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Amide–Ligand Hydrogen Bonding in Reverse Micelles

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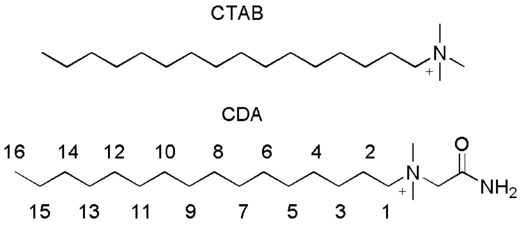
One approach to modeling the second coordination shell of metalloproteins is to pair amide-containing counterions with metal complexes to form hydrogen bonds in the solid state. In a more general approach, we have designed a surfactant counterion that can sustain hydrogen bonding interactions with metal complexes in solution. The surfactant is cationic and incorporates an amide as part of its headgroup to form hydrogen. The surfactant forms hydrogen bonding reverse micelles that accommodate anionic metal complexes in their polar core. In reverse micelles containing an iron(III) hexacyanide complex, spectroscopic evidence suggests that the anion is confined to the polar core region in solution. Single-crystal X-ray diffraction data on the surfactant ferricyanide system reveals a layered structure with interdigitated alkyl chains and an extensive network of hydrogen bonds that link amide groups to the cyanide ligands and to neighboring headgroups.

Reverse micelles (RMs) are employed for drug delivery, in the formation and shape control of nanoparticles, as sequestering agents for enzymes, and for catalysis.[1−7] In these applications, the surfactant or lipid headgroup of the host RM can be designed for specific interactions with the RM guest. We have synthesized surfactants to study amide−ligand hydrogen bonds related to those encountered at protein active sites.[8] The surfactants form RMs designed to mimic the second coordination shell of metalloprotein active sites.

Chart 1. Cations of the Surfactants CTAB and CDA-Cl



Metal complexes and organic chromophores have been employed as probes of the polarity of water-swollen (water core) reverse micelles (reverse microemulsion droplets).[9,10] In such studies, light absorption and fluorescence measurements have provided insight into the structure and polarity of the water phase as a function of proximity to the polar headgroup interface. Surfactants at low concentration in media of low polarity form reverse micelles whose cores consist of closely associated headgroups. These are so-called dry reverse micelles.[11] In this paper, we present the results of experiments on a dry RM system formed by the surfactant acetamidocetyldimethylammonium chloride (CDA-Cl, Chart 1)[12,13] (**1**). The surfactant CDA-Cl is synthesized by the reaction of cetyldimethylamine with equimolar chloroacetamide in refluxing CH_3CN. It is chemically related to the well-known surfactant cetyltrimethylammonium bromide (CTAB) from which it differs by the replacement of one methyl group by an acetamido group chosen for its H-bond donor character.

A ternary phase diagram (Figure 1) of the CDA-Cl/$CHCl_3$/H_2O system confirms the existence of reverse microemulsion (L_2) and microemulsion (L_1) single phase domains. Multiphase domains exist in the region between these L_1 and L_2 domains, and liquid crystalline domains likely exist at higher

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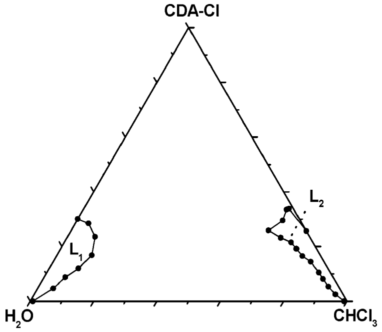

Figure 1. Phase diagram of the CDA-Cl/$CHCl_3$/H_2O ternary system at 22 °C.

CDA-Cl levels. Dynamic light scattering (DLS)[14,15] data on CDA-Cl in chloroform (CDA-Cl/$CHCl_3$ 5.5:94.5 w/w at 20 °C) show reverse micelles with a mean radius of 1.2 nm. This surfactant/solvent ratio lies within the L_2 (reverse microemulsion) region of the phase diagram. DLS data on CDA-Cl (0.01 M) in water show micelles with a mean radius of 6.47 nm. This concentration lies within the L_1 region of the phase diagram.

