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NMR Characterization of the Structure and Dynamics of a Cavitand–SDS Complex

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A combination of NMR spectroscopy and molecular modelling yields the structure of the host–guest complex formed between sodium dodecyl sulfate and a cavitand. Nuclear Overhauser enhancements and ring-current shifts indicate that bound SDS adopts two conformations. Molecular modelling and an analysis of exchange-broadened NMR line shapes support the kinetic model for the binding.

Keywords: Host–guest systems; Ring-current shift; Conformation; Chemical exchange

INTRODUCTION

A prominent feature of supramolecular chemistry is the formation of complexes between host and guest molecules. The study of these interactions has greatly expanded our understanding of molecular recognition [1]. Considerable effort has been devoted to the synthesis and characterization of novel, vase-shaped hosts called cavitands [2]. One cavitand structure examined in detail consists of derivatized benzimidazole rings attached to a resorcinarene ring (Fig. 1). In a series of papers, Rebek *et al*. have systematically examined the structural basis for the tight binding of hydrophobic ligands such as sodium dodecylsulfate (SDS) [3–5]. A striking feature of the proton NMR spectrum of bound SDS is a series of well resolved, upfield shifted peaks for the methyl and methylene protons. We have used this result as the basis for a determination of the structure in water of the SDS–cavitand complex from NMR data. This effort also yielded information on the dynamics of the formation of the complex.

The NMR spectra of the complex result from a complicated interplay of structure, thermodynamics, and dynamics which must be understood in order to find conditions suitable for a structural determination. We report several new features of this system. As shown in Fig. 2, the crucial upfield-shifted peaks for bound SDS are broadened by chemical exchange and are only detected when the ratio of SDS to cavitand is less than or equal to one. As the ratio approaches one, the peaks are only seen at lower temperatures, e.g. 2°C. Furthermore, the spectra show two signals each for the methyl and methylene protons which merge into one as the temperature and the SDS concentration are raised.

The striking dependence of the NMR line shape on concentration and temperature supports the mechanism developed by the Cram and Rebek groups for host–guest interactions [6,7]. The cavitand can exist in a closed or vase conformation, C, and an open or kite form, C′. The aliphatic methine proton at the base of the cavitand, observed at 5.7 ppm for closed form and 3.9 ppm for the open form, is diagnostic for the position of the equilibrium [6]. In the cavitand–SDS system, the closed form predominates; the methine signal in both free and complexed cavitand is found at 5.54 ppm as a sharp triplet which integrates to two protons. As shown in Fig. 3, solvent molecules in the cavity prevent direct binding of the SDS and the cavitand must first convert to the open form where removal of solvent molecules is a facile process. Free SDS then binds to the open form to form a complex, SC′, which closes.

$$\mathrm{C} \leftrightarrows \mathrm{C}' \tag{1}$$

$$\mathrm{S} + \mathrm{C}' \leftrightarrows \mathrm{SC}' \tag{2}$$

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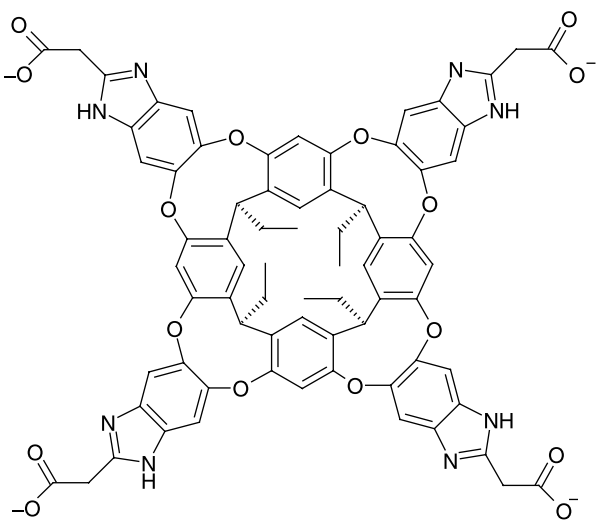

FIGURE 1 Structure of the cavitand examined in this study.

