Supramolecular assistance of [2+2] photocycloaddition for cross-photodimerization

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Received 25 January 2017

[2+2] Photocycloaddition (PCA) of alkenes is an important reaction as it is used in several areas of fundamental and applied research. Due to its significance, there are numerous articles and reviews in chemical literature that document various aspects of this reaction – such as application in synthesis, photopolymerization, materials research, etc. Despite its importance, the vast majority of the reports are focused on the reaction between identical alkenes (homo-dimerization), while PCA between non-identical alkenes (cross-dimerization) has been grossly under-explored. In this review we have compiled the reports on cross-dimerization reactions affected through supramolecular methods, which can be broadly classified based on two broad approaches: (a) crystal-engineering or (b) templation in solution or slurry. Both methods are based on the utilization of favorable intermolecular interaction between non-identical alkenes, and the use of a templating agent that promotes hetero-alkene arrangement in the ground state, which, upon photoexcitation yield the cross-dimer selectively.

Keywords: [2+2] Photocycloaddition, photodimerization, supramolecular, alkenes, crystal-engineering, templation

Photocycloaddition (PCA) of alkenes (2+2) is one of the oldest, well-studied, and practically most utilized organic photochemical reactions. The applied-chemistry significance of this reaction ranges from its use as a key intermediate step in synthetic organic chemistry1-3, to photopolymerization4,5, data-storage technology6,7, and materials research8-10. The biological significance of this reaction is underscored by the role of this reaction in photo-induced DNA damage and cancer11,12, and prevalence of cyclobutane-containing natural compounds resembling structures of photodimeric compounds13,14. The importance of this reaction to the scientific community is evident from the sheer number of publications involving this reaction. There are also numerous reviews that address the general aspect of this reaction, as well as those that specifically focus on its specific aspects, including its application to organic synthesis1,3,15,16, the reaction in solid-state and crystal engineering17,18, photopolymerization19,20, and mechanistic photochemistry21,22. The vast majority of the photocycloaddition literature has reported the reaction between two identical alkenes, which can be classified as homo-dimerization (Scheme I, left). There are very few instances, and no dedicated review, that has attempted to focus on the reactions of non-identical alkenes (cross-dimerization, Scheme I, right). This mini review attempts to compile intermolecular photocycloaddition reactions between non-identical alkenes assisted through supramolecular methods that would not occur otherwise. Selective cross-PCA between non-identical alkenes is essential for a mechanistic understanding of the reaction and the logical next step in expanding its applied-chemistry significance. This review is also intended to highlight the fact that this reaction is under-explored and hence there is scope for the discovery of new knowledge.

[2+2] Photocycloaddition reaction is symmetry-allowed excited state reaction that results in cyclobutane product based on the Woodward-Hoffman rules. Direct excitation of alkenes to the first excited state (of $\pi-\pi^*$ character) is generally understood to lead to cycloaddition reaction from the excited singlet state (S1); triplet-sensitized alkenes have also been observed to yield photodimerization. In both cases, the dimeric product could provide dimeric products through direct or biradical intermediates2. However, due to its bimolecular nature, PCA is precluded by the unimolecular photoisomerization reaction when ever possible, such as in the case of linear alkenes or larger cycloalkenes (C8 or higher). Moreover, depending on the symmetry of the reacting alkenes, as many as
twelve stereo- and regioisomeric dimers can result in homo-dimerization reaction; the number is even higher in the case of cross-dimerization. Thus, the efficient and selective transformation of alkene to a photodimeric product does not typically occur spontaneously and achieving selective outcome is a difficult task.

Improving quantum efficiency and selectivity of PCA has been a major pursuit for supramolecular photochemists, and some highly interesting and creative methods have been devised that can affect near quantitative conversions in solid-state and solutions. These methods are based on the pre-orientation strategy wherein the reacting alkenes are supramolecularly juxtaposed before photoexcitation. Stereoselectivity in supramolecular-assisted PCA is the direct result of relative pre-orientation of the reactants. Supramolecular control to affect selective cross-photodimerization would require selective juxtaposition of the non-identical alkene. The limited number of cross-photodimerization reports in chemical literature is primarily due to challenges associated with meeting this requirement. Works that have reported selective cross-PCA of alkenes fall under one of the two broad classes of supramolecular approach: (a) crystal engineering, and (b) templation in solution. Both the approaches are based on taking advantage of complementarity in electronic and spatial characteristics of the photosubstrates in the ground state. Herein, we document the instances of supramolecular-assisted selective cross-[2+2]photocycloaddition reactions reported in the literature.

