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A Review on the Crystal Engineering Based Templated Synthesis of Cyclobutane Rings in Solid Phase

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INTRODUCTION

Alicyclic compounds are important scaffolds found in synthetic organic chemistry, natural products chemistry, medicinal chemistry, pharmaceutical chemistry, biological chemistry, biotechnology, supramolecular chemistry and material chemistry etc.[1]Cyclobutane ring is one of the crucial scaffold among various kinds of smaller ringcompounds. Thus, gaining importance among the synthetic chemists which is partly because of its synthetic challenges and potential applications.

Synthesis of cyclobutane in good yield is ever challenging and a numbers of methodologies have been devised namely cope rearrangement, ring closing metathesis, [2+2]photodimerisation etc. to name a few and majority of the reactions were carried out in the solution phase.The solution phase synthetic methods of cyclobutane involving [2+2] photocycloadditionreactionare not always a good process context of green chemistry and moreover separation of the products are found to be tedious process. Finding of suitable solvent system and the photon source for the success of [2+2] photocycloaddition are not always straight forward. The disadvantage of poor regio and stereo-chemical control associated with the liquid phase phorodimerisation could be improved by performing the reaction in the confined media.[2]With the development of solid state synthetic techniques and understanding of the solid state reactivity of the molecules, synthetic solid state photochemistry are growing exponentially in recent past. The present review highlights the recent development of the solid state [2+2] photodimerisation reactions utilising the concepts of supramolecular chemistry and crystal engineering.

Topochemical Principle

Studies on the [2+2] photodimerisation reactions revealed that all multiple bonds are not equally reactive in the crystalline solid phase and the analysis of the crystal structure of the compounds indicated that a pair of multiple bonds fringed parallelly at a distance of ~ 4.00 Å could only participate in the dimerisation reaction. This is popularly referred to as topochemical principle[3] and Schmidt et.al.[4] have proved it in a systematic photodimerisation studies on three polymorphic cinnamic acid crystals (α, β and γ forms). (Figure-1).

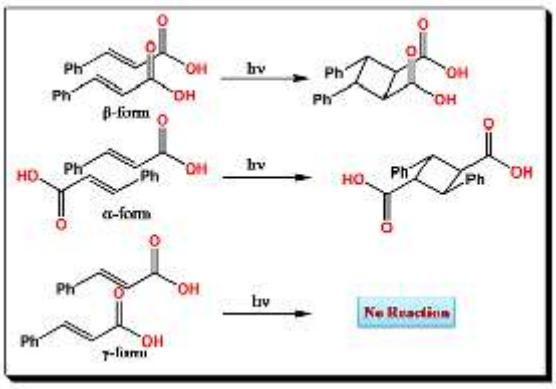

Figure1: Topochemical studies on cinnamic acids.

The reports on synthesis of various complicated macrocyclesindicated that template effect[5] was of paramount important in bringing the far reached reacting centres within approachable proximity. Thus understandably, olifinic bonds could be forced to be within the topochemical distance in the solid state by templating foreign molecules and could be identified by utilising the concept of supramolecularsynthons and crystal engineering. According to Prof. Desiraju "supramolecularsynthons are structural units within supermolecules (crystal) which can be formed and/or assembled by knownor conceivable synthetic operations involving intermolecular interactions"[6] and on the other hand crystal

engineering is defined by the same author as'the understanding of intermolecular interactions in the context of crystals packing and in the utilisation of such understanding tothe design new solids with desired physical and chemical properties".The concept has already been demonstrated in pharmaceutical co-crystal NLO materials,photoreactions, organo gels etc. Prof.Zaworotko defined the term co-crystal as 'the crystalline complex of two or more neutral molecular constituents bound together in the crystal lattice through non-covalent interactions, often including hydrogen bonding'. Various supramolecular homo- and hetero-synthons have been utilized in fetching two molecules containing olifinic bond(s) closely by suitable co-crystal formers in the solid state. Templated co-crystals on photoirradiation undergo facile [2+2] cycloaddition reaction and removal of template after the photo reaction resulted into the desired cyclobutane derivatives.

