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Chiral Molecular Clips Control Orthogonal Crystalline Organization

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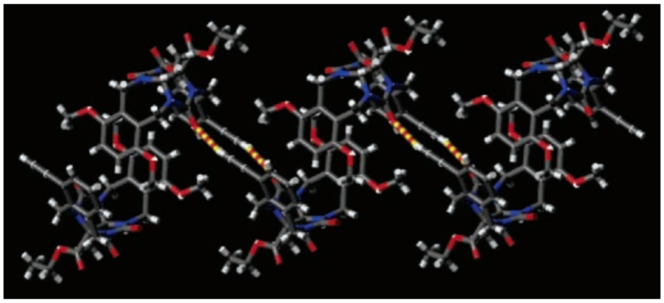
ABSTRACT



Chiral molecular clips constitute a robust system for crystal engineering studies and undergo several levels of orthogonal organization including heterochiral dimerization, H-bond or metal–ligand mediated tape formation, and longitudinal packing of the tapes.

The functions of Nature's macromolecules—especially proteins—are determined to a large extent by their precise three-dimensional structures.[1] Consequently, although the constitution of these biological oligomers can be adequately described by their primary (1°) sequence, their functions are properly determined only by their secondary (2°, e.g., α-helix or β-sheet), tertiary (3°), and quaternary (4°) structures which involve folding, self-assembly, and higher order organization of lower order structural elements. Inspired by the remarkable characteristics of these natural systems, supramolecular chemists have designed non-natural folding oligomers that adopt well-defined 2° structures[2] and begun to control their functions (e.g., host−guest, folding−unfolding, dimerization). For chemists interested in materials properties, this same inspiration focused attention on the field of crystal engineering.[3] By understanding how 1° (e.g., molecular) structure translates into crystalline order, it should be possible to control desirable properties (e.g., nonlinear optics, density, and solubility). Therefore, a major goal of many crystal engineering studies has been the development of robust synthons (e.g., H-bonding, π−π interactions, metal−ligand interactions) that allow one to control the relative orientation of molecules in the crystal.[3] Fewer studies have been directed toward the development of robust sets of orthogonal synthons to allow for precise control over molecular ordering.[4] In this

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paper, we demonstrate that chiral molecular clips[5] based on glycoluril constitute a robust supramolecular synthon that controls enantioselective heterochiral dimerization followed by H-bond or metal−ligand mediated supramolecular polymerization that mimics some of the essential elements of hierarchical organization seen in natural systems.

The popularity of glycoluril as a building block in supramolecular chemistry can be traced to the pioneering work of Nolte and Rebek on molecular clips[5a] and capsules,[6] respectively, and is currently fuelled by interest in the cucurbit[*n*]uril family[7] of macrocycles. It was not until recently, however, that the potential of glycoluril building blocks in crystal engineering studies was realized.[8] To investigate the robustness of glycoluril molecular clips[5a,8d,e] as an orthogonal synthon toward programmed crystalline organization, we synthesized compounds (±)-**1**−(±)-**6** (Figure 1 and Supporting Information) by Pd-catalyzed coupling reactions of terminal acetylenes with iodo-clip (±)-**1**. The critical design elements in choosing targets (±)-**2**−(±)-**6** included the following: (1) one 1,4-dimethoxyxylylene wall to induce dimerization;[8d,e] (2) a second differentially substituted aromatic wall that yields chiral, but racemic, clips; and (3) the presence of functional groups (C≡CH, OCH_3, NH_2, pyridyl) with the potential to engage in H-bonding or metal−ligand interactions.

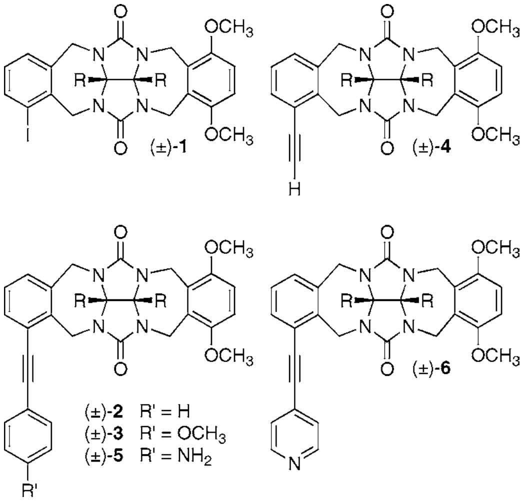

Figure 1. Molecular clips used in this study (R = CO_2Et).

