**Title:** Templating and Catalyzing [2 + 2] Photocycloaddition in Solution Using a Dynamic G-Quadruplex

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# Templating and Catalyzing [2 + 2] Photocycloaddition in Solution Using a Dynamic G-Quadruplex

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***Abstract***. *We describe a templating/covalent capture strategy that enables photochemical formation of 8 cyclobutanes in one noncovalent assembly. This process was characterized by experiment and quantum mechanical/molecular mechanics (ONIOM) calculations. Thus, KI and 16 units of 5′-cinnamate guanosine form a G-quadruplex where C=C π bonds in neighboring $G_4$-quartets are separated by 3.3 Å, enabling [2+2] photocycloaddition in solution. This reaction is efficient (>90% yield), regio- and diastereoselective. Since all components are in dynamic equilibrium this photocycloaddition is catalytic in $K^+$.*

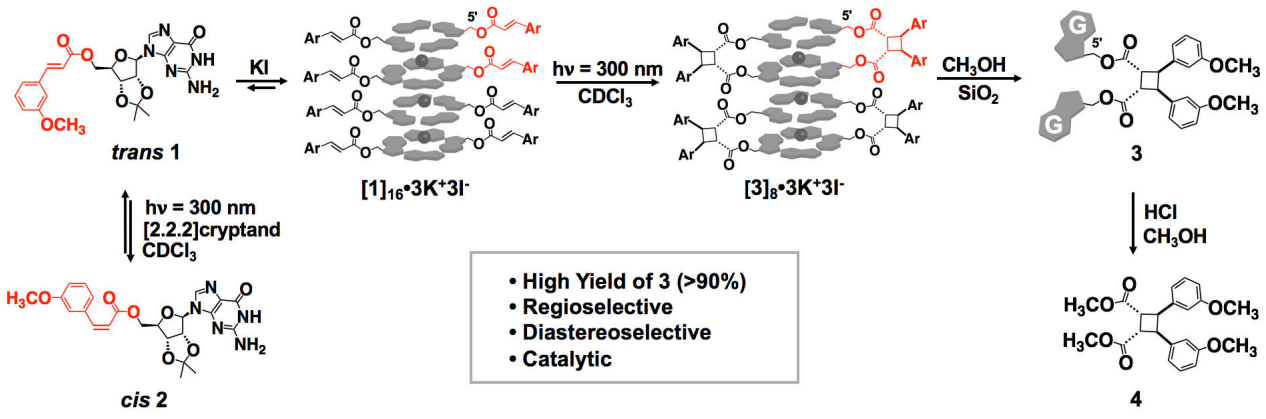
Close location of reactants is crucial for bond formation. Intramolecular reactions are faster than their intermolecular versions.[1] Enzymes hold reactants in proximity long enough for bonds to be made.[2] Supramolecular templating relies on non-covalent interactions to orient reactants for formation of covalent or mechanical bonds.[3-6] This templating/covalent capture process would be even more valuable if products were able to exchange with reactants, so that the process becomes catalytic.[7]

We report that *trans*-5′-(3-methoxycinnamoyl)-2′,3′-isopropylidene guanosine (**1**) and KI self-assemble in solution to give a complex, $[\mathbf{1}]_{16}\bullet 3K^+3I^-$, that forms new C-C σ bonds upon photoirradiation, giving $[\mathbf{3}]_8\bullet 3K^+3I^-$, a species with 8 subunits of cyclobutane **3** (**Scheme 1**). The $K^+$ cation templates formation of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$, whose 5′-alkene sidechains are positioned for [2+2] photocycloaddition. Cyclobutane **3** is made in high yield (>90%) by exposing a dilute solution of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ to light, either from a lamp or the sun. This templating/covalent capture approach enables regio- and stereoselective synthesis of **3**. Importantly, this [2+2] photocycloaddition is catalytic in $K^+$ since reactant **1** and product **3** are in dynamic equilibrium with G-quadruplexes, and QM/MM calculations reveal that incorporation of **1** into the G-quadruplex is favored over incorporation of cyclobutane **3**.

