Self-Assembly

DOI: 10.1002/ange.201002665

Topology Selection and Tautoleptic Aggregation: Formation of an Enantiomerically Pure Supramolecular Belt over a Helix**

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The understanding of self-assembly processes is one of the most important areas of today's science,[1] and the assembly of monomers to discrete cyclic structures by hydrogen bonding is one of the major areas of supramolecular chemistry.[2–5] Despite developments in the field, there are still important issues to be addressed in the design of supramolecular structures. One such issue is the self-assembly of cyclic cavities that have enantiomerically pure skeletons derived from enantiomerically pure monomers, where the challenge is to favor cyclic aggregation over helical polymerization. Both the cyclic and helical topologies can have important applications. Self-assembled cavity compounds can be used for applications in catalysis and recognition, and helical aggregates can transport compounds in their interior. For the same "angle bar" (Figure 1, center), the position of the hydrogen-bonding motif will influence the likelihood to form a cyclic structure. Another issue has to do with the economical and practical aspects of the synthesis of the monomers. For monomers to be able to form extended stable cyclic aggregates, robust complementary hydrogen-bonding motifs must be introduced at each terminus. In heteroleptic aggregation, there are two different monomers, and within each monomer the termini have the same hydrogen-bonding pattern, which is complementary to that of the other monomer type (Figure 2, left). In homoleptic aggregation, there is only one type of monomer, and the monomers aggregate through a self-

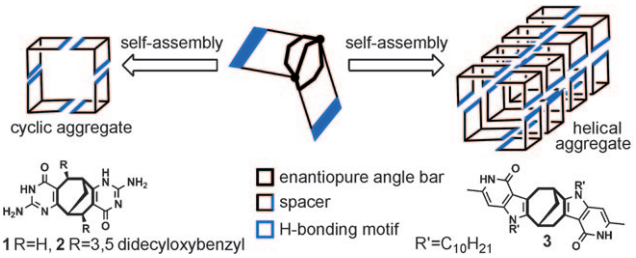

Figure 1. The properties of the construction elements lead to cyclic or helical self-assembly depending on the position and orientation of the hydrogen-bonding motif.

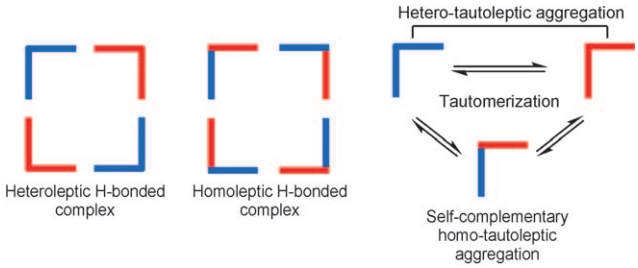

Figure 2. Heteroleptic, homoleptic, and tautoleptic aggregation and their interconversion.

complementary hydrogen-bonding motif, with one half at each terminus (Figure 2, center). The first approach needs the synthesis of two different types of symmetric monomers. The second needs the synthesis of only one type of monomer, however often with two different but complementary termini. We now suggest a third approach—namely, tautoleptic aggregation. This approach is based on the use of one single symmetric monomer that acquires self-complementarity by tautomerization. Two cases can be distinguished (Figure 2, right): In the homo-tautoleptic case, one side of a self-complementary hydrogen-bonding pattern (for example, DDA in a three hydrogen-bonding system, where D represents the H donor and A the acceptor) is located at one terminus of one single monomer and the other side (AAD) is located at the other terminus. In the hetero-tautoleptic case, the same side (DDA) of a self-complementary H-bonding motif is found at both termini of one monomer and the other side (AAD) is found at both termini of a second monomer.

Tautoleptic aggregation would require the least synthetic effort in terms of covalent synthesis of chiral building blocks, in that only one dissymmetric monomer has to be synthesized. Moreover, molecular systems that are inherently non-self-complementary, such as three-hydrogen-bond motifs, can now

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[**] We thank the Swedish Foundation for Strategic Research, the Crafoord Foundation, the Swedish Research Council, the Royal Physiographic Society, and NordForsk for financial support. We thank François Paoloni and Mark Ingratta for GPC measurements and Anders Sundin and Robert Vácha for discussions concerning computational aspects of this project.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201002665.

become self-complementary and can thereby aggregate using one type of monomer.

We now report on the first selective assembly by tautoleptic aggregation of an enantiomerically pure cavity, that is, a supramolecular belt, from one enantiomerically pure monomer containing one inherently non-self-complementary motif. We also show that the positioning of the hydrogen-bonding motif is important for the topological selectivity in the assembly of a cyclic structure over a helical one using enantiomerically pure C_2-symmetric monomers.

