The influence of ethylene glycol chains on the thermodynamics of hydrogen-bonded supramolecular assemblies in apolar solvents†

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Substitution of hydrogen bond directed supramolecular assemblies with ethylene glycol chains leads to a reduction in the association constant in apolar solvents, where the reduction of the association constant is dependent on the length of the aliphatic spacer connecting the hydrogen bonds and the ethylene glycol chain.

Recently, the effect of short ethylene glycol (EG) monomethyl ether chains on two distinct supramolecular assemblies has been independently reported by Bouteiller *et al.*[1] and Araki *et al.*[2] In both cases, the dominant secondary interaction responsible for the formation of the non-covalent assembly is hydrogen bonding. In the first report, Bouteiller discusses the influence of EG tails on the supramolecular polymerization of EG substituted bis-ureas in polar and apolar solvents, while in the second example Araki discusses the influence of EG tails on the formation of giant supramolecular vesicles composed of hydrogen-bonded sheet structures of guanosine derivatives. These two examples have in common that the microscopic (formation of vesicles) and macroscopic properties (viscosity) of the thermodynamically formed supramolecular assembly are highly dependent on the creation of a hydrophobic pocket that shields the hydrogen bonds[3] from the EG moiety.

This communication aims to generalize the findings reported by Bouteiller and Araki by further evaluating the effect of short ethylene glycol monomethyl ether (EG) groups on the self-assembly of two frequently used supramolecular motifs, the ureido-pyrimidinone (UPy) unit and the benzene-1,3,5-tricarboxamide (BTA) unit. Aliphatic derivatives of both systems have been studied in detail by our group.[4,5] We here rationalize the behavior of the EG functionalized self-assembling units and discuss the implications of these findings for design rules of novel synthetic supramolecular assemblies in which short EG units are indispensable to impart solubility in polar and apolar solvents.

The UPy motif forms a self-complementary quadruple hydrogen bonded (Fig. 1) motif for which a very high dimerization constant ($K_{\mathrm{dim}} = 6 \times 10^7$ M^{-1} in CHCl$_3$) has been measured.[4b] Remarkably, the ^{1}H-NMR spectrum of tri-EG monomethyl ether substituted UPy **1a** (in which the EG chain is connected *via* a C$_2$ spacer) in dry CDCl$_3$ shows two signals at a concentration of 0.1 mM at $\delta = 5.82$ and 5.86 ppm. This is in contrast to the butyl substituted UPy where only a signal at $\delta = 5.82$ ppm is observed at this concentration.[3a] Dilution experiments (Fig. 2) reveal that at high concentrations only a single signal is present at $\delta = 5.82$ ppm, indicating that the additional signal at $\delta = 5.86$ ppm at low concentrations originates from monomeric ureido-pyrimidinone species.

DOSY NMR on a solution of **1a** (0.5 mM in CDCl$_3$) indeed confirms that the second signal at $\delta = 5.86$ ppm belongs to a faster diffusing species (Fig. 2, inset). Based on the ratio of the two diffusion constants, a molecular weight ratio of 1.85 was calculated, in close agreement with the fact that the additional signals originate from the 6[1*H*]-pyrimidinone monomeric form. Furthermore, concentration dependent infrared (IR) measurements performed on a solution of **1c** in CDCl$_3$ revealed significant changes in the amide I and amide II regions, indicative of a rearrangement of the hydrogen bond array. Based on the integral ratio between the monomeric and dimeric signals in the ^{1}H-NMR spectrum, a K_{dim} of 3 ($\pm$ 0.5) $\times 10^4$ M^{-1} for **1a** was calculated. This value of K_{dim} is approximately 1000 times lower than the dimerization constant of an aliphatic substituted ureido-pyrimidinone.[3b]

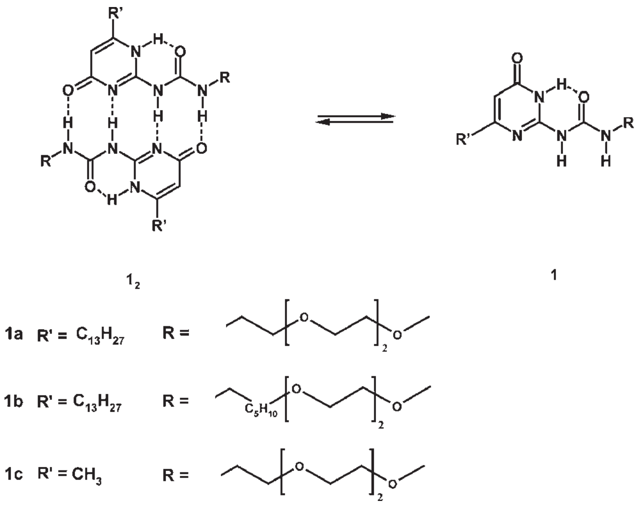

Fig. 1 Equilibrium of triethylene glycol substituted UPy **1a**, **1b** and **1c** in their 4[1*H*] dimeric and 6[1*H*] monomeric forms.

