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Encapsulation of Sodium Alkyl Sulfates by the Cyclotriveratrylene-based, $[Pd_6L_8]^{12+}$ Stella Octangula Cage.

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We have previously described a cyclotriveratrylene (CTV)-based complex, $[Pd_6L_8]^{12+}$, that forms a highly symmetric stella octangula cage. Here we report on the ability of this system to host sodium salts of three alkyl sulfates; octyl (SOS), dodecyl (SDS) and tetradecyl (STS). ^{1}H NMR chemical shift and diffusion coefficient measurements reveal that two molecules of alkyl sulfate reside in the cage, though rapid exchange between cage and bulk solvent is apparent. Host:guest association constants have been determined and support for the internalisation of the sulfates is available from 2D ROESY and NOESY data.

There is considerable interest in the development of supramolecular hosts with internal spaces capable of such features as guest encapsulation[1], catalysis[2], and separation or trapping tasks[3]. The drive towards such nano-vessels has seen successes in the development of both hydrogen-bonded 'organic' structures[4] and those in which assembly is based around a metal ion[5]; referred to as co-ordination cages. Co-ordination cages involving a variety of metals including iron, copper, platinum and palladium have been developed with a variety of ligand species[6]. A number of these have also been investigated for their hosting capability. For example, recently a series of nano-balls in which the metal was Cu, Fe, Zn, Cd, or Mn, has been shown to have tunable gas or solvent hosting capability[7]. An Fe^{II} based $[M_4L_6]$ system has been shown to encapsulate small anionic molecules[8]. Conversely $[M_4L_6]$ systems built around Ga^{III}, Fe^{III}, and Ti^{IV} have been shown capable of binding a range of cationic species though with differing consequences for the shape and size of the host in the resultant host-guest complex[9]. There is such intense activity in the development of supramolecular cages that they are the subject of a number of recent review articles[10].

The majority of metallo-cage host-guest systems reported to date arise due to the energetically favoured incorporation of a guest molecule in a preformed host. However there are some recent examples in which the host has been made to form around an 'associated' guest. For example, a $[Pd_2L_4](BF_4)_4$ system has been described which can undergo light-triggered opening and closing to enable uptake and release of a guest anionic species[11]. A much larger, palladium-based, cage has been shown to form following the covalent linkage of a molecule of the protein ubiquitin to one of the 24 ligands in the resultant $[Pd_{12}L_{24}]$:ubiquitin cage[12].

Supramolecular cages based on cyclotriveratrylene (CTV) co-ordination with Pd^{II} have been a focus of this group with a number of X-ray crystallographic and NMR spectroscopic studies reported[13]. Amongst the largest of these systems shown to also exist in solution phase is the stella octangula cage formed by the co-ordination between six naked Pd^{2+} atoms and eight rim 'decorated' CTV ligands (L) (Figure 1)[13b,14].

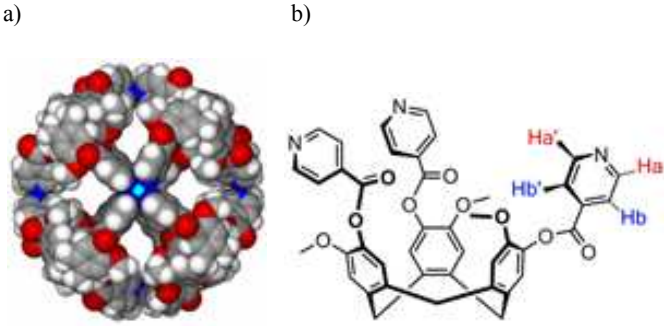


Figure 1. (a) A space filling representation of the stella octangula structure of $[Pd_6L_8]^{12+}$, determined by X-ray crystallography[13b] showing four of the windows. (b) The rim-decorated CTV-based ligand (L) with labels for protons referred to in the text. (c) The structural formula of sodium dodecyl sulfate (SDS) showing numbering referred to in the text.

The stella octangula cage has a diameter of approximately 3.1 nm as measured from the centres of the basal hydrogen atoms of the $-(CH_2)-$ planes for diametrically opposed ligands[13b]. There are eight

'windows' on the surface, although it is apparent in the X-ray structure[13a,b] that these windows are partially blocked by the –OMe groups of each ligand. Nevertheless the presence of these windows and the size of the internal space has lead to an interest in studying the encapsulation potential of this particular $[Pd_6\mathbf{L}_8]^{12+}$ system.