Cyclobutanes, found in natural products and synthetic drugs,[8] can be prepared by [2+2] photocycloaddition of alkenes. Cyclization is best when 2 C=C bonds align in parallel, with reacting atoms held less than 4.2 Å apart.[9] If the alkenes are dispersed in solution, cyclobutane formation is usually disfavored and the major photoreaction is *trans-cis* isomerization about the C=C bond.[10] Often, [2+2] cycloaddition occurs better in the solid-state than in solution, especially if the alkene crystallizes so that topological requirements for dimerization are satisfied.[9,11] But, solid-state reactions suffer if the crystal degrades during irradiation. Synthetic methods that enable high yields of [2+2] cycloaddition in solution are particularly valuable.

Templating strategies enable [2+2] photocycloaddition in solution.[12] One approach is to covalently tether 2 alkenes,[13] so that C=C groups populate conformations that can dimerize. Another approach is to use non-covalent interactions to organize C=C bonds for reaction. Molecular containers can facilitate [2+2] photocycloaddition of alkenes, often with good regio- and stereoselectivity.[14-16] The host sequesters alkenes so that they dimerize upon irradiation. Sometimes, these reactions are catalytic as cyclobutane product exchanges with reactants, enabling turnover.[17] Intermolecular H-bonding of 2 alkenes to a template can also trigger [2+2] cycloaddition of cinnamate esters in solution,[18,19] and some of these H-bonding templates act as catalysts.[19,20] Our goal was to use a G-quadruplex, a robust H-bonded assembly, as a supramolecular template to orient multiple cinnamates for photodimerization in dilute solution.

Guanosine derivatives, in the presence of $K^+$, form the H-bonded $G_4$-quartet,[21] The $G_4$-quartets then stack to give G-quadruplexes made of multiple $G_4$-quartet layers occupied with stabilizing cations. The rigid $([G]_4\bullet K^+)_n$ core can induce the 5′-sidechains to adopt well-defined conformations. We recently described $G_{16}\bullet 3K^+$ hexadecamers made from 5′-benzoyl G analogs that have extensive interlayer H-bonds and π-π interactions on the assembly's exterior.[22] We reasoned that the interlayer separation of ca. ~3.3 Å would be ideal for [2+2] photocycloaddition of 5′-cinnamate esters radiating from the G-quadruplex.[23] We were encouraged by findings that 1) light can control assembly and disassembly of G-quadruplexes,[24] and 2) C8-modified analogs undergo [2+2] photocycloaddition within the G-quadruplex core.[25] We envisioned that attaching reactive olefins to the 5′-sidechain, rather than to C8 in the core, would enable facile release of cyclobutane product after formation. We also postulated that the [2+2] process might be catalytic, since G monomers are in dynamic exchange with G-quadruplex subunits.[26] We studied 5′-*meta*-methoxy cinnamate **1**, since *meta*-methoxy cinnamic acid does not photodimerize, either in the solid-state or in solution.[26]




**Scheme 1.** Cinnamate **1** and KI form a H-bonded G-quadruplex $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ that undergoes [2+2] photocycloaddition to give $[\mathbf{3}]_8\bullet 3K^+3I^-$ containing cyclobutane **3**. When excess [2.2.2] -cryptand is added, in order to sequester $K^+$, irradiation of **1** gives only isomerization about the C=C bond resulting in a mixture of *trans* **1** and *cis* **2**. Cyclobutane *β*-truxinate **3**, can be isolated and further reacted to give **4**.

We characterized self-assembly of **1** by NMR and CD spectroscopy, mass spectrometry and X-ray crystallography. A 1:1 mix of KI and *trans* **1** in $CDCl_3$ gave quantitative formation of a $D_4$-symmetric hexadecamer $[\mathbf{1}]_{16}\bullet 3K^+3I^-$, based on splitting of $^1H$ NMR signals into pairs of equal intensity (**Fig. S16**).[26,28] We also observed interlayer NOEs consistent with close contacts between C=C bonds in the "outer" and "inner" $G_4$-quartets (**Fig S20**). Formation of the hexadecameric G-quadruplex was further supported by ESI-MS, showing a major, triply charged peak at 2617.4 m/z, indicating a mw of 7852.2 for $[\mathbf{1}]_{16}\bullet\ 3K^+$ (**Fig. S22**).