Our starting point was that isocytosine and some derivatives thereof form dimers in $CHCl_3$ by tautomerization, resulting in self-complementary DDA–AAD hydrogen-bonding systems.[6–11] Accordingly, we have designed a monomer **1** containing one isocytosine unit at each end of an enantiomerically pure C_2-symmetric angle bar, the bicyclo[3.3.1]nonane system (Figure 1, bottom left). Molecular modeling at the semi-empirical level (see the Supporting Information) indicated that a cyclic tetramer $\mathbf{1}_4$ is favored and that its quadratic cavity would have a width of approximately 13 Å from face to face in hetero- and homotautoleptic aggregation (Figure 3). The calculations also suggested the possible formation of a stable cyclic pentamer but excluded a trimer or a hexamer as stable species.

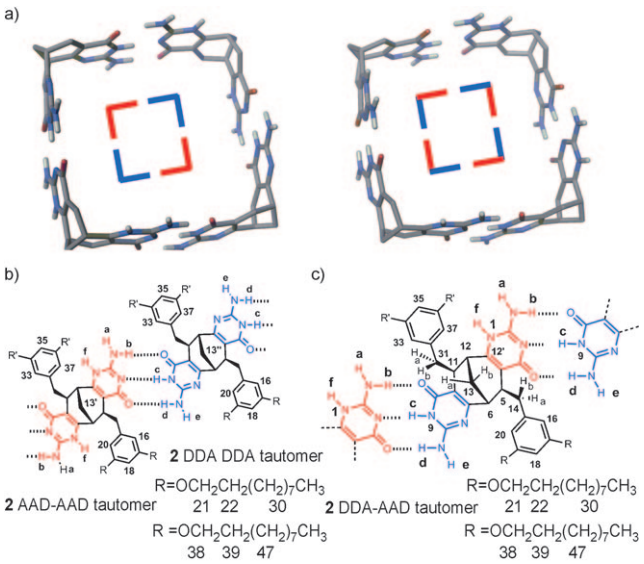

Figure 3. a) Molecular modeling at the semi-empirical level of two possible types of tetrameric aggregates $\mathbf{1}_4$ of monomer **1**: Two different monomers AAD–AAD and DDA–DDA, respectively (left, hetero-tautoleptic aggregation), and one monomer DDA–AAD (right, homo-tautoleptic aggregation). b,c) The targeted monomer **2** and its numbering for hetero- (b) and homo-tautoleptic (c) aggregation.

To obtain the necessary solubility for **1** in $CHCl_3$, we added branched 3,5-didecyloxybenzyl groups to **1**. The resulting compound **2** is shown in Figure 1, bottom left, and its synthesis and full characterization are given in the Supporting Information.

The characterization of **2** and its self-aggregation in $CHCl_3$ was performed partly by NMR spectroscopy. The ^{1}H NMR spectrum of **2** in $CDCl_3$ shows a doubling of all resonances in a 1:1 ratio, thus indicating the presence of either a 1:1 mixture of two different C_2-symmetric monomers in a DDA–DDA—AAD–AAD hetero-tautoleptic aggregate (Figure 3b) or of one monomer with C_1 symmetry in a DDA–AAD homo-tautoleptic aggregate (Figure 3c). By using NOESY spectra, it is evident from NOE interactions of the centrally positioned protons that the doubling of all resonances detected in the ^{1}H NMR spectra is due to only one monomer of C_1 symmetry. Thus, H-13a gives a NOESY crosspeak with only one of the benzylic protons H-31b, whereas H-13b interacts with another benzylic proton H-14b. However, both H-13a and H-13b give NOESY crosspeaks with H-12 as well as with H-6 (Figure S30 and Figure 3c). This evidence shows that all the mentioned resonances originate from protons belonging to one and the same molecule and thus that the structure of **2** in the aggregate is the DDA–AAD tautomer as depicted in Figure 3c. This finding is supported by the fact that the resonances of H-13a and H-13b exhibit a typical AB quartet pattern (Figure 4), showing that there is

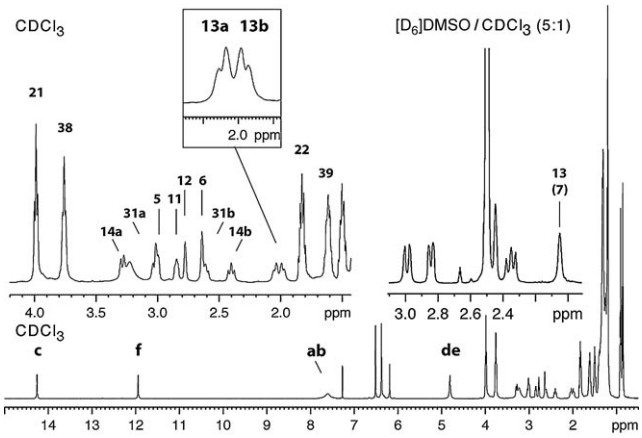

Figure 4. ^{1}H NMR spectra of **2** in $CDCl_3$ and $[D_6]DMSO/CDCl_3$ (5:1).

