Design, synthesis and self-association behavior of water soluble self complementary facial amphiphiles

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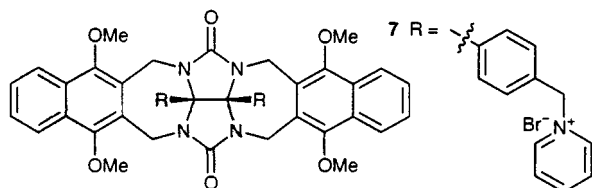*E-mail: li8@umail.umd.edu*
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Self-complementary facially amphiphilic derivatives of glycoluril are useful building blocks for hydrophobic self-assembly in water; we describe the design, synthesis and characterization of six dimeric self-assembled structures with values of K_S up to 1840 M^{-1} in pD 7.4 buffered D$_2$O.

Nature employs the hydrophobically driven self-assembly of amphiphilic molecules such as phospholipids, polypeptides and oligonucleotides to form functional structures like cell membranes, α-helical coiled coils that regulate transcription, DNA and viral capsids.[1] Ultimately, chemists would like to prepare synthetic structures that are as structurally and functionally complex as these natural systems. In efforts toward this goal some chemists have focused on the preparation of amphiphiles with novel geometries and studied their aggregation behavior in water.[2] Others are trying to deduce the rules governing the use of highly directional interactions like hydrogen bonds and metal–ligand interactions in non-polar solvents (CHCl$_3$).[3] The use of the hydrophobic effect to form designed self-assembled structures in water has received less attention.‡ Here we describe our initial efforts toward the use of self-complementary facial amphiphiles **1–6** as building blocks for self-assembly in water. Our goal is to develop the hydrophobic effect as a strong, directional, and predictable non-covalent interaction in water much as hydrogen bonds are now used routinely in chloroform.

Our design of **1–6** was based on the observation of Nolte that water soluble glycoluril derivative **7** aggregated in water to give cigar shaped aggregates with dimensions on the order of 1 μM. This result was attributed to the interaction of the water solubilizing groups with the hydrophobic cavity of another molecule of **7**.[4] We reasoned that if we replaced the hydro-


phobic aromatic solubilizing groups with strictly hydrophilic carboxylate groups, we would be able to eliminate their secondary hydrophobic interactions and form well-defined dimeric structures. We decided, therefore, to use derivatives of glycoluril as building blocks for our studies since: (i) well-established synthetic precedents were available, (ii) we could impart solubility in neutral water by attaching carboxylates or ammonium groups to the convex face of the molecule, and (iii) the glycoluril subunits lead to curvature that creates a cleft-like geometry that allows dimerization.[5,6]

Scheme 1 outlines the synthetic procedures used to prepare **1—6**.[4–6]§ The self-complementary facial amphiphiles **1–6** all have good solubility in pD 7.4 buffered D$_2$O (>5 mM). We

synthesized **1** and **2** to allow us to test the influence of the charge on the convex face of the molecule on its self-association constant (K_S). Compounds **3–6** were synthesized in order to assess the influence of methoxy substituents on K_S and to investigate possible orientational preferences in **3·3** and **4·4**.

We obtained single crystals of **15** by slow evaporation of a benzene solution. Fig. 1 shows an ORTEP plot of the structure of **15** in the crystal.¶ The important features of this structure are: (i) the disposition of the ethyl ester groups on a single face of the molecule (facially amphiphilic), (ii) the formation of a hydrophobic cleft, at least in the solid state, due to the *anti* conformation of the xylylene units with respect to the ethoxycarbonyl substituents on the convex face,[7] and (iii) the distance between the centers of the phenyl rings of 6.35 Å is suitable for the complexation of an aromatic ring. The solvating benzene ring partially fills the cleft of **15** by interacting with the xylylene wall in an edge-to-face type manner (Fig. 1).

