

Automated Recognition, Sorting, and Covalent Self-Assembly by Predisposed Building Blocks in a Mixture

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Conventional molecular recognition involves the formation of complexes or supramolecular arrays using noncovalent forces; because it is generally reversible and under thermodynamic control, it naturally includes proof-reading to remove errors. Here, we extend this idea to the synthesis under thermodynamic control of robust, fully-covalent molecules. Thermodynamics have been used to control a number of syntheses; for example, calix[4]arenes and calix[4]resorcinarenes are both prepared¹ under thermodynamic control, while reversible imine-forming reactions are used in a variety of contexts.² We now show that, by utilizing thermodynamic control, even in complex mixtures where a myriad of products could be produced, suitably predisposed building blocks can recognize each other and covalently self-assemble efficiently to give excellent yields of macrocyclic structures.

The monomer **1**, derived from cinchonidine, can be cyclized virtually quantitatively into the trimer **2** by transesterification using methoxide ion.^{3,4} Control experiments and unambiguous stepwise synthesis of other cyclic oligomers⁵ confirm that this chemistry is reversible and under thermodynamic control; there are no kinetic barriers to formation of higher oligomers. A wide distribution of cyclic oligomers is predicted by the conventional theoretical model that assumes no rigidity or strain in the macrocyclic products,⁶ but our result, which is represented schematically in Figure 1a, demonstrates the exceptional stability of the trimer. Equivalently, we would say that this alkaloid monomer unit is effectively predisposed to stabilize the trimer.

Predisposition must be carefully distinguished from preorganization: the latter generally refers to the ground state of a monomer whose conformation holds the reactive groups in close proximity, thereby favoring one pathway over alternatives. Preorganization in covalent chemistry is therefore a kinetic process. Predisposition, on the other hand, should be thought of as a strong conformational or structural preference expressed by the building block once incorporated into a larger structure, giving rise to a thermodynamic preference for a particular product. This is demonstrated by the cyclization of the cinchonidine monomer **1** which possesses several degrees of conformational freedom, especially around the C₈–C₉ and C₉–C_{4'} bonds: in **1**, ³J_{H₈H₉ is 3.8 Hz, similar to that in cinchonidine}

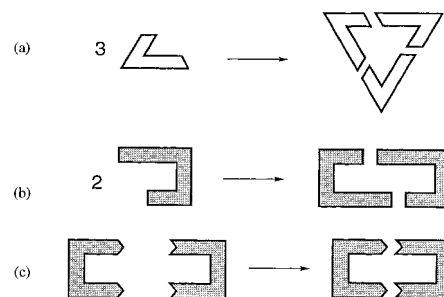
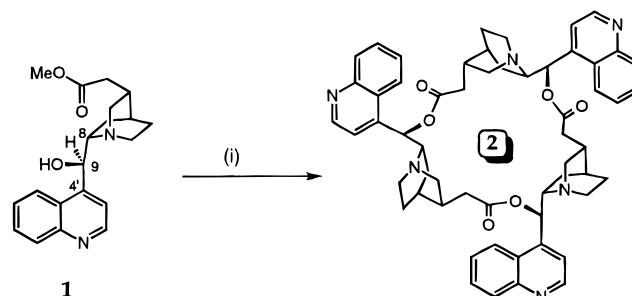


Figure 1. Recognition and covalent assembly by predisposed building blocks: (a) self-assembly of a trimer; (b) self-assembly of a homodimer; (c) assembly of a heterodimer.

Scheme 1^a



^a (i) KOMe, 18-Crown-6, toluene, reflux. Concentration of **1** is 5 mM.

itself,⁷ while in the cyclic trimer ³J_{H₈H₉ is 10.5 Hz, indicating that the conformational relationship between the two halves of the cinchonidine moiety has altered substantially. This demonstrates that the preferential formation of cyclic trimer cannot be due to preorganization of the monomer unit. Conceptually, this is similar to the idea that certain amino acid residues in a peptide are helix-forming or zipper-inducing; these properties are not necessarily reflected in the conformational preferences of free amino acids in solution.⁸}

The schematic representation of Figure 1a immediately leads to corresponding cartoons for other oligomers and shapes such as homo- and heterodimers (Figure 1b and c). For experimental realization of these schemes, we turned to the xanthene derivatives **3–5**;⁹ these appeared to possess the necessary predisposition as their ester and hydroxyl groups are arranged in a parallel fashion on a rigid framework. Subjecting the hydroxy ester **5** to the standard conditions of Scheme 1 indeed led rapidly and quantitatively to the homodimer **6**, while an equimolar mixture of diester **3** and diol **4** quantitatively gave the heterodimer **7**. Both of these new macrocycles are non-planar, domed molecules with large barriers to inversion. The symmetry and rigidity of **6** and **7** are apparent from model building, computer modeling, and the appearance of their ¹H NMR spectra.¹⁰

Given the efficiency of these self-assembly processes, we naturally asked whether they would still operate in complex

