



## Self-Association and Self-Assembly of Molecular Clips in Water

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(Received 15 July 2001; in final form: 31 August 2001)

**Key words:** amphiphiles, electron microscopy, receptors, self-assembly

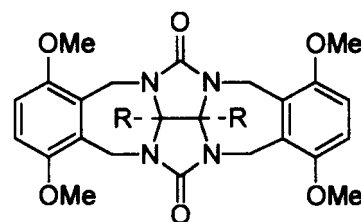
### Abstract

Molecular clips functionalized with two sodium or ammonium benzoate groups self-assemble in water by means of a hydrophobically driven dimerization reaction. Depending on the counter ions, this self-assembly stops at the stage of the dimer (sodium) or continues to generate large nanometer-sized aggregates (ammonium). The molecules in the latter aggregates are proposed to be 'glued' together by multiple hydrogen bonds between the ammonium counter ions and the benzoate groups of the clips.

### Introduction

Most synthetic amphiphiles reported in the literature have a similar topology. They contain a compact, polar head-group to which one or more tails are attached [1]. Upon aggregation in water they can form a wide variety of nano-sized structures, e.g., micelles, bilayers, and vesicles. Although these amphiphiles of the 'classical type' have received considerable attention during the past decades, more recently there appears to be an increasing interest in the development of amphiphilic molecules with a strongly deviating topology [2]. Examples are the 'facial amphiphiles' which are rigid molecules that do not contain aliphatic tails and possess two oppositely directed polar and apolar 'faces'. Their self-association behaviour in water has been well documented [3]; however, no studies of the aggregate morphology of these compounds have been reported to date.

In our laboratory molecular clips which are receptors with a rigid, U-shaped cavity, have been studied as hosts for 1,3-dihydroxybenzene guests [4]. In the absence of these guests the clip molecules form dimeric structures, in which one cavity side-wall of a clip is buried in the cavity of its dimeric partner and *vice-versa*. An example of this interaction is observed in the crystal structure of the neutral compound **Me-1** (Figure 1) [5]. In this paper we describe the self-association and self-assembly of the charged compounds **Na-1** and **NH<sub>4</sub>-1** (Figure 1a) in water. These clips are functionalized on their convex side with water-soluble benzoate groups and as a result of this they are expected to behave as facial amphiphiles in which the receptor cavities form the hydrophobic face.



**Me-1** R = *p*-C<sub>6</sub>H<sub>4</sub>COOMe

**Na-1** R = *p*-C<sub>6</sub>H<sub>4</sub>COO<sup>-</sup> Na<sup>+</sup>

**NH<sub>4</sub>-1** R = *p*-C<sub>6</sub>H<sub>4</sub>COO<sup>-</sup> NH<sub>4</sub><sup>+</sup>

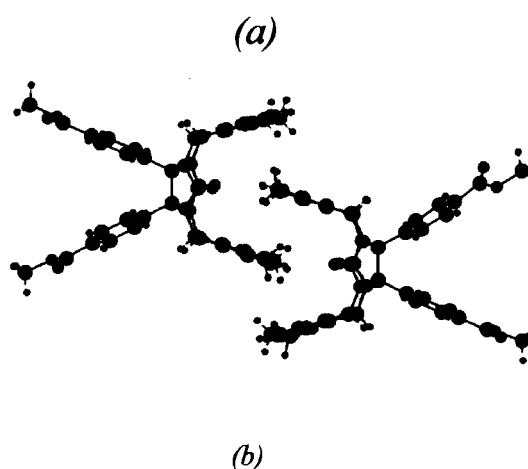


Figure 1. (a) Structures of the benzoic acid functionalised molecular clips. (b) Crystal structure of compound **Me-1** showing the dimeric arrangement of the molecules.

