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Metal-Controlled Aggregation-Deaggregation in Calix[4]arene-Based Self-Assemblies

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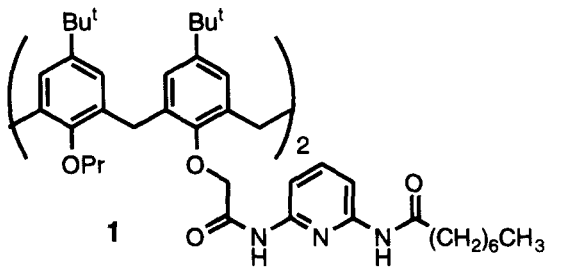
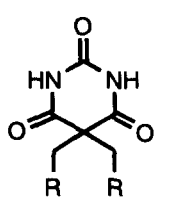
Abstract: Supramolecular self-assemblies of complementary components **1** or **2** (calix[4]arene derivatives with two or four 2,6-diaminopyridine units, respectively) and **3** (5,5-dialkyl barbituric acids) in chloroform-acetonitrile solution were confirmed by ^{1}H NMR spectroscopy and light scattering. While derivative **1** interacts with **3** only after addition of Na^+ cation, which disrupts intramolecular hydrogen bonds, compound **2** creates a complex with **3** even without the presence of Na^+ cation, indicating much weaker intramolecular bonds in this derivative.

The phenomenon of molecular self-assembling attracts recently great attention.[1-3] It is believed that in near future it can serve as a synthetic route to molecular devices[4] and to other nanostructures[5] with defined shapes and/or functions. There are several forces that we can use for generation of such self-assembled structures; among them hydrogen-bonding[6,7] and ligand-to-metal interactions [8] seem to be most promising.

We have realized, that suitably substituted calix[4]arene can serve as an appropriate "monomer" for creating polymeric structures based on intermolecular hydrogen bonds. To achieve as strong as possible hydrogen-bonding interactions we used here a 2,6-diaminopyridine structural motive, which should create three intermolecular hydrogen bonds with 5,5-disubstituted barbituric acid because of the entire mutual complementarity .

Previously, we demonstrated that the direction of carbonyl groups in calix[4]aryl esters and amides can be controlled by bound metal cations.[9] By this conformational change one can create "open" sites for intermolecular hydrogen bonds from "closed" sites for intramolecular hydrogen bonds. This conformational change takes place because the coordination of the carbonyl groups to metal cations results in the exposure of the hydrogen-bonding sites to the medium. If this concept is skillfully combined with the above-mentioned self-assembled system, one may be able to control an equilibrium between "monomer" and "polymer".

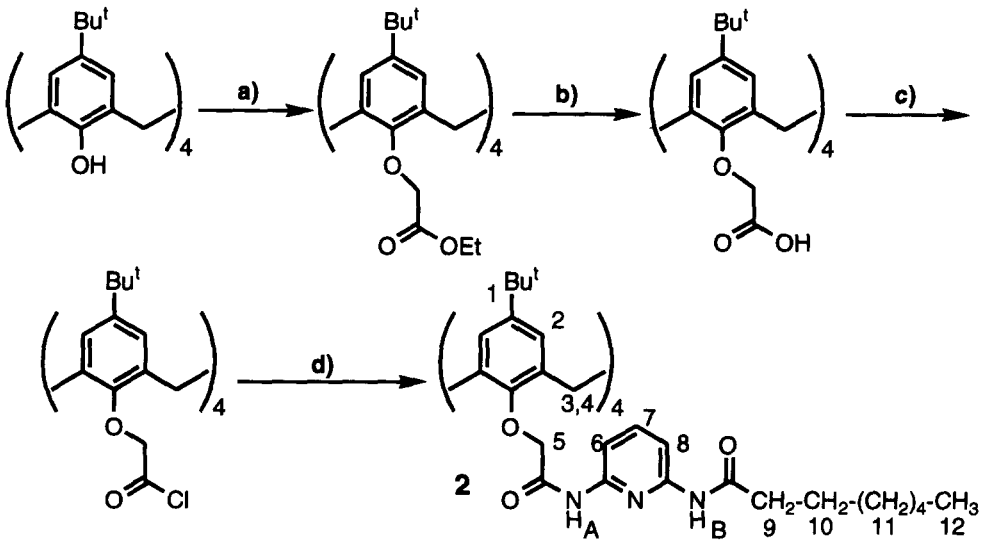




3a R = CH_3
3b R = $(CH_2)_6CH_3$

Bis(2,6-diaminopyridine) derivative **1** was prepared according to the known procedure.[9] The preparation of tetrakis derivative **2** is depicted[10] in Scheme 1. Tetrakis(ethoxycarbonylmethyl) derivative was

obtained by alkylation of starting calix[4]arene with ethyl bromoacetate. Hydrolysis and reaction with $(COCl)_2$ offered appropriate tetrakis chloride of carboxylic acid, which after reaction with monoacyl-substituted 2,6-diaminopyridine yielded derivative **2** in 35 % yield.



