## Oxetane Ring Enlargement through Nucleophilic Trapping of Radical Cations by Acetonitrile

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Oxidative electron transfer cycloreversion of *trans,trans*-2-cyclopropyl-4-methyl-3-phenyloxetane, using triphenylthiapyrylium perchlorate as a photosensitizer, leads to distonic 1,4-radical cations; subsequent cleavage gives rise to fragmentation products (pathway a), whereas nucleophilic trapping by acetonitrile affords a ring expanded oxazine (pathway b).

Photocycloaddition of carbonyl compounds to alkenes (Paterno–Büchi photoreaction) provides a straightforward entry to oxetanes, which are versatile building blocks for organic synthesis.<sup>1</sup> Cycloreversion (CR) of oxetanes can occur through cleavage of the two bonds formed in the photocycloaddition reaction, yielding the starting materials or, more interestingly, the formal metathesis products.<sup>2</sup> This CR can be initiated by photosensitized electron

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Semiempirical AM1 and PM3 calculations on the photoenzymatic repair of (6-4) DNA photoproducts by photolyases<sup>6</sup> point to a nonconcerted, two-step mechanism for cleavage of oxetane radical cations *via* initial C–C bond cleavage. In addition, DFT calculations at

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Scheme 1. Analysis of the Reaction Pathways Involving C–C and O–C Bond Breaking of Oxetane Radical Cation  $1^{++}$ , in the Absence and in the Presence of Acetonitrile, Together with Selected UMP2/6-31G(d)/PCM(Acetonitrile) Relative Energies (in kcal mol<sup>-1</sup>)



the UB3LYP/6-31G\* level point to CR taking place in a concerted but asynchronous process, where C–C breaking is more advanced than O–C breaking at the transition state.<sup>7</sup> Experimental work on the PET CR of 2,3-diphenyloxetanes with (thia)pyrylium salts are in better agreement with an initial O–C<sub>2</sub> cleavage.<sup>4b</sup>

With this background, we have undertaken an experimental and theoretical investigation on the PET CR of oxetane **1**. The choice of **1**, bearing a cyclopropyl group at  $C_2$ , was based on several reasons: (i) replacement of H by cyclopropyl in an alkyl cation does not result in a decreased charge density on the involved carbon atom,<sup>8</sup> (ii) aryl substitution is associated, instead, with the charge delocalization typical of benzylic cations,<sup>4</sup> and (iii) anodic oxidation of cyclopropylmethyl iodide to the corresponding carbocation, followed by Ritter reaction with acetonitrile and eventual hydrolysis, affords *N*-(cyclopropylmethyl)acetamide as a trapping product.<sup>9,10</sup>

The target oxetane **1** was obtained by Paternò–Büchi photocycloaddition of *trans-β*-methylstyrene (**2**) and cyclopropanecarboxaldehyde (**3**). Sensitized photolysis of **1** was performed in the presence of catalytic (10%) amounts of 2,4,6-triphenylthiapyrylium perchlorate (**TPTP**), in acetonitrile/N<sub>2</sub> at  $\lambda_{max} = 350$  nm (Gaussian distribution). The course of the reaction was followed by GC-MS and <sup>1</sup>H NMR spectroscopy. Conversion of **1** was nearly quantitative after 180 min of irradiation (see Supporting Information, SI, p S18). Three products were found in a photomixture: **2** + **3** (35%) and a solvent adduct **4** (60%). The structure of **4** was assigned as *cis,trans*-4-cyclopropyl-2,6-dimethyl-5-phenyl-4*H*-5,6-dihydro-1,3-oxazine, on the basis of NMR experiments (SI, pp S9–S11) including NOE measurements (SI, pp S12 and S13). These data indicate that  $H_2$ ,  $H_3$  and the CH<sub>3</sub> group are within the same face of the oxazine plane (Figure 1).



**Figure 1.** Structural assignment of the acetonitrile adduct **4**. NOE interactions and relevant chemical shifts.

When the PET CR of **1** was perfomed in deuterated acetonitrile the deuterated analog (*cis*,*trans*-4-cyclopropyl-2-(methyl- $d_3$ )-6-methyl-5-phenyl-4*H*-5,6-dihydro-1,3-oxazine) was obtained (see SI, pp S14–S17). Using benzonitrile as solvent, the corresponding nitrile adduct was also detected by MS (M<sup>•+</sup> = 291, SI, p S19).

