Stacked Assemblies Hot Paper

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Two- and Three-Tiered Stacked Architectures by Covalent Assembly

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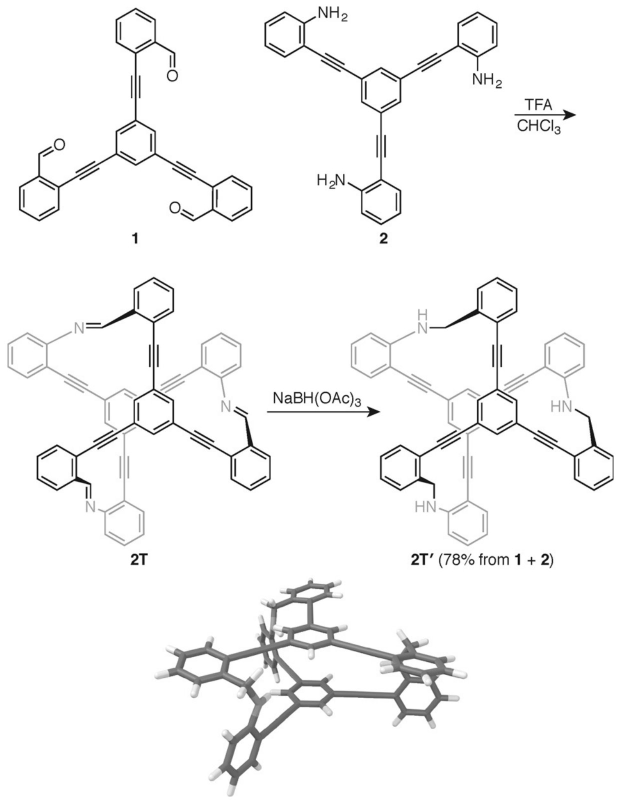
Abstract: *Simple discotic cores functionalized with reactive arms have been assembled into two- and three-tiered covalent stacks through imine formation. The targets are obtained in good yields, but competing formation of misassembled byproducts highlights some of the challenges inherent to the thermodynamically controlled assembly of rigid, compact, three-dimensional architectures. The structures comprise a central stack of arenes surrounded by a triple helix of interconnected arms. The racemization rate is strongly dependent on the number of tiers, suggesting cooperative conformational coupling in these multi-tiered structures.*

Dynamic covalent chemistry (DCC) is a powerful approach to the synthesis of large organic molecules. Because its reversibility allows for error-checking, many bonds can be formed in a single assembly step.[1] Thus, remarkable examples of macrocycles, cages, ladders, and more-complex architectures have been prepared using DCC.[2–10] We are interested in the general problem of using DCC to assemble discotic monomers into multi-tiered stacks; formally, this corresponds to the creation of fused cages. General strategies toward such structures, essentially multitiered cyclophanes,[11–13] would enable the efficient synthesis of finite stacks of chromophores[14] and tubular structures through the stacking of macrocycles.[15] Discrete discotic stacks have been prepared, for example, by using coordination chemistry[16,17] or in the solid state.[18] However, fully organic, solution-phase multi-tiered architectures, while already known to have interesting electronic properties,[19–21] are typically prepared using stepwise, often low-yielding syntheses.[11–13,22,23] Herein, we show that imine formation can be used to assemble two- and three-tiered stacked architectures. The strategy is effective considering the complexity of the products, although unexpected side-products are formed, underscoring the challenges of assembling rigid, three-dimensional molecules at equilibrium. The stacks are triple helices, with conformational dynamics that depend strongly on the number of tiers.

Our synthetic strategy is to functionalize a core structure (benzene for these proof-of-principle studies) with arms bearing aldehyde and amino coupling partners. We began with the assembly of two-tiered stack **2T** (Scheme 1). In the presence of trifluoroacetic acid (12 mol %) in chloroform-*d*, monomers **1** (10 mm) and **2** (1.1 equiv) assemble to give **2T**, as judged by ^{1}H NMR (see the Supporting Information). Only signals corresponding to **1**, **2T**, and a partially assembled diimine (that is, **2T** but with one uncoupled aldehyde/amino pair) are observed. The reaction proceeds quickly, with high conversion after only 15 min, and approximately 90 % **2T** after 24 h. For isolation purposes, the imines were reduced with $NaBH(OAc)_3$, and compound **2T′** was obtained in 78 % overall yield.