a) $BrCH_2COOEt$, K_2CO_3, reflux; b) THF-H_2O, $N(CH_3)_4OH$, 100°C;
c) $(COCl)_2$, CCl_4, reflux; d) 2-octanoylamino-6-aminopyridine, Et_3N, THF.

Scheme 1. Preparation of calix[4]arene derivative **2**. (The δ_H values are recorded in Ref. 10 using the numbers in the above structure.)

Interaction of compound **1** or **2** with diethyl (**3a**) or dioctyl (**3b**) barbituric acids was studied with the help of ^1H NMR spectroscopy in $CDCl_3$ or $CDCl_3$-CD_3CN solution. Derivative **1** possesses characteristic singlets of -NH- protons at 9.03 (A) and 10.07 (B) ppm (Fig. 1a), which are influenced neither by a change in the concentration nor by the presence of barbituric acid derivative (Fig. 2a). On the other hand, addition of 1 equiv. of $NaClO_4$ caused a dramatical high field shift of NH signals (Fig. 1b) to 8.31 and 9.14 ppm, respectively. The low δ_H values for the NH protons can be explained by the presence of intramolecular hydrogen bonds in **1**, which are stronger than six theoretically possible intermolecular hydrogen bonds between **1** and **3**. After addition of cations these bonds are disrupted because of the change in the conformation[9]. This new conformation is suitable for intermolecular hydrogen-bonding interactions and addition of **3** results in the low field shift of both NH signals (Fig. 1c), indicating the presence of three hydrogen bonds.

Binding isotherms (Fig. 2b) were obtained by titration of **1** (2.5×10^{-3} mol dm^{-3}) in the presence of 1 equiv. of $NaClO_4$ with **3a** or **3b** in $CDCl_3$ - CD_3CN = 9:1 v/v at room temperature. Titration curves were analyzed according to the double reciprocal equation and the appropriate association constants for 1:1 complexes were calculated.[11] We obtained K_a = 55 dm^3mol^{-1} for diethyl barbituric acid **3a** and K_a = 150 dm^3mol^{-1} for dioctyl derivative **3b**. The higher value in case of **3b** is caused by higher lipophilicity of this derivative, where hydrophobic interactions of long alkyl chains with those in **1** can take place.

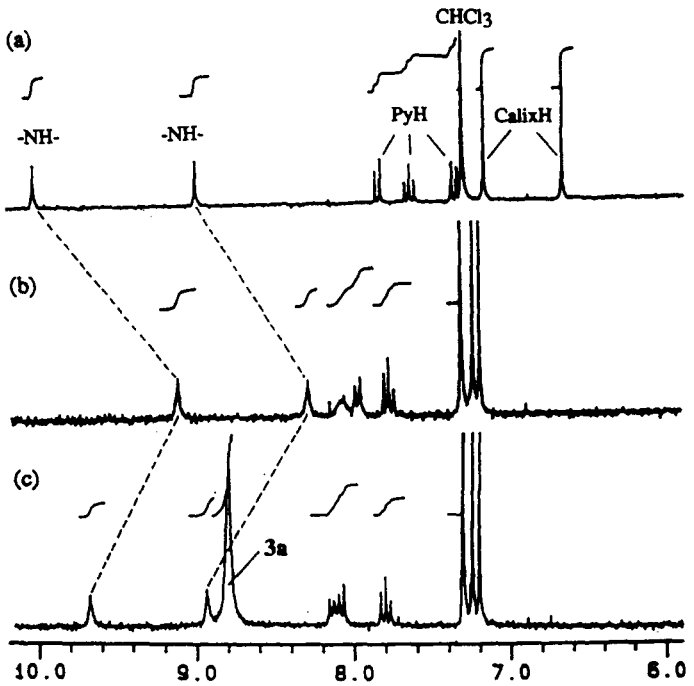


Fig. 1. a) ^1H NMR spectrum of **1**, (250 MHz, $CDCl_3$-CD_3CN=9:1 v/v, c=2.5 x 10^{-3} mol dm^{-3}): b) The same in the presence of 1 equiv. of $NaClO_4$: c) The same as b) after addition of 5 equiv. of **3a**.

