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Cyclophanes and Ladderanes: Molecular Targets for Supramolecular Chemists

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We show that principles of supramolecular chemistry applied in the solid state provide a means to conduct target-oriented molecular syntheses. The syntheses are achieved using molecules that function as linear templates. The templates control molecular organization in the solid state by juxtaposing appropriately functionalized olefins for [2 + 2] photodimerization. We reveal that the linear templates can be used to construct a [2.2]cyclophane and [*n*]-ladderanes (where $n = 3, 5$) as targets.

Keywords: Target-oriented synthesis; Supramolecular chemistry; Linear template; Solid-state reactions; Cyclophane; Ladderane

INTRODUCTION

The main goal of the synthetic organic chemist is to control the formation of covalent bonds [1]. A major impetus for this goal is the ability to construct molecular targets (i.e. molecules designed for a purpose) [2]. The ability of organic chemists to construct targets was significantly advanced by the concept of retrosynthetic analysis by Corey [3]. The concept enables organic chemists to organize chemical transformations into a synthetic route, or blueprint, that dictates the construction of a molecule by way of molecular synthons. Such a route is optimized if the blueprint minimizes the number of reaction steps and maximizes the yield of the target [3,4]. The concept of retrosynthetic analysis has enabled organic chemists to access molecules of considerable complexity and industrial importance [5].

On the other hand, the supramolecular chemist focuses on the study and control of molecular organization, which is governed by the noncovalent bond (e.g. hydrogen bond) [6,7]. Interests in utilizing single and multiple noncovalent bonds to dictate molecular organization have led to the identification of reliable structure-forming units known as supramolecular synthons [8]. The final product of such a noncovalent, or supramolecular, synthesis is an assembly of molecules, which typically forms in a single step, that is assumed to correspond to the global thermodynamic minimum and is intended to serve a specific application [9]. The range of applications is wide, and can include the formation of covalent bonds [10–13]. An inspiration for the design of such assemblies of molecules, or molecular assemblies [10–13], has originated from the highly complex structures and functions of molecules and assemblies encountered in Nature. The tools of Nature used to direct the formation of covalent bonds have been templates in the form of enzymes and DNA [14]. Such templates typically operate by organizing substrates, within a ternary complex, into a position suitable for reaction (Scheme 1) [15]. The ability of Nature to use molecules to direct the formation of covalent bonds has recently led us to ask whether it is possible for supramolecular chemists to use noncovalent bonds to direct the formation of covalent bonds so as to construct molecular targets.

CONTROLLING REACTIVITY VIA LINEAR TEMPLATES

Synthetic molecules that direct the formation of covalent bonds similar to templates of Nature are

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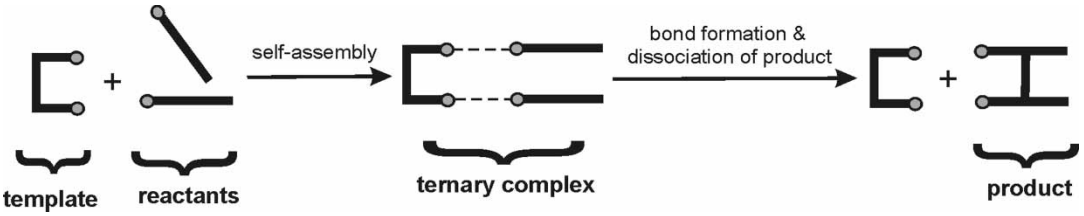


SCHEME 1

relatively rare. The most notable and recent examples include the pioneering work of Kelly *et al.*, who devised a bifunctional reaction template, or a linear template, that directs an S_N2 reaction [16], and later Bassani and coworkers, who used a similar principle to direct a [2 + 2] photodimerization (Fig. 1) [18]. The success of each method relied on the ability of the template to orient, via hydrogen bonds, two reactants linearly within a ternary complex for reaction. The task was made difficult because of problems of entropy, specifically dissociation equilibria of the complex, product inhibition, and also solvent effects. Each of these effects, which are familiar to the supramolecular chemist, interfered with the ability of the template to assemble the reactants so as to achieve the necessary hydrogen-bonded assembly for reaction [19]. Indeed, these observations suggest that, in order to design a linear template that efficiently directs the formation of covalent bonds, issues related to the dynamic nature of molecular complexes associated with the liquid phase should be addressed [20].

