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ORIGINAL ARTICLE

Effect of covalent functionalization of C_{60} fullerene on its encapsulation by water soluble calixarenes

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Abstract The molecular encapsulation of functionalized fullerenes (substituted fulleropyrrolidines) with water-soluble calixarenes was studied by photoluminescence and quantum-chemical methods. The results show that both the thiacalix[4]arene-tetrasulfonate and calix[6]arene-hexasulfonate are able to overcome the natural water-repulsive character of fullerenes. However, the functionalization of calixarenes and fullerenes induces significant changes in the molecular encapsulation processes, and the obtained thermodynamic behavior of the complex formation highlights the importance of the entropy. Our results can contribute to the development of the synthesis and design of functionalized calixarenes supporting their application in pharmaceutical and food chemistry.

Keywords Complex formation · Molecular capsules · Functionalized fullerenes

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Introduction

The parent unfunctionalized fullerenes are known as practically insoluble compounds in water. This behavior hinders their application in several practically important fields indicating the importance to increase the water solubility of fullerene derivatives [1]. Inclusion of C_{60} within cavity of water-soluble hosts [2–5] is found to be one of the most fruitful method to overcome the solubility problems. Furthermore, covalent functionalization of C_{60} with hydrophilic, ionic [6, 7] or non-ionic [8, 9] organic moieties or electrochemical/chemical reduction of C_{60} to a water-soluble anion [10] have also been utilized to improve the solubility of C_{60} fullerene. Accordingly, in our previous work [11] the inclusion complexes of calixarene derivatives with C_{60} fullerene were investigated by photoluminescence (PL) and quantum-chemical methods. The results show highly efficient extraction of parent C_{60} fullerene into water by sulfonated thiacalix[4]arene and calix[6]arene sodium salts.

However, covalent functionalization of C_{60} is applied to widening their applicability in e.g., possible pharmaceutical use [12], therefore it was obvious to investigate how the functionalization inhibits or supports the molecular encapsulation. In this work the effect of the two different pyrrolidine-substitution patterns, used for the covalent functionalization of C_{60} fullerene, on the molecular encapsulation by sulfonated thiacalix[4]arene **1a** and calix[6]arene **1b**, is studied (Fig. 1). The significant role of the entropy was analyzed according to the internal molecular moving and by the solvent properties. The functionalized fullerenes possess a pyrrolidine fragment fused to the parent C_{60} bearing an *N*-phenyl or *N*-methyl substituent in **2a** and **2b**, respectively (Fig. 2). Additionally, a hydrophilic group is attached in position-2 in both

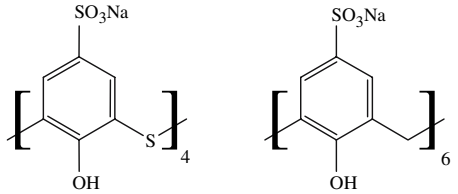

Fig. 1 Sulfonated thiacalix[4]arene **1a** and calix[6]arene **1b** investigated in this work

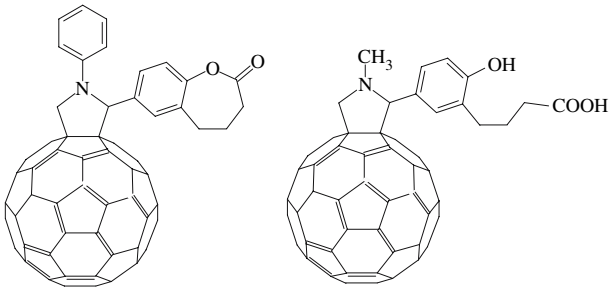

Fig. 2 Substituted fulleropyrrolidines (*N*-phenyl, left: **2a** and *N*-methyl, right: **2b**) studied in this work

cases. The complexation behavior and the factors controlling the thermodynamic and kinetic stability were studied by photoluminescence and quantum-chemical method [13].

Materials and methods

General

All chemicals were commercially available and used without further purification. ^{1}H-spectra were recorded at room temperature using a Bruker Avance 400 and a Bruker DRX-500 spectrometer instruments operating at 400 MHz and 500 MHz, respectively, with TMS or DSS as internal standard. Mass spectra were measured on an Agilent 1100 Series LC/MSD system equipped with an electrospray ionization interface (ESI). FT-IR and UV–vis spectra were obtained with a Jasco FT/IR-660 plus.

