COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Interactions between a surfactant and cavitand in water blur distinctions between host and guest

Laurent Trembleau and Julius Rebek Jr*

The Skaggs Institute For Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA. E-mail: jrebek@scripps.edu; Fax: +1 858 784 2876; Tel: +1 858 784 2250

Received (in Columbia, MO, USA) 17th September 2003, Accepted 29th October 2003
First published as an Advance Article on the web 28th November 2003

The complexation of a water-soluble cavitand and sodium dodecyl sulfate micelles is studied using NMR diffusion ordered spectroscopy.

Cavitands are open-ended molecular hosts capable of binding guests with high selectivity and affinity.[1–3] For example, water-soluble cavitand **1**[3] (Fig. 1) binds acetylcholine with an association constant $> 10^4$ M^{-1}, but larger ammonium derivatives are rejected. Moreover, long alkyl chains of surfactants like sodium dodecyl sulfate (SDS) are also recognized by the cavity with high affinity.[4] In that case, the alkyl chain guests adopt a coiled conformation in order to better fill the hydrophobic cavity and maximize the CH–π interactions with the aromatic surface of the host. Here, we show that the roles of host and guest are reversed above the critical micellar concentration (cmc) of SDS: the cavitand is bound within micelles of the surfactant.

We examined the ^{1}H NMR of 1 mM solutions of **1** in D_2O in the presence of increasing amounts of SDS (Fig. 2). When one equivalent (or less) of SDS is present, the cavitand and surfactant form a kinetically stable complex, and exchange of the SDS in and out of the cavity is slow on the NMR time scale (Fig. 2d). Unexpectedly, the rate of the in/out exchange becomes fast on the NMR time scale when a slight excess of surfactant (*ca*. 1.3 equiv.) is present. The upfield signals for the bound guest (between +1 and −5 ppm) disappear as the chemical shifts of free and bound species are averaged. In the presence of 10 mM of SDS, the NMR signals of the host appear broad and slightly shifted upfield (Fig. 2c). At high concentration (20–40 mM), a new set of broad signals appear in the NMR spectra (Fig. 2b). All the signals are shifted upfield except the benzylic methine protons at ~5.5 ppm. Higher concentrations of surfactant have no effect on the chemical shifts of the signals. According to the amphiphilic characteristics of cavitand **1**, we assumed that it could be included in SDS micelles above the cmc (~8.3 mM at 20 °C),[5,6] as indicated by the broadness and the shifting of the signals.

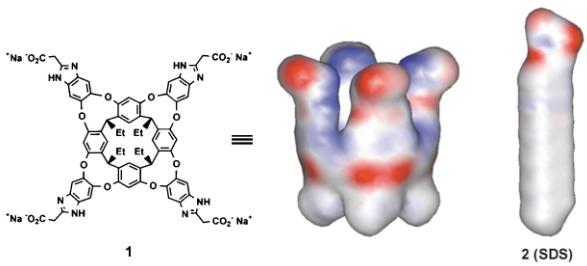

Fig. 1 Structure of cavitand **1** and electrostatic surface representation of **1** and sodium dodecylsulfate (SDS) **2**.

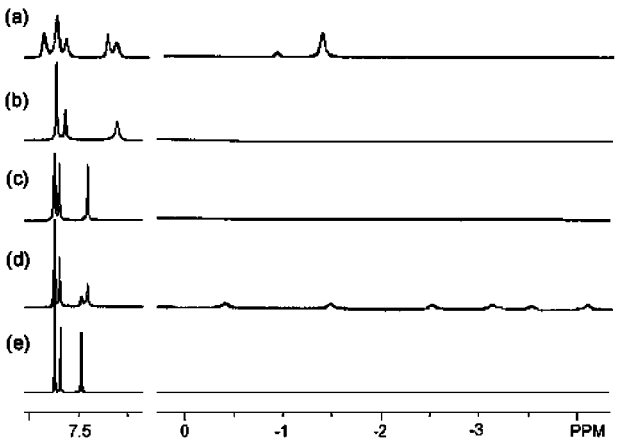

Fig. 2 ^{1}H NMR spectra (D_2O, 300 K, 600 MHz) of the aromatic and upfield region of: a) **1** (1 mM) + SDS (40 mM) + acetylcholine (1 mM); b) **1** (1 mM) + SDS (40 mM); c) **1** (1 mM) + SDS (1.3 mM); d) **1** (1 mM) + SDS (0.6 mM); e) reference spectrum of **1** (1 mM).

To test this hypothesis, we undertook a series of NMR measurements using diffusion ordered spectroscopy (DOSY).[7,8] First, diffusion coefficients were determined for cavitand **1** and SDS solutions alone. The apparent hydrodynamic radii of the species were calculated using the Stokes–Einstein equation (Table 1). The diffusion coefficient of **1** shows no changes between 0.2 mM and 4 mM in accordance with the presence of monomeric species in solution. An equimolar solution of **1** and SDS gives a similar diffusion coefficient for both components indicating the formation of a 1 : 1 complex. This is in agreement with the previous observations by ^{1}H NMR.[4] The calculated hydrodynamic radius of 10 Å is consistent with that expected for a roughly spherical cavitand/surfactant complex.