TEMPLATE-CONTROLLED SOLID-STATE REACTIVITY

We have recently investigated whether linear templates can operate in the organized environment of the solid state. We anticipated that problems of entropy and solvent could be largely circumvented by allowing a linear template to operate in an environment unable to exhibit the degree of dynamic molecular motion encountered in solution. Indeed, the solid state is typically characterized by both a high degree of molecular order and relatively small molecular movements [21,22]. These features suggested to us that the solid state would be sufficiently rigid to support the formation of a molecular assembly, yet sufficiently flexible to allow

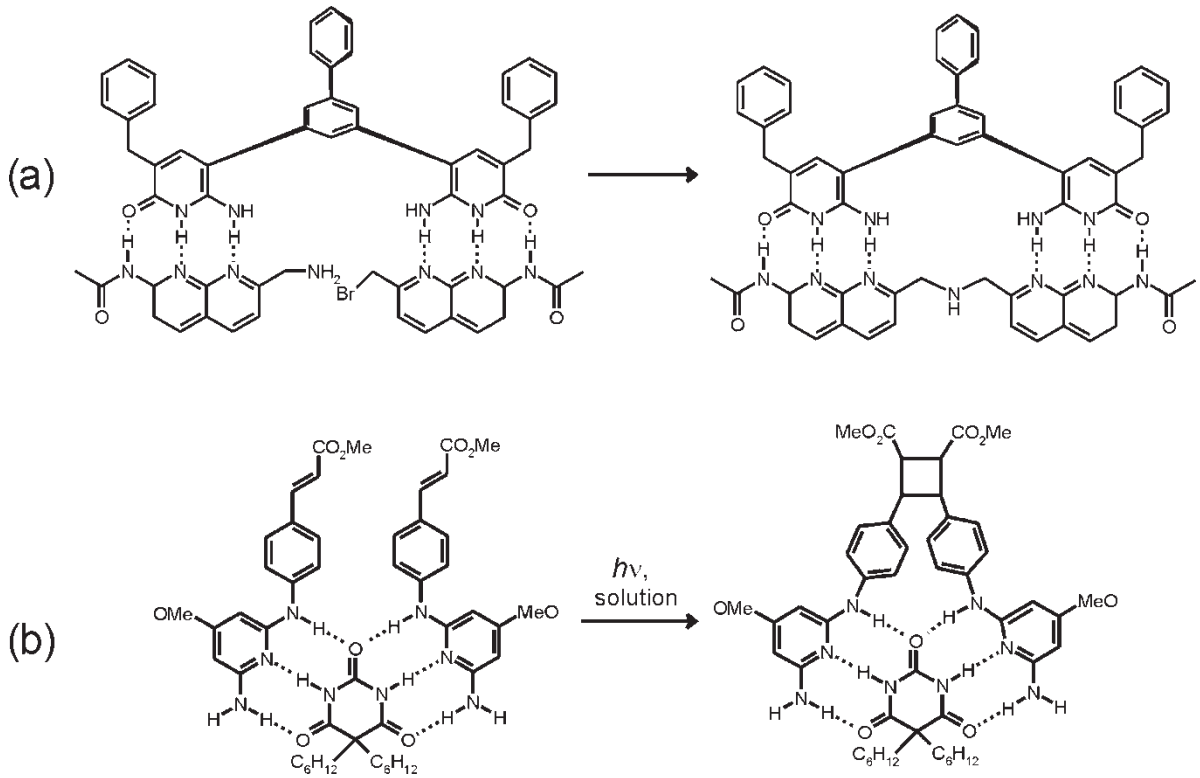


FIGURE 1 Template systems of (a) Kelly *et al.* [16], involving an S_N2 reaction, and (b) Bassani and coworkers [17,18], involving a [2 + 2] photodimerization.

