Tetrahedron 64 (2008) 8292–8300

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Modulating chemical reactivity using a photoresponsive molecular switch

Hema D. Samachetty, Vincent Lemieux, Neil R. Branda *

4D LABS, Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby, BC, Canada V5A 1S6

ARTICLE INFO

Article history:
Received 10 March 2008
Received in revised form 6 May 2008
Accepted 9 May 2008
Available online 14 May 2008

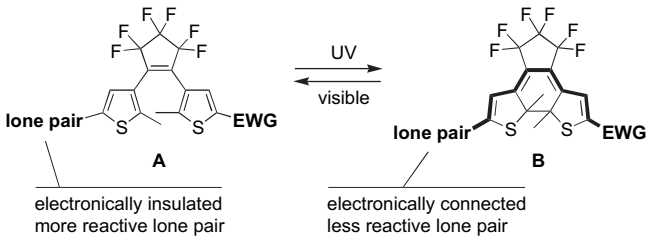
ABSTRACT

The kinetics of an alkylation reaction are used to probe the effect of an electron-withdrawing pyridinium group on the nucleophilicity of a free pyridine in a photoresponsive dithienylcyclopentene (DTCP) derivative in order to demonstrate effective and reversible control over chemical reactivity. The kinetic data support the hypothesis that the ring-open isomer of the DTCP (**1o**) is more reactive than its ring-closed counterpart (**1c**) due to electronic communication between the two pyridine groups existing only in the latter isomer. The rates of the alkylation reactions of bis(pyridine) versions of the photochromic compounds are also evaluated to provide a better understanding of the through-bond and the through-space effects of the groups located at the ends of the linearly conjugated π-electron backbone. The use of the two DTCP isomers (**1o** and **1c**) as nucleophilic catalysts is also suggested in preliminary investigations.

1. Introduction

The incorporation of photoresponsive molecular backbones into chemical reagents and catalysts offers the possibility to turn a reaction 'on' and 'off' on command using light as an external stimulus. This approach to introduce regulation has the potential to advance synthetic methods and polymerization techniques as well as the controlled delivery of biochemical reagents. At the beginning of the new millennium, catalysis-based chemical synthesis accounted for approximately 60% of the current chemical products and 90% of the chemical processes[1] representing a rich area to introduce control at the molecular level. In the life-science realm, the controlled delivery of biochemical reagents to induce an in vitro or in vivo cellular response continues to be a versatile and important experimental technique.[2] Site-selective drug-delivery will also benefit from the regulation of molecular structure and function by converting a therapeutic from its initially inactive (or significantly less active) form to its active form after it reaches the target tissue.[3] This unmasking can be achieved through processes such as metabolism, hydrolysis or by using an external trigger such as light, assuming photoresponsive architectures are incorporated into the molecular design.[4]

Photoresponsive compounds containing the dithienylcyclopentene (DTCP) backbone are particularly well suited to modulate chemical reactivity because they undergo rapid and reversible cyclization reactions, when exposed to UV and visible light, between two isomers (**A** and **B** in Scheme 1) that have distinct geometric and electronic properties.[5] Another appealing property of this photoresponsive architecture is the fact that the ring-open (**A**) and ring-closed (**B**) isomers tend to exhibit excellent thermal stability across a wide range of temperatures providing potential candidates for use as the 'on' and 'off' functions to start and stop chemical reactions using light. Several research groups have demonstrated this potential use of dithienylethene derivatives by taking advantage of the geometric and electronic changes to regulate substrate binding affinities,[6] the stereochemical outcome of a catalytic reaction,[7] relative acidity,[8] retro-Diels–Alder reactions[9] and the Bergmann cyclization.[10]



Scheme 1. The reversible photocyclization reaction of the dithienylcyclopentene backbone.

Scheme 1 also illustrates a specific approach to regulate chemical reactivity, in this case nucleophilicity. The two thiophenes in the ring-open isomer **A** are electronically insulated from each other such that any nucleophilic lone-pair electrons located on one side of the molecular backbone will not sense the electronic effects of an electron-withdrawing group located on the other side. Photocyclization of **A** to the ring-closed isomer (**B**) creates a linearly conjugated π-electron pathway connecting the two groups (shown in bold in Scheme 1), allowing the lone-pair electrons to be subjected to the electronic 'pull' of the electron-withdrawing group,

* Corresponding author. Tel.: +1 778 782 8061; fax: +1 778 782 3675.
E-mail address: nbranda@sfu.ca (N.R. Branda).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.05.050

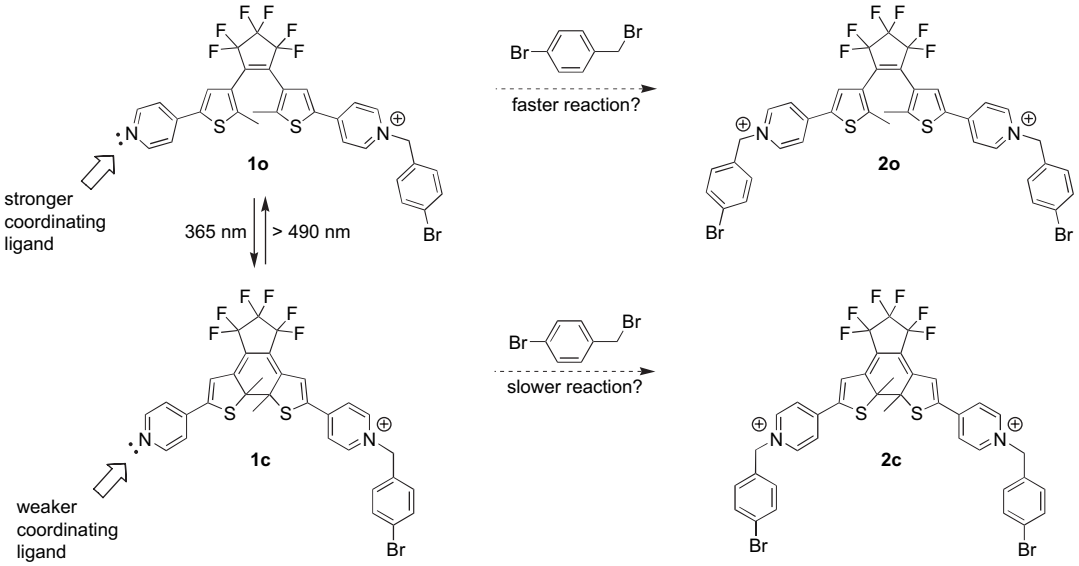
thus lowering their nucleophilic strength. Consequently, the ring-open isomer **A** is expected to react faster with an electrophile than its ring-closed counterpart **B**. We have already applied this strategy to photoregulate the coordinating ability of a pyridine ring decorated onto a DTCP backbone and have shown that ring-open isomer **1o** (Scheme 2) forms a more stable coordination complex with a ruthenium porphyrin than ring-closed counterpart **1c**.[11]

In the current paper, we use the kinetics of an alkylation reaction to probe the effect of the electron-withdrawing pyridinium group on the nucleophilicity of the free pyridine in photoresponsive dithienylcyclopentene (DTCP) **1o** and demonstrate effective and reversible control over chemical reactivity. This pyridine compound is particularly pertinent owing to the ubiquitous role of pyridines as nucleophilic catalysts in synthesis and biochemical processes.[12] The focus of this paper is the model alkylation reaction of both DTCP isomers with 4-bromobenzyl bromide to produce derivatives **2o** and **2c** as also shown in Scheme 2. Through an examination of the rates of this model reaction, the difference in chemical reactivity of this interesting compound is demonstrated.