Synthesis of **1a** and **1b** host compounds

Both host compounds were synthesized as described in the literature. Thus, thiacalix[4]arene-tetrasulfonate salt **1a** was obtained by the *ipso* sulfonation of *p-tert*-butylthiacalix[4]arene [14], while calix[6]arene-hexasulfonate salt **1b** was prepared by direct sulfonation of the parent calix[6]arene with concentrated sulfuric acid [15]. The functionalized C_{60} fullerenes (**2a** and **2b**) were prepared as published earlier [16].

Thiacalix[4]arene tetrasulfonate (**1a**): ^{1}H NMR (500MHz, D_2O, DSS): δ 7.99 (s, 8H. Ar*H*); ^{13}C NMR: δ 157.9, 132.8, 132.0, 118.30 (Ar*C*).

Calix[6]arene-hexasulfonate (**1b**): ^{1}H NMR (500MHz, D_2O, DSS): δ 7.57 (s, 12H. Ar*H*), 4.04 (s, 12H, CH_2); ^{13}C NMR: δ 156.4, 137.7, 130.8, 129.1 (Ar*C*), 33.7 (*C*H_2).

The synthesis of **2a** and **2b**

*Compound **2a***

A solution of C_{60} (132.50 mg, 0.184 mmol), *N*-phenylglycine (55.63 mg , 0.368 mmol) and 2,3,4,5-tetrahydro-2-oxo-1-benzoxepin-7-carboxaldehyde (69.92 mg, 0.368 mmol) in toluene (300 mL) was refluxed for 3.5 h. After cooling the resulting solution was evaporated to dryness. The crude product was purified by column cromatography (silica, toluene). Yields: 33%.

Selected data for **2a:** ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ 7.46–6.60 (m, 8H), 5.29 (s, 1H), 5.19 (d, J = 5.5 Hz, 1H), 5.14 (d, J = 5.5 Hz, 1H), 1.90–1.00 (m, 6H) ppm.

FT-IR (ATR system):(ν, cm^{-1} 2921, 2851, 1596, 1496, 1462, 1427, 1262, 1215, 1184, 962, 813, 734. MS (APCI): *m/z* 999.

*Compound **2b***

To a solution of *N*-methyl-2-(2-oxo-benzoxepin)-fulleropyrrolidine (69.00 mg, 0.075 mmol) in $CHCl_3$ (10 mL) was added 0.6 M KOH (3 mL) and the mixture was refluxed for 1 h. After cooling the reaction mixture was evaporated to dryness and the residue extracted with $CHCl_3$. The chloroform solution was dried on anhydrous sodium sulphate and the crude product obtained after evaporation of the solvent under reduced pressure was purified by column cromatography (silica, toluene). Yields: 23%

Selected data for **2b**: ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ 7.75–6.75 (m, 3H), 5.34 (s, br, 1H), 4.97 (d, J = 9.3 Hz, 1H), 4.85 (s, 1H), 4.24 (d, J = 9.3 Hz, 1H), 2.82 (s, 3H), 2.80–1.80 (m, 6H) ppm.

FT-IR (ATR system):(ν, cm^{-1} 3386, 2920, 2850, 2779, 1736, 1712, 1461, 1438, 1259, 1092, 1018, 798. MS (APCI): *m/z*. 956 (calcd. for [M + H]$^+$ 956).

Apparatus for PL measurements

A highly sensitive Fluorolog τ3 spectrofluorometric system (Jobin-Yvon/SPEX) was used to investigate the

photoluminescence (PL) spectra of the different solutions. For data collection a photon counting method with 0.4 s integration time was used. Excitation and emission bandwidths were set to 1 nm. 1 mm layer thickness of the fluorescent probes with front face detection was used to eliminate the inner filter effect.

The fluorometric experiments were carried out at pH ~ 6.9 using phosphate buffer/0.025 mol/kg disodium hydrogen phosphate (Merck) + 0.025 mol/kg potassium dihydrogen phosphate (Merck); pH 6.873, 6.843 and 6.823 at temperatures of 20, 30 and 40 °C, respectively.

The equilibrium conformations of calixarene derivatives and their complexes with fullerene derivatives were studied with semi-empirical AM1 (Austin Model) method, followed by ab initio MP2/6–31++G calculations. Fletcher-Reeves geometry optimization method was used for the investigation of the conformers. Calculations were carried out with the HyperChem Professional 7 [17] and Gaussian 03 program package [18].