$$SC' \leftrightarrows SC \tag{3}$$

If one invokes the steady-state approximation for the intermediate SC′, the mechanism outlined above yields an informative expression for the pseudo first-order rate constant for the time rate of change of free SDS. If one also assumes that binding of SDS does not appreciably shift the equilibrium between the open and closed forms, i.e. $K_1 \approx 1/K_3 = K_O \ll 1$, the expression simplifies to $k^{(1)} = K_O k_2([C] + 1/K_2)$. Refer to the supplemental information for a derivation. If $k^{(1)}$ is comparable with the difference between the Larmor frequencies of free and bound SDS, $|\nu_S - \nu_{SC}|$, the peaks for the two forms broaden and greatly diminish in amplitude. This was observed to be the case when SDS is present in excess and free C has a very low concentration. In contrast, if the cavitand is present in excess, the concentration of C and therefore $k^{(1)}$ greatly increase. The dynamics determining the NMR spectrum now shifts towards the fast-exchange regime where a peak appears at a weighted average position. In the case of methylene protons on carbons 1 through 4 where the Larmor frequencies of the bound and free form are virtually identical, one is always in the rapid-exchange regime.

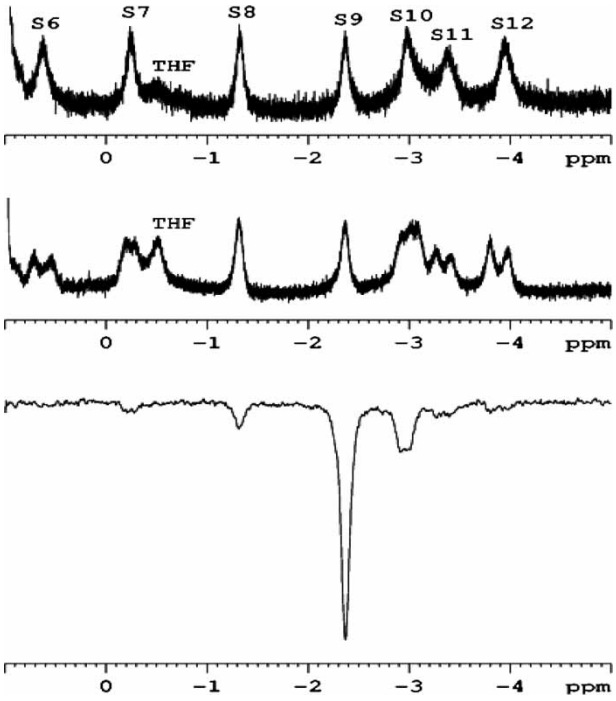

FIGURE 2 400 MHz proton spectra in aqueous 0.5 mM SDS, 2 mM cavitand of the upfield shifted protons on carbons 6–12 (S6–S12) of bound SDS. Top, 1D spectrum at 294 K; middle, 1D spectrum at 274 K; bottom, nOe difference spectrum at 275 K. The S9 methylene was inverted by a selective 180° pulse followed by a 400 ms delay. THF marks a signal due to bound THF. We number the carbons in SDS starting with the carbon adjacent to the sulfate group as number 1 and the methyl carbon therefore as number 12.

Trembleau and Rebek concluded from an nOe between the S12 methyl and S9 methylene protons that the conformation of the C9–C10–C11–C12 dihedral angle is gauche [3]. We report several lines of evidence that show the presence with bound SDS of the both the gauche and fully extended (all anti) conformers in equal amounts. Under conditions of excess cavitand, e.g. [C]/[S] = 4, we observed a pair of equal-area peaks for the protons on carbons 6, 7, 10, 11, and 12 which we assign to the two conformers. A careful examination of the 2D-NOESY spectrum at 275 K shows a strong exchange peak which demonstrates exchange between the two species. Using non-linear regression, we fit the 1D line shapes for the 5 pairs of peaks to the model of Gutowsky and Holm [8]. Within experimental error, all yielded the same rate constant, $260 \pm 50\,s^{-1}$.