**Cross-dimerization in the crystalline or organized solid-state**

Crystal engineering refers to the fabrication of organized solid-state structures with desired physicochemical properties. The idea of controlling molecular alignment in molecular crystals to control product selectivity in photochemical reaction – topochemistry – was originally established by G. M. J Schmidt\(^2^3\). The reduced translational, rotational and vibrational freedom of the pre-aligned molecules in the crystalline state resulted in remarkable reaction selectivity and, in some cases, kinetic enhancements. Through his pioneering work on photodimerization of cinnamic acids in the crystalline state Schmidt established the famous topochemical postulate, which requires that reacting centers (in this case alkene bonds) should be no farther than 4.2 Å for chemical transformation to occur. Thus, the crystal engineering approach for cross-dimerization should meet the topochemical postulate; also, the cross-alkene proximation should also be realized. This could be achieved either through the (a) choice of reacting alkenes such that non-covalent interaction between non-identical alkenes is more favorable (exergonic) than identical alkene interactions, or (b) through the use of the auxiliary components, such as molecular templates or macrocyclic hosts.

One of the earlier examples that demonstrated cross-dimerization in the crystalline state was reported by Maekawa et al.\(^2^4\). Mixed crystals formed in ethanol solution between ethyl and propyl esters of α-cyano (4-ethenyl) cinnamates (1a and 1b), which yielded the [2,2] paracyclophane cross-dimer (Scheme II) in...
quantitative yield (3). The photoreaction proceeded in two steps through intermediate product 2 wherein PCA at each alkene group occurred sequentially to afford the cross-dimer. The reaction was also found to be highly photoreactive as near-quantitative conversion of single-crystals were observed within few-hours of irradiation. Co-crystals of the compounds in ratios of (1a to 1b) 70:30 to 5:95 afforded the cross-dimer in noticeable quantities.

The authors noticed that despite the structural similarity between the two compounds, the structure of the mixed crystal was markedly different from that of the individual compounds. There was no discussion pertinent to the rational-design aspect of the molecular arrangement that leads to the formation of the cross-dimer.

A more rational design approach to forming cross-dimer in the crystals was reported by Desiraju’s group\(^{25}\), in their photodimerization reaction (Scheme III) between 3,5-dinitrocinnamic acid (4) and 3,5-dimethoxycinnamic acid (5). Irradiation of the crystals resulting from the solution of the donor (5) and acceptor (4) in ethanol yielded a dimeric product in high yields. The arrangement of the reactants in crystalline state was deduced from the structure of the product, which was identified to be the cross-dimer 6.

The authors rationalize that \(\pi-\pi\) donor-acceptor interaction between the electron-rich and deficient rings of D and A is responsible for the co-facial pro-reactive orientation. The existence of operative charge-transfer interaction in the designed crystal was established retroanalytically based on the electronic spectra of the cross-dimer product, which showed red-shifted absorptions, compared to its monomer analogs: dinitrobenzene and dimethoxybenzene, due to the presence of internal CT components.

The instance of \(\pi-\pi\) co-facial stacking in the crystalline state of non-identical alkenes, resulting in cross-dimerization, was demonstrated by Coates et al. (Scheme IV)\(^{26}\). This work established the perfluoro-phenyl motif, which was being explored then, as a reliable supramolecular synthon for crystal engineering (Scheme IV). Crystallization of perfluorostilbene (7) and stilbene (8) from ethanol yielded co-crystals with the non-identical alkenes stacked co-facially, which resulted in more than 98% conversion to yield cross-dimer (9) upon irradiation. Similarly, co-crystals of perfluoro-cinnamic acid (10) and cinnamic acid (11) contained the non-identical alkenes in co-facial arrangement resulting in more than 87% photochemical conversion to yield 12. Due to the co-facial stacking, syn isomer of the cross-dimer was