To disclose the nature of the **TPTP** excited state involved in the PET process, quenching experiments were carried out. Thus, the fluorescence intensity of **TPTP** decreased upon addition of increasing amounts of **1** (Figure 2A). The quenching rate constant  $k_q(S_1)$  was obtained from the Stern–Volmer analysis;<sup>11</sup> it was found to be  $2.6 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ ,

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indicating a nearly diffusion-controlled process (Figure 2A, inset). In addition, laser flash photolysis (LFP) of **TPTP** ( $\lambda_{exc} = 355$  nm, MeCN/N<sub>2</sub>) gave rise to the typical triplet-triplet absorption (Figure 2B, inset); its monitoring at 600 nm, in the presence of **1**, revealed no dynamic quenching, although the end-of-pulse absorbance clearly decreased with increasing concentrations of **1** (Figure 2B). The combined fluorescence and LFP results indicate that the reaction takes place from the singlet excited state of the photosensitizer. This agrees well with the estimation of the free energy changes associated with electron transfer from both excited states (SI, p S21) using the Rehm–Weller relationship.<sup>12</sup>



**Figure 2.** (A) Fluorescence spectra of **TPTP** at 0.03 mM concentration ( $\lambda_{exc} = 435$  nm, MeCN/air) in the presence of increasing amounts of **1**; inset: Stern–Volmer plot to obtain  $k_q(S_1)$ . (B) Decay traces of the T–T absorption of **TPTP** (0.06 mM) measured at 600 nm in the presence of increasing amounts of **1**: 0 mM (black), 1 mM (red), 3.5 mM (green) and 5 mM (blue); inset: transient absorption spectrum of **TPTP** (0.06 mM) recorded 0.2  $\mu$ s after the laser pulse.

The proposed PET mechanism is outlined in Scheme 1. In principle, cleavage of  $C_2-C_3$  (a) or  $O-C_2$  (b) can occur. Following pathway (a), a distonic 1,4-radical cation with spin and charge located in  $C_3$  and  $C_2$ , respectively, would be formed. This should be favored through stabilization of the carbocationic site by oxygen as an oxonium ion. Subsequent  $O-C_4$  bond cleavage would afford  $2^{*+}$  and 3;

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eventually, back-electron transfer from the thiopyranyl radical to  $2^{\bullet+}$  would lead to  $2^{\cdot13}$  The competitive route (b) would involve formation of a different distonic 1,4-radical cation with spin located in the oxygen and charge in C<sub>2</sub>. The higher degree of charge localization in this intermediate would favor nucleophilic attack of acetonitrile at C<sub>2</sub>, leading to the corresponding nitrilium derivative; ring closure and back-electron transfer would justify formation of the observed product 4. The absence of 5 and 6 in the photomixture indicates that trapping of the C<sub>2</sub> located carbocation by acetonitrile occurs faster than C<sub>3</sub>-C<sub>4</sub> bond cleavage. In addition, the initial *trans* arrangement of phenyl and cyclopropyl groups in 1 is no longer maintained in 4, so C<sub>2</sub>-C<sub>3</sub> bond rotation must occur along the reaction path.

In order to rule out the possibility that the ring expansion observed under PET conditions results from the wellknown acid catalyzed process,<sup>14</sup> due to the presence of adventitious acid traces generated by partial hydrolytic ring opening of **TPTP**, a series of control experiments were performed. Thus, **1** was irradiated in deuterated acetonitrile for 120 min in the presence of **TPTP**, and the reaction mixture was analyzed by <sup>1</sup>H NMR. At this stage, formation of **2**, **3**, and **4**-*d*<sub>3</sub> was clearly observed (compare Figures 3A and 3B). Interestingly, after an additional 120 min in the dark, no significant changes in the <sup>1</sup>H NMR spectrum were noticed (Figure 3C).



**Figure 3.** <sup>1</sup>H NMR spectra of deuterated acetonitrile solutions of (A) **1** (8 mM) + **TPTP** (0.8 mM) before irradiation; (B) **1** (8 mM) + **TPTP** (0.8 mM) after 120 min of irradiation at  $\lambda_{max}$  = 350 nm; and (C) **1** (8 mM) + **TPTP** (0.8 mM) after 120 min of irradiation at  $\lambda_{max}$  = 350 nm plus 120 min in the dark.

Conversely, when catalytic amounts of HClO<sub>4</sub> were added to a freshly prepared solution of **1** in the same solvent, <sup>1</sup>H NMR measurements revealed formation of **4**- $d_3$  and a total absence of **2**, **3**, **5**, or **6**. The results of these control experiments unambiguously prove that different

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mechanisms operate in the PET and acid catalyzed processes.