The $[Pd_6\mathbf{L}_8]$ cage is only soluble in DMSO which presented problems in selecting potential guest molecules. DMSO molecules are of course inside the cage and these are in fast exchange with the bulk solvent; ^{1}H NMR has not been able to detect encapsulated DMSO. To overcome the unfavourable entropic barrier for encapsulation, a guest was sought which had some hydrophobicity characteristics whilst still being capable of solubilisation in DMSO. The sodium alkyl sulfate salts fitted these criteria, and the encapsulation of three such salts has been characterized here.

The stella octangula cage was prepared by combining six equivalents of $[Pd(CH_3CN)_4](BF_4)_2$ and eight equivalents of **L** in d_6-DMSO. It was noted that the rate at which the symmetric, and homochiral, cage[15] was formed depended on the history of the Pd(II) species. Mixing the palladium salt with **L** at room temperature resulted in a homochiral cage after a period of many days (see ESI). In contrast the cage formed within 24 h if the stock palladium solution was heated and then added when cool to the ligand. This is in line with the numerous reports of Pd-based coordination cages being formed following heating (at temperatures ranging from 313 - 363 K), of solutions of the Pd salt (primarily $[Pd(CH_3CN)_4](BF_4)_2$) in the presence of ligand.[11,12,15,16,] It was also noted that old (unheated and room temperature stored) Pd/DMSO stock solutions when added to fresh ligand solutions lead to the homochiral cage within the same 24 h time period (see the ESI). Both of these observations are consistent with the suggestion[17] that polar solvents such as DMSO could behave like a ligand; the consequent Pd:DMSO interaction facilitating Pd:ligand (**L**) exchange. For guest encapsulation studies the alkyl sulfate salt was added at the same time as the stocks of ligand and palladium were combined and subsequent measurements made at least 24 h later.

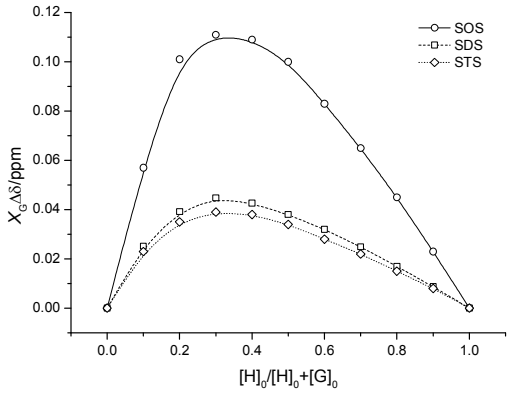
A range of cage and guest concentrations was investigated for each of three alkyl sulfates; octyl (SOS), dodecyl (SDS), and tetradecyl (STS) sulfate, using ^{1}H NMR spectroscopy and chemical shift, diffusion coefficient and 2D ROESY and NOESY measurements.

Using a fixed total sample concentration of 2.5 mM and different cage (host, **H**) : detergent (guest, **G**) ratios, ^{1}H NMR chemical shift changes were monitored for both the guest and host molecules and subsequently Job's[18] plots created from these data (figure 2(a) and ESI). For each of the alkyl sulfates examined, the Job's plots suggested a **H:G** ratio of 1:2; the maximum in the curve is apparent at a relative host concentration of approximately 33%. The data shown in figure 2 are for the chemical shift of the terminal methyl group (H4) in each of the guests. The shift changes are small but there is a trend depending on the length of the alkyl chain (see the ESI). While these data are highly reproducible and logical trends are apparent, the use of Job's plots with systems of stoichiometry other than 1:1 while common is reported to be unreliable[19]. Consequently an alternative 'titration' approach to investigating these systems was adopted.

Proton NMR chemical shift changes in the spectra of samples prepared with a fixed host concentration of 0.5 mM and guest concentrations over the range 0.5-10.0 mM were measured and the data were modelled[20] to establish **H:G** association constants (figure 2(b) and ESI). The chemical shift variation for the guest molecules in the absence of host was also measured to ensure changes were not due to guest-guest interactions over the concentration range utilized.

Table 1 shows the fitted values for the cumulative association constants, β. The first association constant ($K_{a1} = \beta_1$) is consistently higher (ca. 10^4 M^{-1}) than the second stepwise constant ($K_{a2} = \beta_2/\beta_1$ ca. 10^2 M^{-1}); the cumulative association constant (β_2) in each case being in excess of 10^5 M^{-2}. In adopting relatively low concentrations in these experiments we are able to offset concerns associated with using NMR for studying systems having high K_a values[19].

a)