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**Scheme III** — CT interaction between(3',5'-dinitrophenyl)-4-(2',5'-dimethoxyphenyl) cyclobutane-1,2-dicarboxylic acid leading to hetero-alkene arrangement for cross-dimerization in solid-state

**Scheme IV** — Phenyl and per-fluorophenyl moieties as synthons in crystal engineering
obtained in both cases. The stacking between perfluorophenyl-phenyl stacking interaction is considered to be due to VanderWaals and electrostatic forces resulting from reverse charge distributions, and not due to charge-transfer-type interaction. The work also featured the PCA between non-identical dienes 13 and 14 based on the same concept to yield oligomeric cross-dimeric product 15.

A more recent example of cross-dimerization, based on the relatively new approach of using molecular templates to crystal engineering, was reported by McGillivray’s group (Scheme V)\(^{27}\). They reported the efficient cross-dimerization between 4-methylstilbene (16) and 4-chlorostilbene (17). Stacked hetero-alkene pre-organization in the solid-state was achieved by the use of co-crystallized resorcinol templates with the reactants, from a solution of acetonitrile which resulted in a hydrogen-bonded 1:1:1 ternary complex of the components (16•17). The template’s hydrogen-bonding interaction with stilbazole nitrogens directed the head-to-head (H-H) arrangement of alkenes. Because resorcinol is homoditopic, there is a lack of supramolecular differentiation between homo- and hetero-stacking arrangements; consequently, the alkene arrangement in the crystals involved a (statistical) mixture of hetero- and homo-stacking arrangements. Therefore, irradiation of the crystals yielded a mixture of cross-dimer (57%, 18) in slight excess of the two homo-dimers. Stereochemistry of the dimers in both cases was \textit{syn} H-H. The authors also note that in the absence of the template, co-crystallization of the reactants alone did not yield the hetero-alkene arrangement.

Another example in the line of mixed-crystals yielding selective cross-dimerization (Scheme VI) is the reaction between 4-methoxy-6-methyl-2-pyrone (19) and maleimide (20) (Ref 28). The formation of 57% of the \textit{endo} cross-dimer (21) was rationalized by the formation of a ground-state complex of the charge-transfer type interaction. Analysis of the crystal structure also revealed the importance of hydrogen bonding contacts between the maleimide hydrogen and the carboxy units in the pyrone. Solution phase irradiation, however, yielded a mixture of products (21-a, 22, 23) with a small amount of the \textit{endo} product 21.

A similar example of charge-transfer complex in the ground state leading to cross-dimerization is that of the reaction between acenaphthylene (24), a well-studied photosubstrate, with tetra-cyano ethylene (25, Scheme VII)\(^{29}\). Crystals obtained from an equimolar solution of the compounds in acetonitrile were irradiated with light in the visible region (500 nm or higher), which corresponds to the excitation of the CT band, yielded cross-dimer 26 in yields upward of 80%, indicating an efficient photoreaction. Irradiation of the crystals with lower energy light source (400 nm or less) yielded the acenaphthylene homo dimer predominantly with minor amounts of the cross dimer (~5%).
Interestingly, no noticeable amount of cross-dimer resulted from solution irradiation. The PCA between tryptamine (27) and trans-3-nitrocinnamic acid (28) was demonstrated by Ito et al. (Scheme VIII)30.

In their first ever report on the PCA of an N-unsubstituted indole, they showed that the ion-dipole interaction between the oppositely charged ammonium unit in indole and the carboxylate unit of 3-nitrocinnamate could be used to bring the reacting alkene moieties together for efficient cross-dimerization at 83% yield for 29.

A remarkable case of asymmetric photochemistry through complete stereo-controlled alignment of cross-alkene pairs was reported by Vaida et al. (Scheme IX)31. Mixed-crystals of trans-cinnamamide (30) and trans-cinnamic acid (31) was obtained from ethyl acetate solution. XRD analysis of the crystals showed that the mixed crystals consisted of two

Scheme VII — Reaction betweenacenaphthylene and tetracyanoethylene in solid-state

Scheme VIII — Cross-dimerization between indole and cinnamic acid based on ion-ion interaction

Scheme IX — Absolute asymmetric photochemistry using centrosymmetric single crystals
“enantiomorphous halves”. Irradiation of each enantiomorphous half separately resulted in optically active dimers, corresponding to the precursor alignment. The enantiomeric excesses were 40% in one case and 60% for the other (32-a and -b).