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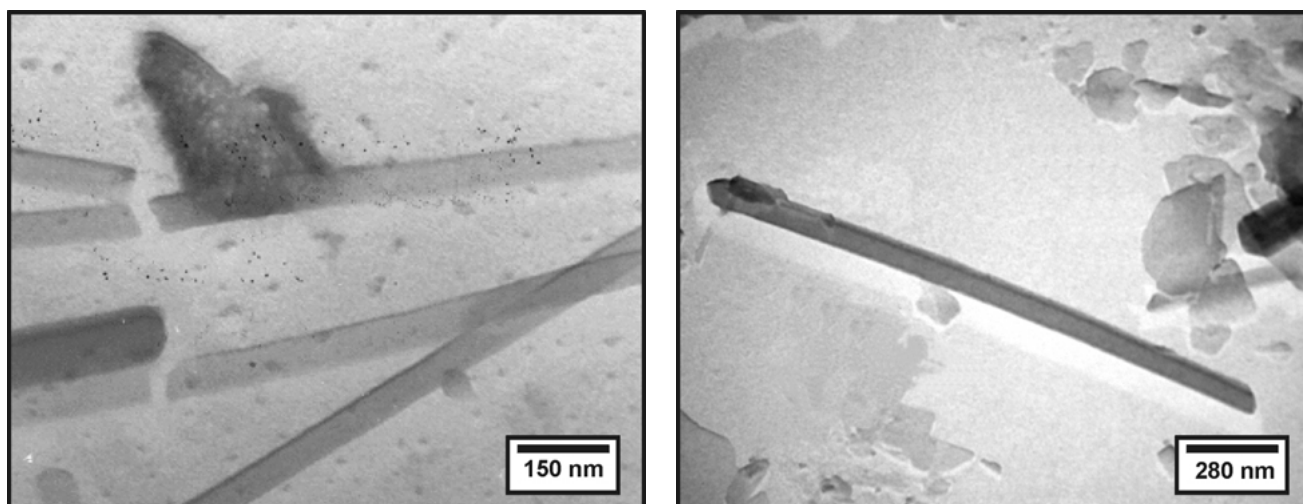


Figure 2. Transmission electron micrographs of the aggregates formed by  $\text{NH}_4\text{-1}$  in water (samples were platinum shadowed).

## Results and discussion

The synthesis of the benzoate functionalized clips **1** will be described elsewhere [6]. The self-association properties of **Na-1** and  $\text{NH}_4\text{-1}$  in water were investigated with the help of  $^1\text{H}$  NMR dilution experiments. There appeared to be large solubility differences between the two salts, i.e., **Na-1** was soluble in water up to relatively high concentrations ( $>30$  mM), whereas  $\text{NH}_4\text{-1}$  hardly dissolved at all. For this reason, a reliable NMR dilution titration could only be carried out on the sodium salt. For **Na-1**,  $^1\text{H}$  NMR spectra were recorded of samples having concentrations varying between 0.2 and 10 mM. Upon increase of the concentration, the signals of the protons of the cavity side-walls and those of the methoxy groups displayed large upfield shifts. These shifts are in line with the formation of a dimeric structure similar to that shown in Figure 1b for **Me-1**. The calculated dimerization constant for **Na-1** ( $K_{\text{dimer}} = 630 \text{ M}^{-1}$ ) appeared to be much higher than the  $K_{\text{dimer}}$  of the methyl ester derivative **Me-1** in chloroform ( $K_{\text{dimer}} = 18 \text{ M}^{-1}$  [5]). In the case of **Na-1**, however, hydrophobic effects [7] enhance the self-association process, because the two hydrophobic cavities try to minimize their exposure to the aqueous environment. Although the strength of dimerization of  $\text{NH}_4\text{-1}$  could not be determined by a similar dilution titration,  $^1\text{H}$  NMR spectra of low concentrated solutions of this compound ( $\sim 0.3$  mM) in water showed shifts of the cavity side-wall and methoxy proton signals which were comparable to those of **Na-1**. This indicates that also in the case of  $\text{NH}_4\text{-1}$  dimerization of the cavity parts of the molecules occurs.