In distinction from compound **1**,compound**2** possesses the dependence of chemical shifts of -NH- signals on the concentration of barbituric acid derivative even in the absence of Na^+ cation. It means that intramolecular hydrogen bonds of **2** are arranged in different way and they are much weaker than those in compound **1**. In such case the presence of Na^+ cation is not necessary for the formation of intermolecular 3 new hydrogen bonds (per pyridine unit) with barbituric acid derivative.

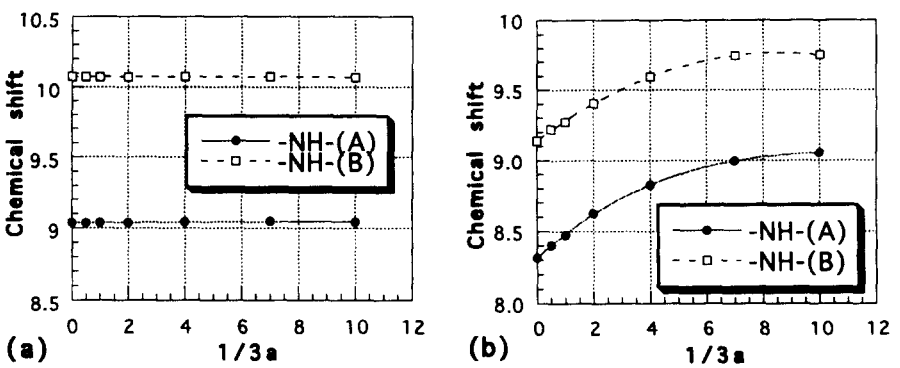


Fig. 2. a) NMR titration curves of δ_{NH} in **1** ($CDCl_3$-CD_3CN=9:1 v/v, c = 2.5 x 10^{-3} mol dm^{-3}): b) The same in the presence of 1 equiv. of $NaClO_4$.

Light scattering was used to determine the molecular mass of self-assembled species. While an equimolar mixture of $NaClO_4$ and **2** (c=2.5 x 10^{-3} mol dm^{-3}, $CHCl_3$:CH_3CN=9:1 v/v, 20℃) exhibited the average size of diameter 1.8 nm, after addition of 2 equiv. of **3a** the diameter increased up to 6.8-7.4 nm. We believe that in the presence of Na^+ cations the hydrogen-bonding sites in **2** (the same situation is in **1**) are exposed to the medium and then **2** (or **1**) and **3a** create oligomeric clusters.

In conclusion, Na^+ can act as a trigger to change the conformation of **1** or **2** and to construct the oligomeric clusters in the presence of complementary **3**.

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10. Preparation of **2**: A solution of the corresponding acyl chloride calix[4]arene derivative in 30 ml THF was added dropwise to a solution of 1.33 g of 2-amino-6-octanoylaminopyridine and 0.8 ml of Et_3N in 15 ml of dry THF during 1 h at room temperature. Reaction mixture was then stirred under nitrogen for 50 h, poured into water, extracted with $CHCl_3$ and dried over $MgSO_4$. After chromatography on 80 g of SiO_2 (hexane-AcOEt=7:3 v/v) and crystallization from acetone we obtained 0.64 g of **2** (35%), m.p.: 123-124 ℃. ^1H NMR spectrum (250 MHz, $CDCl_3$): δ 0.86 t (6.90 Hz, H-12), 1.10 s (H-1), 1.25 brs (H-11), 1.61 m (H-10), 2.23 t (7.78 Hz, H-9), 3.37 d (13.09 Hz, H-3), 4.51 d (13.19 Hz, H-4), 4.81 s (H-5), 6.88 s (H-2), 7.53 t (8.02 Hz, H-7), 7.69 d (7.90 Hz, H-8 or 6), 7.89 d (7.82 Hz, H-6 or 8), 8.77 s (A or B), 9.20 s (B or A). EA calcd. for $C_{104}H_{140}N_{12}O_{12}$: C, 71.35; H, 8.08; N, 9.60%. Found: C, 71.55; H, 8.15; N, 9.32%.
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