Determination of the thermodynamic parameters using the PL signal

Job's method was applied at four different temperatures in the range of 20–35 °C with a step size of 5 °C in order to determine the thermodynamic properties. The quantitative evaluation of the Job's curves (where C refers to the calixarene host **1a** or **1b**; G is one of the C_{60} fullerene derivative (**2a** or **2b**) guest; CG and C_2G are the individual types of complexes formed in the studied systems; K_1 and K_2 denote the formation constants of the individual complexes, respectively) needs to apply the following considerations. Assuming that the observed PL signal varies linearly with the concentrations, ΔF in such a system is described by Eq. 1

$$\Delta F = f_{CG}[CG] + f_{C_2G}[C_2G] \quad (1)$$

wherein $\Delta F = F - F_0$ is the difference between the PL intensity obtained with the calixarene-functionalised-C_{60} system and the PL intensity of the calixarene with the same concentration. The measures of the PL signals, f_{CG} and f_{C2G} could be observed for the individual C_iG (i = 1, 2) species relative to the PL signal of pure calixarene of the same concentrations. By definition,

$$f_{C_iG} = \left.\frac{F([C]) - F([C_iG])}{F([C])}\right|_{[C_iG]=[C]} \quad (i = 1,2) \quad (2)$$

Using Eqs. 3 and 4 as expressions for the total concentration of the calixarene, the theoretical change of the PL signal can be obtained by Eq. 5,

$$C_0 = [C] + K_1[C][G] + 2K_1K_2[C]^2[G] \quad (3)$$

$$G_0 = [G] + K_1[C][G] + K_1K_2[C]^2[G] \quad (4)$$

$$F - F_0 = \frac{G_0\left\{f_{CG}K_1[C] + f_{C_2G}K_1K_2[C]^2\right\}}{1 + K_1[C] + K_1K_2[C]^2} \quad (5)$$

wherein C_0 is the analytical concentration of calixarene, [C] is the equilibrium concentration of calixarene, G_0 and [G] are the analytical and equilibrium concentrations of the fullerene derivative, respectively, K_i (i = 1,2) is the complex formation constant. By using Eq. 5, K_1 and K_2 as well as f_{CG} and f_{C2G} could be optimized iteratively: First, Eq. 3 and 4 are solved numerically for given values of K_1 and K_2 and the f_{CG}, f_{C2G} coefficients. Then, the application of the equilibrium concentration of the fullerene derivative for the given parameters enabled the determination of the theoretical change in the PL signal.

It has to be noted, that the K_i values are extraction constants rather than association constants (K_{ass}) which are related by the equation

$$K_{ass} = K_i \cdot K_d \quad (6)$$

where K_d is the distribution coefficient of fullerene derivative from toluene to water.

However, it is known that the equilibrium in similar systems strongly depends on the temperature.[14] The thermodynamic parameters for the individual complexes can be determined by a straightforward method from Eq. 7 (van't Hoff equation):

$$\ln K_i = -\frac{\Delta G_i}{RT} = -\frac{\Delta H_i}{RT} + \frac{\Delta S_i}{R} \quad (i = 1,2) \quad (7)$$

where ΔG_i is the Gibbs free energy change, ΔS_i the entropy change and ΔH_i the enthalpy change associated with complex formation.

Using Eq. 7, inserting this expression for the formation constants into the Eqs. 3–5, the fluorescence change in Eq. 5 can be expressed as a function of the ΔH_i, ΔS_i values and the f_{CG}, f_{C2G} coefficients.

The thermodynamic parameters associated with the K_i values were determined from the Job's curves (Figs. 3 and 4) by an iterative solution of Eq. (1–5) using the expression of K_i values from the van't Hoff equation (Eq. (7)).