The substitution of chloride ion[16] in CDA-Cl by $[Fe(CN)_6]^{3-}$ yields the complex $(CDA)_3[Fe(CN)_6]$ (**2**). Structural and dynamical information on **2** was obtained by the comparison of ^{1}H NMR spectra of RMs in 1:99 (w/w) solutions (L_2 phase) of (i) **1** and (ii) **2** in $CDCl_3$. Evidence for RM formation in the **2**:$CDCl_3$ system is the observation of $[Fe(CN)_6]^{3-}$ solubilization in $CDCl_3$ resulting in a clear yellow homogeneous solution. The average size of RMs in the **2**:$CDCl_3$ system has yet to be determined by DLS because complex **2** gives homogeneous solutions only at low concentrations that are weakly scattering.

The $[Fe(CN)_6]^{3-}$ paramagnet ($S = 1/2$) broadens a subset of the CDA protons, specifically those of the amide, Cα, ammonium methyl group and the methylene C1 of the cetyl chain.[17,18] The C2−C16 protons show no broadening. Selective proton resonance broadening for protons in the vicinity of the headgroup shows that the $[Fe(CN)_6]^{3-}$ ions are essentially confined to the cluster core.

The RM structure of **2** is disrupted in DMSO as substantiated by ^{1}H NMR data. In this solvent, the amide proton signals display splittings characteristic of acetamide in a diamagnetic environment with a resonance at 7.6 ppm (d, 2H).[19] Additionally, the spectrum in DMSO shows a slight broadening of all the CDA protons. This broadening is indicative of the dissociation of the RM structure that exposes all of the surfactant protons to dipolar broadening interactions with the $[Fe(CN)_6]^{3-}$ anion.

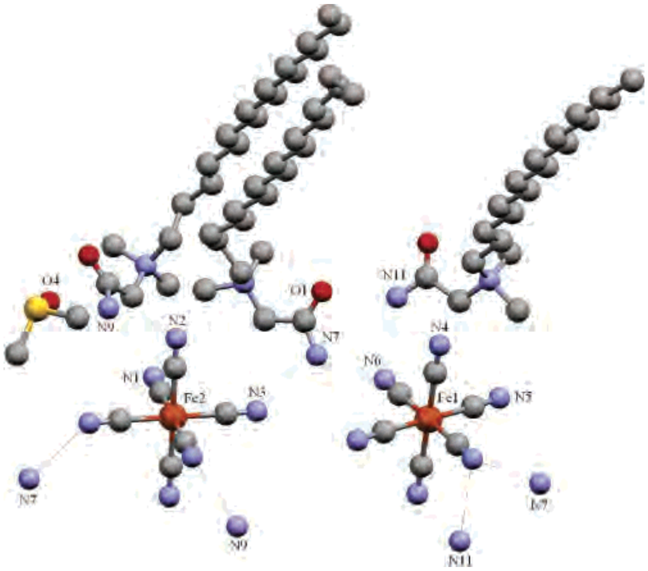

Figure 2. Crystal structure showing amide-cyanide hydrogen bonding in $(CDA)_3[Fe(CN)_6]$·DMSO. Hydrogen atoms and surfactant chains that are related by inversion to the surfactants shown in the figure are omitted for clarity.

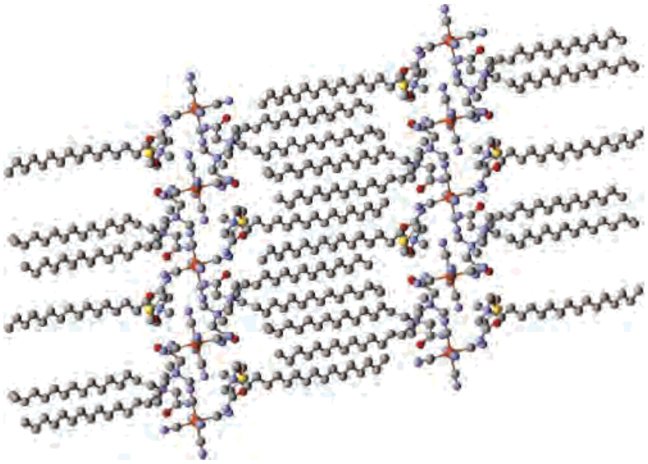

Figure 3. Crystal structure of $(CDA)_3[Fe(CN)_6]$·DMSO, partial packing diagram.