X-ray diffraction of single crystals confirmed that 16 units of **1** and 3 equiv of KI form a $D_4$-symmetric hexadecamer (**Fig. S23** and **Table S2**). The G-quadruplex core and most 5′-cinnamate sidechains were well defined, whereas the aryl rings and some cinnamate sidechains were disordered. In terms of its H-bonded core, the solid-state structure of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ is similar to other G-quadruplex structures.[22,29] Importantly, X-ray data revealed that 5′-ester carbonyls from one $G_4$-quartet form H-bonds with exocyclic amines ($N^2H_B$ donor) projecting from neighboring $G_4$-quartets (**Fig. S23**). These $N^2H_B$--O=C interlayer H-bonds clamp together $G_4$-quartets in $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ so that C=C bonds from the "outer" layer stack on C=C bonds from the "inner" layer (**Fig. 1A**). Thus, carbons α to the ester (C1 and C1′ in **Fig. 1B**) are separated by just 3.3 Å. This orientation of alkenes in $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ would predict formation of a symmetrical *syn* head-to-head dimer upon photoirradiation.[14]

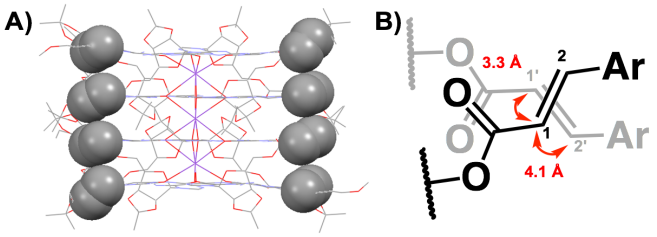



**Figure 1.** A) From X-ray structure of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$. View highlights stacked C=C bonds (space-filling). B) Illustration indicates distances between atoms in stacked alkenes. Formation of a σ bond between C1 and C1′ (3.3 Å distance) upon photoirradiation leads to regioselective formation of β-truxinate **3**.

Because aryl rings and some C=C bonds were disordered in the X-ray structure of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$, we performed ONIOM calculations,[30] using a hybrid density functional (WB97XD)[31] in combination with a semi-empirical method (PM6),[32] to optimize the structure of a $[\mathbf{1}]_8\bullet K^+$ fragment. The ONIOM (QM:MM) approach, combining the accuracy of DFT calculations with the lower computational cost of molecular mechanics, has been used to calculate geometry for a DNA G-quadruplex.[33,34]

Due to the many atoms in $[\mathbf{1}]_{16}\bullet 3K^+3I^-$, we computed structures for $G_8\bullet K^+$ octamers that contain 2 (rather than 4) $G_4$-quartet layers. Since it is $D_4$-symmetric the 2 $G_8\bullet K^+$ octamers that make up $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ are identical, so we reasoned that analysis of an octamer would help better understand the structure of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$. The computed model for octamer $[\mathbf{1}]_8\bullet K^+$, which provided insights lacking from the X-ray structure, revealed that the 3-methoxy aryl rings do not π-stack. Other aspects of the calculated model agreed with the X-ray structure for $[\mathbf{1}]_{16}\bullet 3K^+$. First, interlayer H-bonds between 5′-ester carbonyls and exocyclic amino protons ($N^2H_B$ donor) were similar (Table S4). Second, the C=C bonds from the "outer" $G_4$-layer stack on C=C bonds from the "inner" $G_4$-layer with *s-cis* conformations in both crystal structure and calculated model. We also located a minimum-energy structure for $[\mathbf{3}]_4\bullet K^+$, the G-quadruplex formed by a net 4 [2+2] photocycloadditions. As described in **Fig. S33** formation of 4 cyclobutane rings significantly destabilized this $[\mathbf{3}]_4\bullet K^+$ assembly relative to $[\mathbf{1}]_8\bullet K^+$.