Scheme 1. Assembly of two-tiered stacks **2T**/**2T′**. The molecular model is of **2T′** (B3LYP/6-31G(d)).

We then attempted to prepare the analogous three-tiered structure (Scheme 2). The target (reduced) stack **3T′** was indeed obtained from **2** and **3** in 39 % yield. However, unlike for the synthesis of **2T′**, a different, major product was isolated in 51 % yield. NMR assignments, based on a rich ROESY spectrum, suggest that this product is $\mathbf{3T_{iso}}'$, a twofold symmetric three-tiered structure with the "wrong" connectivity. ^{1}H NMR monitoring (Scheme 2) indicates that the reaction mixture at equilibrium consists of a mixture of primarily misassembled imine $\mathbf{3T_{iso}}$ and a species with six imine/aldehyde peaks that likely represents a precursor to **3T** with a free aldehyde/amine pair. This set of products is obtained quickly (< 15 min, see the Supporting Information)

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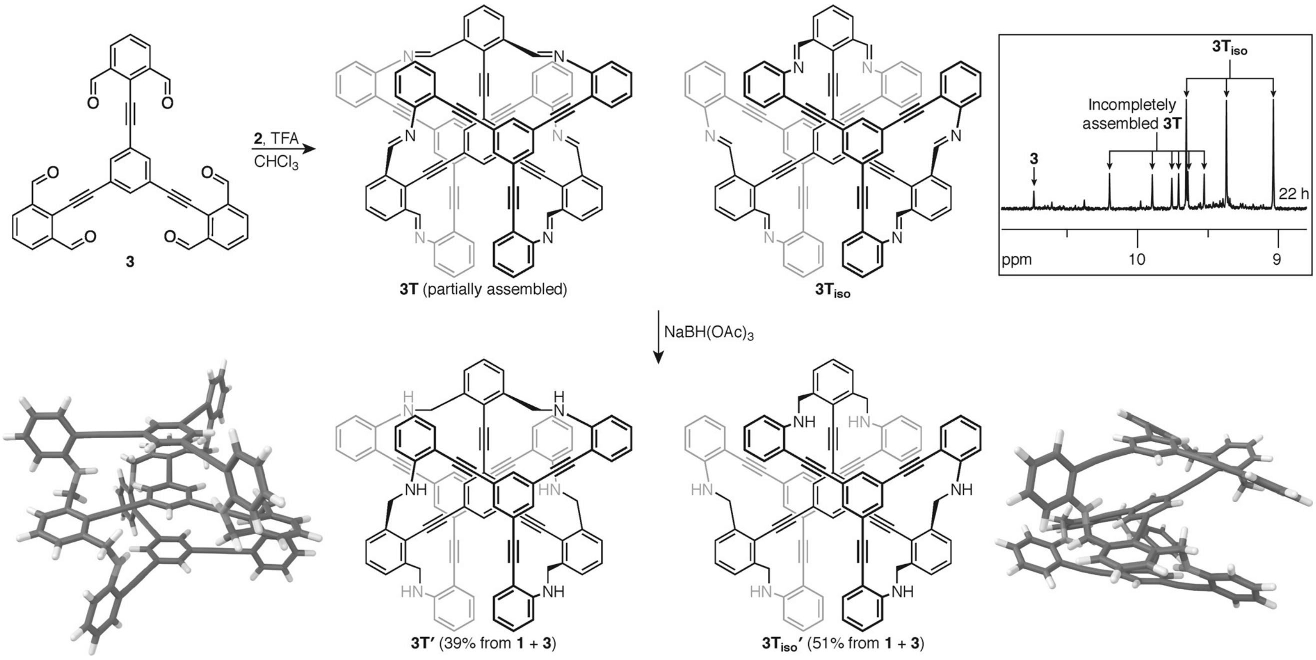