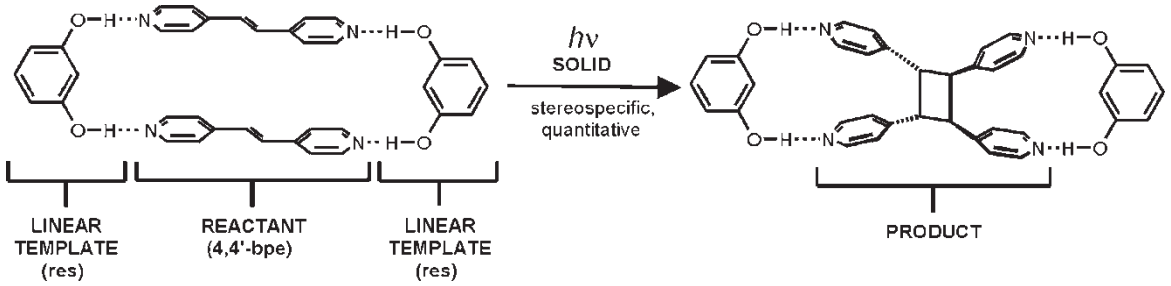
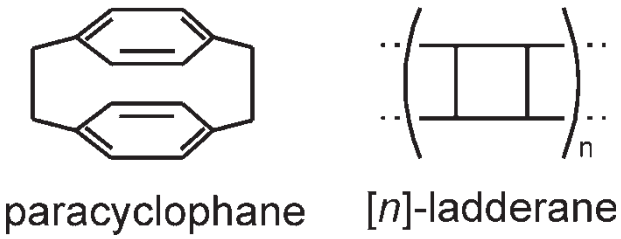


FIGURE 2 Template-controlled solid-state [2 + 2] photodimerization of 4,4′-bpe.

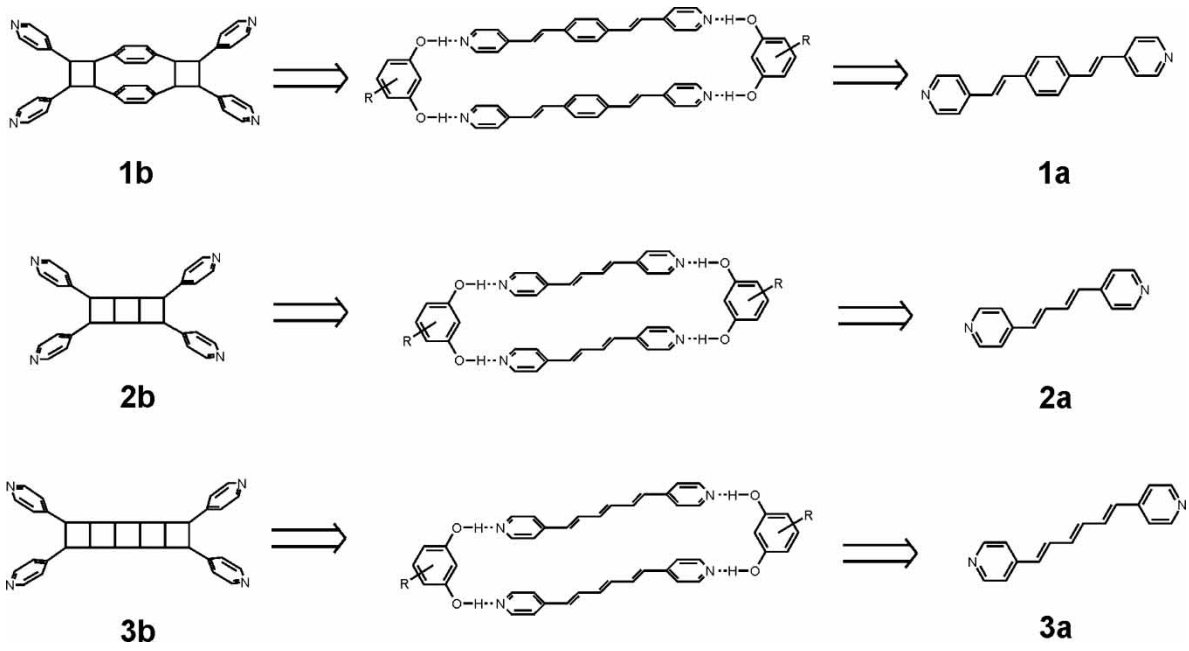
atomic movements necessary to form covalent bonds [21–23].

By following such reasoning, we have shown that linear templates can be used in the solid state to direct the [2 + 2] photodimerization [24,25]. Specifically, simple molecules based on resorcinol (res) have been used to position carbon–carbon double (C═C) bonds linearly in geometries suitable for the photoreaction [26–28]. This is illustrated by the co-crystallization of res with *trans*-1,2-bis(4-pyridyl)-ethylene (4,4′-bpe), which produced a crystalline solid, of composition 2(4,4′-bpe)·2(res), constructed of discrete four-component molecular assemblies held together by four O—H···N hydrogen bonds (Fig. 2). The diol organized the C═C bonds of 4,4′-bpe in parallel and at a distance of 3.65 Å, a geometry that satisfies the requirements of Schmidt for photoreaction [26]. UV irradiation of the solid produced a product, *rctt*-tetrakis(4-pyridyl)cyclobutane (4,4′-tpcb), with a stereochemistry that corresponds to the stereochemistry of the reactants within the hydrogen-bonded assembly. The photoproduct was also shown to form in 100% yield and in gram quantities [27,28].