The PET reactions of oxetane **1** were submitted to theoretical calculations at the UMP2(FC)/6-31G(d) level.<sup>15</sup> Due to the intermediacy of positively charged species, solvent effects (acetonitrile) were considered using Tomasi's polarized continuum model (PCM).<sup>16</sup>

The stationary points found along the potential energy surface (PES) of the O–C and C–C bond breaking of  $1^{++}$  are depicted in Scheme 1, together with the corresponding relative energies. Energy profiles of selected reaction paths can be found in Figure 4. Since energy barriers for bond cleavage involving C<sub>4</sub> are between 7 and 15 kcal mol<sup>-1</sup> higher than those involving C<sub>2</sub>, they will not be discussed further.



Figure 4. Relative energies of the transition states and intermediates involved in the PET reactions of 1<sup>•+</sup>; inset: relative free energy of transition state, TS22.

Starting from  $1^{\bullet+}$ , ring splitting to give  $2^{\bullet+} + 3$  or  $5^{\bullet+} + 6$ , as well as ring enlargement affording oxazine 4, takes place *via* a stepwise mechanism. The initial C<sub>2</sub>-C<sub>3</sub> or O-C<sub>2</sub> bond-breaking energy barriers associated with TS11 and TS21 are 15.0 and 16.0 kcal mol<sup>-1</sup>, respectively. Regarding the corresponding intermediates, formation of IN11 is slightly exothermic (-0.5 kcal mol<sup>-1</sup>), while that of IN21 is endothermic (8.0 kcal mol<sup>-1</sup>). Breaking of the O-C<sub>4</sub> bond at IN11 yielding  $2^{\bullet+} + 3$  (which would

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complete a formal cycloreversion to the starting materials employed for the Paterno-Büchi synthesis of 1) proceeds through a barrier of only 5.6 kcal  $mol^{-1}$ . The reaction path toward  $5^{\bullet+}$  + 6, which constitutes a formal metathesis cycloreversion, shares the starting stationary point (IN21) with ring enlargement to oxazine  $4^{\bullet+}$ . From this saddle point, the energy barrier for  $C_3 - C_4$  bond breaking, to give  $5^{++}$  + 6 through TS24, is 32.8 kcal mol<sup>-1</sup>, which rules out the possibility of formal metathesis cycloreversion. In the presence of acetonitrile as solvent, intermediate IN21 undergoes a nucleophilic attack at C<sub>2</sub> giving rise to IN22 via TS22. In the energy profile, TS22 is below IN21; however, considering the entropy contribution due the bimolecular nature of this step, a free energy barrier of 5.3 kcal  $mol^{-1}$  is obtained. A conformational equilibrium is established between IN22 and IN23 before intramolecular nucleophilic attack, which yields 4<sup>•+</sup>. No transition state TS23 could be found over the PES at UMP2(FC) level; however, this stationary point was confirmed by using density funcional methodogy at UB3LYP/6-31G(d)/PCM (acetonitrile) or UM06-2X/6-31G(d)/PCM (acetonitrile) levels. Backelectron transfer (BET) could take place from the thiapyranyl radical to 4<sup>•+</sup> or to IN23/IN24 to give an alkoxide, which is an excellent nucleophile and would cyclize onto the electron-deficient carbon of the nitrilium moiety in an essentially barrierless process.

To further the energetic discussion, both TS12 and TS22 are below the transition states of the first step. Therefore, the kinetic control exerted by the initial ring opening, together with the small energy difference found between TS11 and TS21 and the activation barrier of the process yielding  $5^{\bullet+} + 6$  (formal metathesis), explains the experimentally observed formation of the cycloreversion products 2 and 3, in addition to oxazine 4.

In summary, initial  $O-C_2$  bond cleavage of the oxetane ring under PET conditions leads to a distonic 1,4-radical cation, which is trapped by acetonitrile to give a ring expanded oxazine adduct. This is a new reaction, which formally constitutes the creation of a six-membered heterocyclic ring from C=C, C=O, and C=N units. In addition, splitting of the oxetane radical cation, through stepwise cleavage of the C<sub>2</sub>-C<sub>3</sub> and O-C<sub>4</sub> bonds, results in a retro-Paterno-Büchi reaction.

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**Supporting Information Available.** Additional experimental details, <sup>1</sup>H and <sup>13</sup>C NMR spectra (including DEPT and NOESY); computational methods; geometry of the stationary points (Cartesian coordinates); structures of the transition states and intermediates involved in the PET CR of 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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