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An Enantiomeric Discrimination In Aqueous Mixed Chiral Micelles Through Hydrogen Bonding

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Abstract: Self-assembling molecular receptor comprising a chiral surfactant amide placed in a rigid micellar environment recognizes the different amide enantiomeric forms in water solution by means of hydrogen bonding.

Hydrogen bonding is a fundamental force in molecular recognition by biological macromolecules.[1-3] Since it is known that amide enantiomeric discrimination is caused by hydrogen bonding[4] and that weak hydrogen bonding occurs in micellar environments[5,6] we reasoned that a self-assembling molecular receptor consisting of a chiral amide in a micellar environment[7] might recognize the different enantiomeric forms by means of hydrogen bonding. Here we report these results.

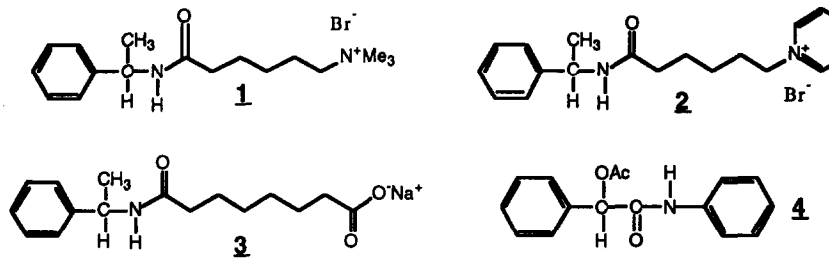

Figure 1

The compounds studied (Figure 1)[8] **1-3** are chiral and possess surfactant properties. Their aqueous solutions show change of chemical shift in ^{1}H NMR spectra[9] around 10^{-2} M with little or no change within a range of concentrations 10^{-3} to 10^{-4} M. This behavior is characteristic for surfactant molecules in water media.[6] Typical physical properties of surfactant molecules **1-3** are shown with **3R** in Figure 2. and **1S** in Figure 3. The drastic change in signals shape (aromatic protons) and chemical shift (aliphatic protons) is observed around the critical micellar concentration (10mM). A similar effect was observed at rather low concentration (~0.5 mM) of **1S** in equimolar aqueous counterion surfactant (Figure 3). In our previous study we discovered that mixed micelles formed

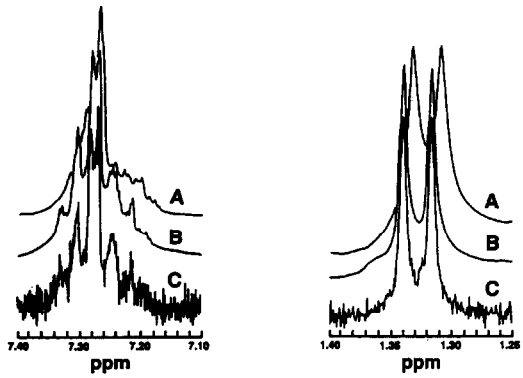

Figure 2. Chemical shifts of aromatic and methyl protons of 1000 mM (**A**), 10 mM (**B**), and 0.1 mM (**C**) aqueous **3R**

much stronger aggregates and the physical effects of critical micellar concentration can be observable at significantly lower concentration.[11] This two spectroscopic characteristics of chiral molecules **1-3** undoubtedly demonstrate their surfactant ability.

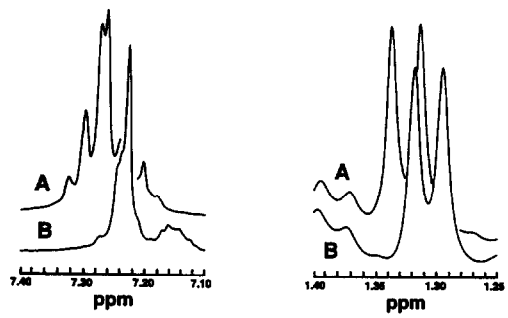

Figure 3. Chemical shifts of aromatic and methyl protons of **1S** (0.5 mM) in water (**A**) and equimolar aqueous SDS (**B**)

As a probe for studying hydrogen bond formation, and consequently enantiomeric recognition in micellar media, amide **4** was chosen because the chemical shift of the proton on the chiral center is in a clear region of the ^{1}H NMR spectra. We were not able to see any difference in the ^{1}H NMR spectra of water solutions (20 mM) of various ratios of optically active surfactants **1R-1S**, **2R-2S**, or **3R-3S**.

Attempts to determine any kind of chiral recognition between racemic chiral probe **4** (3mM) in various aqueous solutions of **1R**, **1S**, **2R**, **2S**, **3R**, and **3S** were unsuccessful. A possible explanation is that micellar structures thus formed are too loose to protect against penetration of water molecules into the micellar structure.[10] Therefore, the formation of hydrogen bonding between the amides (**4** and **1R**, **1S**, **2R**, **2S**, **3R**, or **3S**) and water molecules will be much more favored over amide-amide hydrogen bonds. To overcome this problem chiral micelles of enantiomericly pure surfactants and achiral counterion surfactants, sodium dodecyl sulfate (SDS) or cetyltrimethylammonium bromide (CTAB), were employed. It is well documented that so formed micelles have more rigid structures which exclude high concentrations of water from the micellar aggregates.[6,11] The chemical shifts for the hydrogen on the chiral center of **4R** and **4S** (3:2) in water solutions of **1R** (20 mM) and SDS (20 mM)[12] are shown in Figure 4.