We first examined photochemical properties of monomeric *trans* **1** in $CDCl_3$. UV-vis spectroscopy showed a band with $\lambda_{max}$ of 285 nm extending to 315 nm, due to the π-π* transition for 5′-cinnamate (**Fig. S14**). Monomeric **1** did not dimerize in solution. To ensure there was no G-quadruplex present during irradiation excess [2.2.2]-cryptand was added to sequester any rogue $Na^+$ or $K^+$ cations. When a solution of *trans* **1** (10 mM) and cryptand (100 mM) in $CDCl_3$ was irradiated for 1 h with 300 nm light we observed only isomerization to give a 56:44 photostationary mix of *trans* **1** and *cis* **2** (**Fig. S15**) With no cations available to form G-quadruplexes, there was no [2+2] cycloaddition of **1**. The situation changed when KI was added to a solution of *trans* **1**, as a *single* cyclobutane stereoisomer **3** formed upon irradiation with 300 nm light. As described below, formation of β-truxinate **3**, which occurs via a net head-to-head and *syn* dimerization of stacked *trans* olefins, requires a templating $K^+$ cation. Irradiation of a 0.625 mM solution of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ in $CDCl_3$ (10 mM of **1**) resulted in broadening of $^1H$ NMR signals (**Fig. S24**), likely due to formation of mixed G-quadruplexes containing **1** and cyclobutane **3**. This broadening made it difficult to monitor reaction progress by $^1H$ NMR.

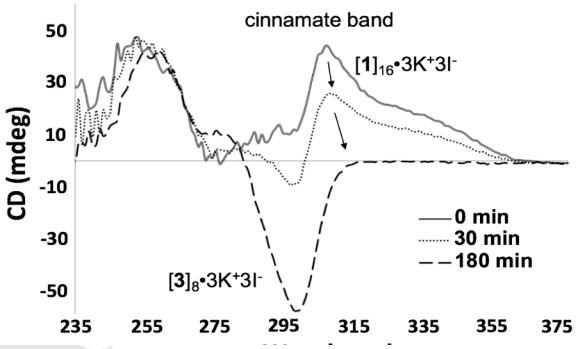



**Figure 2.** CD spectra before and after photoirradiation of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$. Aliquots were removed from the reaction mixture at t= 0, 30, and 180 min and diluted to 12.5 μM in $CHCl_3$. The cinnamate's C=C π bond in $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ shows an induced CD band at 307 nm. As the [2+2] cycloaddition proceeds this CD band at 307 nm disappears and a new negative band near 295 nm appears for the stacked $G_4$-quartets in the product $[\mathbf{3}]_8\bullet 3K^+3I^-$.

The [2+2] photoreaction could be followed in $CDCl_3$ using CD spectroscopy, a sensitive probe of helical structure.[35] **Figure 2** shows transformation of the CD spectrum for $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ into a new CD signature upon irradiation. The starting $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ has 2 intense positive bands, one at 260 nm for stacked $G_4$-quartets and one at 307 nm for cinnamate's π bond, which clearly senses the core's helical chirality. Importantly, the spectrum of the photoproduct (t=180 min) did not show cinnamate's CD band at 307 nm, indicating that all C=C π bonds in $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ had reacted to produce a new G-quadruplex $[\mathbf{3}]_8\bullet 3K^+3I^-$, with its own distinct CD signature being a negative exciton centered at 280 nm. ESI-MS of this new complex showed a major signal for a triply charged species at 2617.58 m/z, consistent with the structure of $[\mathbf{3}]_8\bullet 3K^+3I^-$ (mw 7852.7) (**Fig. S22**).