Using the Merck Molecular Force Field and Spartan Version 04, we constructed models for the SDS–cavitand complexes [11]. The construction of these structures was guided by the model for the complex described by Trembleau and Rebek [3]. The fully extended form is energetically more stable and the molecular energies of the gauche and fully extended forms at the global minimum differ by 2.1 kcal. Our calculations show a low barrier for internal rotation of the bound SDS about its long axis. Given its length, the SDS cannot tumble inside the cavity. In contrast, Hooley *et al.* show from an NMR study of the binding of alkanes to the cavitand that shorter alkanes such as n-hexane adopt a helical conformation in the cavitand and are able to tumble rapidly [12]. In the case of the fully extended conformer, the methyl carbon is 2.9 Å from the plane defined by the 4 aliphatic methine carbons at the base of the cavitand; with the gauche, it is 3.6 Å. In these models carbons 7–12 are embedded in the cavitand and carbon 6 is located at its mouth. Their

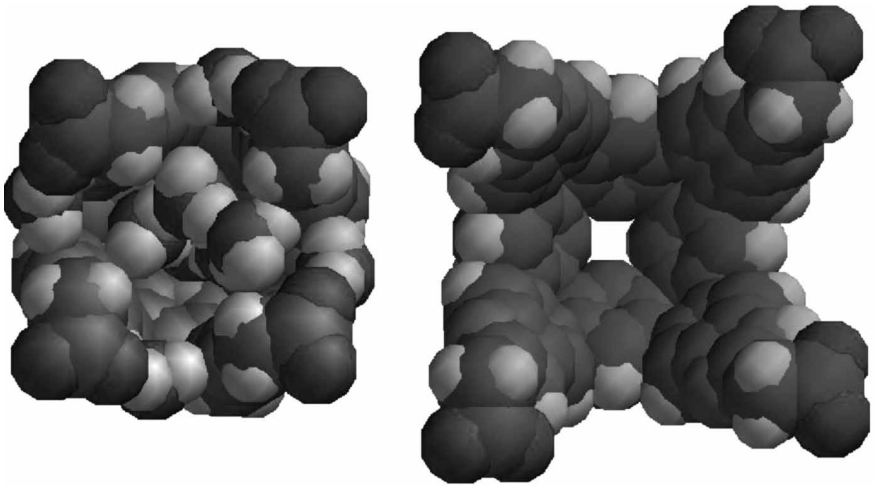

FIGURE 3 Closed (left) and open (right) forms of the cavitand in a space filling format. The closed form is filled with solvent molecules.

corresponding protons are shifted upfield by the fields generated by cavitand ring currents We employed the structural parameters from these models, e.g. the distance of each methylene proton from the aromatic rings, to calculate the upfield shifts of each proton from the model of Johnson and Bovey, whose utility has been demonstrated in protein NMR [9,10]. We fit the observed upfield shift, $\delta(bound) - \delta(free)$, for the protons on carbons 6–12 to the calculated value to a linear model with zero intercept. The excellent correlations, illustrated in Fig. 4 with $R > 0.995$, $s < 0.23$ ppm, and 6 degrees of freedom, provide quantitative strong support for our three-dimensional models of the pair of conformers.

The nuclear Overhauser effect (nOe) has been the principal source of structural constraints in protein NMR [13]. nOe's turned out to be less useful in the elucidation of the SDS–cavitand complex because exchange broadening of the crucial SDS upfield-shifted protons significantly reduced the signal-to-noise ratio. Sharp cross peaks between cavitand protons dominated the NOESY spectra with mixing times ranging from 300 ms to 500 ms. Cross peaks involving the SDS ligand were very weak and had intensity comparable with artifacts (see the Appendix). Because the upfield-shifted SDS peaks are well resolved, we obtained data sets with acceptable signal by performing a series of one-dimensional experiments. We employed the transient NOE method involving a selective 180° pulse followed by a delay interval to validate the NOESY results [14]. Success with the method requires selective inversion of spin(s) and a difference between spectra acquired via on- and off-resonance irradiation [15]. Spin diffusion was ruled out with a set of transient NOE experiments and delays of 100, 200, and 300 ms where the nOe's increased monotonically and non-sigmoidally with delay time.

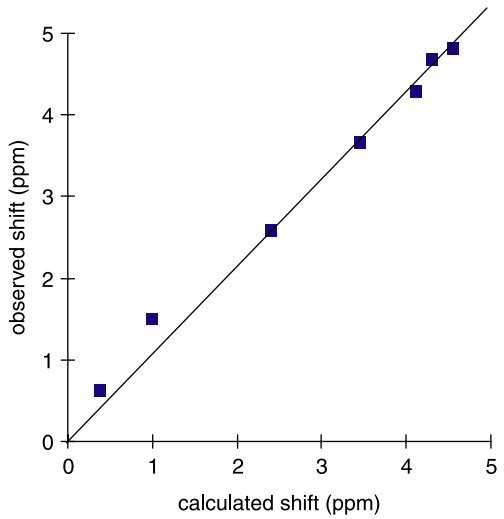

FIGURE 4 Fit of the average upfield shift of SDS protons on carbons 6–12 to the shift calculated for the all extended conformer via the model of Johnson and Bovey.