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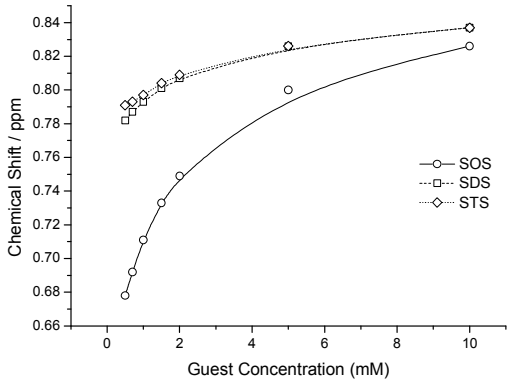

Figure 2. (a) Job's plot constructed using the data for the H4 protons of the guest (**G**) indicating that binding is 1:2 **H:G** for each type of guest. (b) ^{1}H chemical shift change (proton H4) with host concentration fixed (at 0.5 mM) and the guest concentration varied (from 0.5-10.0 mM). (d_6 DMSO solution, 293 K).

The models generated are consistent with the 1:2 **H:G** complex determined from the Job's approach and show a similar trend in association constants with change in alkyl chain length; with SOS displaying the tightest binding.

Further support for the presence of 1:2 **H:G** complexes was provided by the analysis of diffusion coefficients determined through the collection of DOSY data sets for cage:SDS samples, with fixed host concentration and SDS concentration over the range 0.5-10 mM (figure 3 and ESI). The diffusion coefficient for SDS in the absence of cage was monitored over a similar concentration range.

Table 1. Fitted cumulative association constants for the host: guest systems.

Guest	β_1 / M^{-1} (H + G Ö HG)	β_2 / M^{-2} (H +2G Ö HG_2)
SOS	5,000± 400	1,000,000± 130,000
SDS	2,000± 700	500,000± 300,000
STS	1,000± 60	130,000± 20,000

The uncertainties are estimates of the standard deviation calculated by HypNMR[20].

As expected the diffusion coefficient measured for the cage was almost invariant with change in SDS concentration (figure 3 and ESI). In contrast the diffusion coefficient for SDS increased from approximately 1.8 x 10^{-10} m^2s^{-1} to approximately 2.3 x 10^{-10} m^2s^{-1} as its concentration was increased; the larger number being similar to the diffusion coefficient measured for SDS in the absence of cage.

While these data have not been modelled there is an apparent plateau in the diffusion coefficient for the SDS molecule at a **H:G** ratio of 0.5 (i.e. 1:2 host:guest). This result is reproducible, the same 'saturation' point being observed with a range of host concentrations.

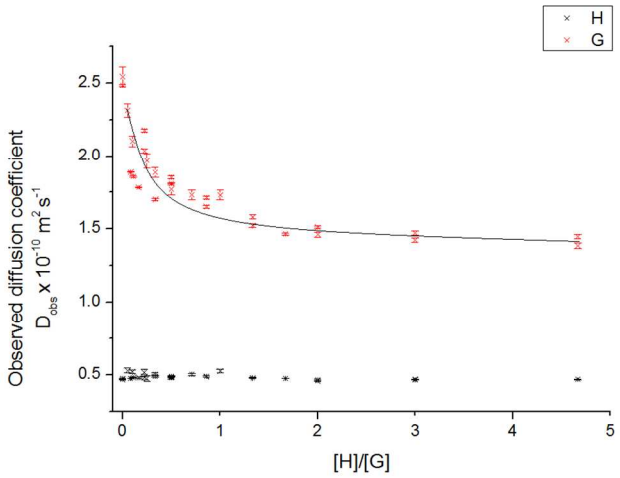

Figure 3. Plot of diffusion coefficient against host:guest concentration ratio ([**H**]/[**G**]). The curve for the guest flattens from a [**H**]:[**G**] ratio of 1:2. (d_6 DMSO solutions at 293 K.).

There have been a number of reports of SDS encapsulation[21] or simply sulfate anion association[8b,22]. In these reports the host/receptor molecules have a much smaller 'cavity' than the interior of the stella octangula cage. Consequently the proximity of the SDS alkyl tail to, for example, aromatic residues of the 'host' is much greater resulting in significant ring current induced chemical shifts for the alkyl protons and/or discrimination between free and bound SDS molecules[21]. In the current study the two 'associated' detergent molecules are in fast exchange with the bulk solvent hence a time averaged chemical shift is detected. Nevertheless it is possible to provide evidence in support of encapsulation, as opposed to some 'external' association, as a result of the NMR observation of through-space connections between detergent and host.

