Molecular Recognition between Uncharged Molecules in Aqueous Micelles

James S. Nowick,* Thomas Cao, and Glenn Noronha

Contribution from the Department of Chemistry, University of California, Irvine, California 92717-2025

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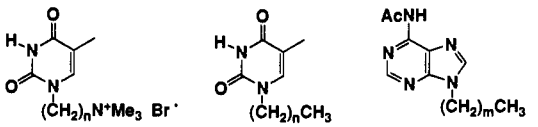
Abstract: Micelles provide microenvironments that permit hydrogen bonding to occur between small molecules in aqueous solution. 1-Alkylthymine derivatives **2** hydrogen-bond (base-pair) with N^6-acetyl-9-alkyladenine derivatives **3** in the presence of sodium dodecyl sulfate (SDS) micelles but base-stack with the adenine derivatives in the absence of SDS. When the adenine–thymine interactions are analyzed by ^{1}H NMR titration, the adenine and thymine groups play different roles in the binding process; the thymine derivative acts as a receptor, whereas the adenine derivative acts as a ligand. For base pairing to be observed, the alkylthymine derivative must be sufficiently hydrophobic to be largely incorporated within the micelles. This requirement reflects the thymine group's role as the spectroscopic probe in the ^{1}H NMR titration studies. In contrast, the adenine derivative may be considerably less hydrophobic and need not be largely incorporated within the micelles. More lipophilic adenine derivatives are bound with greater observed binding constants (K_{obs}), and a linear relationship is observed between log K_{obs} and log K_{ow} (where K_{ow} is the octanol–water partition coefficient of adenine **3**). These observations are consistent with a model in which the adenine derivative partitions between the exterior and interior of the micelles and the thymine binds the intramicellar adenine. These studies establish that uncharged hydrogen-bonding receptor molecules can incorporate into micelles to form *supramolecular receptors* that bind hydrogen-bonding ligands in aqueous solution.

Hydrogen bonding[1] contributes only modestly to the free energy of association of small, uncharged solute molecules in aqueous solution.[2] For this reason, hydrogen bonding has historically played a limited role in molecular recognition in aqueous systems. Instead, molecular receptors based upon cyclodextrins[3] and cyclophanes[4] have relied heavily upon hydrophobic interactions in the binding of substrates. Only within the past few years have strategies for achieving hydrogen bonding between small molecules in aqueous solution begun to emerge. In general, these strategies have relied upon hydrophobic interactions to facilitate hydrogen bonding: aromatic surfaces,[5] monolayer–water interfaces,[6] and the interior of bilayer membranes[7] have been shown to provide suitable microenvironments for hydrogen bonding in aqueous solution.

We recently introduced a new strategy to achieve hydrogen bonding between small molecules in aqueous solution.[8] In this strategy, an amphiphilic derivative of one compound is incorporated into a surfactant micelle; the micelle provides a microenvironment that permits the compound to hydrogen-bond to a complementary compound. Thus, alkylammonium derivatives of thymine (**1a–d**) incorporate into sodium dodecyl sulfate (SDS) micelles, and the resulting supramolecular assemblies bind adenine derivatives by means of hydrogen bonding (base pairing). In the absence of SDS, base pairing does not occur. This strategy provides a means to achieve molecular recognition between charged and neutral species in aqueous solution.



1a n = 4 **1b** n = 6 **1c** n = 8 **1d** n = 10

2a n = 1 **2b** n = 3 **2c** n = 5 **2d** n = 7

3a m = 1 **3b** m = 2 **3c** m = 3 **3d** m = 4

We now report that hydrogen bonding occurs between *uncharged* molecules when micelles are present. Alkylthymine derivatives **2** base-pair with adenine derivatives **3** in the presence of SDS but base-stack with adenine derivatives in its absence. By varying the alkyl substituents of the adenine and thymine derivatives, we find that hydrophobic effects also contribute to binding. Because of the differing roles of the thymine and adenine molecules in the binding process, there are different requirements