Solutions of complex **2** in DMSO at maximal concentration are in fact supersaturated under ambient conditions. Within a period of hours, transparent yellow crystals are deposited from the solution. Single-crystal X-ray diffraction analysis of the crystals reveals the formula unit to be $(CDA)_3[Fe(CN)_6]$·DMSO[20] (Figures 2 and 3). The structure is remarkable because it exhibits a combination of charge pairing and hydrogen bonding association between the $[Fe(CN)_6]^{3-}$ anion and the cationic headgroup of the sur-

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[20] Crystal data for $(CDA)_3[Fe(CN)_6]$·DMSO follow: $C_{68}H_{135}FeN_{12}O_4S$, fw = 1272.79, T = 218(2) K, yellow plate, triclinic, $P\bar{1}$, a = 11.6444(15) Å, b = 14.3461(17) Å, c = 24.658(3) Å, α = 74.053(3)°, β = 77.117(2)°, γ = 83.995(3)°, V = 3856.8(8) Å^3, D(calc) = 1.096 Mg/m^3, Z = 2. All crystals examined diffracted weakly due to the expected high thermal activity of the long alkyl chains. The asymmetric unit consists of three cations, two-half anions located on inversion centers, and a molecule of DMSO. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in idealized locations. $R1$ = 10.89%, $wR2$ = 25.52%. Bruker P4 diffractometer with APEX CCD detector. All software contained in Bruker SMART, SAINT, and SHELXTL libraries (Bruker AXS, Madison, WI).

factant and likely reflects the structural relationship of the headgroups and anionic guests in the corresponding RMs.

The hydrocarbon regions of the asymmetric unit are aligned as two sets of three parallel chains that are related by a center of inversion (Figure 2). For clarity, only one set of parallel chains is shown. The polar cationic headgroups of CDA form a well-defined layer in contact with a layer of ferricyanide anions. The polar headgroups maintain close contact through charge pairing and hydrogen bonding with the ferricyanide ions.

The amide groups each serve as N−H donors to two H-bond acceptors, accounting for a total of six hydrogen bonds in the asymmetric unit. Amide N7 forms a bifurcated H-bond with the N3 (2.930 Å) and N6 (3.088 Å) atoms of cyanide ligands bound to Fe2 and Fe1, respectively. Amide N9 forms a similarly bifurcated H-bond to O4 (2.832 Å) of DMSO and N1 (2.948 Å) of a cyanide ligand bound to Fe2. Last, amide N11 donates H-bonds to carbonyl O1 (2.953 Å) and an aforementioned cyanide N6 (2.960 Å).

Overall, the crystal structure reveals a bilayer, containing the $[Fe(CN)_6]^{3-}$ anions in a planar hydrophilic region (Figure 3). The ferricyanide plane is overlayered by the cationic headgroups of the CDA counterions. van der Waals interactions between the cetyl chains of CDA favor close packing and interdigitation of the extended nonpolar alkyl tails of neighboring surfactant molecules. The interdigitated bilayer structure in the crystal is a common morphology of surfactants in their crystalline forms, as reported earlier for CTAB and SDS.[21,22] The formation of $[Fe(CN)_6]^{3-}$ layers in the crystal is promoted by the $(CDA)^+$ surfactants, as shown by comparison with the structure of $(Et_4N)_3[Fe(CN)_6]$ that displays no bilayer structure.[23]

In summary, we have shown that **1** forms RMs in chloroform. These RMs can incorporate anionic metal complexes with hydrogen bonding to the ligands as exemplified by the $[Fe(CN)_6]^{3-}$ anion. ^{1}H NMR data suggest that the paramagnetic metal complex is largely confined by ion pairing and hydrogen bonding to the region near the surfactant headgroups in the RMs.

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Supporting Information Available: Crystallographic data of $(CDA)_3[Fe(CN)_6]$DMSO (CIF) and experimental preparations and characterizations for all surfactants and L_1 and L_2 domain phase boundaries (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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