To investigate if the self-association of the carboxylate amphiphiles would result in the formation of aggregates on a mesoscopic scale, samples of **Na-1** and  $\text{NH}_4\text{-1}$  in water were investigated with the help of transmission electron microscopy (TEM). Compound **Na-1** remained completely soluble in water up to high concentrations ( $>30$  mM). TEM studies on these solutions did not reveal the presence of large aggregates. In contrast, when  $\text{NH}_4\text{-1}$  (0.25%, w/v) was dissolved in water, a turbid dispersion was obtained, which is indicative of the presence of large aggregates. The addition

of 5% (v/v) acetone to this dispersion led to a clearance of the solution, apparently as a result of the dissociation of the assemblies. TEM studies on the dispersions revealed that  $\text{NH}_4\text{-1}$  formed well-defined aggregates with an elongated rectangular shape and rounded corners (Figure 2). Their dimensions typically were 1500–2500 nm  $\times$  70–100 nm. An electron diffraction experiment indicated that the observed structures were not crystalline.

The fact that compound  $\text{NH}_4\text{-1}$  forms nano-sized aggregates whereas **Na-1** does not, implies that the ammonium ions in the former aggregates play an important role in the self-assembly process. It is well known that these ions can form very strong hydrogen bonds with carboxylate anions [8]. To investigate this, reflectance infrared studies on cast films of dispersions of  $\text{NH}_4\text{-1}$  were carried out. A C=O stretching vibration at  $1680 \text{ cm}^{-1}$ , corresponding to the carboxylate functions, and a relatively sharp N—H stretching vibration at  $3160 \text{ cm}^{-1}$  of the ammonium ions indicate the presence of well-defined hydrogen bonding interactions between these functions. An X-ray powder diffractogram of a cast film of the compound showed a clear repeating distance of  $\sim 9.75 \text{ \AA}$ , and in addition a very complex reflection pattern which indicated an ordering of the molecules in an as yet unresolved 3-dimensional lattice.

A possible model of self-assembly for clips **Na-1** and  $\text{NH}_4\text{-1}$  is presented schematically in Figure 3. Based on the  $^1\text{H}$  NMR data, we may conclude that an important intermolecular interaction is the ‘face-to-face’ dimerization, in which two receptor cavities are mutually filled (Figure 3a). In a subsequent process, these dimeric units can form a long, one-dimensional array, in which the hydrophobic aromatic surfaces of the receptor cavities have minimized their exposure to the aqueous phase and all the hydrophilic carboxylate groups are directed outwards (Figure 3b). A similar bilayer-like ordering has been observed in the solid state for related receptors functionalized with long aliphatic tails [5]. In a third process, which probably occurs cooperatively with the growth of the dimeric array, the ammonium cations can act as a ‘glue’ by forming hydrogen bonds and stitch the bilayers together to generate a 2-dimensional (2D) sheet (Figure 3c).