As anticipated, the diffusion coefficient of SDS decreases with increasing concentration. Below the cmc (*ca*. 3.7 mM), SDS is essentially monomeric and diffuses at the high rate of 4.2×10^{-6} cm^2 s^{-1}. At concentrations above the cmc, monomers and micelles exist in a dynamic equilibrium.[9] Thus, if N is the aggregation number:

$$N\mathrm{SDS(aq)} \leftrightarrows \mathrm{SDS}_N\mathrm{(aq)} \quad (1)$$

In a fast exchange regime, the observed diffusion coefficient is the mole fraction weighted average of the diffusion of the individual species (eqn. 2).

$$D_{\mathrm{SDS(obs)}} = X_{\mathrm{SDS}}D_{\mathrm{SDS}} + X_{\mathrm{Micelle}}D_{\mathrm{Micelle}} \quad (2)$$

At 40 mM concentration and 30 °C, the diffusion coefficient of SDS is 1.3×10^{-6} cm^2 s^{-1} and the micelle's apparent hydrodynamic radius is 15.4 Å. At the same concentration of SDS and at 1 mM of cavitand **1**, the diffusion coefficient of **1** also

Table 1 Diffusion coefficients[a] and hydrodynamic radius of cavitand **1** and SDS species in D_2O solutions

Solutions (C in mM)	Viscosity[b] η (cp)	$D/10^{-6}$ cm^2 s^{-1}	r/Å
Cavitand **1** (0.2)	0.98	2.2	10.2
Cavitand **1** (4)	0.98	2.3	9.8
1/SDS (2/2)	0.98	2.2/2.2	10.2
SDS (3.7)	0.98	4.2	5.3
SDS (10)	0.99	3.4	6.5
SDS (20)	1.03	1.9	11.3
SDS (40)	1.11	1.3	15.4
1/SDS (1/40)	1.11	0.8/1.1	24.8/18.0

[a] Average (± 10%) of three consistent DOSY experiments at 30 °C and 400 MHz; [b] Viscosities were determined at 30 °C using an Ostwald viscometer.

DOI: 10.1039/b311424d

decreases to 0.8×10^{-6} cm^2 s^{-1}. This corresponds to a hydrodynamic radius of ~25 Å, a value in agreement with previous determinations of SDS micelle radius using X-ray scattering.[10] ^{1}H NMR experiments and NMR diffusion data show that the cavitand is associated with the micelles.

A molecular model of a micelle incorporating one molecule of cavitand is shown in Fig. 3. The hydrophobic moiety of **1** is expected to be located in the core of the micelle with the carboxylate groups on the surface. NMR experiments show that no surfactant is in the cavitand or that the complex is not kinetically stable on the NMR time scale. But **1** still binds acetylcholine with relatively high affinity (Ka ~ 1700 M^{-1}) while embedded in the micelles (Fig. 2a).

In summary, cavitand **1** in water incorporates SDS at low concentrations, but above the critical micellar concentration the surfactant incorporates the cavitand. At intermediate concentrations the relationship is undefined. The NMR diffusion experiments showed that the micelles remain approximately spherical upon incorporation of **1**,[6] with an aggregation number close to 60. Given the relative concentrations, we expect more than two molecules of cavitand to be included in each micelle. These experiments augur well for the study of synthetic receptors in membrane-like environments.

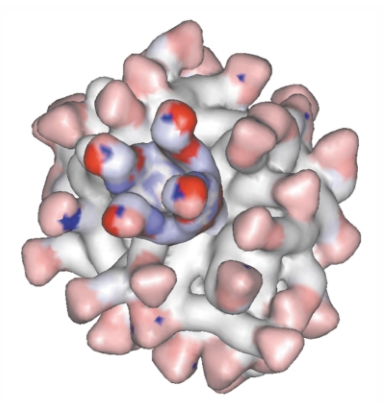

Fig. 3 Surface representation of a mixed micelle composed of SDS and cavitand **1** (Hyperchem 7.0, Charmm27 force field).[11]

We are grateful to the Skaggs Institute for Research and the NIH (GM 27932) for financial support. We thank Dr Laura B. Pasternack for valuable advice and her help with the DOSY experiments. L.T. is a Skaggs Postdoctoral Fellow.

Notes and references

1 D. J. Cram, *Container Molecules and their Guests, Royal Society of Chemistry*: Cambridge, 1994.
2 D. M. Rudkevich, G. Hilmersson and J. Rebek Jr., *Eur. J. Org. Chem.*, 1999, 1991–2005.
3 L. Trembleau, F. Hof, E. Ullrich and J. Rebek Jr., *Angew. Chem., Int. Ed.*, 2003, **42**, 3150.
4 L. Trembleau and J. Rebek Jr., *Science*, 2003, **301**, 1219–1220.
5 N. J. Turro and A. Yekta, *J. Am. Chem. Soc.*, 1978, **100**, 5951.
6 K. Goodling, K. Johnson, L. Lefkowitz and B. W. Williams, *J. Chem. Ed.*, 1994, **71**, A8.
7 K. F. Morris and C. S. Johnson Jr., *J. Am. Chem. Soc.*, 1992, **114**, 3139–3141.
8 Examples of micelle studies using pulsed-field-gradient diffusion methods: P. Stilbs, *Prog. NMR Spectrosc.*, 1987, **19**, 1–45; D. A. Kallick, M. R. Tessmer, C. R. Watts and C. V. Li, *J. Magn. Reson. Ser. B.*, 1995, **109**, 60–65; K. F. Morris, C. S. Johnson Jr. and T. C. Wong, *J. Phys. Chem.*, 1994, **98**, 603–608; A. Chen, D. Wu and C. S. Johnson Jr, *J. Phys. Chem.*, 1995, **99**, 828–834; X. Gao and T. C. Wong, *Biophys. J.*, 1998, **74**, 1871–1888.
9 A. H. Roux, D. Hetu, G. Perron and J. E. J. Desnoyers, *Solution Chem.*, 1984, **13**, 1; Jan B. F. N. Engberts and M. J. Blandamer, *Chem. Commun.*, 2001, 1701–1708.
10 R. Itri and L. Q. Amaral, *J. Phys. Chem.*, 1991, **95**, 423–427.
11 HyperChem(TM), Hypercube, Inc., 1115 NW 4th Street, Gainesville, Florida 32601, USA.