Scheme 2. Assembly of three-tiered stacks **3T**/**3T′** and misaligned isomers **3T$_{iso}$**/**3T$_{iso}$′**. The molecular models are of **3T′** and **3T$_{iso}$′** (B3LYP/6-31G(d)). Top right: ^{1}H NMR spectrum (22 h) of the mixture of **3**, **3T$_{iso}$**, and an incompletely assembled stack.

and is unchanged with extended reaction times; thus it appears that **3T′** is not obtained directly from **3T**, but rather assembly is only completed during reduction. We do not believe that **3T$_{iso}$** is kinetically trapped, as it was still the major product on heating, and DFT calculations predict it to be more stable than **3T** (Supporting Information).

We also examined the alternate route to three-tiered stacks with the same ABA stacking pattern. Surprisingly, as shown in Scheme 3, when monomer **4** (the *tert*-butyl groups were included for synthetic convenience, but should not influence assembly) is combined with **1**, ^{1}H NMR monitoring indicates that assembly stops at the two-tiered stack **2T$_B$**, leaving one equivalent of **1** unreacted. After reduction, we obtained the partially assembled **2T$_B$′** in 52 % yield as the only isolable product. Attempts to construct **3T$_B$′** by a subsequent reductive amination of **2T$_B$′** with additional **1** were unsuccessful.

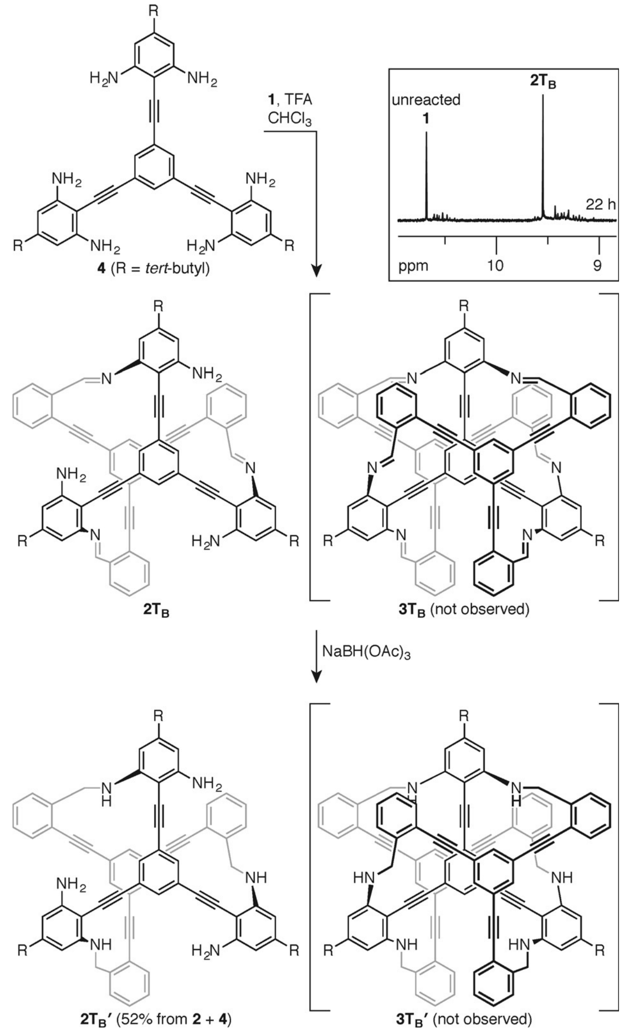
The isolation of **3T$_{iso}$** and **2T$_B$** highlights some of the challenges of designing systems for assembly at equilibrium. Taken together, the byproducts suggest that there is a small amount of strain inherent to the basic **2T**/**3T**/**3T$_B$** architecture, likely because of the twisting of the arms out of conjugation with the central arene unit and subtle angle strain in the final assemblies. The target architectures are fairly rigid and compact, which allows only limited flexibility to relieve such strain.

Nevertheless, the strategy described here is an efficient route to multi-tiered, multi-component covalent structures: despite their complexity, compounds **2T′** and **3T′** are each available in only three total steps from commercially available starting materials.