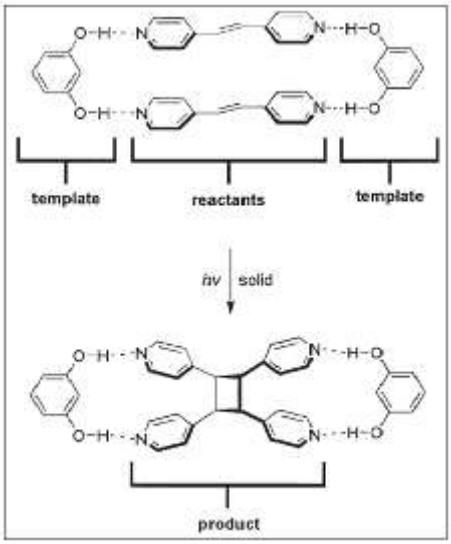

Figure 2:Resorcinol templated photodimerisation reaction

Macgillivaryet.al. utilised linear templatesto bring the olefinic double bond within the topochemical regime for a successful [2+2] photodimerisation in the solid state. For this purpose, he anticipated that rigid molecules with two hydrogen bond donor groups separated at a distance compairable to that of the topochemicalguidelines could serve a template and had designed a 2:1 binary co-crystal comprised of anthraquinone (**1**) and a linear template, resorcinol. The crystal structure revealed that double bond in anthraquinone moiety forced to be within the topochemical distance by the template which undergown [2+2] photodimerisation reaction by using UV light.

The strong supramolecularhetero synthons had been exploited in the synthesis of cocrystals derived from trans-1,2-bis(4-pyridyl)ethylene (4,4'-bpe) and resorcinol where a discrete four-component 1:1 complex (4,4'-bpe:resorcinol) held together in the crystal lattice by O-H···N hydrogen bonds. The template, resorcinol positioned two 4,4'-bpe moiety suitable for [2+2] photocyclo addition reaction (Fig. 2) of topic in current chemistry). In an another report he had also utilised unsaturated dicarboxylic acids to template **bpe** for the same purpose in the same report. Single crystal to single crystal (*sc-sc*) transformation is a remarkable technique in avoiding synthetic steps of a chemical transformation. MacGillivray et. al had demonstrated that bifunctional hydrogen-bond donor 1,8-naphthalenedicarboxylic acid (1,8-nap) to force unsaturated dicarboxylic acids namely fumaric acid to span within the suitable distance for [2 + 2] photodimerisation (figure 3).

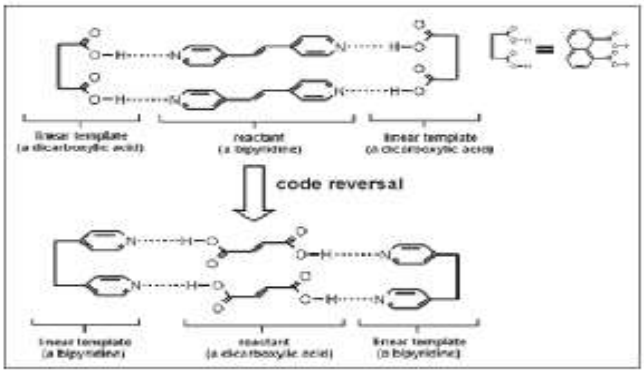

Figure 3: 1,8-naphthalenedicarboxylic templated photodimerisation reaction of fumaric acid

The pyridine-carboxylic acid hetero synthons were used to design of several functional co-crystals or salts and host–guest complexes. It was exploited to template the [2 + 2] reaction of two types of olefins (1) bis-pyridyl ethylene and (2) fumaric acid or muconic acid. In the first case, the template contains two –COOH functional groups, and in the second case it contains two 4-pyridyl groups. These groups are placed conveniently such that the two olefins come within the reactive distance with the correct reactive alignment(Figure 4).

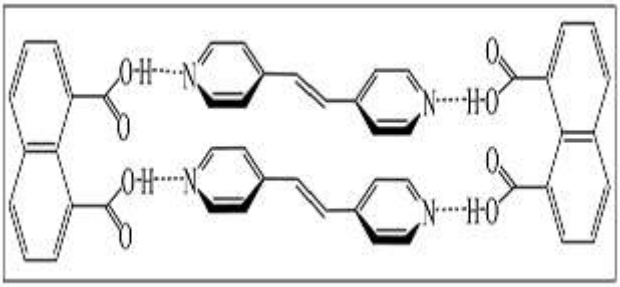

Figure 4: 1,8-naphthalenedicarboxylic templated photodimerisation reaction of *bis*-pyridyl ethylene

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