We performed dilution experiments to investigate the self-association behavior of **1–6**.[8] In these experiments, ^{1}H NMR spectra were obtained at a series of concentrations and changes
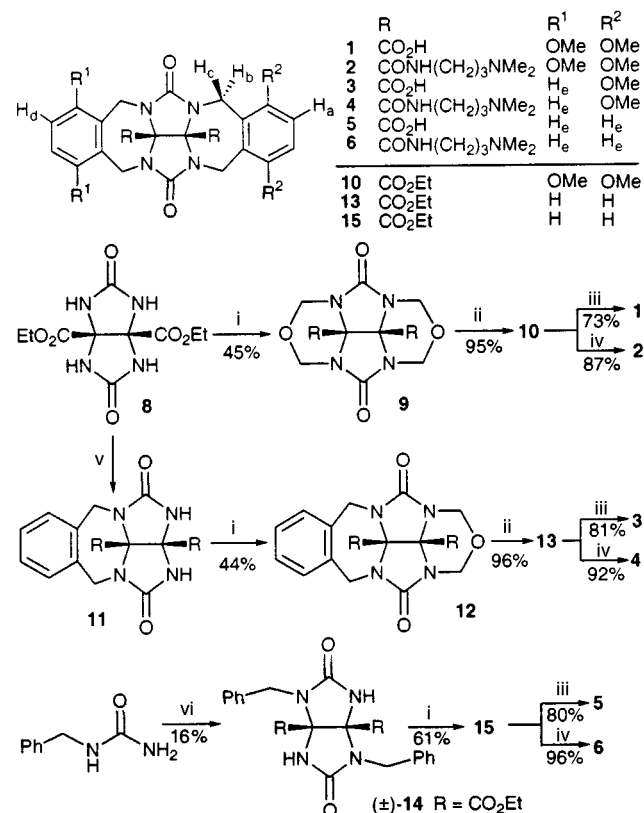
Scheme 1 *Reagents and conditions*: i, TFA, (CH$_2$O)$_n$, reflux; ii, TFA, Ac$_2$O, C$_6$H$_4$(OMe)$_2$, reflux; iii, MeOH, H$_2$O, LiOH, 60–65 °C; iv, H$_2$N(CH$_2$)$_3$NMe$_2$, 70–90 °C; v, DMSO, Bu^{t}OK, C$_6$H$_4$(CH$_2$Cl)$_2$; vi, PhH, TFA, (EtO$_2$CCO)$_2$, reflux.
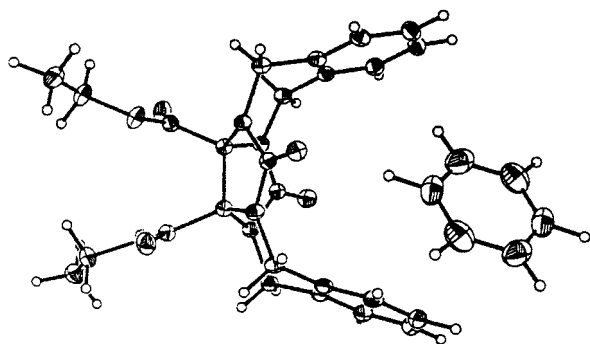
Fig. 1 Crystal structure of $\mathbf{15}\cdot(C_6H_6)_{0.25}$ with 30% probability ellipsoids.

| Compound | $K_S{}^a/M^{-1}$ | $\Delta\delta^b$ | | | $\Delta G°/$ kcal mol^{-1} |
		H_a	H_d	H_e	
1	1840	1.22	^{c}		−4.5
2	1530	1.41	^{c}		−4.3
3	140	1.48	0.61	0.12	−2.9
4	130	1.79	0.73	0.37	−2.9
5	^{d}	^{d}	^{cd}	^{d}	^{d}
6	^{d}	^{d}	^{cd}	^{d}	^{d}

^{a} The error in the determination of K_S is $\approx 15\%$; the corresponding error in $\Delta G°$ is ≈ 0.1 kcal mol^{-1}. All dilution experiments were performed in 100 mM phosphate buffered D_2O (pD = 7.4) at 25 °C. ^{b} Based on the calculated values of the chemical shift for the dimer and the monomer. ^{c} H_a and H_d are symmetry equivalent. ^{d} The observed changes in chemical shift up to 5 mM are negligible.