To better understand the structures of **2T′** and **3T′**, their geometries were optimized by DFT. At the B3LYP/6-31G(d) level, the optimized structures (Schemes 1 and 2) are highly symmetrical. The structure of **2T′** is reminiscent of recent (two-tiered) cages from Zhang[24] and Katoono.[25] For both **2T′** (C_3) and **3T′** (D_3), the stacked central arenes are twisted by 28° and separated by 4.15 Å. Recognizing that aromatic interactions should play an important role in these structures, we also optimized their geometries at the dispersion-corrected B97-D/TZV(2d,2p) level (Supporting Information),[26] widely used to study aromatic stacking.[27] For **2T′**, the resulting geometry is similar to that from B3LYP/6-31G(d), but with the two rings separated by 3.48 Å and twisted by 41°, suggesting effective stabilization from aromatic stacking. For **3T′**, the cofacially stacked D_3-symmetric structure is a second-order transition state. The optimized conformer is similar but unsymmetrical, allowing the arenes to achieve a more-stable offset stacked geometry.

For these helical architectures, racemization should occur via twisting (Figure 1, top). The conformational dynamics of **2T′** and **3T′** are surprisingly different, however. For **2T′** at room temperature ([D$_8$]toluene), only one ^{1}H NMR signal is observed for the diastereotopic methylene protons (CH$_2$NH). Cooling the solution causes little change until shortly before all of the signals broaden around −50 °C (Supporting Information). In contrast, the two methylene protons of **3T′** are clearly distinguishable by ^{1}H NMR at room temperature (Figure 1); thus, interconversion between the (*M*)- and (*P*)-enantiomers of **3T′** is slow on the NMR timescale. On heating, the signals broaden, nearly reaching coalescence at 370 K, corresponding to a free energy of activation of $\Delta G^{\neq}{}_{370} \approx 17\ \text{kcal mol}^{-1}$.

This contrast between the two- and three-tiered structures is remarkable. For **2T′**, either the behavior parallels that of **3T′**, but 1) the methylene NMR signals are coincidentally



Scheme 3. Attempted assembly of three-tiered stack $3T_B$. Top right: ^{1}H NMR monitoring of the assembly of **1** (2 equiv) and **4**.

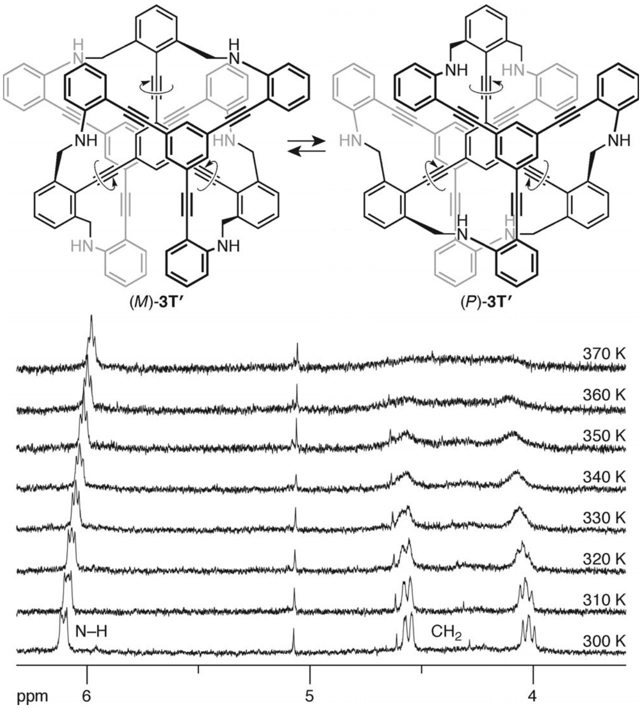


Figure 1. VT ^{1}H NMR of **3T′** ([D$_8$]toluene, 500 MHz).