A section of the ROESY spectrum for a cage:SDS mixture is shown in figure 4. There is a very small amount of free ligand (**L**) apparent in the 1D spectrum (see ESI) and the ligand is clearly visible in the ROESY data set. Over a range of spin-locking times exchange between free ligand and cage was not detected (see ESI). Strong through-space connections are seen between protons on the cage pyridyl ring, and weaker rOes were detected between Hb/Hb' and protons along the alkyl chain. The Ha/Ha' protons display through-space connections to H1 and the H3 SDS protons. The CH_3 protons of the phenyl OMe group display a strong rOe to the H3 SDS protons and a much weaker connection to the H2 protons (see ESI). Over a range of sample concentrations and nOe/rOe build-up times no through-space connections were detected between the basal $-CH_2-$ protons and the SDS tail; the X-ray diffraction structure reveals that the basal $-CH_2-$ protons point towards the exterior/solvent[13b]. Similar observations were made for the cage:SOS system (see ESI). No through-space connections were observed between free ligand and SDS (or SOS).

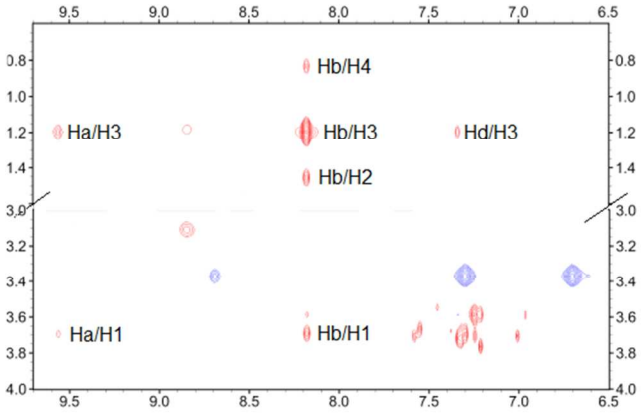

Figure 4. Section of a 2D ROESY spectrum for a 1:10 **H:G** mixture (**G** is SDS) with through space connections in red and exchange peaks in blue; note the cross peaks with an F1 chemical shift of ca. 3.4 ppm indicate exchange with the signal for water in the DMSO solution. See ESI for equivalent data for the cage alone (^{1}H frequency 500 MHz, 293 K, d_6 DMSO solution, 300 ms spin-lock time).

During the period of the rOe measurements the SDS and SOS molecules are in close proximity to both aromatic rings of the cage subunits[23]. Initially rationalization of the observation of close spatial proximity between the Hb/Hb' proton and **all** of the alkyl protons including the methyl terminus does not appear obvious. However such an observation has been made in other host:guest systems. These were explained through invoking a model in which the guest molecule rotates around its long axis over the timescale of the Overhauser measurement[24]. The dimensions of the cavity of the stella octangula cage are such that alkyl sulfate 'long-axis' rotation is indeed feasible and could therefore explain the rOe observations referred to. Additionally a simple molecular modelling approach in which SDS conformation was permitted to energy minimize in a static cage was supportive of the range of interactions detected (see ESI).

Herein the encapsulation of detergent molecules, octyl, dodecyl, and tetradecyl sulfate sodium salts, by the $[Pd_6(\mathbf{L})_8](BF_4)_{12}$ supramolecular cage has been demonstrated. To the best of our knowledge, this is the first example of encapsulation of these detergent molecules in such a large metallo-cage. Such accommodation is permissible according to the packing considerations proposed by Mecozzi and Rebek[25]; we have estimated the (internal) van der Waals volume of the cage and that of the detergents; 2050 A^3 for cage cf. 214 A^3 for SDS (see ESI for details), and consequent packing coefficients of 0.10 (10%)

and 0.21 (21%) for 1 and 2 encapsulated molecules respectively, both within the reported 55% limit[25].

ESI-MS spectra for the cage in the presence of SDS (see ESI) provide clear evidence of an interaction; however, the data cannot easily be used to determine stoichiometry due to rapid exchange and the low population of the host:guest complex. It was not possible to explore slower exchange regimes due to the constraint of working in DMSO, but it may be possible to gain further insight using a closely related system. Recently we have synthesized a modified stella octangula system, in which an –OPr group replaces the –OMe[26]. This modification renders the cage soluble in a variety of solvent systems, offering the potential for studying interactions with these and perhaps other amphipathic molecules under a wider range of experimental conditions.

Notes and references

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Electronic Supplementary Information (ESI) available: Details on sample preparation for NMR data collection; NMR data collection parameters; dissociation constant determination; and sample NMR spectra and further Job's plot information See DOI: 10.1039/c000000x/

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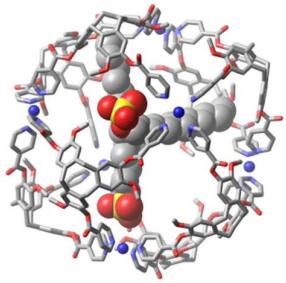

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