Table I tabulates the nOe's consistently observed in the series of 1D and 2D experriments discussed above. The checkerboard pattern of intrachain nOe's is consistent with the interproton distances calculated for a fully extended SDS chain. We have replicated the nOe between the protons on carbons 9 and 12 reported by Trembleau and Rebek [3]. However, as Fig. 2 shows, the nOe, which is diagnostic for a gauche conformation about the C9–C10–C11–C12 dihedral angle, is barely detectable and is weaker than the other intrachain nOe's We conclude from this result as well as the presence of pairs of signals and the ring-current calculations that two conformers, the gauche and the fully extended, are present in significant amounts.

The weak nOe's between the phenyl protons in the cavitand support the structure of the fully extended SDS conformation that was used in the ring-current calculations. In particular, the average distance between the SDS methyl protons and the phenyl

TABLE I nOe's between cavitand and SDS protons. Measured at 275 K with 0.5 mM SDS and 2 mM cavitand

Irr[†]	S6	S7	S8	S9	S10	S11	S12	ϕ_A[‡]	ϕ_B[¶]
S6		X	X						
S7	X		X	X					
S8	X	X		X	X				
S9		X	X		X	X	X		
S10			X	X		X	X		X
S11				X	X		X		
S12				X	X	X		X	
ϕ_A							X		
ϕ_B					X				

[†] In the 1D difference experiments, this proton is inverted. X, a weak or very weak nOe is observed in a 1D difference experiment between the irradiated proton and the proton(s) identified by the column label or a cross-peak between the pair of protons is observed in a NOESY spectrum. [‡] nOe to the phenyl proton at the base of the cavitand ($\delta = 7.54$ ppm). [¶] nOe to the phenyl protons on the resorcinarene ring ($\delta = 7.85$ ppm).

protons at the based of the cavitand was calculated to be 3.8 Å. In the model structure, the S10 methylenes are closest to the two protons on the resorcinarene ring as confirmed by the weak nOe.

The combination of NMR spectroscopy and molecular modelling has defined the structure of the SDS–cavitand complex. The dependence of the NMR line shape on temperature and concentration lends qualitative support to Rebek's model for binding. Although considerable effort has been invested in the characterization of the binding of ligands to the cavitand host, the elucidation of the thermodynamics and kinetics of this process has been at best semi-quantitative. A full quantitative treatment of this host–guest system, which will require work at micromolar concentrations, is a worthy object for future work.

MATERIALS AND METHODS

SDS was purchased from Aldrich and was used without further purification. The cavitand was provided by Professor Rebek of the Scripps Institute in La Jolla, California. THF is used in its synthesis. Integration of the proton spectrum of 2 mM cavitand shows tight binding of two moles of THF. Upon complexation with SDS, the THF molecule bound at the mouth of the cavitand is retained but the THF bound in the cavity is displaced.

All NMR measurements were performed on a Bruker 400 MHz spectrometer with an Avance DPX console and a dual proton/carbon-13 probe. All work was conducted in 99.96 atom% D_2O (Aldrich). Chemical shifts were referenced to the residual HDO peak whose chemical shift with respect to TSP was determined as a function of temperature in a separate set of measurements.

TPPI phase-sensitive NOESY spectra were acquired with presaturation of the HDO signal. The relevant acquisition and processing parameters were TD(1), 256; TD(2), 4096; d1, 2.0 s; SW, 22 ppm in both dimensions; NS, 320; SI(1) = SI(2) = 2048. A squared cosine windowing function was used in both dimensions. The nOe difference experiments were performed with 104 cycles. In each cycle, the frequency for inversion channel was set on-resonance for 64 scans and then well off-resonance, e.g. 12 ppm, for an additional 64 scans. The total accumulated fid for each data set was Fourier transformed without and phased identically before calculating the difference spectrum. Pulse lengths of 7, 50, and 100 ms were employed for the 180° inversion pulse.

Acknowledgements

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