only one monomer and that one is of C_1 symmetry, since H-13a and H-13b are obviously not chemically equivalent. In contrast, if **2** would assemble by hetero-tautoleptic aggregation (Figure 3b), the two different monomers would be of C_2 symmetry, and H-13a and H-13b would then be chemically equivalent. In fact, in $[D_6]DMSO/CDCl_3$ (5:1), monomer **2** is of C_2 symmetry, and the H-13a and H-13b resonances are chemically equivalent (Figure 4 and Figure S31 in the Supporting Information). Moreover, the ^{13}C NMR spectrum of **2** in $CDCl_3$ shows a doubling of all carbon resonance frequencies in the bicyclo[3.3.1]nonane framework except for the centrally positioned C-13 (all of the same intensity and line width), which gives one resonance peak only (Figure S22 in the Supporting Information), thus supporting homo-tautoleptic aggregation. In contrast, in the case of hetero-tautoleptic aggregation of monomer **2**, two resonances for C-13 would have been expected, one for each of the two different monomers (Figure 3b).

The hydrogen-bonding motif in **2** in $CDCl_3$ is partly characterized by the properties of the NH proton resonances

in the NMR spectrum (see Figure 4, bottom). The ^{15}N-^{1}H HMQC spectrum shows the bonding from H-c at $\delta =$ 14.33 ppm to one nitrogen atom displaying a chemical shift of $\delta = 150.2$ ppm and from H-f at $\delta = 12.23$ ppm to the nitrogen atom with a resonance at $\delta = 146.3$ ppm, whereas the signal from the two protons H-d and H-e, which have the same chemical shift $\delta = 4.83$ ppm at 300 K, correlates to one nitrogen chemical shift at $\delta = 65.7$ ppm (Figure S29 in the Supporting Information). The H-a/H-b resonance at $\delta =$ 7.58 ppm has a line width that is too large to give correlations to nitrogen shifts in the HMQC spectra. A change of the sample temperature from 300 to 200 K resulted in splitting of the chemical shifts for each of the NH_2 groups into individual resonances for each proton (Figure S41 in the Supporting Information). The chemical shifts of H-c and H-f as well as the temperature dependence of the chemical shifts for NH_2 H-a/H-b and H-d/H-e pairs are consistent with previous evaluations of hydrogen-bonding motifs in an isocytosine dimer in $CDCl_3$.[9,11] By comparing the spectra at different temperatures it is also evident that the strength of the hydrogen bonds differs between the two amino groups in the DDA–AAD tautomers, with a stronger bond for the NH_2-b than for the NH_2-d proton. Thus, the NH_2-a/b protons are frozen out into two individual chemical shifts at higher temperature than the NH_2-d/e protons, and their chemical shifts are more strongly separated (Figure S41 in the Supporting Information). This difference in hydrogen-bonding strength can be either a result of different electron distribution in the two tautomers, which would change donor and acceptor properties of the hydrogen bond, or be due to a distorted geometry of the hydrogen-bonding motif, a geometry that is required for the formation of the cyclic aggregate.

In the ROESY spectra in $CDCl_3$ (Figure S27 in the Supporting Information), a strong cross peak between the resonances of protons H-c and H-f was observed, despite the rather long H···H distance (4.8 Å), thus clearly demonstrating intermolecular interactions between monomers of **2**. However, the NH hydrogen atoms that take part in the hydrogen bonding most probably undergo chemical exchange with each other in a tautomerization–dissociation–association mechanism, in analogy with the similar guanidine–cytosine hydrogen-bonding pair.[12,13] The aforementioned spectral features are absent in hydrogen-bond-competing solvents like DMSO, in which compound **2** exists as the monomeric C_2-symmetric species DDA–DDA or AAD–AAD or a mixture thereof, as evaluated on the basis of the symmetry of the ^{1}H and ^{13}C NMR spectra in $[D_6]DMSO/CDCl_3$ (5:1; Figure 4 and Figure S32 in the Supporting Information).