We were fortunate to be able to obtain X-ray quality crystals of (±)-**1**−(±)-**6** by recrystallization from CH_2Cl_2 with MeOH or CH_3CN as cosolvent and solve their structures. Figure 2a shows the structure of (±)-**1** in the crystal.

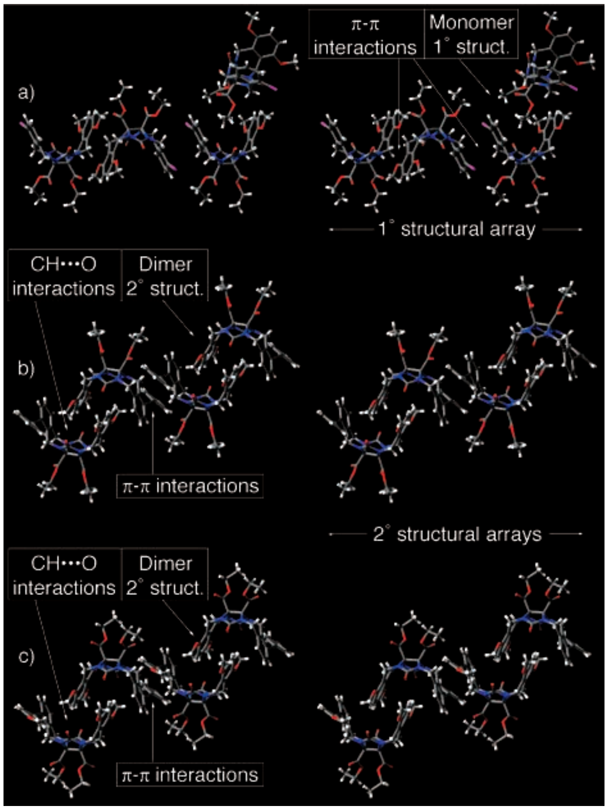

Figure 2. Cross-eyed stereoviews of the X-ray crystal structures of (a) (±)-**1**, (b) (±)-**2**, and (c) (±)-**3**. Color coding: C, gray; H, white; N, blue; O, red; I, purple.

In contrast to (±)-**2**−(±)-**6** (vide infra) and six other 1,4-dimethoxyxylylene walled clips prepared previously by us,[8e] (±)-**1** does not undergo CH•••O and $\pi-\pi$ interaction mediated cleft−cleft dimerization in the crystal. Instead, (±)-**1** undergoes $\pi-\pi$ interactions along the *ab* diagonal to yield a tape-like array[3f] of the monomeric building unit (e.g., 1° structural array). Interestingly, the $\pi-\pi$ interactions occur between identical aromatic walls (e.g., Ar−I with Ar−I) of molecules of **1** of opposite handedness (e.g., (+)-**1**•••(−)-**1**•••(+)-**1**). The clefts of (±)-**1** are filled by CO_2Et groups from molecules of (±)-**1** in an adjacent tape.

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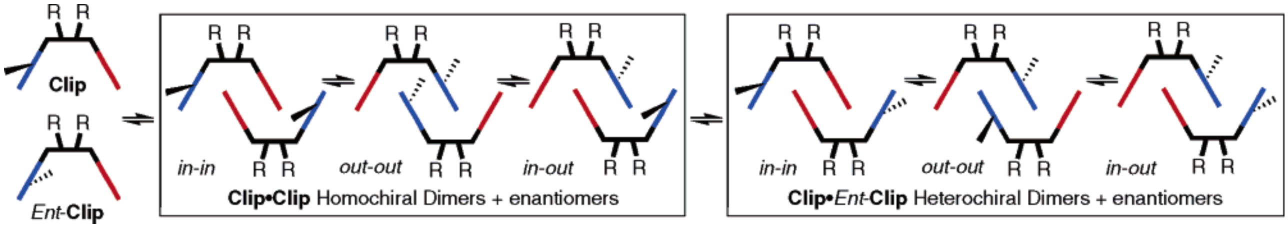
Scheme 1. Schematic Representations of the Six Diastereomeric Dimeric Clips That Are Possible upon the Self-Association of Racemic Molecular Clips: Color Code: Red, Dimethoxyxylylene Wall; Blue, Monosubstituted Xylylene Wall