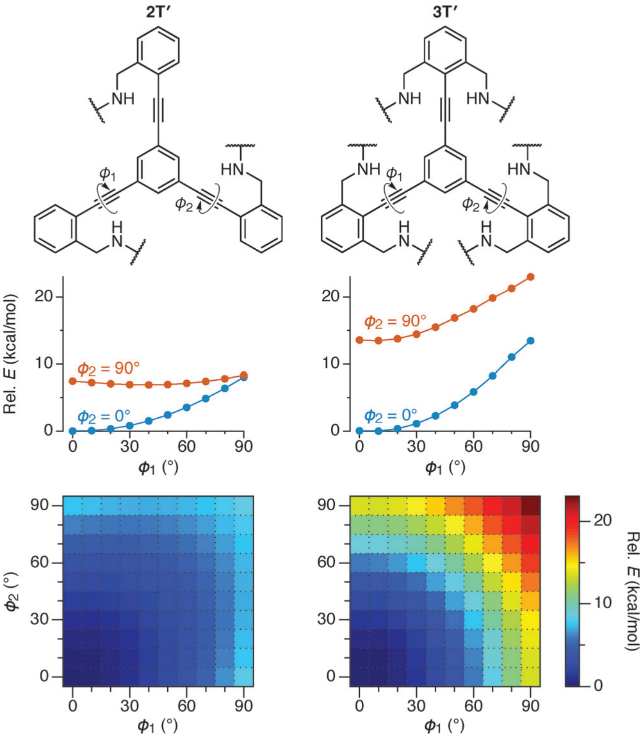


Figure 2. PM6 conformational energy surfaces for rotation about ϕ_1 and ϕ_2 in **2T′** and **3T′**. Middle: relative energy vs. ϕ_1 for limiting values of ϕ_2. Bottom: Heat map of the conformational energy as a function of both ϕ_1 and ϕ_2.

isochronous, or 2) (*M*)- and (*P*)-**2T′** interconvert quickly; or 3) the conformational behavior is distinct from **3T′** in that many conformational states are sampled. DFT calculations (B3LYP/6-31G(d)) suggest that the diastereotopic protons in both **2T′** and **3T′** should have nearly identical chemical shifts. Option 1 is therefore unlikely. To better understand the conformational behavior, we calculated the conformational potential energy surface (PES) of **2T′** and **3T′** using the semi-empirical PM6 method. We focused on rotation about two of the three aldehyde-derived arms, as defined by the dihedral angles ϕ_1 and ϕ_2 in Figure 2, near the global energy minimum ($\phi_1 \approx \phi_2 \approx 0°$). The calculations did not identify any additional conformers for **2T′**; thus, option 3 is unlikely. The two-tiered stack therefore likely adopts well-defined enantiomeric conformers that interconvert quickly. The VT NMR results indicate that the barrier to racemization for **2T′** must be at least $\approx 10\,\text{kcal mol}^{-1}$ below that of **3T′**, assuming a negligible $\Delta S^{\neq}$. The additional aromatic stacking interaction in **3T′** can only account for a fraction of this difference. The third tier must also add an element of coupling that is not present in **2T′**; that is, conformational changes in **3T′** are slower because one part of the molecule cannot move without perturbing another in these rigid, interconnected structures.

This hypothesis is fully consistent with the PM6 calculations. First, the overall energy minimum for **2T′** is indeed much shallower than that of **3T′**. Secondly, there is a flexibility to **2T′**, manifested in ϕ_1 and ϕ_2, that is absent for **3T′**. For **2T′**, once one arm has rotated, it costs little additional energy to rotate the second (note the flat dependence of E on ϕ_1 once $\phi_2 = 90°$). In contrast, for **3T′**, rotation about the second arm is nearly as difficult as for the first. This additional coupling between the tiers suggests that architectures of this basic form become more rigid as their size increases.

In summary, we have developed a simple strategy for the synthesis of two- and three-tiered stacked architectures using DCC. While misaligned and incompletely assembled compounds have also been obtained, the method is efficient considering its brevity and the structural complexity of the products. The conformational behavior of the two- and three-tiered structures is quite different, with the additional tier affording much slower conformational racemization. Computational results show that the additional tier deepens the energy wells for the most-stable conformers and increases conformational coupling between the subunits. Efforts to expand this strategy to taller stacks, other discotic cores, and more-flexible arms are currently underway.

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Keywords: conformational analysis · discotic stacks · dynamic covalent chemistry · imine formation · self-assembly

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