To follow photocycloaddition of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ in $CDCl_3$ by $^1H$ NMR, aliquots were removed, $CDCl_3$ was evaporated and the residue dissolved in DMSO-$d_6$, a solvent that breaks up H-bonded assemblies. Chemical shifts of cinnamate's *meta*-$OCH_3$ distinguished competing reactions, isomerization of *trans* **1** to *cis* **2** and [2+2] cycloaddition to give cyclobutanes. **Figure 3** shows that after 1 h most of *trans* cinnamate **1** had been converted into a new compound that was not *cis* isomer **2**. After 6 h, photoreaction was complete, with formation of greater than 92% of β-truxinate cyclobutane **3**, a compound whose structure we characterized by $^1H$ and $^{13}C$ NMR and mass spectrometry. We confirmed the identity of photoproduct **3** by converting it to the known dimethyl ester **4**.[15b,36] Cycloaddition of trans **1** in $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ also gave a high yield of cyclobutane **3** when done outdoors in sunlight (**Fig. S28**).

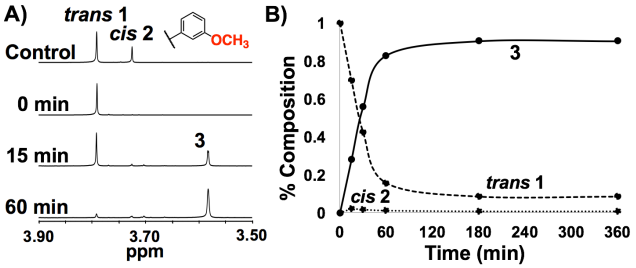



**Figure 3.** A) $^1$H NMR spectra of the *meta* –$OCH_3$ protons during irradiation of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$. The top spectrum is a control experiment done in DMSO-$d_6$ showing that irradiation of monomeric *trans* **1** gives only *cis* **2**. Irradiation of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$ in $CDCl_3$ leads to cyclobutane **3**. B) Graph showing production of cyclobutane **3** upon photoirradiation of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$.

To 1) understand selective formation of β-truxinate **3** and 2) compare relative stabilities of assemblies containing cinnamate **1** and cyclobutane **3** we carried out high-level computations with the ONIOM method ((M06-2X/6-31+G(d,p):B3LYP/6-31G(d)-in $CHCl_3$ (CPCM)//WB97XD-6-31G(d):PM6).[30] **Figure 4** shows energetics of intermediates on a path leading to cyclobutane **3**. The lowest energy complex ($\mathbf{A}_{cis:cis}$) adopts an *s-cis* conformation about each 5′-cinnamate. If concerted photodimerization of pre-organized s-*cis* C=C olefins, which adopt a crisscross orientation, were to occur from this $\mathbf{A}_{cis:cis}$ complex it would predict formation of a 1,3-disubstituted cyclobutane. Experimentally, only *β*-truxinate **3**, a *cis*-1,2-diester, is formed upon irradiation of $[\mathbf{1}]_{16}\bullet 3K^+3I^-$. Concerted formation of *β*-truxinate **3** requires one of the reacting esters to adopt an s-*trans* conformation. Structure $\mathbf{A}_{trans:cis}$, where 1 of 4 pairs of alkenes stacks in a parallel orientation, had a relative energy just 0.1 kcal/mol above $\mathbf{A}_{cis:cis}$ (**Fig. 4**). From the $\mathbf{A}_{trans:cis}$ intermediate, photocycloaddition leads to formation of $\mathbf{A}_{1,2\text{-}syn}$, an intermediate with a relative energy of +3.0 kcal. Release of *β*-truxinate **3** from $\mathbf{A}_{1,2\text{-}syn}$ and incorporation of 2 equiv of *trans* **1** would regenerate the $\mathbf{A}_{cis:cis}$ complex. If stacked olefins were to react directly out of the lowest-energy conformation ($\mathbf{A}_{cis:cis}$) to form $\mathbf{A}_{1,2\text{-}syn}$, it would suggest a step-wise mechanism where initial σ bond formation occurs between C1 and C1' to give a biradical. Subsequent σ bond rotation and coupling of the 2 benzyl radicals (C2 and C2′ in **Fig. 1B**) would form the cyclobutane in G-quadruplex $\mathbf{A}_{1,2\text{-}syn}$. Alternatively, as pictured in **Figure 4**, one 5′-cinnamate sidechain could adopt a conformation that aligns reacting C=C π bonds so that they are oriented face-to-face ($\mathbf{A}_{trans:cis}$). This $\mathbf{A}_{trans:cis}$ species could undergo a concerted cycloaddition to give $\mathbf{A}_{1,2\text{-}syn}$. Regardless of the mechanism, either concerted or stepwise, the consequence of pre-organization of 5'-cinnamate esters in the G-quadruplex is a highly regio- and stereoselective [2+2] photocycloaddition.