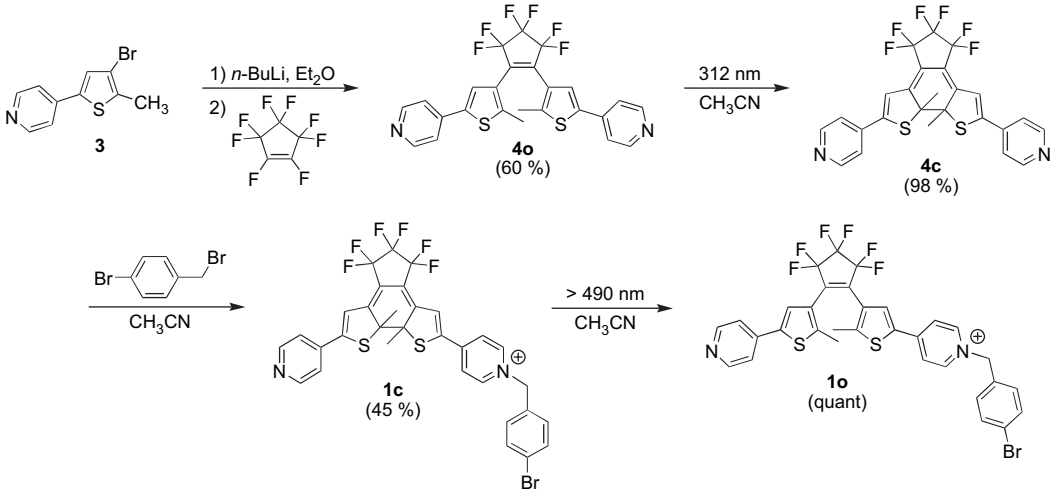
2. Results and discussion

2.1. Synthesis of the monobenzylated DTCP derivatives 1o and 1c

The monobenzylated DTCP **1o** is prepared in four steps as shown in Scheme 3 via the ring-closed isomer of the bis(pyridine) **4o** by lithiating the known pyridylthiophene **3**[13] followed by quenching with octafluorocyclopentene. The direct treatment of the bis(pyridine)'s ring-open isomer (**4o**) with 1 mol equiv of 4-bromobenzyl bromide yields an unacceptable amount of the undesired dibenzylated DTCP (**2o**) as a side product. Higher yields of the monobenzylated derivative can be obtained by alkylating the ring-closed bis(pyridine) **4c**, followed by ring-opening of **1c** to **1o** using visible light. This observation already suggests that the two pyridines in the ring-open isomer (**4o**) react independently from each other while they communicate to a larger extent when the DTCP backbone exists in its ring-closed form. This claim will be further substantiated later in this paper.



Scheme 2. Reversible photocyclization modulates the ability of the pyridine in **1o** and **1c** to act as a coordinating ligand. The alkylations of **1o** and **1c** to generate **2o** and **2c** are the model reactions described in this report.



Scheme 3. Synthesis of ring-closed and ring-open isomers **1c** and **1o**. The counterions are NO_3^-.

The ring-closed isomer **4c** is generated by irradiating an anhydrous CH_3CN solution (5.8×10^{-3} M) of bis(pyridine) **4o** with 312 nm light[14] and monitoring aliquot amounts of the solution by ^1H NMR spectroscopy until no further changes are observed. The progress of the photocyclization reaction is best assessed by monitoring the peak corresponding to the methine C–H of the thiophene rings, which shifts from 7.63 to 7.02 ppm as the solution of **4o** is converted into one containing 98% of the ring-closed isomer **4c**. This photostationary state can then be alkylated with 1.0 mol equiv of 4-bromobenzyl bromide to afford monobenzylated bis(pyridinium) **1c** after purification by column chromatography (silica gel, CH_3CN/H_2O/saturated KNO_3) as its nitrate salt. The ring-open isomer **1o** of the monobenzylated bis(pyridinium) is finally produced by irradiating a CH_3CN solution (2.7×10^{-3} M) of **1c** with visible light[14] to trigger the ring-opening reaction and generate **1o**. Again, the progress of the photoreaction can be monitored using the methine peaks of the thiophene rings, which in this case shift from 7.30 and 7.06 ppm for the ring-closed isomer **1c** to 8.00 and 7.62 ppm for **1o**. The ring-open monobenzylated DTCP (**1o**) can be collected by evaporating the solvent without the need for further purification.

2.2. Photochromic properties of monobenzylated DTCPs 1o and 1c

Irradiating a CH_3CN solution of compound **1o** (2.0×10^{-5} M) with 365 nm light[14] triggers the photocyclization reaction and generates a solution of the ring-closed isomer **1c**. The visual demonstration of this photoreaction is the change in colour of the solution from colourless to greenish-blue due to the formation of the extended π-conjugated backbone in the ring-closed isomer. The corresponding UV–vis absorption spectra show trends that are typical for ring-closing reactions of dithienylethene derivatives (Fig. 1a). The high-energy bands in the spectra become less intense as a broad band centred at 649 nm appears. At a concentration of 2.0×10^{-3} M (in CD_3CN), a photostationary state is reached within 10 min, at which point only the proton signals corresponding to the ring-closed isomer **1c** are observed in the ^1H NMR spectrum.[15] Irradiating the coloured solution with light of wavelengths greater than 490 nm[14] results in the complete regeneration of the ^1H NMR and UV–vis spectra corresponding to the ring-open isomer (**1o**) without observable formation of side-products. The solutions also show no apparent signs of degradation even after prolonged irradiation with either type of light and after 10 cycles of alternating the irradiation with 365 nm light and wavelengths greater than 490 nm to toggle the compound between its ring-open and ring-closed isomers.[16]

2.3. Differences in reactivity of monocations 1o and 1c

The rate constants for all alkylation reactions of the compounds reported in this paper can be estimated using *pseudo*-first-order kinetic analysis[17] by treating CD_3CN solutions of the DTCP compounds with a large excess of 4-bromobenzyl bromide (30 mol-equiv)[18] and monitoring the changes in the concentration of each component during the course of the reaction using ^1H NMR spectroscopy at controlled temperatures. The most convenient signals to monitor in the ^1H NMR spectra are those corresponding to the α-protons of the pyridine and pyridinium rings (protons H_a in Fig. 2), which decrease in intensity during a 24-h period at 22 °C when a solution (2.4×10^{-3} M) of the ring-open isomer of monobenzylated DTCP (**1o**) is treated with the excess of the alkylating reagent.[19] Graphical treatment of the change in concentration of **1o** over time gives the expected linear relationship as illustrated in Figure 2[20] and an apparent *pseudo*-first-order rate constant ($k'_{\mathbf{1o}}$) of $(2.9\pm0.1)\times10^{-5}$ s^{-1}.[21] Treating an equivalent solution of the ring-closed isomer **1c**[22] under identical conditions generates an apparent *pseudo*-first-order rate constant ($k'_{\mathbf{1c}}$) that is just over 3 times smaller, $(9.0\pm0.5)\times10^{-6}$ s^{-1}.

It is clear from these experiments that the ring-open isomer is just over 3 times more reactive as a nucleophile than its ring-closed counterpart. Although these differences appear small, they correspond to a difference in a reaction that is 95% complete in just over 1 day (for **1o**) compared to one that takes just under 4 days (**1c**) to reach the same level of completion. The magnitude of the

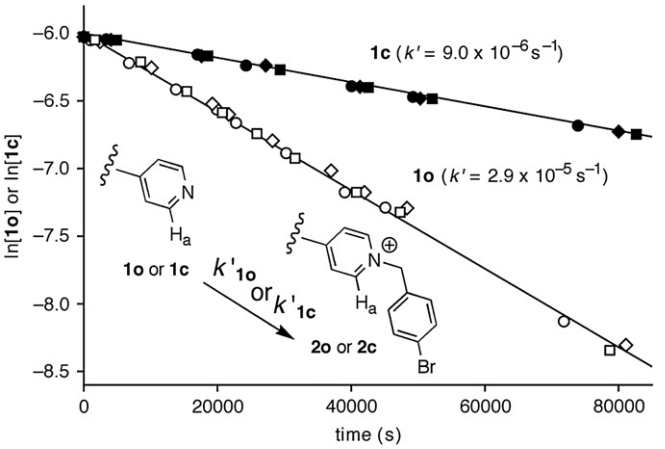


Figure 2. Changes in concentration of monocations **1o** (open symbols) and **1c** (filled symbols) when CD_3CN solutions of them (2.4×10^{-3} M) are treated with excess 4-bromobenzyl bromide. The experiments were performed in triplicate.