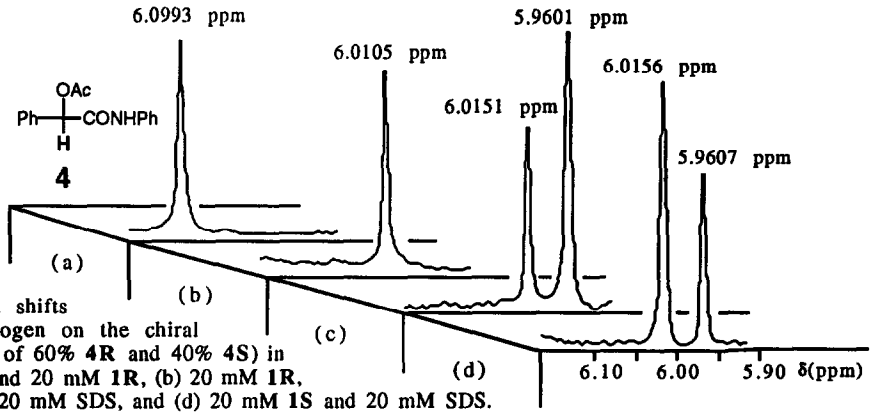

Figure 4. Chemical shifts (ppm) of the hydrogen on the chiral center of 4 (3 mM of 60% **4R** and 40% 4S) in (a) 20 mM CTAB and 20 mM **1R**, (b) 20 mM **1R**, (c) 20 mM **1R** and 20 mM SDS, and (d) 20 mM **1S** and 20 mM SDS.

The micelle between cationic chiral surfactant **1R** and cationic CTAB is open allowing penetration of water molecules deep into the micellar core and resulting in a downfield shift of **4**.[13] The hydrogen bonding between the probe molecule and chiral micelle is precluded and only one signal for **4R** and **4S** is observed (Figure 4, case *a*). The micelle formed solely from **1R** is slightly rigid but still the microenvironment is too polar to provide enantiomeric recognition (Figure 4, case *b*). Only the micelle between SDS and **1R** provides the proper microenvironment for enantiomeric recognition through hydrogen bonding (Figure 4, case *c*). Two signals for the enantiomers of **4** (ratio of R/S is 3/2) are observed with $\Delta\delta$ = 0.045 ppm and their integrals correspond to the enantiomeric composition. Similar results were also observed for micelles for all the other chiral surfactants (**1S**, **2R**, **2S**, **3R**, and **3S**) with the counterion achiral SDS or CTAB respectivelly. The enantiomeric signals for **4** exchange places when changing from the SDS-**1R** to SDS-**1S** micelle (Figure 4, case *d*). The enantiomeric recognition of nonracemic **4** was not observed in either aqueous nonchiral surfactant (CTAB or SDS), or their mixture.

Our data support a model in which the chiral micelles formed between the chiral surfactant and achiral counterion surfactant exclude bulk water from the hydrogen bonding part of the chiral surfactant, thus providing a chiral microenvironment for enantiomeric recognition via hydrogen bonding between a chiral micelle and the dissolved enantiomeric compound. This effect is not observed in either aqueous achiral micelles (the lack of a chiral environment) or in aqueous chiral micelles (the structure is too loose to provide nonaqueous microenvironment).

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8. (S)- or (R)-N-(6-bromohexanoyl)-α-methylbenzylamine (**5**) were prepared from either optically pure (R)- or (S)-α-methylbenzylamine (10 mmol) and 6-bromohexanoyl chloride (10 mmol) in tetrahydrofuran-water (50 + 50 mL) with sodium hydroxide (10 mM) as base. The solvent was evaporated, solid residue was partitioned between chloroform and 10% KOH. The organic layer was evaporated, and solid residue was crystallized from petroleum-ether. Surfactant **1** and **2** was prepared from **5** (5 mmol) with bubbling trimethylamine or adding pyridine (20 mmol) respectively into its chloroform (200 mL) solution. The reaction mixture was kept at O°C for two days. The solvent was evaporated and oily residue was crystallized from chloroform petroleum-ether.
   Surfactant **3** was prepared from either optically pure (R)- or (S)-α-methylbenzylamine 10 mmol) and suberoyl chloride (10 mmol) in pyridine (300 mL) at room temperature. The reaction mixture was kept at room temperature overnight. The solvent was evaporated and residue was dissolved in chloroform (200 mL) and extracted with 10% KOH (3x100 mL). The basic water layer was acidified with conc. HCl and extracted with chloroform (3x100 mL). The chloroform extracts were dried ($MgSO_4$), and evaporated. The semisolid residue was crystallized from chloroform petroleum-ether. The water solution of **3** was prepared from so obtained acid and equimolar amount of sodium hydroxide. The preparation and spectroscopic characterization of **4** is published elsewhere.[4] Structures of all studied compounds were confirmed by ^1H NMR, ^{13}C NMR, and MS (FAB).
9. All ^1H NMR studies were performed at room temperature in D_2O as solvent on a Varian Gemini 300 with the water signal as reference (4.7 ppm).
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13. UV studies of **4** in water and aqueous **1**-**3** with and without corresponding coun terionic surfactant showed that the compound goes deep into the micellar core.

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