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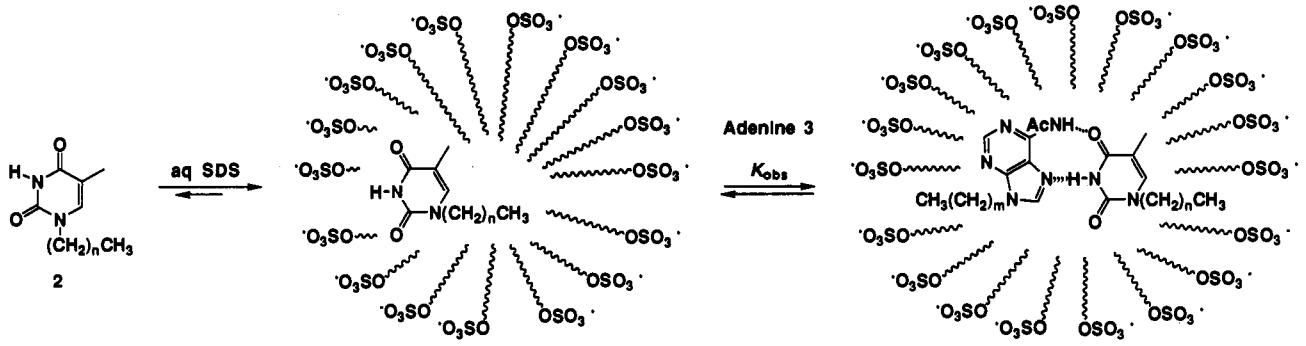
Scheme 1



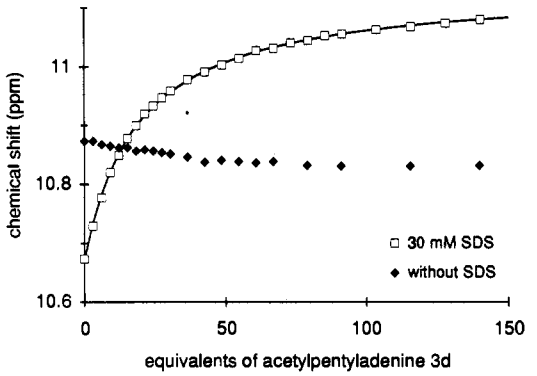


Figure 1. Titration of hexylthymine **2c** with acetylpentyladenine **3d**. Chemical shift of NH group of thymine **2c** vs equivalents of added adenine **3d** in the presence and in the absence of 30.0 mM SDS. The curve is the theoretical 1:1 binding isotherm that best fits the experimental data (K_{obs} = 48.5 M^{-1}, δ_{free} = 10.669 ppm, δ_{bound} = 11.197 ppm). Titrations were performed on a 500-MHz ^1H NMR instrument at 22–23 °C. H_2O or HOD was used as a reference (δ 4.65).

for the hydrophobicities of the two molecules. The thymine derivative acts as a receptor, because it provides the spectroscopic probe for binding in ^1H NMR titration studies. For base pairing to be observed, this compound must be sufficiently hydrophobic to be largely incorporated within the micelles. In contrast, the adenine derivative acts as a ligand. Although the magnitude of the observed binding constant (K_{obs}) depends upon the hydrophobicity of this compound, it need not be largely incorporated within the micelles, and it can be considerably less hydrophobic than the thymine derivative. Scheme 1 provides a pictorial representation of the binding process.

Results and Discussion

Adenine–Thymine Base Pairing in Micelles. When an aqueous solution of alkylthymine **2** and SDS is titrated with an aqueous solution of an N^6-acetyl-9-alkyladenine (**3**) and SDS, the ^1H NMR resonance of the thymine NH group shifts downfield. If no SDS is present, the NH resonance shifts slightly upfield. Figure 1 illustrates these results, as seen in the titration of hexylthymine **2c** with acetylpentyladenine **3d**. These observations suggest that the adenine and thymine derivatives base-pair (hydrogen-bond) in the presence of SDS but that the adenine stacks with the thymine in the absence of SDS.

In a typical titration experiment, aliquots of a solution of adenine **3** (150–200 mM) and SDS (30 mM) in 10% D_2O/H_2O were added to an NMR tube containing a solution of thymine **2** (1.0 mM), AcOH (1.0 mM), and SDS (30 mM) in 10% D_2O/H_2O, and the chemical shift of the thymine NH resonance was monitored by ^1H NMR spectroscopy.[8b] A $1\bar{3}3\bar{1}$ pulse sequence was used to suppress the water peak.[9] The added AcOH lowers the pH of the solution, thus reducing the rate of exchange of the thymine NH group and permitting its chemical shift to be monitored.[10,11] The reduced basicity of the acetylated adenines **3** (with respect to the corresponding unacetylated derivatives) also helps minimize the rate of exchange of the thymine imido proton.