The absorption (UV/Vis) spectrum of **2** (Figure S45 in the Supporting Information) is composed of two bands, one at 232 nm and another at 285 nm in $CHCl_3$.[7] The intensity of the long-wavelength band is dominated by the DDA tautomer, whereas the short-wavelength band is dominated by the AAD tautomer, on the basis of the comparison with the assignment of isocytosine itself in various solvents.[8]

To acquire information about the size and size distribution of aggregates, monomer **2** was subjected to vapor pressure osmometry (VPO) in $CHCl_3$ at 37 °C, 11–53 mM. It showed a constant degree of association of 4.4 ± 0.1 over this concentration range (Figure S43 in the Supporting Information), thus supporting the formation of a tetrameric aggregate.[14]

Further insight into the aggregation of **2** was given by diffusion NMR spectroscopy[15–18] using the bipolar longitudinal eddy delay (BPLED) technique (see the Supporting Information).[19] The value of the diffusion coefficient D was estimated in $CDCl_3$ at three different concentrations (10, 20, and 30 mM) and by monitoring four different proton resonances: H-c, H-f, and the combined H-d/e and H-21/38 resonances. It was found that D is inversely proportional to the viscosity (η; Figure S49 in the Supporting Information), thus strongly supporting a static system on the time scale of NMR spectroscopy and allowing for the determination of a highly accurate value of the hydrodynamic Stokes' radius R_s from D_0 after extrapolation of D to infinite dilution to give $D_0 = 2.71 \times 10^{-10}\ m^2 s^{-1}$ in $CHCl_3$. Using the Stokes–Einstein equation $D_0 = k_b T/(6\pi\eta_0 R_s)$[20] gave $R_s = 13.2$ Å (k_b is the Boltzmann constant, and T is the temperature). The DOSY spectra showed that all proton resonances only gave correlation with one and the same value of D, a significant indication of one type of aggregate.

Owing to the presence of many flexible alkyl chains in the aggregate of **2**, an estimation of R_s based on the size of the aggregate is difficult, as also noted by others for other aggregates.[17,18] We therefore argued that more accurate results would be obtained using molecular dynamics (MD) simulations. Hence, in order to have some correlation between the value of R_s obtained from the DOSY experiment and from size estimation, we performed MD simulations in the isothermal–isobaric ensemble for the tetramer and pentamer solvated in fully atomistic chloroform using the Gromacs 4 package[21] and the proven Gromos forcefield (see the Supporting Information). For the tetramer and pentamer, R_s was found to be 14.0 and 14.8 Å, respectively (see the Supporting Information for details on how R_s was calculated.). Thus the experimental value of R_s from the DOSY experiments, 13.2 Å, corresponds better to the formation of a tetramer than a pentamer.

Gel permeation chromatography (GPC) was performed using a set of *O*-acylated β- and γ-cyclodextrins as standard compounds. These standard compounds are particularly suitable for our purposes in that they not only have the same mass range as the tetramer and the pentamer but they also have the same shape as the self-assembled cyclic structure. GPC confirmed the results obtained from the diffusion NMR spectroscopy studies that the aggregate of **2** is monodisperse, having $M_w/M_n = 1.08$ (M_w is the weight-average molecular weight and M_n the number-average molecular weight). Moreover, the molecular mass of the aggregate was determined to be 4130. This result is consistent with the formation of a tetramer ($M_w = 4366$) and is inconsistent with a pentamer ($M_w = 5457$), thus clearly supporting tetrameric aggregation.

In summary, we have shown an example of the topological selection of an enantiomerically pure cyclic structure over a helical one upon aggregation of an enantiomerically pure monomer **2** containing a self-complementary hydrogen-bonding motif. In fact, when the same chiral angle bar, the bicyclo[3.3.1]nonane framework, was used and a hydrogen-

bonding motif was placed in a different position, the aggregation resulted in helical tubular oligomers (Figure 1, compound **3**).[22] Moreover, for the first time an enantiomerically pure molecular belt has been assembled on the basis of hydrogen bonding, and for the first time an inherently non-self-complementary three-hydrogen-bond motif has been involved in cyclic homoleptic aggregation. In this process enantiomerically pure monomer **2** aggregated by induced tautomerization to include the DDA and AAD hydrogen-bonding motifs of isocytosine at one end each, thus forming an unusually stable cyclic tetrameric structure. For simple dimerizations by tautoleptic aggregation, association constants of isocytosine compounds in $CHCl_3$ are approximately $10^4\,M^{-1}$.[11] However, it is obvious that the formation of the cyclic aggregate of **2** has an association constant that is at least one order of magnitude higher based on dilution titrations and on a competition experiment (Figure S42 in the Supporting Information). The aggregation of planar monomers to defined two-dimensional cyclic structures by induced tautomerization has also been observed,[23,24] but such monomers are not able to display topological diversity as enantiomerically pure monomers. We suggest the term tautoleptic aggregation for all these modes of aggregation. Finally, by the use of tautoleptic aggregation, only one symmetric monomer is to be synthesized compared to more than one monomer for heteroleptic aggregation and one unsymmetrical monomer for homoleptic aggregation, making the first a very attractive concept for self-assembly from an economical and practical view of monomer synthesis.

Received: May 3, 2010
Revised: October 27, 2010
Published online: January 24, 2011

Keywords: H-bonding · molecular belts · self-assembly · tautomerization · topological selectivity

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