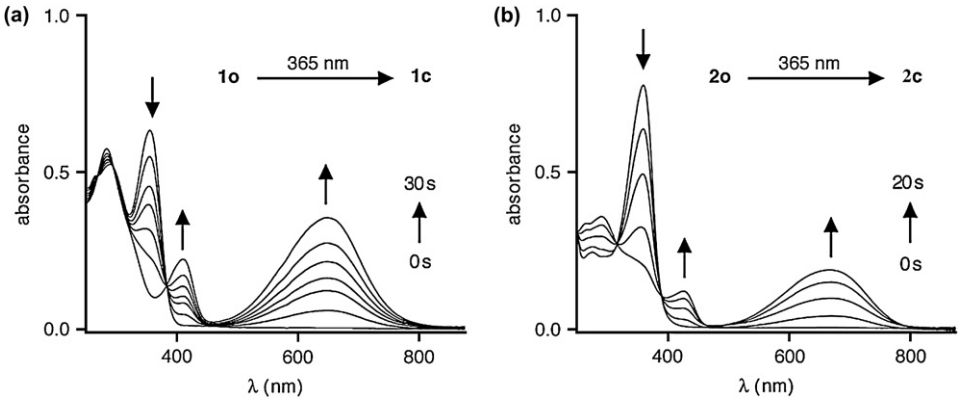


Figure 1. Changes in the UV–vis absorption spectra of CH_3CN solutions (2.0×10^{-5} M) of (a) **1o** and (b) **2o** as they are irradiated with 365 nm light until the photostationary states are reached.

difference in rate constants is also expected and can be ascribed, in part, to the fact that the nucleophilic pyridine ring in the ring-closed isomer **1c** is twisted 20–30° out of co-planarity from the DTCP's linearly π-conjugated backbone as has already been suggested to account for similar differences in the coordinating ability of the two isomers.[11] This structural distortion may reduce the electronic communication between the two ends of the photoresponsive backbone. We can speculate on another factor that may be contributing, in this case, to reduce the reactivity of isomer **1o**. The conformational flexibility of the ring-open isomer allows the compound to adopt a structure where the pyridine and the positively charged pyridinium groups are in close proximity to each other due to electrostatic attraction. This conformation would result in through-space effects detrimental to the reactivity of **1o** such as sterical crowding of the reaction site, a reduction in the electron-rich nature of the pyridine and the creation of charge–charge repulsion in the transition state leading to the formation of the dication **2o**.

The nucleophilicity of the pyridine in DTCP **1** can be modulated while the alkylation reaction progresses by cycling the compound between its ring-open (**1o**) and ring-closed (**1c**) isomers by alternately irradiating solutions of it with UV and visible light (Fig. 3). When a CD_3CN solution (2.4×10^{-3} M) of **1o** is treated with an excess of 4-bromobenzyl bromide (7.3×10^{-2} M, 30 mol equiv) at 22 °C, the alkylation reaction to form **2o** proceeds at a similar rate

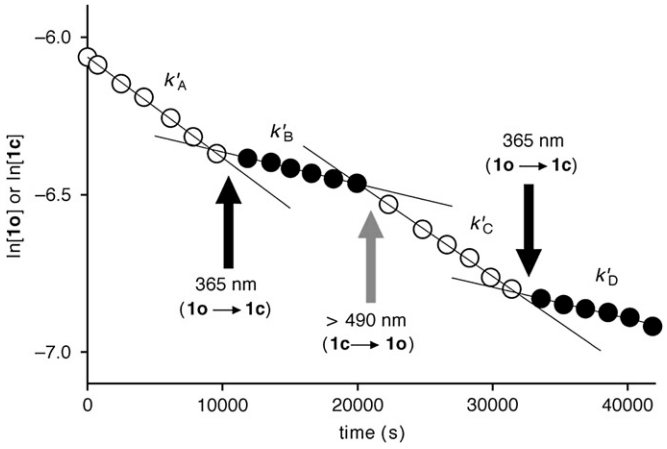


Figure 3. Modulation of the rate of the alkylation reaction of a CD_3CN solution (2.4×10^{-3} M) of DTCP **1** with excess 4-bromobenzyl bromide (30 mol equiv) by alternatively irradiating with UV and visible light at 22 °C.[24]

($k'_A=(3.0\pm0.1)\times10^{-5}$ s^{-1}) as previously measured. After approximately 3 h, the solution can be irradiated with 365 nm light until both the ring-open reactant **1o** and the ring-open product **2o** are completely converted to their respective ring-closed forms as attested by ^{1}H NMR spectroscopy.[23] The rate of the alkylation reaction slows and the apparent *pseudo*-first-order rate constant ($k'_B=(1.0\pm0.1)\times10^{-5}$ s^{-1}) is similar to that measured for pure **1c** described previously. Irradiating this reaction with visible light (greater than 490 nm) after another 3 h regenerates both the ring-open species and the original rate constant ($k'_C=(3.0\pm0.1)\times10^{-5}$ s^{-1}). The system can be modulated again using 365 nm light ($k'_D=(9.9\pm0.1)\times10^{-6}$ s^{-1}). There is no observable degradation of any DTCP species during these photomodulating experiments.

2.4. Differences in reactivity of bis(pyridine)s 4o and 4c

As already mentioned in Section 2.1 of this paper, higher yields of the monobenzylated DTCP are produced when the bis(pyridine) is alkylated in its ring-closed form (**4c**→**1c**). The fact that the reaction of the ring-closed isomer **4c** with 4-bromobenzyl bromide affords monoalkylated **1c** as the predominant product while its ring-open counterpart (**4o**) affords predominantly the dialkylated product (**2o**) suggests that the pyridines in ring-closed **4c** are more reactive than the remaining pyridine in monocation **1c** (this is expected) and that the pyridines in ring-open **4o** are not necessarily more reactive than that in monobenzylated **1o**. An analysis of the rate of the alkylation reactions of **4o**→**1o**→**2o** and **4c**→**1c**→**2c** using consecutive first-order kinetics should shed light on the differences in reactivity of the pyridines in the entire series of DTCP derivatives.

When a CD_3CN solution of the ring-open bis(pyridine) **4o** (4.6×10^{-3} M) is treated with an excess of 4-bromobenzyl bromide (1.2×10^{-1} M, 27 mol equiv) the change in concentration of each species (**4o**, **1o** and **2o**) during the reaction at 22 °C can be monitored by ^{1}H NMR spectroscopy (for the signals corresponding to the α-protons as described previously).[25] The results are presented in Figure 4a and b.

The plots of the relative concentrations of **4o**, **1o** and **2o** against time are consistent with consecutive *pseudo*-first-order kinetics. The concentration of the bis(pyridine) **4o** shows the predicted exponential decay indicative of a *pseudo*-first-order trend. The trend for monobenzylated **1o** is consistent with a situation where the concentration increases to a maximum and then decreases supporting the expectation that the concentration of **1o** is dependent on both the concentration of bis(pyridine) **4o** and the rate of conversion to the bis(pyridinium) **2o**. The shape of the plot for the **2o**

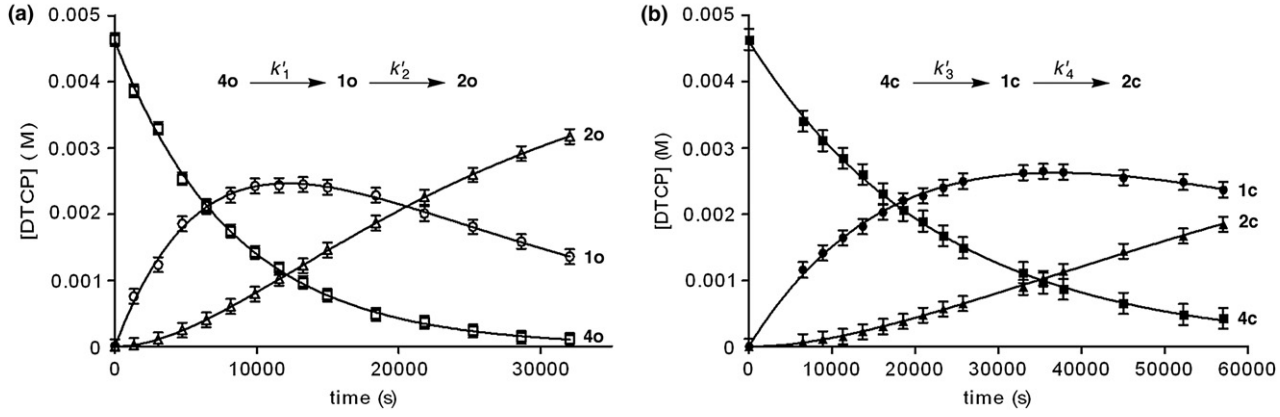


Figure 4. a) Changes in concentration of bis(pyridine) **4o** (□), monocation **1o** (○) and dication **2o** (△) when a CD_3CN solution of **4o** (4.6×10^{-3} M) is treated with excess 4-bromobenzyl bromide. (b) Changes in concentration of bis(pyridine) **4c** (■), monocation **1c** (●) and dication **2c** (▲) when a CD_3CN solution of **4c** (4.6×10^{-3} M) is treated with excess 4-bromobenzyl bromide.