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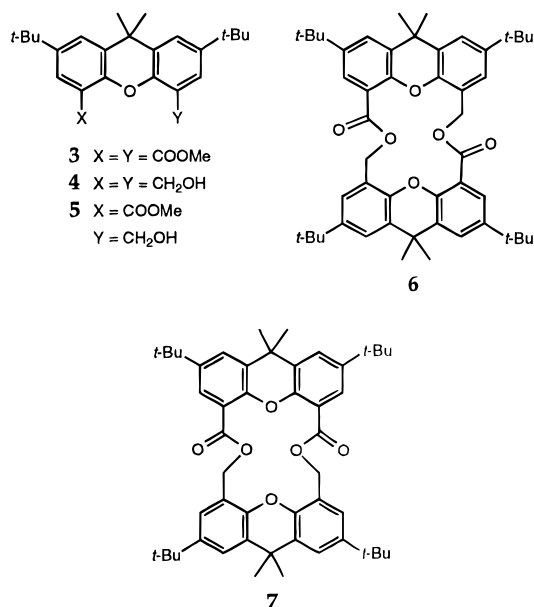
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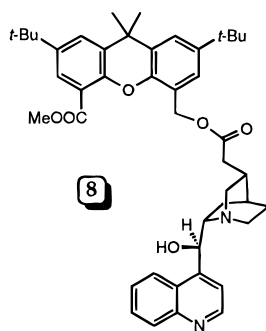
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(10) The symmetry of homodimer **6** leads to diastereotopic methylene signals (10.7 Hz doublets at 5.75 and 5.62 ppm) and two methyl singlets (1.66 and 1.56 ppm), while that of heterodimer **7** gives diastereotopic methylene signals (10.7 Hz doublets at 6.14 and 5.27 ppm) and four methyl singlets (1.74, 1.59, 1.58, and 1.46 ppm).



mixtures. The first bond formation reaction in a mixture of **1** and **5**, for example, is likely to be random, leading to 50% of linear homodimers and 50% of cinchonidine-xanthene conjugates (e.g., **8**), but if all of the bond-formation processes are indeed reversible, then any product lacking unusual stability should be proof-read and consumed. When an equimolar



mixture of hydroxy esters **1** and **5** (2.5 mM each) was subjected to the standard reaction conditions of Scheme 1, the outcome was indeed as predicted: xanthene dimer **6** and cinchonidine trimer **2** were the overwhelming products as detected by TLC, ¹H NMR spectroscopy, and electrospray mass spectrometry. Similarly, the three-component mixture **1**, **3**, and **4** gave almost exclusively trimer **2** and the heterodimer **7**.¹¹

It could perhaps be argued that these experiments would be the result of kinetic control if, for example, the xanthenes **3–5** were more reactive than the alkaloid **1**: once all xanthenes have reacted and been consumed, the cinchonidine molecules that remained could only react with each other. However, when dimer **6** was subjected to the thermodynamic transesterification conditions in the presence of 2 equiv of cinchonidine itself (which lacks the ester group present in **1**), ring-opened

(11) Traces of the mixed cyclic conjugate of **1**, **3**, and **4** ($m/z = 1064$) were detected by electrospray mass spectrometry. However, the presence of basic cinchonidine nitrogens greatly increases the detectability of cinchonidine conjugates relative to **7**, and the mixed conjugate was not detectable by NMR.

conjugates were rapidly formed. There is therefore no apparent kinetic barrier to equilibration. To provide absolute proof of this assertion, the linear conjugate **8** was prepared by Yamaguchi coupling¹² of the appropriate monomer units and was subjected to the thermodynamic transesterification conditions. The only significant products were xanthene dimer **6** and cinchonidine trimer **2**.

These results have several implications. First, this is to the best of our knowledge the first example of intermolecular self-sorting at the covalent level;¹³ a close noncovalent analogy is the self-sorting of metal-coordinated double and triple helices.¹⁴ There is no reason to believe that transesterification is the only suitable reaction for reversible covalent bond-forming and -breaking. For example, transacetalization and olefin metathesis as well as imine formation could well be suitable.

Second, it seems likely that other molecular architectures¹⁵ are similarly accessible, even in a mixture, by this type of reversible chemistry. Squares are an obvious first target: at present these shapes tend to be available either using irreversible covalent chemistry¹⁶ or using less robust coordination chemistry.¹⁷ Third, the intriguing question arises whether naturally-occurring macrolides such as nonactin are also in thermodynamic wells. With so many possible diastereomers, is the only one observed in nature the result of natural selection of the most stable? Finally, one can see that the consequence of relaxing the degree of predisposition, for example by grafting a flexible chain onto a rigid component, is to make accessible several products of comparable energy.³ This system should be amenable to templating under thermodynamic conditions.

In conclusion, we have introduced the notion of predisposition¹⁹ as distinct from preorganization and demonstrated that efficient covalent synthesis and self-sorting can be achieved in a mixture when suitably predisposed building blocks are employed; the result is a "clean" mixture.¹⁸ This idea also has considerable potential for application to the synthesis of a range of robust molecules with interesting architectures.

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(19) **Note Added in Proof.** Since submission of this paper, we have become aware that Constable was used "predisposition" with essentially the same meaning in the context of metal-ligand recognition [Constable, E. C. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., Macnicol, D. D., Vögtle, F., Eds.; Elsevier: New York, 1996; Vol 9, p 218.