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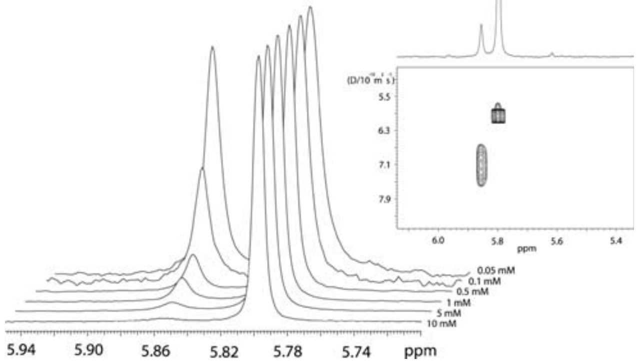

Fig. 2 ^{1}H-NMR spectra at various concentrations of **1a** in $CDCl_3$. The spectrum shows the region where the alkylidene protons resonate. DOSY spectrum of a 0.5 mM solution of **1a** in $CDCl_3$ (inset).

In sharp contrast, ureido-pyrimidinone **1b** in which a hydrophobic hexyl spacer 'protects' the hydrogen bonding array from the polar EG chain does not show any evidence of a diminished dimerization constant (see ESI†).

We then extended our investigations to the effect of short EG chains on the hydrogen bond induced supramolecular polymerization of *N*,*N*′,*N*″-trialkylbenzene-1,3,5-tricarboxamides in apolar solvents. Symmetric trialkyl substituted BTA's are well known to self assemble in one dimensional stacks in alkane solution as a result of threefold, α-helix type intermolecular hydrogen bonding between the amide moieties of neighbor molecules.[6,7] Circular dichroism (CD) measurements of a chiral derivative based on (*R*)-3,7-dimethyloctyl chains showed a pronounced CD-effect ($\Delta\varepsilon = 44\ M^{-1}\ cm^{-1}$) in heptane at a concentration of 6.5×10^{-5} M and the association constant (K_{ass}) was around $5 \times 10^8\ M^{-1}$.[5a] We desymmetrized the BTA motif by replacing one alkyl chain by an oligoEG chain affording compounds **2a,b** (Fig. 3). No CD-effect was observed for chiral **2a** at 6.5×10^{-5} M in heptane and the UV spectrum showed a λ_{max} at 208 nm which is typical for molecularly dissolved BTA species.[5b,7] Increasing the concentration of **2a** to $c = 0.6$ mM, $c = 7.7$ mM and $c = 48$ mM finally resulted in a CD-effect ($\Delta\varepsilon = 37\ M^{-1}\ cm^{-1}$ at $\lambda = 225$ nm) at the highest concentration (Fig. 4a).[8] The CD-effect is similar in size and shape when compared to the chiral derivative based on three (*R*)-3,7-dimethyloctyl chains suggesting that helical order is present in the columns at high concentrations. In addition, the IR spectrum of the 48 mM solution confirmed the presence of threefold intermolecular hydrogen bonding (see ESI†). The loss of the CD-effect at lower concentrations can originate from either the loss of helical stacking within the columns (loss of directionality of the intermolecular hydrogen bonds) or from a significantly reduced K_{ass} of **2a** in alkane solution.

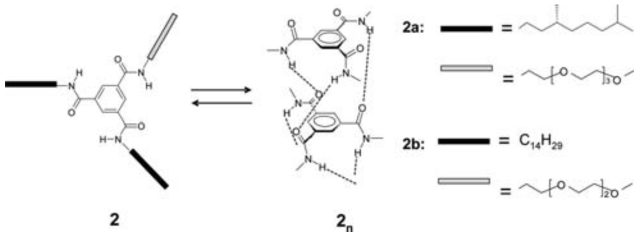

Fig. 3 Chemical structures of BTAs **2** and the threefold intermolecular hydrogen bonds formed upon stacking, resulting in a helical packing of the molecules.