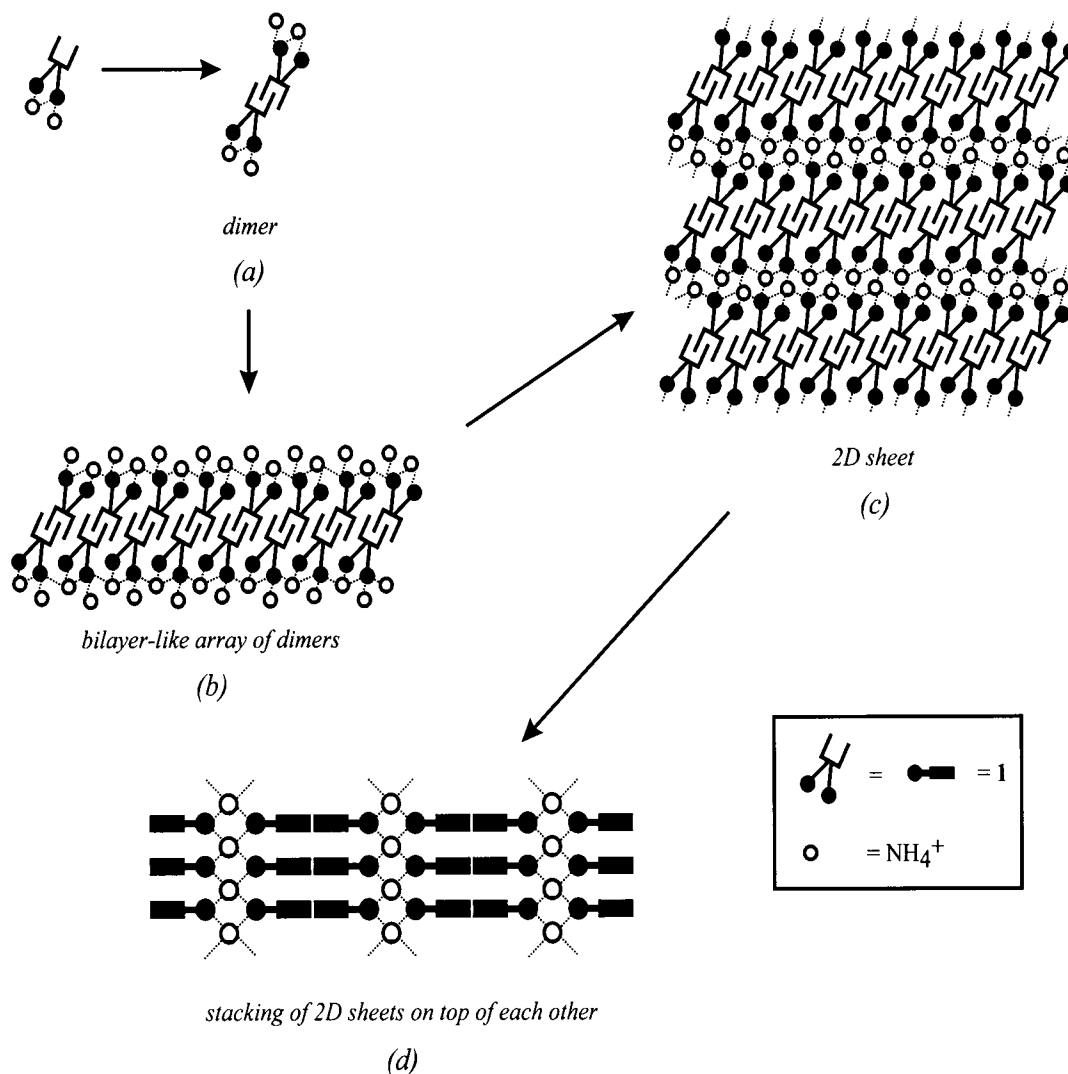


Figure 3. Schematic representation of the proposed ordering of  $\text{NH}_4\text{-1}$ . (a) Formation of a dimer. (b) Assembly of dimers in a one-dimensional array. (c) Stacking of bilayers by the  $\text{NH}_4^+$  ions resulting in the formation of 2D sheets (top view). (d) Stacking of the 2D sheets on top of each other (side-view).

In the case of **Na-1** this stitching cannot occur. Hence, the self-assembly of the latter molecules stops at the stage of the dimer or the dimeric array, and no aggregates on a mesoscopic scale are formed. Finally, it is proposed that the 2D sheets of the ammonium amphiphiles stack on top of each other giving the aggregates their final 3-dimensional shape (Figure 3d). Molecular modeling showed that the thickness of one 2D sheet amounts to approximately 9.2–9.5 Å, a value which corresponds reasonably well with the strong reflection observed in the powder diffractogram of  $\text{NH}_4\text{-1}$  (9.75 Å). A similar stacking of 2D sheets has been observed before for related clip molecules [5, 9]. It is not unlikely that the 2D sheets of amphiphiles are also stitched together by the ammonium ions, which can form, apart from hydrogen bonds with carboxylate functions within the sheets, additional hydrogen bonds with carboxylate functions in different sheets.

## Conclusion

We have demonstrated that water-soluble clips can self-assemble into large mesoscopic aggregates through an ensemble of hydrogen bonding interactions and the hydrophobic effect. Current studies are directed toward fine-tuning the aggregate morphology by changing the size of the receptor side-walls, which controls the strength of the dimerization reaction of  $\text{NH}_4\text{-1}$ .

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