The magnitudes of the association constants (K_{obs}) were determined by nonlinear least-squares fitting of a 1:1 binding isotherm to the titration data.[12,13] Analysis of the data in Figure 1 indicates that hexylthymine **2c** binds acetylpentyladenine **3d** with an association constant of 48 M^{-1} in the presence of 30 mM SDS. The excellent fit of the data to a 1:1 binding isotherm is consistent with the model shown in Scheme 1, in which adenine–thymine base pairing occurs.[14]

Effect of Adenine Chain Length upon Binding. Adenine derivatives bearing longer alkyl chains are bound more strongly than adenine derivatives bearing shorter alkyl chains. Titration of hexylthymine **2c** with acetylalkyladenines **3a–d** reveals association constants of 15, 20, 37, and 48 M^{-1}, respectively (Figure 2). These values correlate logarithmically with the octanol–water partition coefficients of the adenines (0.39, 1.24, 3.5, and 9.6, respectively) according to eq 1 (b = 0.40, c = 1.30, R^2 = 0.974).[8b] This correlation supports a model[8b] in which the adenine derivative

$$\log K_{obs} = b \log K_{ow} + c \qquad (1)$$

partitions between the interior and exterior of the micelles and the thymine groups base-pair with the intramicellar adenine. By this means, both hydrophobic and hydrogen-bonding interactions contribute to binding.

Effect of Alkylthymine Chain Length upon Micellar Incorporation. Whereas the effect of the adenine chain length upon binding is relatively straightforward, the effect of the alkylthymine chain length upon binding is more complex. This section and the

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(11) The precise concentration of AcOH was found to have no significant effect upon the titrations, and concentrations of AcOH ranging from 0.5 to 2.0 mM gave comparable results.

(12) The following equation was used: $\delta_{obs} = \delta_{unbound} + (\delta_{bound} - \delta_{unbound})((([2]_{tot} + [3]_{tot} + 1/K_{obs}) - (([2]_{tot} + [3]_{tot} + 1/K_{obs})^2 - 4[2]_{tot}[3]_{tot})^{1/2})/(2[2]_{tot})$, where δ_{obs} is the observed chemical shift of the NH group of **2**, $\delta_{unbound}$ is the chemical shift of the NH group of **2** in the uncomplexed state, δ_{bound} is the chemical shift of the NH group of **2** in the **2**·**3** complex, $[2]_{tot}$ is the total concentration of **2** in solution, $[3]_{tot}$ is the total concentration of **3** in solution, and K_{obs} is the equilibrium constant for formation of the **2**·**3** complex. The quantities $\delta_{unbound}$, δ_{bound}, and K_{obs} were allowed to vary during the fitting procedure. The quantity δ_{obs} was measured during the titration, and the quantities $[2]_{tot}$ and $[3]_{tot}$ were calculated on the basis of volumes and concentrations of the solutions used in the titration.

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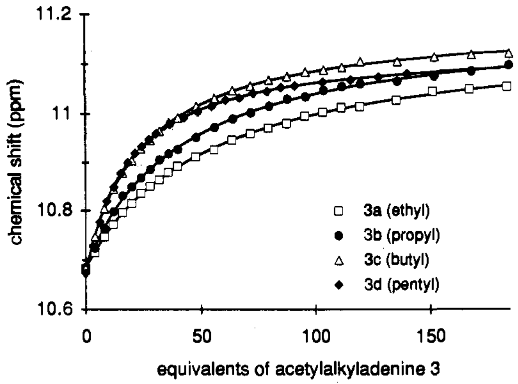

Figure 2. Effect of adenine chain length upon binding. Chemical shift of NH group of alkylthymine **2c** vs equivalents of added acetylalkyladenines **3a–d** at 30.0 mM SDS. The curves are the theoretical 1:1 binding isotherms that best fit the experimental data (**3a**, K_{obs} = 14.5 M^{-1}, δ_{free} = 10.683 ppm, δ_{bound} = 11.326 ppm; **3b**, K_{obs} = 19.8 M^{-1}, δ_{free} = 10.684 ppm, δ_{bound} = 11.311 ppm; **3c**, K_{obs} = 36.6 M^{-1}, δ_{free} = 10.681 ppm, δ_{bound} = 11.252 ppm; **3d**, K_{obs} = 48.5 M^{-1}, δ_{free} = 10.669 ppm, δ_{bound} = 11.197 ppm). Titrations were performed on a 500-MHz NMR instrument at 22–23 °C. H_2O or HOD was used as a reference (δ 4.65).