The X-ray crystal structures of (±)-**2** and (±)-**3** are closely related to one another and display secondary (2°) structural organization based on dimerization of the molecular clips (Figure 2b,c). During the formation of dimeric molecular clips from (±)-**2** and (±)-**3**, it is conceivable that either the homochiral (e.g., (+)-**2**•(+)-**2** and (−)-**2**•(−)-**2**) or the heterochiral ((+)-**2**•(−)-**2**) form could predominate (Scheme 1). Because clips (±)-**2**−(±)-**6** contain two different aromatic walls, there are three diastereomeric arrangements of the homochiral and the heterochiral forms that differ in the disposition (e.g., in−in, in−out, and out−out) of the dimethoxyxylylene walls (Scheme 1). Despite the potential complexity, (±)-**2** and (±)-**3** undergo exclusive heterochiral dimerization via the in−in diastereomer during crystalline organization.[9] We believe that this highly diastereoselective process is controlled by favorable C−H⋯O interactions between the OCH_3 groups of the internal dimethoxyxylylene wall and the ureidyl C=O of the glycoluril building block.[8e,10] These 2° building blocks then form tape-like 2° structural arrays by π−π interactions between the −C≡C−Ar substituted aromatic walls on their external faces. The tape-like 2° structural arrays formed by (±)-**2** and (±)-**3** pack with their long axes parallel to generate extended structures in the solid state. The structures of (±)-**2**−(±)-**3** further define the scope and generality of the solid-state dimerization of dimethoxyxylylene walled molecular clips mediated by C−H⋯O interactions[8e] and display a strong preference for interaction between clips of opposite handedness (e.g., heterochiral dimerization).

To investigate the possibility of using the heterochiral dimerization mediated by C−H⋯O interactions toward orthogonal organization in the solid state, we decided to endow these molecular clips with H-bond donating or metal coordinating functional groups. Accordingly, we prepared and crystallized (±)-**4**−(±)-**6** which contain C≡C−H, Ar−NH_2, and pyridyl functional groups, respectively (Figure 3). Figure 3a shows a cross-eyed stereoview of the structure of (±)-**4** in the crystal. As predicted, the monomeric units of (±)-**4** undergo heterochiral dimerization to yield the in−in diastereomer of the dimeric 2° building block (+)-**4**•(−)-**4** with terminal acetylenic (C≡C−H) groups arrayed roughly antiparallel to one another. These 2° building blocks then undergo H-bond mediated formation of tape-like structures that constitute a tertiary (3°) structural building block. In a similar fashion, (±)-**5** undergoes heterochiral dimerization to yield the in−in diastereomer of the 2° structural building block (+)-**5**•(−)-**5** (Figure 3b). The extended C≡C−Ar−NH_2 arms of (+)-**5**•(−)-**5** then form a H-bonded tape (3° structure) by NH⋯O H-bonds to the glycoluril C=O group. One of the intriguing aspects of both of these H-bond mediated solid-state supramolecular polymerizations is that the C≡C−H and C≡C−Ar−NH_2 arms H-bond to opposing