Results and discussion

It has been shown by acid-base titration [19–21], that calixarenes **1a** and **1b** exist in double protonated form at

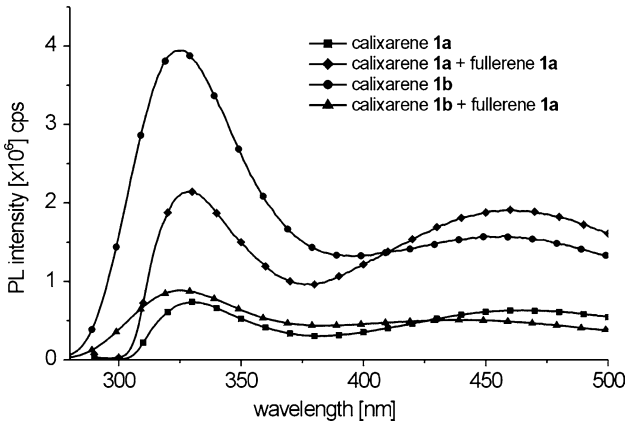

Fig. 3 Spectral changes of calixarene derivatives **1a** or **1b** in the absence and in the presence of 10^{-4} M **2a**

pH 7. It has also been shown, that the distribution curve of $CalixH_2^{4-}$ and the $ThiaCalixH_2^{2-}$ have a wide maximum between pH 6 and pH 8.5 providing excellent conditions for the investigation as host compounds [19–21]. Since no considerable abundance of other species has been observed at the pH range above, pH ~ 6.9 was chosen for the further examinations. To minimize the temperature dependence of the pH, phosphate buffer was used which keeps the pH constant at a wide range of temperature (see Experimental).

In order to investigate the interaction, 10^{-4} M aqueous solution of **1a** or **1b** at around pH = 7, buffered by phosphate buffer and 10^{-4} M toluene solution of fullerene derivatives of **2a** or **2b** were prepared. A two-phase system has been formed, which has been stirred vigorously for 15 min. The samples taken from the aqueous phase were analysed. For the application of Job's method, these solutions were mixed at different molar ratios and the PL spectra of the aqueous phase obtained after phase separation were recorded by using 280 nm and 310 nm wavelengths for excitation and data evaluation, respectively (Fig. 3). Both calixarene derivatives showed lower PL intensity in the absence of the functionalized fullerenes **2a** and **2b**, while no considerable emission of fullerenes has been observed in the absence of calixarenes at 280 nm excitation wavelength. According to our earlier results [13, 19–23] it was concluded that the spectral changes were induced by a weak interaction between the calixarene hosts and the fullerene guest.

For the experimental determination of thermodynamic properties, Job's method was applied at four different temperatures in the range of 20–35 °C with a step size of 5 °C. The method applied successfully earlier is used for the data evaluation [13, 19–23]. The Job's curves obtained suggest that **1a** and **1b** form complexes with the fullerene **2a** with both 1:1 and 1:2 stoichiometries, while complexes containing **2b** fullerene show 1:1 stoichiometry exclusively. The results are summarized in Table 1 and 2.

The thermodynamic parameters associated with the stability constants K_i were determined from the Job's curves and were evaluated by the van't Hoff equation according to our earlier results (see details in Ref. 19–21). Although we used the same host calixarene derivatives as earlier [11], their complexation behavior towards the functionalized fullerenes is quite different. In the case of **1a**