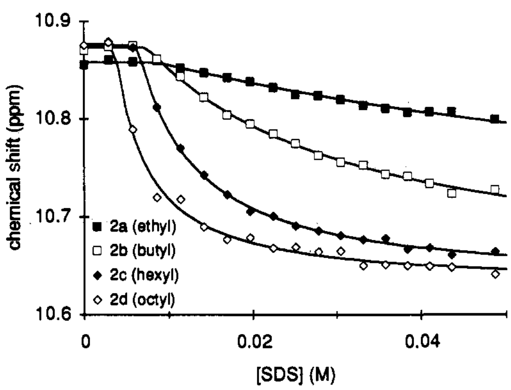

Figure 3. Incorporation of alkylthymines **2** into SDS micelles. Effect of SDS concentration on chemical shift of NH protons in thymines **2a–d**. The curves are the theoretical incorporation isotherms that best fit the experimental data. See text and Table 1 for details. Studies were performed on a 500-MHz ^1H NMR instrument at 21 ± 2 °C. H_2O or HOD was used as a reference (δ 4.65).

following section describe the effect of alkylthymine chain length and incorporation of the thymine group within the micelles upon the binding of adenine derivatives **3**.

Alkylthymines **2** incorporate into SDS micelles. The incorporation of **2** within the micelles was assessed by measuring the chemical shift of the alkylthymine NH groups as a function of SDS concentration. In a typical experiment, aliquots of an 800 mM solution of SDS in 10% D_2O/H_2O were added to an NMR tube containing a solution of thymine **2** (1.0 mM) and AcOH (1.0 mM) in 10% D_2O/H_2O, and the chemical shift of the thymine NH resonance was monitored by ^1H NMR spectroscopy.[15] As shown in Figure 3, alkylthymines bearing longer chains exhibit greater upfield shifting of the NH resonance as the concentration of SDS is increased. These data indicate that thymines bearing longer alkyl chains incorporate more readily within the micelles.

The degree of micellar incorporation was calculated by fitting a micelle–water partition model to the incorporation data.[16] In this model, the ratio of the intramicellar and extramicellar concentrations of the alkylthymine derivative is defined as the micelle–water partition coefficient (K_{part}) and is expressed by eq 2.[17] The variable ρ is the mole fraction of intramicellar **2**, and

$$K_{part} = \left(\frac{\rho}{1-\rho}\right)\left(\frac{V_{aq}}{V_{mic}}\right) \quad (2)$$

V_{aq} and V_{mic} are the relative volumes of water and micelles in the solution. The volume of the micelles was estimated as the product of the concentration of micellar SDS and the partial molar volume of SDS (0.246 L/mol).[18,19] The concentration of micellar SDS was calculated as the difference between the total concentration of SDS and the minimum concentration of SDS at which aggregation of SDS with alkylthymine **2** occurs (cmc_{eff}). Since exchange between the interior and exterior of the micelles is rapid on an NMR time scale, the chemical shift of the thymine NH resonance (δ_{obs}) depends on ρ as shown in eq 3, where δ_{mic} and δ_{aq} are the chemical shifts of intra- and extramicellar thymine. Nonlinear least-squares fitting of these equations to the incorporation data afforded best-fit values for K_{part}, cmc_{eff}, δ_{aq}, and δ_{mic}. These values are shown in Table 1 and were used to create the isotherms plotted in Figure 3. Values of K_{part} of 36, 160, 600, and 1100 were calculated for **2a–d**, respectively.

$$\delta_{obs} = \rho\delta_{mic} + (1-\rho)\delta_{aq} \quad (3)$$

Table 1. Micelle–Water Partition Parameters and Octanol–Water Partition Coefficients for Alkylthymines **2**

	K_{part}[a]	cmc_{eff} (mM)	δ_{aq} (ppm)	δ_{mic} (ppm)	K_{ow}
ethylthymine **2a**	36[b]	8.43[b]	10.858[b]	10.63[b]	0.70[b]
butylthymine **2b**	160	7.38	10.873	10.632	8.2
hexylthymine **2c**	600	6.29	10.876	10.628	86
octylthymine **2d**	1100	3.62	10.876	10.628	1100

[a] Values estimated to be accurate within ±50% based upon analysis of multiple data sets. [b] Values calculated for δ_{mic} = 10.63 ppm.