Another case of charge transfer interaction-based cross-dimerization was reported by Suzuki et al. (Scheme X)\(^32\); electron-deficient BTDA (bis[1,2,5]-thiadiazolotetracyanoquinodimethane, 33) co-crystallized readily with \(\alpha\)-divinylbenzene (34). Irradiation of the system at the charge-transfer band yielded the cross-dimer 35 in a single-crystal-to-single-crystal transformation. Due to the inherent asymmetric arrangement of the compounds in the crystal lattice, the enantiomeric excess was observed upon analysis of product mixture. Enantiomeric excesses as high as 71% at 15°C, and 95% at \(-70°C\) were observed.

**Cross-dimerization reactions in solution or slurry**

The supramolecular mediation of cross-dimerization in solution or slurry phase is based on the host-guest or template approach. Host-guest photochemistry is based on encapsulating reacting alkenes within macrocyclic cavitands through hydrophobic interactions. Extending this approach for cross-dimerization should, thus, involve devising means for selective formation of the 1:1:1 complex over the 1:2 complexes. This is achieved by choosing reactants that are spatially and electronically complementary (Scheme XI).

The first example of a highly efficient instance of cross-dimerization between doubly photoactive alkene pair was reported by Fujita’s groups in their newly synthesized palladium nanocage (Scheme XII)\(^33\). The palladium nanocage 36 synthesized by his group is a...
hemicarcerand constructed based on the coordination of tripyridyl-triazine and ethylene diamine (EDA) ligands with Pd$^{2+}$, wherein the aromatic ligands formed the four alternating faces of the octahedron with the metal ion in the apexes and the EDA capping the external coordination site. The resulting structure contained hydrophobic interior, which encapsulated organic guests predominantly through hydrophobic interactions. The tight spaces within the palladium nanocage were proved to be conducive for selective inclusion of a series of hetero-alkene pairs: acenaphthylene (24) and N-phenyl maleimide (39), acenaphthylene and napthoquinones (37), dibenzosuberenon (42) and disubstituted-N-phenyl maleimides (41). This approach was based on the strategy of size-complementarity selective inclusion of alkenes to form the ternary 1:1:1 complex, which yielded the syn-heterodimers exclusively in the majority of the reactions! Some of the selectivity reported in nanocage (38) is perhaps the highest for the reaction reported in the homogeneous medium for cross-dimerization reactions. The stereochemical selectivity for syn is also explained regarding the spatial constraint, as the anti-dimer (and hence the precursor arrangement) is too large to fit within the cage. Despite its remarkable efficiency, there were no further reports involving the nanocage for PCA (homo and cross). This is perhaps due to the spectral interference from aromatic ligands in the nanocage, which acted as internal absorption filter.

The other instance of cross-dimerization within a macrocyclic cavitand around the same time as Fujita’s work was reported by Furutani et al. In their work, they utilized the cyclodextrin (CD) cavity-mediated asymmetric photocycloaddition between cycloalkenones and ethylene$^{34}$. Cyclodextrins are arguably the most utilized macrocyclic cavitand in host-guest chemistry, especially in supramolecular photochemistry. The three commonly used oligomeric members, α- β- γ-CDs (44, 45 and 46, Figure 1), increase progressively in size and cavaitand volume, are soluble in water and encapsulate small organic molecules through hydrophobic interactions. Furutani’s work employed both size complementarity and concentration-effect to promote the formation of 1:1:1 complex with the three CDs. In the case of the smaller β-CD, the photoactive substrates (cycloalkenones, 47 and 48) were too large to form 1:2 ternary complex, thus the hetero-alkene-pair complex was favored, yielding the cross dimers upon irradiation (50, 51, Scheme XIII). Whereas in the case of the larger γ-CD, which is known to encapsulate two larger organic guests, the hetero-alkene pair