Table 1
Average apparent *pseudo*-first-order rate constants for the alkylation reactions of CD_3CN solutions of DTCP compounds **1** and **4** with an excess of 4-bromobenzyl bromide at 22 °C

Compound		Apparent rate constant (k') (s^{-1})
Bis(pyridine) **4o**	k'_1	$(1.2\pm0.1)\times10^{-4}$
Bis(pyridine) **4c**	k'_3	$(4.6\pm0.3)\times10^{-5}$
Mono(pyridine) **1o**	k'_2	$(5.4\pm0.3)\times10^{-5}$
	$k'_{\mathbf{1o}}$[a]	$(2.9\pm0.1)\times10^{-5}$
	k'_A and k'_C[b]	$(3.0\pm0.1)\times10^{-5}$
Mono(pyridine) **1c**	k'_4	$(1.5\pm0.1)\times10^{-5}$
	$k'_{\mathbf{1c}}$[a]	$(9.0\pm0.5)\times10^{-6}$
	k'_B[b]	$(1.0\pm0.1)\times10^{-5}$
	k'_D[b]	$(9.9\pm0.1)\times10^{-6}$

[a] Obtained from the kinetic analysis of the reaction of **1o** and **1c** as described in Figure 2.
[b] Obtained from the kinetic analysis of the cycling reaction as described in Figure 3.

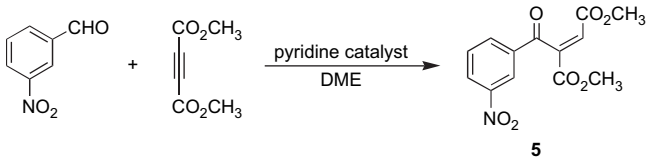
shows the characteristic initial delay in its formation, which is governed by the time required for the monocation **1o** to be generated. Treatment of the data using non-linear least squares regression analyses[26] affords apparent *pseudo*-first-order rate constants of $k'_1=(1.2\pm0.1)\times10^{-4}\ s^{-1}$ and $k'_2=(5.4\pm0.3)\times10^{-5}\ s^{-1}$ as averages of three experiments (Table 1).

A CD_3CN solution of ring-closed bis(pyridine) **4c**[27] treated under identical conditions shows similar changes for the signals corresponding to the α-protons of the pyridine or the pyridinium groups in the ^1H NMR spectra.[16] The plots of the relative concentrations of **4c**, **1c** and **2c** against time are shown in Figure 4b and are consistent with consecutive *pseudo*-first-order kinetics. Treatment of the data using non-linear least squares regression analyses[26] affords apparent *pseudo*-first-order rate constants of $k'_3=(4.6\pm0.3)\times10^{-5}\ s^{-1}$ and $k'_4=(1.5\pm0.1)\times10^{-5}\ s^{-1}$ as averages of three experiments (Table 1).

These experiments illustrate that the pyridine in the bis(pyridine) **4o** reacts approximately 2.1 times faster than the pyridine in monobenzylated **1o** and support the initial argument that through-space interactions between the nucleophile and the electron-deficient pyridinium in **1o** contribute to reduce the nucleophilic strength of **1o**. In the case of the ring-closed forms, the two pyridine rings in both bis(pyridine) **4c** and monocation **1c** are in electronic communication owing to the linear π-conjugated pathway running along the backbone of the DTCP. As expected the pyridine in ring-closed bis(pyridine) **4c** reacts faster (approximately 3.1 times) than the pyridine in ring-closed, monobenzylated **1c**. The fact that the ring-open bis(pyridine) **4o** reacts twice as fast as its ring-closed counterpart (**4c**) can be attributed to the extended delocalization in the latter isomer.

2.5. Photoregulation of catalysis: preliminary observations

As mentioned in Section 1 of this paper, photoresponsive compounds such as DTCP **1** are particularly pertinent candidates for photoregulating chemical reactivity owing to their popularity as nucleophilic catalysts in a wide range of synthetic systems. One only has to be reminded of the widespread use of compounds such as *N*,*N*-dimethylaminopyridine (DMAP) in coupling reactions to be convinced.[12] Preliminary studies using DTCPs **1o** and **1c** demonstrate the potential use of photoresponsive compounds in these applications. The addition of dimethylacetylene dicarboxylate (DMAD) to 3-nitrobenzaldehyde to generate diester **5** is one of many model reactions catalyzed by pyridine compounds and is the one used to show the validity of the approach in this report (Scheme 4) due to the ease with which the product can be analyzed using ^1H NMR spectroscopy.[28]



5

Scheme 4. Pyridine-catalyzed addition of DMAD to 3-nitrobenzaldehyde.

The test reactions are carried out by adding 1.0 and 0.2 mol-equiv of the appropriate DTCP isomer (**1o** or **1c**) to a mixture containing 3-nitrobenzaldehyde and DMAD (1:1) in anhydrous dimethylether (DME). After 2 days, the amount of product **5** formed for each reaction is assessed by analyzing the ratios of the areas under the peaks corresponding to **5** and 3-nitrobenzaldehyde by ^1H NMR spectroscopy.[16] This analysis reveals that 20% of **5** is generated when 1.0 mol equiv of ring-open **1o** is present as compared to 11% when the amount of **1o** is reduced to 0.2 mol equiv, indicating the activity of the DTCP as a catalyst. The background reaction of equimolar amounts of the 3-nitrobenzaldehyde and DMAD in anhydrous DME in the absence of the monobenzylated DTE ligands **1o** and **2o** did not lead to any product formation after 2 days. In the case of ring-closed **1c**, only 4% of product **5** is observed when 1.0 mol equiv of **1c** is present. No observable peaks corresponding to product **5** appear in the spectrum when only 0.2 mol equiv of **1c** is used. These results show that the ring-open isomer **1o** is more effective than the ring-closed isomer **1c** as predicted from the trend observed in the previous studies.

3. Conclusions

In this paper, we have demonstrated the photomodulation of chemical reactivity by analyzing the kinetics of an alkylation reaction. The results indicate that the free pyridine in the ring-open form **1o** reacts approximately 3 times faster than the ring-closed form **1c** under *pseudo*-first-order conditions. Consecutive *pseudo*-first-order kinetics have been used to probe the differences in reactivity between the ring-open (**1o** and **4o**) and the ring-closed (**1c** and **4c**) isomers of the bis(pyridine) and the monobenzylated DTCP to better understand the through-bond and the through-space effects of having two pyridines, and a pyridine and an electron-deficient pyridinium at the external positions of the DTCP backbone. The results suggest that the through-bond communication between the pyridine and the pyridinium of the monobenzylated **1c** and the two pyridine groups of the bis(pyridine) **4c** lowers the reactivity of the pyridine nitrogen to a greater extent than the through-space interaction between the pyridine and the pyridinium in monobenzylated **1o**. Preliminary tests have demonstrated the use of the ring-open and the ring-closed DTCP isomers as nucleophilic catalysts by investigating the reaction of 3-nitrobenzaldehyde with dimethylacetylene dicarboxylate.

4. Experimental

4.1. Materials

All solvents for synthesis were dried and degassed by passing them through steel columns containing activated alumina under nitrogen using a solvent purification system (MBraun). All other solvents were used as received including those for NMR analysis (Cambridge Isotope Laboratories). Column chromatography was performed using silica gel 60 (230–400 mesh) from Silicycle Inc. All reagents and catalysts except for $Pd(PPh_3)_4$ (purchased from Strem) and octafluorocyclopentene (supplied by the Nippon Zeon Corporation) were purchased from Aldrich and used as received.

3-Bromo-2-methyl-5-thiopheneboronic acid[13] was prepared following literature procedures.

4.2. Techniques

Melting points (mp) were measured on a Gallenkamp capillary melting point apparatus. ^{1}H and ^{13}C NMR characterizations were performed on a Varian Mercury 400 instrument working at 400.1 MHz for ^{1}H NMR and 100.6 MHz for ^{13}C NMR or a Bruker TCI 600 instrument working at 600.3 MHz for ^{1}H NMR and 150.5 MHz for ^{13}C NMR. The ^{13}C NMR spectra are ^{1}H-decoupled but ^{19}F-coupled. Assignments were confirmed using ^{1}H–^{1}H COSY and selective 1D NOE experiments when necessary. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane using the residual solvent peak as an internal reference. Coupling constants (J) are reported in hertz. Relaxation measurements (T_1) were performed on the Bruker TCI 600 instrument, with the temperature set to 22 °C and the values are reported in seconds. FTIR measurements were performed using a Perkin Elmer 599B IR spectrophotometer. UV–vis absorption spectroscopy was performed using a Varian Cary 300 Bio spectrophotometer. Low resolution mass spectrometry (LRMS) measurements were performed using a matrix assisted laser desorption/ionization source (MALDI) using a PerSeptive Biosystems Voyager-DE instrument and the MALDI-TOF mass spectra were obtained using 2,5-dihydroxybenzoic acid as the matrix. Microanalyses (Anal.) were performed on a Carlo Erba Model 1106 CHN analyzer.