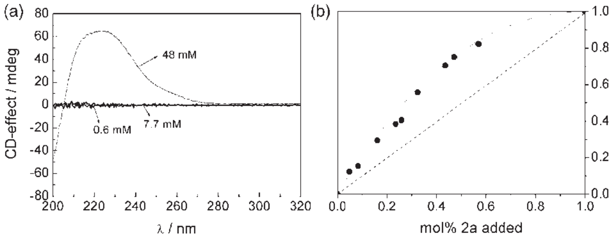

Fig. 4 (a) CD spectra of compound **2a** in decalin at $c = 48.0$ mM, $c = 7.7$ mM and $c = 0.6$ mM. The spectra were measured in a 0.01 mm, 0.1 mm and 1 mm cuvette, respectively. (b) Development of the normalized g_{value} as a function of chiral **2a** added ($c = 48$ mM in decalin).

To estimate the K_{ass} in **2a**, we used the Havinga model which has previously allowed us to estimate the K_{ass} in similar systems.[5a,9] In this model, chiral and achiral derivatives are mixed in different ratios (the "sergeants-and-soldiers" experiment) and the chiroptical response is measured by CD spectroscopy as a function of the enantiomeric excess (ee). If amplification of chirality is present, a non-linear relationship is observed between the chiroptical response and the ee. Comparing the data to values predicted by the Havinga model allows for a rough estimation of K_{ass}. We performed the "sergeants-and-soldiers" experiment on compound **2a** and achiral derivative **2b** at a concentration of 48 mM in decalin. Fig. 4b clearly shows the non-linearity when the normalized g_{value} ($= \Delta\varepsilon/\varepsilon$) is plotted as a function of the amount of **2a** added to a solution of achiral **2b**. The solid line represents the predicted values using a K_{ass} of $21\ M^{-1}$, a significantly lower value than previously found for the trialkyl substituted BTAs.[5a]

The presence of a single oligoEG chain has a dramatic effect on the stability of both the UPy dimerization and the formation of BTA stacks. The large conformational space of an oligoEG chain and the stabilizing effect of intramolecular[10,11] and intermolecular[12] hydrogen bonding on different conformations of the EG chain has lead to unexpected results in supramolecular self-assembling systems before.[13,14] The 1000 fold decrease in K_{dim} for UPy dimerization is most probably the result of stabilization of the 6[1*H*] monomeric form by backfolding of the triEG chain. Previously, Kaifer and Sun reported a generation dependent decrease in K_{dim} in a series of ureido-pyrimidinones substituted with Newkome type dendrimers.[15] In their case, the decrease in K_{dim} was mainly attributed to an increase in steric crowding upon increasing the dendrimer generation. However, in our case steric issues are unlikely to have a pronounced effect on the value of K_{dim}. For the BTA stacks, competition between the intermolecular hydrogen bonds between neighboring molecules and intramolecular hydrogen bonds with the EG chains results in an even higher decrease in the K_{ass}. This competition decreases the cohesive energy between molecules in the stacks which results in a lower K_{ass}.[16]

As the field of supramolecular chemistry is making the transition to the development of supramolecular assemblies that can display structure and properties in water,[17–19] the findings reported in this paper are important to design novel synthetic supramolecular assemblies in which short oligoEG units are used to impart aqueous solubility. Although in water backfolding of the EG chain will not occur due to the preference of the hydrated random coil ''helical'' structure (*gauche–trans–gauche*) of the EG chain,[20] the presence of a hydrophobic spacer of sufficient length is necessary to increase the association constant by providing an apolar microenvironment that prevents hydrogen bonding between water and the hydrogen bonds that constitute the supramolecular assembly.[1,2]

The striking effect of intramolecular shielding of hydrogen bonding patterns found here, may also be responsible for low association constants in other supramolecular systems in apolar solvents after introducing oligoEG chains. More importantly, the results obtained can be generalized; it is most likely that other functional groups containing hydrogen bond donors (amides, ureas and carbamates moieties) or acceptors (esters, ureas, amides or carbamates) will influence the thermodynamics of hydrogen-bond based self-assemblies if the linker connecting the functional groups to the hydrogen bond array is not sufficiently long. The result of the proposed intramolecular competition between hydrogen bond accepting and donating groups in the side chain with the intermolecular hydrogen bonds of any supramolecular assembly will be reflected in significant changes in both microscopic and macroscopic properties compared to their aliphatic derivatives.

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