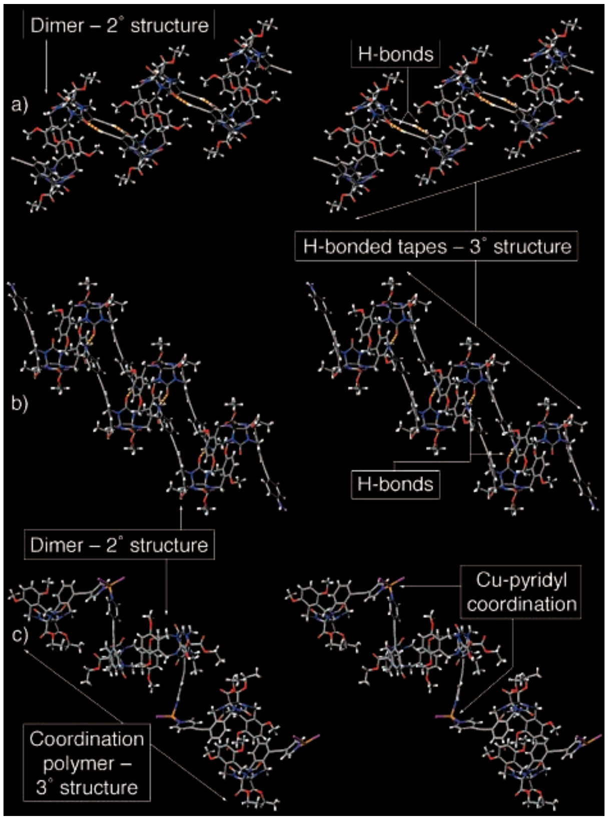


Figure 3. Cross-eyed stereoviews of the X-ray crystal structures of (a) (±)-**4**, (b) (±)-**5**, and (c) (±)-**6**•CuI_2. Color coding: C, gray; H, white; N, blue; O, red; I, purple; Cu, orange; H-bonds, red-yellow striped.

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[9] Crystallization of racemates usually results in the incorporation of both enantiomers rather than conglomerate formation. The unusual observation in this work is that both enantiomers are incorporated during the exclusive formation of the heterochiral dimeric molecular clips. As expected, (±)-**1**−(±)-**6**•CuI_2 crystallize in centrosymmetric space groups ($P2_1/c$, $P2_1/n$, $P\bar{1}$, and $C2/c$) to accommodate such an arrangement.

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glycoluril C═O groups in the dimers (+)-**4**·(−)-**4** and (+)-**5**·(−)-**5**, which requires a geometrical change in one of the OCH_3 groups of the 2° structural determining dimethoxyxylylene wall. The ability of the 2° structure determining C−H···O interactions to accommodate the structural demands of higher order organizing H-bonding groups establishes the orthogonality of these synthons in the solid state and suggests a broad applicability toward crystal engineering.

As a further test of the robustness of the C−H···O mediated molecular clip dimerization as a 2° structural element in crystal engineering, we prepared molecular clip (±)-**6** which bears a pyridyl group suitable for metal−ligand coordination interactions. Figure 3c shows the X-ray crystal structure of (±)-**6**·CuI_2. In a completely predictable fashion based on our previous experience with (±)-**2**−(±)-**5**, (±)-**6** undergoes heterochiral dimerization to yield the in−in diastereomer of (+)-**6**·(−)-**6** as a 2° structural building block. Subsequently, the two pyridyl arms of (+)-**6**·(−)-**6** which are displayed roughly antiparallel to one another undergo metal−ligand coordination interactions with the Cu atoms. This process generates a metallo-supramolecular polymer [(+)-**6**·(−)-**6**−Cu(I_2)−(−)-**6**·(+)-**6**−Cu(I_2)]$_n$. Superficially, the placement of the Cu atoms on opposite sides of the 3° structure of (±)-**6**·(CuI_2) may evoke images of helical DNA or peptide α-helices. Closer inspection reveals that the metallo-supramolecular polymer consists of short helical units of alternating helicity in which two molecules of **6** of the same handedness bind to a given Cu atom in an alternating fashion. In all three cases ((±)-**4**, (±)-**5**, and (±)-**6**·Cu(I_2)), the 3° tape-like structures pack with their long axes parallel to one another.

In conclusion, we find that molecular clips containing a 1,4-dimethoxyxylylene wall (1° structure) interact with each other by C−H···O interactions to yield dimeric (2° structural) building blocks by in−in diastereoselective heterochiral processes. When these 2° structural elements contain functional groups capable of H-bonding or metal−ligand interactions (e.g., (±)-**4**−(±)-**6**), a 3° level of organization is expressed during the formation of tape-like supramolecular polymers. In all cases, the tape-like structures pack with their long axes parallel to one another which may be considered as a 4° level of structural organization. The pronounced robustness, enantioselectivity, and orthogonality of the C−H···O mediated 2° structure and H-bond or metal−ligand mediated 3° structures based on glycoluril derived molecular clips suggests the broad utility of this scaffold in crystal engineering studies.

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Supporting Information Available: Procedures, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds. Crystallographic information files for **1**−**6** (.cif). Enlarged versions of the structures presented in Figures 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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