The increasing values of K_{part} reflect increasing hydrophobicity of alkylthymines with longer alkyl chains. The hydrophobicity of these compounds is also reflected by their octanol–water partition coefficients (K_{ow}, Table 1). As is generally observed for *n*-alkyl homologues, there is a linear relationship between log K_{ow} and the length of the alkylthymine chain (slope = 0.53, R^2 = 1.000).[20] Micelle–water partition coefficients are known to correlate logarithmically with octanol–water partition coefficients (eq 4), where coefficients a and b depend upon the type of compound.[21] Within the limits of experimental error, the micelle–water and octanol–water partition coefficients of compounds **2a–d** obey this relationship (a = 1.72, b = 0.48, R^2 = 0.966).

$$\log K_{part} = a + b \log K_{ow} \quad (4)$$

Role of Micellar Incorporation of Alkylthymines. Incorporation of the thymine receptor group into the micelles is essential to the binding process. When alkylthymines **2a–d** are titrated with acetylpentyladenine **3d**, the NH resonances of the hexyl- and octylthymine derivatives undergo substantial downfield shifting, whereas the NH resonances of the ethyl- and butylthymine derivatives exhibit only modest downfield shifting (Figure 4). Fitting the ^1H NMR titration data to 1:1 binding isotherms reveals limiting downfield shifts ($\delta_{bound} - \delta_{free}$) of 0.04, 0.22, 0.53, and 0.66 ppm for ethyl-, butyl-, hexyl- and octylthymine

(15) The limited solubility of octylthymine **2d** necessitated that the concentration of this compound be lower than 1 mM.

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(19) By these calculations, micelles occupy 0.55% of the volume of pure 30 mM SDS solution (22 mM micellar SDS, cmc = 8 mM).

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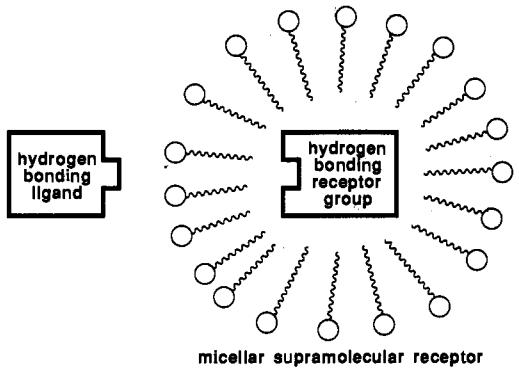


Figure 4. Effect of alkylthymine chain length upon binding. Chemical shift of the NH groups of thymines **2a–d** vs equivalents of added acetylpentyladenine **3d** at 30.0 mM SDS. The curves are the theoretical 1:1 binding isotherms that best fit the experimental data (**2a**, K_{obs} = 590 M^{-1}, δ_{free} = 10.821 ppm, δ_{bound} = 10.861 ppm; **2b**, K_{obs} = 113 M^{-1}, δ_{free} = 10.746 ppm, δ_{bound} = 10.965 ppm; **2c**, K_{obs} = 48.5 M^{-1}, δ_{free} = 10.669 ppm, δ_{bound} = 11.197 ppm; **2d**, K_{obs} = 44.9 M^{-1}, δ_{free} = 10.654 ppm, δ_{bound} = 11.317 ppm). Titrations were performed on a 500-MHz NMR instrument at 22 ± 1 °C. H_2O or HOD was used as a reference (δ 4.65).

derivatives, respectively. These values correlate qualitatively with the degree of micellar incorporation of the thymines (16%, 47%, 78%, and 88%, respectively, at 30 mM SDS, as calculated from the values presented in Table 1).[22] This trend suggests that only the intramicellar **2** is able to participate in base pairing.