By exploiting the inherent modularity of the template method, we have also shown that the approach can be used to organize unsymmetrical reactants to achieve regiospecific control of reactivity [29]. Specifically, co-crystallization of a res with 2,4-bpe produced an unsymmetrical hydrogen-bonded assembly with two molecules of 2,4-bpe oriented in



SCHEME 2



SCHEME 3

a head-to-head geometry. UV-irradiation of the solid produced the corresponding head-to-head photoproduct 2,4-tpcb in 100% yield [30]. Moreover, the fact that the templates occupied the periphery of each solid-state assembly involving 4,4′-bpe and 2,4-bpe suggested to us that the templates could adapt to additional structural changes to the reactants (e.g. size), which may provide synthetic freedoms necessary to construct a target molecule [31].

MOLECULAR TARGETS CONSTRUCTED IN THE SOLID STATE USING LINEAR TEMPLATES

To construct a molecular target using a linear template in the solid state, we focused on molecules with structural elements able to code for the [2 + 2] photodimerization. Once achieved, we would then identify an olefin that may be assembled by a linear template and react within a hydrogen-bonded molecular assembly to form the target molecule. [2.2]Cyclophanes [32] and ladderanes were identified as suitable targets (Scheme 2) [33]. Members of each family of these molecules were recognized as possessing C—C linkages able to code for the cyclobutane rings generated by the template-controlled solid-state approach.

Precursors to a [2.2]paracyclophane and ladderanes were selected from retrosynthetic analyses based on cycloreversions of the corresponding cyclobutane products [34]. Specifically, diolefin **1a** was selected as the precursor to a solid-state assembly that reacts to form the [2.2]-paracyclophane **1b**, while the diene **2a** and triene **3a** were selected as precursors of assemblies that react to form the [3]- and [5]-ladderanes **2b** and **3b**, respectively (Scheme 3). Notably, each target molecule would be considerably longer than 4,4′-tpcb