4.3. Photochemistry

Standard hand-held lamps (312 and 365 nm) used for visualizing TLC plates (Spectroline E-series, 470 μW cm^{-2}) were used to carry out the ring-closing reactions. The power of the light source is given based on the specifications supplied by the company when the lamps were purchased. A light detector was not used to measure the intensity during the irradiation experiments. A 312 nm light source was used for the bis(pyridine) **4o** and a 365 nm light source was used for the monobenzylated bis(pyridinium) **1o** and the dibenzylated bis(pyridinium) **2o**. The ring-opening reactions of the bis(pyridine) **4c**, the monobenzylated bis(pyridinium) **1c** and the dibenzylated bis(pyridinium) **2c** were carried out using the light of a 300 W halogen photo-optic source that was passed through a 490 nm cut-off filter to eliminate higher energy light.

4.4. Synthesis

*4.4.1. 3-Bromo-2-methyl-5-(4′-pyridyl)thiophene (**3**)[13]*

A mixture of THF (50 mL) and a saturated aqueous Na_2CO_3 solution (50 mL, 2 M) was deoxygenated by bubbling N_2 through the solution for 45 min, treated with 4-bromopyridine hydrochloride (2.81 g, 14.4 mmol) and N_2 was bubbled through the solution for an additional 5 min. 3-Bromo-2-methyl-5-thiopheneboronic acid[13] (2.90 g, 13.1 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) were immediately added and the reaction mixture was heated at reflux for 20 h under a N_2 atmosphere. The heat source was removed and the reaction mixture was allowed to slowly cool to room temperature at which time, the aqueous layer was removed and extracted with $CHCl_3$ (3×50 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness in vacuo. The product was purified using a short column (silica, hexanes/EtOAC=6:1, containing 1% of Et_3N) yielding an off-white solid. Recrystallization from EtOAc afforded pyridylthiophene **3** (2.35 g, 70%) as colourless crystals. Mp 80–82 °C (lit. 83 °C).[13] ^{1}H NMR (400 MHz, CD_2Cl_2, δ (ppm)): 8.56 (d, J=5.6 Hz, 2H), 7.38 (d, J=5.6 Hz, 2H), 7.34 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2, δ (ppm)): 150.7, 140.3, 138.1, 136.8, 128.0, 119.3, 110.6, 15.1. FTIR (KBr-cast, ν (cm^{-1})): 3056, 3027, 2910, 1598, 1494, 1412, 1324, 1222, 1159, 1008, 988, 862, 812, 760, 718. LRMS (CI isobutane): m/z 254, 256 $[M+H]^+$.

*4.4.2. 1,2-Bis(2′-methyl-5′-(pyrid-4″-yl)thien-3′-yl)perfluorocyclopentene (**4o**)[13]*

A solution of 3-bromo-2-methyl-5-pyridylthiophene **3** (199 mg, 0.787 mmol) in anhydrous THF (30 mL) was cooled to −78 °C using a dry ice/acetone bath. The solution was treated with n-BuLi (0.32 mL, 2.5 M in hexanes, 0.79 mmol) dropwise under a N_2 atmosphere. The resulting deep red solution was then treated with perfluorocyclopentene (53 μL, 0.40 mmol) through a cooled gas tight syringe whereby the solution turned green. The cooling bath was removed and the solution was allowed to slowly warm up to ambient temperature and quenched with a saturated solution of NH_4Cl (30 mL). The aqueous layer was removed and extracted with CH_2Cl_2 (3×30 mL), the combined organic layers were washed with a saturated solution of $NaHCO_3$ (100 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed using a rotary evaporator. The product was purified by flash chromatography (neutral alumina: activity II–III, hexanes/EtOAc=2:1). Recrystallization of the resulting green solid from EtOAc afforded the bis(pyridine) **4o** (123 mg, 60%) as a white powder. Mp 179–181 °C (lit. 181 °C).[13] ^{1}H NMR (400 MHz, CD_2Cl_2, δ (ppm)): 8.58 (d, J=6.0 Hz, 4H), 7.50 (s, 2H), 7.42 (d, J=6.0 Hz, 4H), 2.01 (s, 6H). ^{13}C NMR (100 MHz, CD_2Cl_2, δ (ppm)): 150.4, 143.4, 140.0, 139.3, 126.1, 124.6, 119.4, 14.5 (8 of 11 carbons found). FTIR (KBr-cast, ν (cm^{-1})): 3070, 3032, 2964, 2856, 1630, 1596, 1552, 1504, 1441, 1413, 1339, 1274, 1222, 1193, 1116, 1056, 989, 964, 896, 815, 740, 691. LRMS (CI isobutane): m/z 523 $[M+H]^+$.

*4.4.3. Photochemical synthesis of the ring-closed isomer of the bis(pyridine) (**4c**)*

A solution of the ring-open isomer of the bis(pyridine) (**4o**) (61 mg, 0.12 mmol) was dissolved in CH_3CN (20 mL) and irradiated with 312 nm light. Aliquots (2 mL) of the reaction mixture were removed via a pipette at regular intervals, concentrated to dryness in vacuo, re-dissolved in CD_3CN and monitored by ^{1}H NMR spectroscopy until a solution containing 98% of the ring-closed form **4c** was obtained. No attempts to isolate the pure ring-closed were made and the remaining 2% was assigned to the ring-open form **4o**. ^{1}H NMR (400 MHz, CD_3CN, δ (ppm)): 8.67 (d, J=6.0 Hz, 4H), 7.52 (d, J=6.0 Hz, 4H), 7.02 (s, 2H), 2.21 (s, 6H).

*4.4.4. Nitrate salt of the ring-closed isomer of 1-[5′-(pyrid-4″-yl)-2′-methylthien-3′-yl]-2-{2‴-methyl-5‴-[N-(4⁗-bromobenzylpyrid)-4⁗-yl]thien-3‴-yl}perfluorocyclopentene (**1c**)*

The ring-open isomer of the bis(pyridine) (**4o**) (61 mg, 0.12 mmol) was dissolved in anhydrous CH_3CN (20 mL) and the solution was irradiated with 312 nm light. Aliquots (2 mL) of the reaction mixture were removed via a pipette at regular intervals, concentrated to dryness in vacuo, re-dissolved in CD_3CN and monitored by ^{1}H NMR spectroscopy until a solution containing 98% of the ring-closed form **4c** was obtained. The resulting dark blue solution was treated with 4-bromobenzyl bromide (29 mg, 0.12 mmol) and left to stir at room temperature for 7 days under a N_2 atmosphere. The solvent was evaporated to dryness in vacuo and purification by flash chromatography (silica, CH_3CN to remove any unreacted **4c** followed by a mixture of CH_3CN/H_2O/a saturated solution of KNO_3=100:1:0.01) afforded the nitrate salt of ring-closed monobenzylated **1c** (39 mg, 45%) as a dark blue solid. Mp 138–140 °C. ^{1}H NMR (500 MHz, CD_3CN, δ (ppm)): 8.72 (d, J=6.5 Hz, 2H), 8.70 (d, J=6.0 Hz, 2H), 8.05 (d, J=6.5 Hz, 2H), 7.65 (d, J=8.5 Hz, 2H), 7.54 (d, J=6.0 Hz, 2H), 7.39 (d, J=8.5 Hz, 2H), 7.30 (s, 1H), 7.06 (s, 1H), 5.74 (s, 2H), 2.24 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD, δ (ppm)): 160.3, 154.5, 151.7, 151.3, 149.5, 149.3, 146.1, 141.5,

133.9, 133.7, 132.2, 126.3, 125.3, 124.5, 122.4, 118.8, 70.0, 67.8, 64.5, 25.8, 25.5 (21 of 26 carbons found). UV–vis (CH_3CN, λ_{max} (nm) ($\log \varepsilon/M^{-1}\,cm^{-1}$)): 649 (4.12). FTIR (KBr-cast, ν (cm^{-1})): 3124, 2930, 2866, 1635, 1596, 1561, 1504, 1474, 1384, 1341, 1276, 1217, 1197, 1129, 1091, 1054, 979, 933, 844, 818, 748. LRMS (MALDI-TOF): *m*/*z* 691, 693 $[M-NO_3]^+$. Anal. Calcd for $C_{32}H_{22}S_2F_6N_3BrO_3$: C, 50.94; H, 2.94; N, 5.57. Found: C, 50.62; H, 3.15; N, 5.30.