Analysis of the data obtained upon titrating **2c** and **2d** with **3d** reveals association constants of 48 and 45 M^{-1}, respectively.[23] Although it is possible to analyze the data obtained upon titrating **2a** and **2b** with **3d**, the binding constants that are calculated (590 and 113 M^{-1}, respectively) are not meaningful, because they reflect the combined effects of base stacking of the extramicellar thymine and base pairing of the intramicellar thymine. Together, these effects produce shallow, flattened binding isotherms and data that best fit 1:1 binding isotherms with high values of K_{obs}.

Estimation of the Intramicellar Association Constants of 2 and 3. We have previously found that hydrophobic interactions and hydrogen bonding contribute to binding as shown in eq 5.[8b] In

$$K_{obs} = K_{part}K_{assoc} \quad (5)$$

this equation, the observed binding constant (K_{obs}) is the product of the micelle–water partition coefficient of the adenine derivative (K_{part}) and the intramicellar association constant (K_{assoc}). If K_{part} of adenines **3** could accurately be determined, it would be possible to calculate K_{assoc} and thus quantify the roles of hydrophobic interactions and hydrogen bonding in the binding process. Unfortunately, the measurement of the micelle–water partition coefficients of adenines **3** by ^1H NMR techniques is subject to complications. Adenines **3** show relatively small changes in chemical shifts upon addition of SDS, which suggests that the degree of micellar incorporation is too small to accurately be determined by micelle incorporation studies. In addition, the adenine ring protons undergo large changes in chemical shift upon protonation of the adenine ring nitrogens, and the protonation state of the adenine ring appears to be sensitive to the presence of SDS. For these reasons, it is not feasible to measure the micelle–water partition coefficients of adenines **3** using the NMR techniques that permitted determination of the micelle–water partition coefficients of thymines **2**.

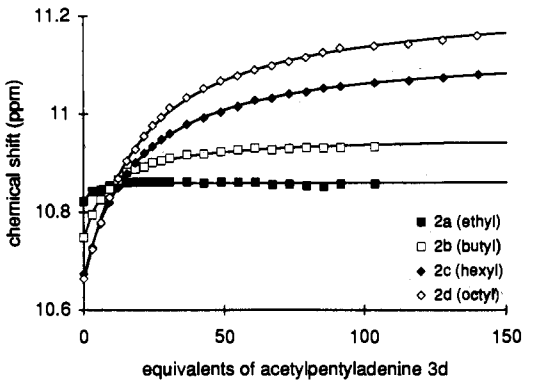
(22) In keeping with these observations, (thyminyloctyl)ammonium bromide (**1c**) incorporates completely in SDS micelles at 30 mM SDS and exhibits 0.73-ppm downfield shifting upon binding acetylpentyladenine **3d** (K_{obs} = 48.8 M^{-1}, δ_{free} = 10.635 ppm, δ_{bound} = 11.367 ppm). For details, see ref 8b.

(23) A similar value (49 M^{-1}) is obtained upon titrating (thyminyloctyl)-ammonium bromide (**1c**) with **3d** (see ref 8b, 22).

On the basis of the known relationship between octanol–water partition coefficients and micelle–water partition coefficients (eq 4), it is possible to estimate the micelle–water partition coefficients of the adenine derivatives. The coefficients a and b have been determined for various classes of compounds including several (aliphatic amides, aliphatic alcohols, aromatic alcohols) that are similar in structure and hydrogen-bonding properties to adenine derivatives **3**.[21,24] For alkylthymines **2**, which are also similar in polarity and hydrogen-bonding properties to the adenines, we calculate coefficients of 1.72 and 0.48 (vide supra). If we take acetylbutyladenine **3c** as a representative example (K_{ow} = 3.5, K_{obs} = 37 M^{-1}), we estimate its micelle–water partition coefficient to be between 10^1 and 10^2. From these values, we calculate K_{assoc} to be roughly 10^0 M^{-1}. This estimate indicates that intramicellar association occurs with an association constant that is roughly 1–2 orders of magnitude lower than the association constant of acetylated adenine derivatives with alkylthymine derivatives in chloroform solution ($K \approx 40$ M^{-1}). The smaller magnitude of the intramicellar association constant is consistent both with a model in which the interiors of micelles are polar and hydrated[25,26] and with the observation that association constants of hydrogen-bonded complexes are diminished in polar and wet solvents.[27]

Conclusion

The incorporation of hydrogen-bonding receptor groups into micelles offers a new strategy for achieving molecular recognition in aqueous solution. In this strategy, the receptor groups and amphiphilic surfactant molecules self-assemble to form micelles that function as *supramolecular receptors* for hydrogen-bonding ligands. The following cartoon provides a working model for these receptors, illustrating key features without addressing the precise location or number of hydrogen-bonding receptor groups within the micelles or the dynamic structure of the micellar supramolecular receptors.