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**Figure 1 — Chemical structure and representation of cyclodextrins**

**Scheme XIII — Cycloaddition of enone to ethylene, within cyclodextrins**
complex was favored when a large excess of ethylene was used. As expected, the photoexcitation of the complexes afforded the cross-dimers exclusively. Moreover, the authors also evaluated the asymmetric outcome of these reactions, as the nano space of cyclodextrins are chiral in nature due to the glucopyranose building units that make up the cavitand. The yields in the reactions were modest, ranging between 2% to 22%; asymmetric induction was low as well, though there was a general trend towards higher enantiomeric excess in reactions from the γ-CD complexes than the β-CD complexes; α-CD was too small to form ternary complex, due to which no PCA was noticed.

The latest instance of cavitand-mediated cross-dimerization was reported by our group35. The larger cavity of γ-CD 46 was employed to affect the predominant photocycloaddition between cinnamic acids and coumarins (Scheme XIV). Coumarins and cinnamic acids are both highly photoactive substrates and are especially known for their photocycloaddition reactions. Therefore, directing selective cross-dimerization would require significant control in complex assembly. This was achieved by performing the complexation in the slurry, rather than solution phase, as the solid-state-like characteristics of slurry would result in reduced freedom for molecule and hence greater control in controlling their arrangement.

Irradiation of the complexes equimolar mixtures of coumarin/cinnamic acid/γ-CD yielded the cross-dimer in the majority of the cases explored; the cinnamic acid (52), 6-methyl coumarin (53) pair afforded the highest cross-dimer (54) proportion. The presence of cross-dimer in the product mixture was established through NMR analysis; stereochemistry of the cross-dimer is speculated to be based on computational analysis of the product geometry, which is most likely syn H-H isomer (Figure 2). It was observed that the selectivity in favor of cross-dimer products was proportional to the size complementarity between the guests; alkene-pairs,

Scheme XIV — Cross photodimerization between cinnamic acids and coumarins

Figure 2 — Energy-minimized structures of dimers within γ-CD cavity
where only one of the alkenes contained an alkyl substituent on the aromatic ring, yielded the most cross dimer, whereas combinations with both or neither containing alkyl substitutes yielded less cross dimer. Moreover, there are also indications that electronic interactions might also be in play as all coumarin-cinnamic acid combinations yielded the cross-dimer as the major product. The only instances of highly-selective homodimerization was in alkene pairs with strong pro-homoalkene interactions, such as trifluoromethyl and hydroxyl groups which engage in halo-halo and hydrogen bonding interactions respectively.

An interesting approach to cross-dimerization through the use of bio-inspired scaffold is the work by Doi et al. (Figure 3)\textsuperscript{36}. Their strategy for promoting PCA involved covalently attaching carboxy stilbenes (55-a, b, c, e, f) and stilbazoles (55-c, d) onto the base surrogate D-threoninol (56), which can then be covalently implanted into a DNA strand. Spontaneous assembly of DNA duplex with the non-identical stilbazoles in complementary strands yielded cross-dimers in high yields. The efficiency of this method in pre-aligning the reactants is evidenced by the observation of PCA even in cases of photo-inactive alkenes, such as nitro-stilbene. They noticed that pairs with closer HOMO(donor)-LUMO(acceptor) placements had higher quantum efficiency, indicating the possibility of electronic interaction in the ground-state.

**Conclusion**

As presented through the literature-reported instances of cross-dimerization reaction, selective intermolecular [2+2] photocycloaddition between two non-identical alkenes can be achieved efficiently through the application of supramolecular principles. The extent of molecular control exercised in solid-state is much more conducive for this purpose, due to which majority of the reactions have been reported in the crystalline state. However, the unpredictable nature of crystal growth renders this method less general than its solution-phase counterpart; this is emphasized by the fact that the reactions are substrate-specific, and slight variations in the substrate structure need not necessarily yield the same outcome. While there are only a few instances of solution/slurry phase reaction, the method is more general, reliable, and tolerates structural changes around the core photosubstrate. The limited number of cross-dimerization instances highlight the need for more detailed exploration of this reaction, which also promises opportunities in photochemistry and its application.

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