*4.4.5. Photochemical synthesis of the nitrate salt of the ring-open isomer of the monobenzylated DTCP (**1o**)*

The nitrate salt of the ring-closed isomer of monobenzylated DTCP (**1c**) (29 mg, 38 μmol) was dissolved in anhydrous CH_3CN (15 mL) and irradiated with light of wavelengths greater than 490 nm until a colourless solution was observed. Aliquots (2 mL) of the reaction mixture were removed via a pipette, concentrated to dryness in vacuo, re-dissolved in CD_3CN and monitored by ^1H NMR spectroscopy until complete disappearance of the peaks corresponding to the ring-closed isomer **1c** (methine peaks of the thiophene rings at 7.30 and 7.06 ppm) was observed. The solvent was evaporated to dryness yielding the nitrate salt of the ring-open monobenzylated DTCP **1o** (28 mg, 97%) as an off-white solid. ^1H NMR (500 MHz, CD_3CN, δ (ppm)): 8.60 (d, J=7.0 Hz, 2H), 8.57 (d, J=6.0 Hz, 2H), 8.06 (d, J=7.0 Hz, 2H), 8.00 (s, 1H), 7.65 (d, J=8.5 Hz, 2H), 7.62 (s, 1H), 7.51 (d, J=6.0 Hz, 2H), 7.36 (d, J=8.5 Hz, 2H), 5.69 (s, 2H), 2.11 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (150 MHz, CD_3CN, δ (ppm)): 151.2, 150.7, 148.9, 145.7, 145.3, 145.2, 140.7, 140.3, 136.1, 134.0, 133.1, 132.7, 132.2, 127.9, 126.6, 126.5, 126.4, 126.3, 124.2, 123.7, 62.8, 15.3, 15.0 (23 of 26 carbons found). UV–vis (CH_3CN, λ_{max} (nm) ($\log \varepsilon/M^{-1}\,cm^{-1}$)): 356 (4.37).

*4.4.6. The bis(hexafluorophosphate) salt of 1,2-bis(2′-methyl-5′-[N-(4‴-bromobenzyl)-pyrid-4″-yl]thien-3′-yl)perfluorocyclopentene (**2o**)*

The ring-open isomer of the bis(pyridine) (**4o**) (25 mg, 48 μmol) was dissolved in anhydrous CH_3CN (15 mL), treated with 4-bromobenzyl bromide (13 mg, 96 μmol) and then heated under reflux for 18 h under a N_2 atmosphere. The heating source was removed and the mixture was allowed to slowly cool down to room temperature. The solvent was removed in vacuo and the reaction mixture was sonicated with Et_2O (3×10 mL) to remove any unreacted 4-bromobenzyl bromide. The product was collected by vacuum filtration, washed with Et_2O (3×5 mL) and left to dry yielding the dibenzylated DTCP as the bromide salt. The green solid was dissolved in the minimum amount of EtOH (1 mL) and a saturated solution of NH_4PF_6 was added. The resulting pale green precipitate was collected by vacuum filtration, washed with copious amounts of water and left to dry yielding the bis(hexafluorophosphate) salt of the dibenzylated DTCP **2o** (52 mg, 96%) as a very pale green solid. Mp 230–232 °C. ^1H NMR (400 MHz, CD_3CN, δ (ppm)): 8.67 (d, J=6.8 Hz, 4H), 8.08 (d, J=6.8 Hz, 4H), 8.00 (s, 2H), 7.64 (d, J=8.4 Hz, 4H), 7.38 (d, J=8.4 Hz, 4H), 5.63 (s, 4H), 2.11 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, δ (ppm)): 151.7, 149.3, 145.5, 136.3, 133.3, 133.4, 132.5, 132.0, 127.7, 124.4, 123.9, 63.5, 15.4 (13 of 16 carbons found). UV–vis (CH_3CN, λ_{max} (nm) ($\log \varepsilon/M^{-1}\,cm^{-1}$)): 360 (4.59). FTIR (KBr-cast, ν (cm^{-1})): 3139, 1638, 1553, 1518, 1470, 1441, 1407, 1339, 1276, 1227, 1193, 1149, 1115, 1056, 988, 964, 844, 815, 748. LRMS (MALDI-TOF): *m*/*z* 691, 693 $[\mathbf{1o}-PF_6]^+$. Anal. Calcd for $C_{39}H_{28}Br_2F_6N_2S_2(PF_6)_2$: C, 40.64; H, 2.45; N, 2.43. Found: C, 40.74; H, 2.42; N, 2.23.

*4.4.7. Photochemical synthesis of the ring-closed isomer of the dibenzylated DTCP (**2c**)*

The ring-open isomer of the dibenzylated DTCP (**2o**) (2 mg) was dissolved in CD_3CN (0.7 mL) and transferred into an NMR tube. The solution was irradiated with 365 nm light and monitored by ^1H NMR spectroscopy. The progress of the photocyclization was assessed by monitoring the methine peaks of the thiophene rings (8.00 ppm for the ring-open isomer **2o** as opposed to 7.35 ppm for the ring-closed form **2c**) until the peak corresponding to the ring-open isomer **2o** was no longer observed. ^1H NMR (400 MHz, CD_3CN, δ (ppm)): 8.80 (d, J=6.4 Hz, 4H), 8.12 (d, J=6.4 Hz, 4H), 7.67 (d, J=8.0 Hz, 4H), 7.41 (d, J=8.0 Hz, 4H), 7.35 (s, 2H), 5.72 (s, 4H), 2.28 (s, 6H). UV–vis (CH_3CN, λ_{max} (nm) ($\log \varepsilon/M^{-1}\,cm^{-1}$)): 670 (4.03).

4.5. Fitting of the collected data

Linear least squares regression analysis of the data for the independent reaction of the ring-open and the ring-closed isomers of the monobenzylated dithienylcyclopentene (DTCP) (**1o** and **1c**) with an excess of 4-bromobenzyl bromide and the in situ reaction of both the ring-open and the ring-closed isomers of the monobenzylated DTCP (**1o** and **1c**) with an excess of the 4-bromobenzyl bromide were performed using the commercially available Excel Data Analysis Tool Package. Non-linear least squares regression analysis of the data for the reaction of both the ring-open (**4o**) and the ring-closed (**4c**) isomers of the bis(pyridine) with an excess of the 4-bromobenzyl bromide were completed using a free trial version of GraphPad Prism Software.

4.6. Kinetic analysis

All data were treated using *pseudo*-first-order kinetic analysis by adding an excess of 4-bromobenzyl bromide and using the following equation:

$$\frac{d[DTCP]}{dt} = k'[DTCP]$$

where $k'=k$[4-bromobenzyl bromide].

Graphical treatment of the data by plotting the natural log of the concentration of [DTCP] against time gives a straight line with a slope of $-k'$ where k' is the *pseudo*-first-order rate constant.

$$\ln[DTCP]_t = -k't + \ln[DTCP]_0$$

4.6.1. Experiment to ensure pseudo-first-order kinetics

The validity of using *pseudo*-first-order kinetics was determined by monitoring three samples of different concentrations (1.9, 2.8 and 3.8 mM) of DTCP **1o**. The apparent *pseudo*-first-order rate constants (k') were calculated to be $(2.9\pm0.1)\times10^{-5}$, $(2.9\pm0.1)\times10^{-5}$ and $(2.8\pm0.1)\times10^{-5}$ s^{-1}.