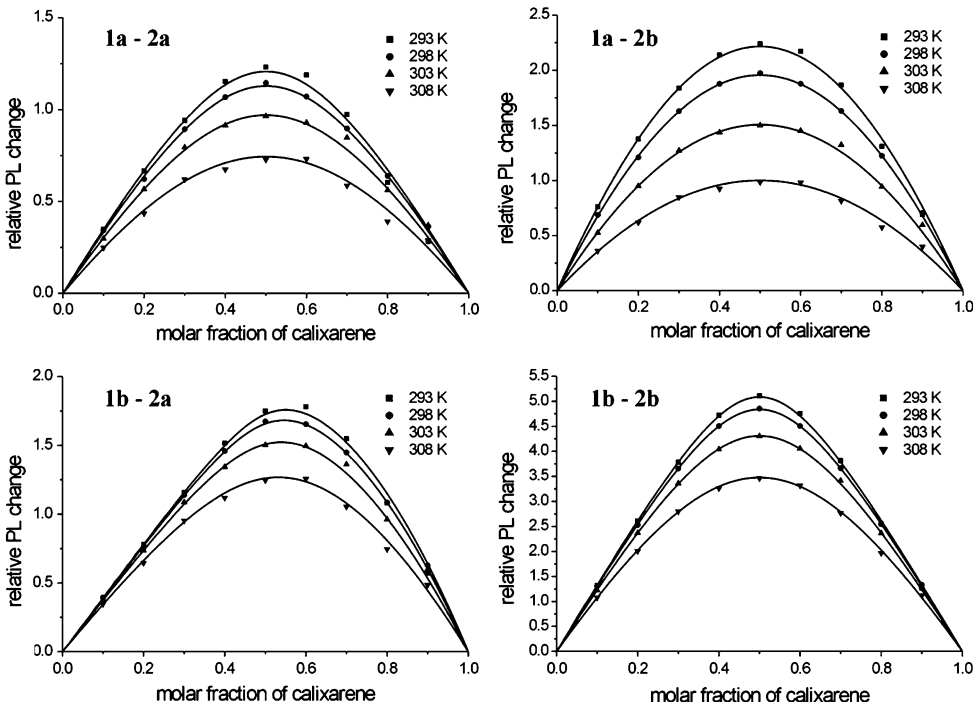

Fig. 4 PL titration curves (Job's plots) of **1a** or **1b** calixarenes with **2a** or **2b** fullerenes

Table 1 Thermodynamic parameters of complexation of calixarene **1a** with **2a** and **2b** fullerene

Species interacted	Conformation (see Fig. 5)	Stoichiometry	Log K_i	ΔG^o (kJ mol^{-1})	ΔH^o (kJ mol^{-1})	ΔS^o (J K^{-1} mol^{-1})
1a with **2a**	A1	1:1	4.73 (5)	–27.00 (8)	–35.52 (5)	–28.57 (3)
1a with **2a**	A2	2:1	2.34 (5)	–5.81 (8)	–27.31 (5)	–72.16 (3)
1a with **2b**	B1	1:1	3.92 (5)	–22.39 (9)	–30.73 (5)	–27.96 (4)

Table 2 Thermodynamic parameters of complexation of calixarene **1b** with **2a** and **2b** fullerene

Species interacted	Conformation (see Fig. 6)	Stoichiometry	Log K_i	ΔG^o (kJ mol^{-1})	ΔH^o (kJ mol^{-1})	ΔS^o (J K^{-1} mol^{-1})
1b with **2a**	C1	1:1	5.35 (5)	–30.55 (8)	–41.55 (5)	–36.88 (3)
1b with **2a**	C2	2:1	2.94 (5)	–16.78 (8)	–21.45 (4)	–15.67 (3)
1b with **2b**	D1	1:1	5.10 (5)	–29.11 (8)	–39.95 (5)	–36.35 (3)

calixarene, the Gibbs free enthalpy change obtained during the first complexation step with **2a** is similar than it was found for the complexation of the parent C_{60} fullerene with **1a** calixarene [11]. In this case the enthalpy and entropy also show similar values. However, during the coordination of a second calixarene **1a** molecule to the calixarene—fullerene complex, much less free enthalpy change is found compared to the coordination to the parent fullerene. This observation reflects that the mechanism of formation of **1a**-**2a** complexes with 2:1 stoichiometry is preferably based on the complexation of the phenyl substituent of the **2a** fullerene since the coordination of second **1a** molecule to the fullerene ball itself is sterically hindered. The stability of these complexes with 2:1 stoichiometry is very weak (free enthalpy change is 5.81 kJ/mol) especially if we consider that the average kinetic energy of particles around room-temperature is approx. 3.8 kJ/mol. It is not surprising if we consider the bulky structural fragment attached to the pyrrolidine ring adjacent to the phenyl substituent. This steric arrangement hinders the phenyl to be embedded into the cavity of **1a** by stronger π–π interactions.

The **1a** calixarene forms complexes with **2b** fullerene with 1:1 stoichiometry. This property is probably due to the steric hindrance of the hydrophilic moiety of the **2b** fullerene considering the coordination of the second **1a** calixarene to the fullerene ball. Furthermore, **2b** fullerene doesn't possess an aromatic ring as **2a** fullerene does. Due to the steric hindrance resulted by the functionalization of C_{60}, no similar 'bowl-shaped' structure of molecular encapsulation is observed as it was found earlier during the complexation of the parent C_{60} fullerene [11].