Since computation indicated that cyclobutane formation destabilizes the G-quadruplex, we reasoned that the system could be catalytic in $K^+$ if cinnamate **1** in solution were to expel cyclobutane **3** from the assembly (**Fig. 4**). We tested for catalysis by monitoring [2+2] cycloaddition of *trans* **1** to **3** under conditions with insufficient $K^+$ to fully complex *trans* **1**. We conducted these reactions on a relatively large scale (194 mg of **1** in 40 mL of $CHCl_3$), so that a) ratios of **1** (mw 483.4) and KI (mw 166) could be determined by weight and b) we could demonstrate the synthetic utility of this process. **Figure 5** shows that photocycloaddition is sensitive to $K^+$ concentration. Addition of excess $K^+$ (1:1 KI to **1**) gave relatively fast cycloaddition (>90% yield of **3** after 6 h). The [2+2] cycloaddition was slower, but still gave high yields of **3**, for a sample with a 1:64 ratio of KI to **1**. Initially, the reaction mixture was heterogeneous, but became clear as insoluble **1** was converted into soluble **3** **(Fig. S30).** That reaction with a 1:64 ratio of KI to **1** gave 90% yield of product indicated that photocycloaddition is catalytic in $K^+$.

We were perplexed by a control wherein cycloaddition of cinnamate **1** to give **3** occurred even when *no* KI was added (**Fig. 5**). We suspected that production of **3** under these conditions was due to the ability of **1** to scavenge adventitious $Na^+$ or $K^+$ from solvent or glassware to form photoreactive G-quadruplex $[\mathbf{1}]_{16}\bullet 3M^+$. Our hypothesis was supported by comparing elemental analyses of freshly prepared **1** with material subjected to the sample preparation protocol used prior to irradiation, a process that involves 1) suspending **1** in $CDCl_3$, 2) sonication and 3) overnight stirring in $CDCl_3$. Elemental analysis of purified **1** indicated a $Na^+$: **1** ratio of 1:157 and a $K^+$: **1** ratio of 1:820 (**Table S3**). The concentration of these cations increased after the sample preparation protocol, showing a $Na^+$: **1** ratio of 1:55 and a $K^+$: G **1** ratio of 1:431. Our hypothesis that adventitious cations template formation of reactive G-quadruplexes was supported by an experiment wherein excess [2.2.2]-cryptand (140 mM) was added to a suspension of **1** (10 mM) in $CDCl_3$. Photoirradiation of that sample for 48 h showed no formation of cyclobutane **3** (**Fig. 5**). Overall, the data in **Figure 5** allows us to conclude that [2+2] photocycloaddition of cinnamate **1** is catalytic with regard to $K^+$. An individual cation enables multiple turnovers of guanosine 5′-cinnamate **1** to give high yields of diguanosylcyclobutane **3**.