The present experiments establish that *uncharged* hydrogen-bonding receptor groups can incorporate in micelles and that the resulting supramolecular receptors can hydrogen-bond to complementary ligands. Although the adenine and the thymine groups both incorporate into the micelles to varying degrees, the alkylthymines are considered to be the receptors, because the thymine groups serve as the spectroscopic probes for binding. For

(24) Aliphatic alcohols, a = 0.51, b = 0.86; aliphatic amides, a = 1.40, b = 0.28; phenols, a = 0.59, b = 0.75; halogenated phenols, a = 0.76, b = 0.66.

(25) (a) Muller, N.; Birkhahn, R. H. *J. Phys. Chem.* **1967**, *71*, 957. (b) Menger, F. M.; Jerkunica, J. M.; Johnston, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4676. (c) Menger, F. M. *Acc. Chem. Res.* **1979**, *12*, 111. (d) Menger, F. M.; Chow, J. F. *J. Am. Chem. Soc.* **1983**, *105*, 5501. (e) Menger, F. M.; Doll, D. W. *J. Am. Chem. Soc.* **1984**, *106*, 1109.

(26) For alternative models, see: (a) Wennerström, H.; Lindman, B. *J. Phys. Chem.* **1979**, *83*, 2931. (b) Dill, K. A.; Flory, P. J. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 676. (c) Fromherz, P. *Chem. Phys. Lett.* **1981**, *77*, 460.

(27) For recent examples, see: (a) Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 678. (b) Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 1398. (c) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369.

significant binding to be observed, the hydrogen-bonding receptor group must be largely incorporated within the micelles. In the current system, we find that this component must have an octanol–water partition coefficient of ca. 10^2 or greater for sufficient micellar incorporation and binding to occur. The supramolecular receptors bind the ligands by a combination of hydrogen-bonding and hydrophobic interactions, and increasingly hydrophobic ligands are bound with larger binding constants (K_{obs}). Estimation of the relative roles of hydrophobic and hydrogen-bonding interactions in a representative case suggests that hydrophobic interactions contribute a factor of ca. 10^1–10^2 to K_{obs}. Since micelles are known to solubilize and incorporate a variety of molecules, this strategy should be widely applicable to the recognition of small molecules in aqueous solution.[28]

Experimental Section

Materials. High-purity sodium dodecyl sulfate was purchased from Mallinckrodt (GenAR grade). 1-Alkylthymines **2** were prepared by alkylation of 5-methyl-2,4-bis(trimethylsiloxy)pyrimidine.[29] N^6-Acetyl-9-alkyladenines **3** were prepared from adenine as described previously.[8b] Compounds **2** and **3** exhibited satisfactory IR, ^{1}H NMR, and high-resolution mass spectral and/or elemental analyses.

Procedures and Instrumentation. ^{1}H NMR titration and incorporation data were collected on a General Electric GN-500 (500 MHz) NMR spectrometer using a $1\bar{3}3\bar{1}$ pulse sequence.[9] Octanol–water partition coefficients were determined spectrophotometrically using a Shimadzu UV160U UV–visible spectrophotometer.[30] Detailed procedures for the collection and analyses of these data are described in ref 8b and 13.

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(28) Preliminary experiments support this conclusion. Titration of an aqueous SDS solution of a bis Kemp's triacid imide derivative of 3,6-diaminocarbazole (compound **6** from: Conn, M. M.; Deslongchamps, G.; de Mendoza, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 3548) with 9-ethyladenine reveals an association constant of ca. 5000 M^{-1}. We estimate an uncertainty of a factor of 2 in this number because of the low solubility of this compound in aqueous SDS solution and the low signal-to-noise ratio in the ^{1}H NMR spectra collected during titration studies. We thank M. M. Conn, G. Deslongchamps, and J. Rebek, Jr., for providing a sample of this compound.

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