The **1b** calixarene forms stable complexes with both **2a** and **2b** fullerene with at most 2:1 and 1:1 stoichiometry, respectively. The 2:1 complexes of **1b** calixarene are much stronger with **2a** fullerene than was found for $(\mathbf{1a})_2$-**2a** calixarene-fullerene complex. This property might be explained by the different cavity shape, i.e., different inclination of the opposite rings of **1a** and **1b** calixarenes. To clarify these unexpected results, quantum chemical investigations were performed to determine the stable conformations of the calixarene-fullerene complexes. It can be clearly seen from Fig. 5 and 6 that in both cases the aromatic moiety of **2a** fullerene is located within the two opposite rings of calixarene hosts. In an earlier work we showed that more stable complexes are formed when the inclination between the aromatic rings of the calixarene and the guest's moiety is small. This is in agreement with our present result, where more stable calixarene–fullerene complexes with 2:1 stoichiometry are formed in case of **1b** host compared to the **1a** host.

We can generally state that calix[6]arene-hexasulfonate **1b** forms much more stable complexes with both fullerene derivatives (**2a**, **2b**) than thiacalix[4]arene-tetrasulfonate **1a** calixarene does. This property is mainly determined by stereochemical backgrounds: (i) the fullerene ball can lie more deeply in the cavity of **1b** where the six-membered ring form π–π interaction with the aromatic rings of the fullerene ball, and (ii) during the interaction of the 'second' **1b** host molecule with the phenyl substituent of **2a** the opposite rings of the **1b** calixarene lie nearly parallel supporting stronger formation of a sandwich-like complex with the *N*-phenyl substituent. The latter phenomenon was investigated earlier in detail [22].

The significant role of the entropy

In a first view, it is surprising, that the entropy term during complex formation of **1a** or **1b** with **2a** shows quite different behavior: in the case of **1a** host the reduction of entropy in the second coordination step is $\sim$2.5 times higher compared to the first coordination step (–28.57 JK^{-1} mol^{-1} vs. –72.16 JK^{-1} mol^{-1}). In contrast, in the case of **1b** host, the entropy change obtained in the second

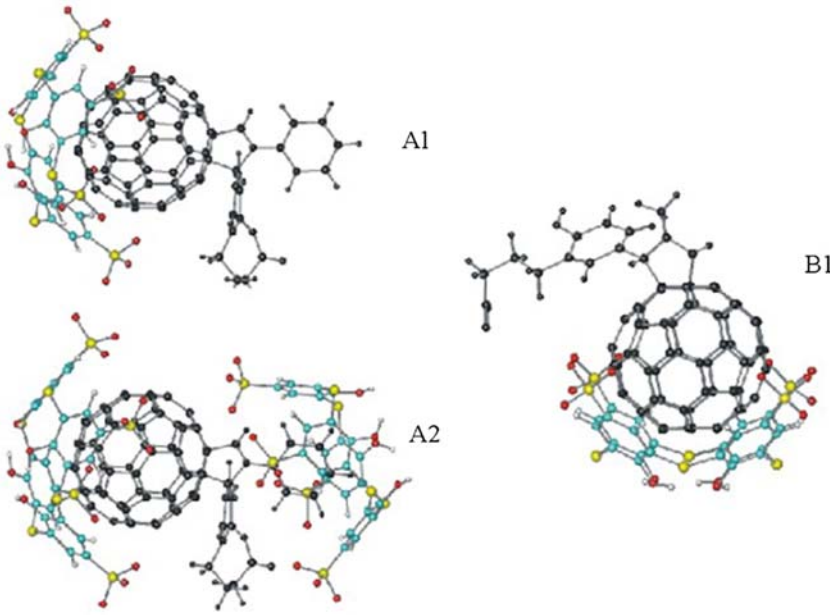

Fig. 5 Fullerene derivatives **2a** (left) and **2b** (right) encapsulated by thiacalix[4]arene-tetrasulfonate (**1a**)