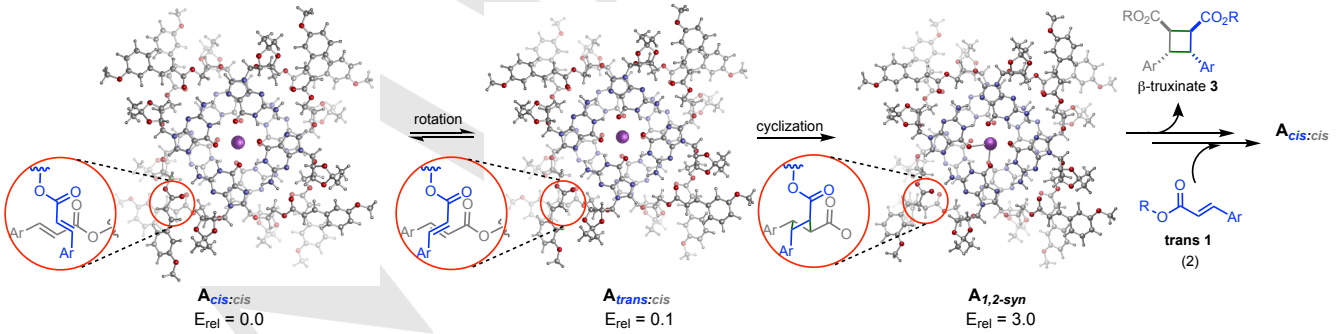



**Figure 4.** A proposed pathway for [2+2] photocycloaddition of *trans* **1** to give β-truxinate **3**, as templated by the G-quadruplex. Using the ONIOM method, optimized structures and energies were calculated for a series of $G_8\bullet K^+$ octamers. This particular pathway involves bond rotation of a cinnamate ester in $\mathbf{A}_{cis:cis}$ to give $\mathbf{A}_{trans:cis}$, which undergoes concerted [2+2] photocycloaddition, to give cyclobutane-containing $\mathbf{A}_{1,2\text{-}syn}$. Exchange of *trans* **1** with β-truxinate **3** in $\mathbf{A}_{1,2\text{-}syn}$ would make this process catalytic.

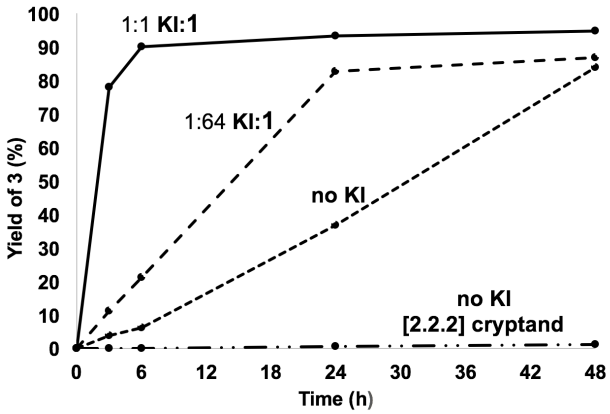



**Figure 5.** Graph showing production of **3** as a function of irradiation time. Reactions were performed by continuous irradiation (hv=300 nm) of samples containing **1** (193.6 mg, 10 mM) in 40 mL of $CHCl_3$ with various amounts of added KI. The control experiment contained [2.2.2] cryptand (140 mM) to sequester any adventitious cations. Aliquots were removed at different times, the solvent was evaporated and the residue was dissolved in DMSO-$d_6$ for subsequent NMR analysis.

In summary, we have demonstrated that the self-assembled G-quadruplex enables regio- and stereoselective formation of cyclobutanes, in dilute solution, by organizing 5′-cinnamate esters for [2+2] photocycloaddition. The templating $K^+$ cation is required for photocycloaddition; without $K^+$ cinnamate ester **1** undergoes only *cis*/*trans* isomerization upon photoirradiation. Because of the pre-organization of 5′-cinnamate side-chains in the G-quadruplex, cyclobutane **3** is produced in high yield and with excellent regio- and diastereoselectivity. Importantly, this photocycloaddition is catalytic in $K^+$, since reactants and products can exchange between solution and G-quadruplex assembly. Our ongoing research is now focused on exploring the scope of reactions that can take place on the periphery of the G-quadruplex, since this rigid core is an ideal for organizing reactive groups so that they are close in space and time.

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