that occurred in the chemical shifts of the different protons were monitored. The shifts in the ^1H NMR resonances were then fitted to the theoretical equation governing self-association of two molecules.[8]‖ For example, when the concentration of **2** is 0.2 mM, the resonance for H_a (Scheme 1) is broadened and appears at δ 6.45, which is close to the chemical shift observed for this proton in CDCl$_3$ (δ 6.73). At a concentration of 5 mM, H_a resonates at δ 5.78, indicating more extensive dimerization at that concentration. The upfield direction of this shift suggests that the H_a protons are proximal to an aromatic ring in the complex. In these experiments, we observe a single broadened resonance for each set of protons in the monomer and the dimer. This observation indicates that the monomer and dimer are in the fast exchange regime on the NMR time scale.

Table 1 summarizes the results of our studies. The values of K_S reported are the results of duplicate dilution experiments at a series of at least seven different concentrations and are averaged over all of the protons undergoing significant complexation induced shifts (> 0.1 ppm). Evaluation of each of these different protons gave similar values of K_S. Based on the values of K_S and $\Delta\delta$ we are able to draw the following conclusions. First, in all three cases—compare **1** with **2**, **3** with **4**, and **5** with **6**—the carboxylic acid and the amine derivatives have approximately equal self-association constants. This result indicates that the charged groups on the convex face of the amphiphile are merely solubilizing groups and do not alter the dimerization process. Second, compounds with greater numbers of methoxy substituents have higher self-association constants. Compounds **5** and **6** undergo no concentration dependant changes in chemical shift up to 5 mM, indicating that self-association does not occur at these concentrations. We rationalize the differences in K_S by the increase in the amount of hydrophobic surface area in **1** and **2**.[9] Third, we suggest that dimers **3·3** and **4·4** are oriented such that each dimethoxyphenyl ring is complexed in the cavity of the second molecule. We base this suggestion** on the higher values of $\Delta\delta$ for H_a and lower values of $\Delta\delta$ for H_d or **3** and **4** when compared to the $\Delta\delta$ for H_a of **1** and **2** (Table 1). Those protons that are complexed within the hydrophobic cavity experience the anisotropic effect of two phenyl rings, whereas those that are on the outside of the cavity only feel the effect of one phenyl ring. This type of selectivity could allow the orientation of several components in larger self-assembled structures.

We have shown that facially amphiphilic derivatives of glycoluril containing water solubilizing carboxylate or ammonium groups can be used as a platform for the study of hydrophobic self-assembly in water. Self-complementary facial amphiphiles **1**–**4** self-associate in aqueous solution to give dimers. The self-association constant and the orientation of the molecules in the dimeric complex are influenced by the number of methoxy groups in the monomer. Ongoing investigations are directed toward the design and synthesis of compounds with more solubilizing groups and larger amounts of hydrophobic surface area that dimerize with higher values of K_S and reduced exchange rates, as well as the covalent connection of several

molecules of **6** to allow for self-assembly rather than simple dimerization.

Notes and references

‡ The 1 : 1 host–guest properties of water-soluble cyclodextrins, calixarenes and cyclophanes are well known.
§ New compounds were characterised by ^1H NMR, ^{13}C NMR, IR, MS, melting point and HR-MS or elemental analysis.
¶ *Crystal data* for **15**: $[C_{26}H_{26}N_4O_6][C_6H_6]_{0.25}$, M = 510.04, monoclinic, a = 17.973(2), b = 14.284(3), c = 19.986(4) Å, β = 106.050(11)°, V = 4931.1(14) Å^3, T = 173(2) K, space group $P2_1/c$, Z = 8, D_X = 1.374 g cm^{-3}, μ(Mo-Kα) = 0.098 mm^{-1}, $F(000)$ = 2148, $R(F)$ = 7.22%, $wR(F^2)$ = 14.55% for all 11315 independent reflections. CCDC 182/1481. See http://www.rsc.org/suppdata/cc/1999/2549/ for crystallographic data in .cif format.
‖ Vapor pressure osmometry measurements are in good agreement with a monomer–dimer equilibrium.
** The ROESY spectrum of **4** does not allow us to make firm conclusions regarding the detailed geometry of **4·4**.

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