, S.; Thompson, D. H.; Ko, Y. H.; Kim, K.; Yui, N. *Org. Lett.* **2006**, *8*, 3159−3162.

(19) Ambrogio, M. W.; Pecorelli, T. A.; Patel, K.; Khashab, N. M.; Trabolsi, A.; Khatib, H. A.; Botros, Y. Y.; Zink, J. I.; Stoddart, J. F. *Org. Lett.* **2010**, *12*, 3304−3307.

(20) Angelos, S.; Yang, Y.-W.; Patel, K.; Stoddart, J. F.; Zink, J. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 2222−2226.

(21) Liu, J.; Du, X. *J. Mater. Chem.* **2010**, *20*, 3642−3649.

(22) (a) Pessêgo, M.; Moreira, J. A.; Garcia-Rio, L. *Chem.—Eur. J.* **2012**, *18*, 7931−7940. (b) Pessêgo, M.; Basilio, N.; Moreira, J. A.; García-Río, L. *ChemPhysChem* **2011**, *12*, 1342−1350.

(23) Wyman, I. W.; Macartney, D. H. *Org. Biomol. Chem.* **2009**, *7*, 4045−4051.

(24) Wyman, I. W.; Macartney, D. H. *J. Org. Chem.* **2009**, *74*, 8031−8038.

(25) Gamal-Eldin, M. A.; Macartney, D. H. *Org. Biomol. Chem.* **2013**, *11*, 1234−1241.

(26) Honig, B.; Nicholls, A. *Science* **1995**, *268*, 1144−1149.

(27) (a) Mock, W. L. *Top. Curr. Chem.* **1995**, *175*, 1−24. (b) Gerasko, O. A.; Samsonenko, D. G.; Fendin, V. P. *Russ. Chem. Rev.* **2002**, *71*, 741−760. (c) Wheat, N. J. *Aust. J. Chem.* **2006**, *59*, 354−354. (d) Kim, K.; Selvapalan, N.; Ko, Y. H.; Park, K. M.; Kim, D.; Kim, J. *Chem. Soc. Rev.* **2007**, *36*, 267−279. (e) Isaacs, L. *Chem. Commun.* **2009**, 619−629.

(28) Connors, K. A. In *Binding Constants. The Measurement of Molecular Complex Stability*; John Wiley & Sons: New York, 1987; pp 189−215.

(29) Miyake, K.; Yasuda, S.; Harada, A.; Sumaoka, J.; Komiyama, M.; Shigekawa, H. *J. Am. Chem. Soc.* **2003**, *125*, 5080−5085.

(30) Menger, F. M.; Wrenn, S. *J. Phys. Chem.* **1974**, *78*, 1387−1390.

(31) Woolford, R. G. *Can. J. Chem.* **1962**, *40*, 1846−1850.

(32) Wu, D.; Chem, A.; Johnson, C. S. *J. Magn. Reson.* **1995**, *115*, 260−264.