A solution of the ring-open isomer (**1o**) of the monoalkylated DTCP (1.0 mg, 1.3 μmol) in CD_3CN (0.70 mL) was prepared and transferred into an NMR tube. The solution was treated with an excess of 4-bromobenzyl bromide (13 mg, 52 μmol) and the sample was immediately placed in the NMR instrument, which was already set to 22 °C. The sample was kept in the probe throughout the reaction and the progress of the reaction was monitored over a period of 24 h. By measuring the relative integrals of the areas under the peaks corresponding to the starting monobenzylated DTCP **1o** and the dibenzylated DTCP **2o** generated, the mole fractions $\chi_{\mathbf{1o}}$ and $\chi_{\mathbf{2o}}$ (corresponding to the monobenzylated DTCP **1o** and the dibenzylated DTCP **2o**, respectively) were obtained. From these values, a plot of the natural log of the concentration of **1o** against time was obtained allowing the apparent *pseudo*-first-order rate constant, k', to be determined using linear least squares regression analysis of the data. The alkylation reaction was repeated twice more following the described procedure using a solution of the ring-open isomer (**1o**) of the monoalkylated DTCP (1.5 mg, 2.0 μmol) in CD_3CN (0.70 mL) and a solution of the ring-open isomer (**1o**) of the monoalkylated DTCP (2.0 mg, 2.7 μmol) in CD_3CN (0.70 mL), all the

while keeping the concentration of the 4-bromobenzyl bromide (13 mg, 52 μmol, 7.3×10^{-2} M) constant. The calculated apparent *pseudo*-first-order rate constants were very similar for all three samples regardless of the initial concentration of the monobenzylated DTCP **1o** consistent with a *pseudo*-first-order pattern.

4.6.2. Kinetics experiments for the alkylation reaction of the ring-open isomer (*1o*) of the monobenzylated DTCP under pseudo-first-order conditions

A stock solution (2.4×10^{-3} M) of the ring-open isomer (**1o**) of the monoalkylated DTCP (12 mg, 16 μmol) in CD_3CN (6.5 mL) was prepared and a known volume of that solution (0.70 mL, 1.71 μmol) was transferred into an NMR tube. The solution was treated with an excess of 4-bromobenzyl bromide (13 mg, 52 μmol) and the sample was immediately placed in the NMR instrument, which was already set to 22 °C. The sample was kept in the probe throughout the reaction and the progress of the reaction was monitored by ^{1}H NMR spectroscopy over a period of 24 h. By measuring the relative integrals of the areas under the peaks corresponding to the starting monobenzylated DTCP **1o** and the dibenzylated DTCP **2o** generated, the mole fractions $\chi_{\mathbf{1o}}$ and $\chi_{\mathbf{2o}}$ (corresponding to the monobenzylated DTCP **1o** and the dibenzylated DTCP **2o**, respectively) were obtained. From these values, a plot of the natural log of the concentration of **1o** against time was obtained allowing the apparent *pseudo*-first-order rate constant, $k'_{\mathbf{1o}}$, to be determined using linear least squares regression analysis of the data. To test the reproducibility of the results, the alkylation reaction was repeated twice following the described procedure using samples prepared from the same stock solution (2.4×10^{-3} M) of the ring-open isomer **1o** in CD_3CN. From these values, the average apparent *pseudo*-first-order rate constant, $k'_{\mathbf{1o}}$, for the alkylation reaction of the ring-open isomer (**1o**) of the monobenzylated DTCP was calculated to be $(2.9\pm0.1)\times10^{-5}$ s^{-1}.

4.6.3. Kinetics experiments for the alkylation reaction of the ring-closed isomer (*1c*) of the monobenzylated DTCP under pseudo-first-order conditions

The same volume (0.70 mL, 1.71 μmol) of the stock solution (2.4×10^{-3} M) of the ring-open isomer (**1o**) of the monoalkylated DTCP (12 mg, 16 μmol) in CD_3CN (6.5 mL), used for the previous experiment, was transferred into an NMR tube. The solution was irradiated with 365 nm light until the methine peaks of the thiophene rings corresponding to the ring-open isomer **1o** (8.00 and 7.62 ppm for the ring-open isomer **1o** as opposed to 7.30 and 7.06 ppm for the ring-closed form **1c**) were no longer observed, as monitored by ^{1}H NMR spectroscopy. The resultant dark bluish solution was treated with an excess of 4-bromobenzyl bromide (13 mg, 52 μmol) following the same procedure used for the ring-open isomer **1o** and the progress of the reaction was monitored under the same conditions for 24 h. Graphical treatment of the data by plotting the natural log of the concentration of monobenzylated DTCP **1c** against time followed by a linear least squares regression analysis of the data gave the apparent *pseudo*-first-order rate constant, $k'_{\mathbf{1c}}$. To test the reproducibility of the results, the alkylation reaction was repeated twice following the described procedure using samples prepared from the same stock solution (2.4×10^{-3} M) of the ring-open isomer (**1o**) in CD_3CN. From these values, the average apparent *pseudo*-first-order rate constant, $k'_{\mathbf{1c}}$, for the alkylation reaction of the ring-closed isomer (**1c**) of the monobenzylated DTCP was calculated to be $(9.0\pm0.5)\times10^{-6}$ s^{-1}.

4.6.4. In situ photomodulation of the alkylation reaction of the ring-open (*1o*) and the ring-closed (*1c*) isomers of the monobenzylated DTCP under pseudo-first-order conditions

A stock solution (2.4×10^{-3} M) of the ring-open isomer (**1o**) of the monoalkylated DTCP (1.8 mg, 2.4 μmol) in CD_3CN (1.0 mL) was prepared and a known volume of that solution (0.70 mL, 1.67 μmol) was transferred into a quartz NMR tube. The solution was treated with an excess of 4-bromobenzyl bromide (13 mg, 52 μmol) following the same procedure used for the ring-open isomer **1o** and the ring-closed isomer **1c** and the progress of the reaction was monitored under the same conditions at regular intervals of time by ^{1}H NMR spectroscopy. After about 3 h, the NMR tube was irradiated with 365 nm light until the peaks corresponding to the ring-open reactant **1o** (monobenzylated DTCP) and the ring-open product **2o** (dibenzylated DTCP) were no longer observed. The sample was quickly placed in the NMR probe and the progress of the reaction was monitored under the same conditions at regular intervals of time. After another 3 h, the sample was irradiated with light of wavelengths greater than 490 nm until the peaks corresponding to the ring-closed species were no longer observed. Such in situ switching by alternating irradiation at 365 and >490 nm over 3 h intervals was repeated. Graphical treatment of the data in a similar fashion to the method already described for the reaction of independent solutions of the ring-open (**1o**) and the ring-closed (**1c**) isomers showed that the apparent rate constants for the two ring-opening steps are very close in value ($k'_A=(3.0\pm0.1)\times10^{-5}$ s^{-1} and $k'_C=(3.0\pm0.1)\times10^{-5}$ s^{-1}) and that of the two ring-closing steps are also similar ($k'_B=(1.0\pm0.1)\times10^{-5}$ s^{-1} and $k'_D=(9.9\pm0.1)\times10^{-6}$ s^{-1}).

4.6.5. Kinetics experiment for the alkylation reaction of the ring-open isomer (*4o*) of the bis(pyridine) under consecutive pseudo-first-order conditions

A stock solution (4.6×10^{-3} M) of the ring-open isomer (**4o**) of the bis(pyridine) (5.1 mg, 9.7 μmol) in CD_3CN (2.1 mL) was prepared and a known volume of that solution (0.70 mL, 3.3 μmol) was transferred into an NMR tube. The solution was treated with an excess of 4-bromobenzyl bromide (22 mg, 87 μmol) following the same procedure used for the alkylation reactions of the ring-open (**1o**) and the ring-closed (**1c**) isomers of the monobenzylated DTCP and the progress of the reaction was monitored under the same conditions for 10 h. By measuring the relative integrals of the areas under the peaks corresponding to the starting bis(pyridine) **4o**, the generated monobenzylated DTCP **1o** (as an intermediate) and the generated dibenzylated DTCP **2o**, the mole fractions $\chi_{\mathbf{4o}}$, $\chi_{\mathbf{1o}}$, and $\chi_{\mathbf{2o}}$ (corresponding to the bis(pyridine) **4o**, the monobenzylated DTCP **1o** and the dibenzylated DTCP **2o**, respectively) were obtained. From these values, a plot of the relative concentrations for all three species (**4o**, **1o** and **2o**) against time was obtained. The average apparent *pseudo*-first-order rate constants, $k'_{\mathbf{1o}} = (1.2\pm0.1)\times10^{-4}$s^{-1} and $k'_{\mathbf{1o}} = (5.4\pm0.2)\times10^{-5}$s^{-1}, corresponding to the two consecutive *pseudo*-first-order alkylation steps, were obtained after non-linear regression analysis of the data.