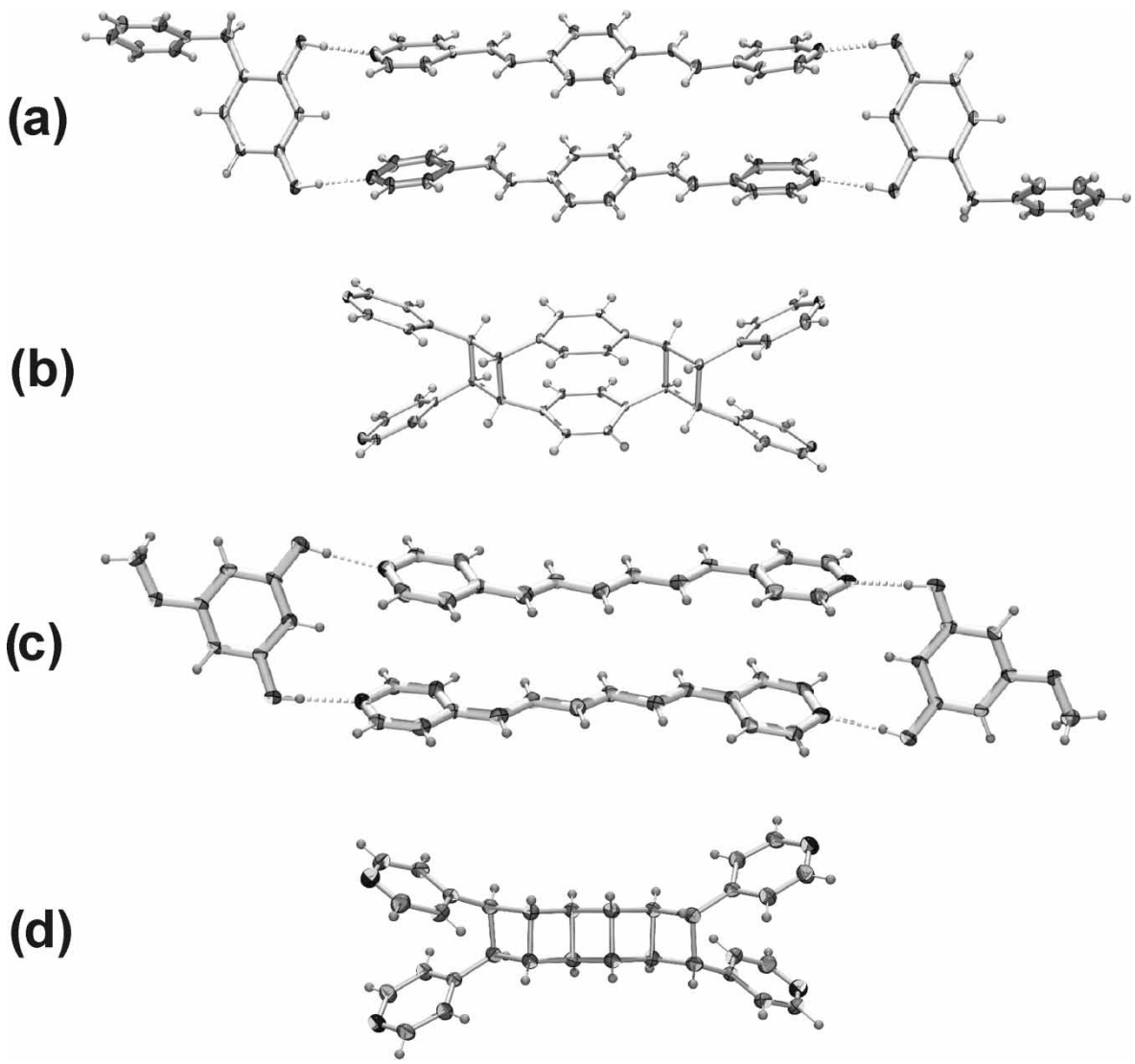


FIGURE 3 ORTEP representations of: (a) 2(4-bn-res)·2(**1a**), (b) the [2.2]paracyclophane target **1b**, (c) (5-OMe-res)·2(**3a**) and (d) the [5]-ladderane target **3b**.

and 2,4′-tpcb, which would allow us to begin to test the tolerance of the assembly process to lengthening of the reactants and products.

That a res organizes **1a** for [2 + 2] photodimerization to give **1b** was realized by a single-crystal X-ray structure analysis of a co-crystal involving 4-benzylresorcinol (4-bn-res) as the template in 2(4-bn-res)·2(**1a**) (Fig. 3a). In this assembly, both C═C bonds of the diolefin were organized parallel and separated by 3.77 and 3.91 Å. Moreover, UV-irradiation of the solid produced the targeted product **1b**, regiospecifically in gram quantities and 100% yield [19]. The structure of the target was identified via single-crystal X-ray structure analysis and ^{1}H NMR spectroscopy (Fig. 3b). Similar to 2(4-bn-res)·2(**1a**), single-crystal X-ray structure analyses of two solids involving 5-methoxyresorcinol (5-OMe-res) as the template in 2(5-OMe-res)·2(**2a**) and 2(5-OMe-res)·2(**3a**) revealed the ability of the res to organize the two polyenes for reaction (Fig. 3c). The C═C bonds of each solid were organized parallel, with separations ranging from 3.78 and 3.82 Å [2(5-OMe-res)·2(**2a**)] and 3.69 and 3.97 Å [2(5-OMe-res)·2(**3a**)], respectively. UV-irradiation of both solids produced the targeted [3]- and [5]-ladderanes in gram quantities and 100% yield. The structures of both targets were also confirmed via single-crystal X-ray diffraction and ^{1}H NMR spectroscopy (Fig. 3d). Whereas the synthesis of **2b** represents the first example of a quantitative construction of a [3]-ladderane framework in the solid state, the synthesis of **3b** represents the sole quantitative synthesis of a [5]-ladderane [35,36].

CONCLUSIONS AND OUTLOOK

Linear templates provide a means to direct chemical reactivity in the solid state to form molecular targets. Targets of the approach have involved a [2.2]paracyclophane and ladderanes. That a cyclophane and ladderanes have been targets of linear templates has been achieved via retrosynthetic analyses that involve structural elements derived from hydrogen-bonded molecular assemblies. Thus, the idea of a molecular synthon has been applied to a supramolecular synthesis [1,6]. Our future efforts will focus on further generalizing the template method to control molecular organization so as to construct molecular targets of increasing structural complexity.

Acknowledgements

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