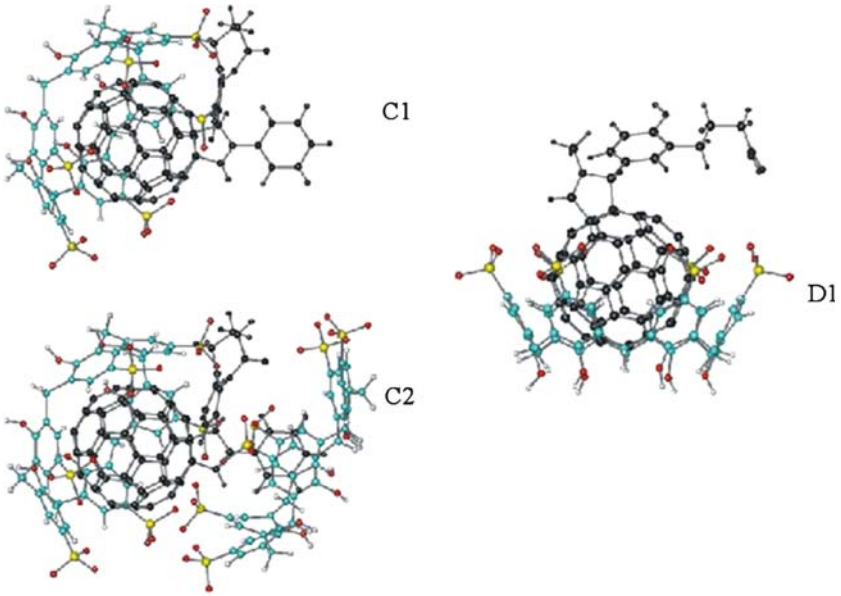

Fig. 6 Fullerene derivatives **2a** (left) and **2b** (right) encapsulated by calix[6]arene-hexasulfonate (**1b**)

coordination step is ~2.35 times lower compared to the entropy change during the first coordination step (–36.88 JK^{-1} mol^{-1} vs. –15.67 JK^{-1} mol^{-1}). In the former case, we can use our recent model for the interpretation [24]: the degree of freedom of the molecules during complexation can decrease because (i) a higher ordered system (complex) can be formed and (ii) the rotation of the complex is decreased compared to the free molecules before the complex was formed. This is because the moment of inertia of the complex is higher than that of the free molecules and the average kinetic energy associated to the rotational freedom is the same in both cases. Because of the above effect the 1:1 complex has slower rotation than the free (uncomplexed) fullerene. As a result, the reduction in the rotational freedom of a calixarene molecule during complex formation is higher in the second coordination step, which resulted in higher reduction of entropy in the second coordination step.

The entropy change obtained in case of complex formation of **1b** calixarene with **2a** fullerene has probably a completely different background. Both the **1a** and **1b** calixarenes have cyclic hydrogen bonds at their lower rim, due to their phenolic OH groups. However, this hydrogen bond was found to be much weaker in case of **1b** calixarene [19–21], resulting a more flexible molecular structure. During the first coordination step of complex formation,

the fullerene introduces deeply into the cavity of the calixarenes reducing the flexibility of the skeleton of the calixarenes. However, this process affect the flexibility of the **1b** calixarene to higher extent, since the rigid structure of **1a** calixarene is stabilized by the relatively strong cyclic hydrogen bonds at the lower rim. Therefore, the flexibility of **1a** calixarene doesn't change much when it interacts with the fullerene ball. This idea is in agreement with the experimental entropy values (Tables 1 and 2), where higher entropy reduction is observed during the first coordination step of formation of **1b**-**2a** complexes compared to the formation of **1a**-**2a** complexes. In contrast, the entropy change obtained during the second coordination step between **1a** and **2a** resulting in $(\mathbf{1a})_2$-**2a**, is higher than that the second step leading to $(\mathbf{1b})_2$-**2a** complex. This is because the flexible skeleton of **1b** calixarene doesn't change much during the process when the aromatic ring of **1a** fullerene enters into the calixarene cavity. As a result, small entropy change can be observed in this case.

Conclusion

In summary, we can conclude that water-soluble tetrasulfonated thiacalix[4]arene (**1a**) and hexasulfonated calix[6]arene (**1b**) form complexes with functionalized C_{60} fullerene **2a** exhibiting 2:1 stoichiometry. The **1a** and **1b** calixarenes form complexes with **2b** fullerene with 1:1 stoichiometry exclusively because of the steric hindrance of the hydrophilic moiety of **2b** fullerene, that inhibits the coordination of a second calixarene molecule, and the lack of the phenyl moiety to be embedded into the cavity of the second host molecule. The results show the deterministic character of entropy on the stability of the complexes, however in a significantly different manner in cases of complex formation with **1a** or **1b** calixarene hosts. Our observations can contribute to the design and synthesis of functionalized fullerenes able to overcome their natural water-repulsive character by molecular encapsulation with water-soluble species.

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