4.6.6. Kinetics experiment for the alkylation reaction of the ring-closed isomer (*4c*) of the bis(pyridine) under consecutive pseudo-first-order conditions

The same volume (0.70 mL, 3.3 μmol) of the stock solution (4.6×10^{-3} M) of the ring-open isomer (**4o**) of the bis(pyridine) (5.1 mg, 9.7 μmol) in CD_3CN (2.1 mL), used for the previous experiment, was transferred into an NMR tube. The solution was irradiated with 313 nm light by monitoring the methine peaks of the thiophene rings (7.63 ppm for the ring-open isomer **4o** as opposed to 7.02 ppm for the ring-closed form **4c**) until a solution containing 98% of the ring-closed isomer **4c** was observed. Without attempting to isolate the pure ring-closed isomer **4c**, the solution was treated with an excess of 4-bromobenzyl bromide (22 mg, 87 μmol) following the same procedure used for the ring-open isomer and the progress of the reaction was monitored under the same conditions for 17 h. Graphical treatment of the data by plotting the

relative concentrations of the bis(pyridine) **4c**, the monobenzylated DTCP **1c** and the dibenzylated DTCP **2c** against time, followed by non-linear least squares regression analysis of the data, gave the average apparent *pseudo*-first-order rate constants, $k'_{\mathbf{3c}} = (4.6 \pm 0.3) \times 10^{-5} s^{-1}$ and $k'_{\mathbf{4c}} = (1.5 \pm 0.1) \times 10^{-5} s^{-1}$, corresponding to the two consecutive *pseudo*-first-order alkylation steps.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.050.

References and notes

1. Valkenberg, M. H.; Holderich, W. F. *Catal. Rev.* **2002**, *44*, 321–374.
2. *Dynamic Studies in Biology: Phototriggers, Photoswitches and Caged Biomolecules*; Goeldner, M., Givens, R., Eds.; Wiley-VCH: Weinheim, Germany, 2005.
3. Saltzman, W. M. *Drug Delivery: Engineering Principles for Drug Therapy*; Oxford University Press: New York, NY, 2001.
4. (a) McCoy, C. P.; Rooney, C.; Jones, D. S.; Gorman, S. P.; Nieuwenhuyzen, M. *Pharm. Res.* **2007**, *24*, 194–200; (b) Denny, W. A. *Eur. J. Med. Chem.* **2001**, *36*, 577–595.
5. (a) Special issue on photochromism: Irie, M. *Chem. Rev.* **2000**, *100*, 1685–1716; (b) Irie, M. In *Molecular Switches*; Feringa, B. L., Ed.; Wiley-VCH: Weinheim, Germany, 2001; pp 37–62; (c) Irie, M. In *Photochromic and Thermochromic Compounds*; Crano, J. C., Guglielmetti, R. J., Eds.; Plenum: New York, NY, 1999; Vol. 1, pp 207–222; (d) Tian, H.; Yang, S. *Chem. Soc. Rev.* **2004**, *33*, 85–97; (e) Tian, H.; Wang, S. *Chem. Commun.* **2007**, 781–792.
6. (a) Takeshita, M.; Uchida, K.; Irie, M. *Chem. Commun.* **1996**, 1807–1808; (b) Kawai, S. H. *Tetrahedron Lett.* **1998**, *39*, 4445–4448; (c) Takeshita, M.; Irie, M. *J. Org. Chem.* **1998**, *63*, 6643–6649; (d) Mulder, A.; Jukovic, A.; van Leeuwen, F. W. B.; Kooijman, H.; Spek, A. L.; Huskens, J.; Reinhoudt, D. N. *Chem.—Eur. J.* **2004**, *10*, 1114–1123.
7. Sud, D.; Norsten, T. B.; Branda, N. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2019–2021.
8. (a) Kawai, S. H.; Gilat, S. L.; Lehn, J.-M. *Eur. J. Org. Chem.* **1999**, 2359–2366; (b) Odo, Y.; Matsuda, K.; Irie, M. *Chem.—Eur. J.* **2006**, *12*, 4283–4288.
9. (a) Lemieux, V.; Branda, N. R. *Org. Lett.* **2005**, *7*, 2969–2972; (b) Lemieux, V.; Gauthier, S.; Branda, N. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 6820–6824.
10. Sud, D.; Wigglesworth, T. J.; Branda, N. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 8017–8019.
11. Samachetty, H. D.; Branda, N. R. *Chem. Commun.* **2005**, 2840–2842.
12. (a) Vaidya, R. A.; Mathias, L. J. *J. Am. Chem. Soc.* **1986**, *108*, 5514–5520; (b) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129–161; (c) Bender, M. L.; Turnquest, B. W. *J. Am. Chem. Soc.* **1957**, *79*, 1652–1655.
13. Gilat, S. L.; Kawai, T.; Lehn, J.-M. *Chem.—Eur. J.* **1995**, *1*, 275–284.
14. All ring-closing reactions were carried out using the light source from a lamp used for visualizing TLC plates at 312 or 365 nm (Spectroline E series, 470 W cm^{-2}). The ring-opening reactions were carried out using the light of a 300 W halogen photo-optic source passed through a 490 nm cut-off filter to eliminate higher energy light.
15. The signals in the ^1H NMR spectra of both isomers were assigned using ^1H–^1H COSY and selective 1D NOE experiments.
16. See Supplementary data for details.
17. The treatment of all data using *pseudo*-first-order kinetic analysis should be valid assuming all substitution reactions of the DTCP derivatives with DTCP **1o** proceed by an S_N2 pathway, which exhibit overall second-order kinetics. Adding a sufficiently high concentration of the alkylating reagent so that its concentration remains constant during the course of the reaction reduces the reaction to one governed by *pseudo*-first-order kinetics. However, one important assumption for this to hold true is that there is no significant back reaction. The term apparent *pseudo*-first-order rate constant will be used throughout this paper in order to take into account any back reaction where the apparent *pseudo*-first-order rate constant refers to the sum of the forward *pseudo*-first-order rate constant and the backward *pseudo*-first-order rate constant.
18. The validity of using *pseudo*-first-order kinetics was determined by monitoring three samples of different concentrations (1.9, 2.8 and 3.8 mM) of 4-bromobenzyl bromide. The apparent *pseudo*-first-order rate constants (k') were calculated to be $(2.9\pm0.1)\times10^{-5}$, $(2.9\pm0.1)\times10^{-5}$ and $(2.8\pm0.1)\times10^{-5}$ s^{-1}, respectively.
19. The time delay during the ^1H NMR acquisition was set 5 times larger than the largest longitudinal relaxation T_1 value to ensure that the peak intensities of protons H_a in **1o** and **1c** correspond to the number of protons present and allows the relative number of different protons to be determined by measuring the areas under the peaks.
20. Linear regression was performed using the *Microsoft Excel Data Analysis Tool Package*.
21. All kinetic experiments were done in triplicate.
22. A CD_3CN solution of the photostationary state containing at least 98% of ring-closed **1c** was prepared using the same stock solution (2.4×10^{-3} M) of the ring-open isomer (**1o**) used for the kinetic analysis by irradiating it with 365 nm light until complete ring cyclization was achieved as monitored by ^1H NMR spectroscopy.
23. The photochemical cycling studies on independent solutions of the monobenzylated DTCP (**1**) and the dibenzylated DTCP (**2**) indicate that both DTCP compounds can be toggled between their ring-open and their ring-closed isomers numerous times without observable degradation and that both the ring-closing and ring-opening reactions proceed with a high photostationary state. See Supplementary data for details.
24. The data was collected from nine integrations of the areas under the peaks in the ^1H NMR spectra. Error was estimated as 2%, which is less than the size of the circles plotted for each data point in the figure.
25. These studies were carried out in the absence of an internal standard because the ^1H NMR spectra of the bis(pyridine), the monoalkylated DTCP and the dialkylated DTCP showed no apparent signs of degradation during the course of the reaction.
26. The least squares regression analysis was performed using the software GraphPad Prism.
27. This solution was prepared by irradiating the solution of **4o** in an NMR tube with 312 nm light until complete ring cyclization was achieved as monitored by ^1H NMR spectroscopy.
28. Nair, V.; Pillai, A. N.; Menon, R. S.; Suresh, E. *Org. Lett.* **2005**, *7*, 1189–1191; (b) Nair, V.; Shreekanth, A. R.; Abhilash, N.; Biju, A. T.; Remadevi, B.; Menon, R. S.; Rath, N. P.; Srinivas, R. *Synthesis* **2003**, 1895–1902.