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Stepwise Cycloreversion of Oxetane Radical Cations with Initial C−O Bond Cleavage

Miguel A. Miranda* and M. Angeles Izquierdo

Departamento de Química/Instituto de Tecnología Química UPV- CSIC, Universidad Politécnica de Valencia, Camino Vera s/n, Apdo. 22012, 46022, Valencia, Spain

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Cycloreversion (CR) of oxetanes by photoinduced electron transfer (PET) has attracted considerable interest, as this process appears to be involved in the enzymatic repair of the (6−4) photoproducts of the DNA dipyrimidine sites by photolyase.[1] Although photoreducing sensitization is the mode usually operating in biological systems,[2] the photooxidative approach is considered to be relevant for DNA repair therapies.[3] Further, CR of oxetane radical cations is known to occur in the gas phase (MS), where the molecular ions are hardly detected due to their instability under the ionization conditions.[4]

Nonconcerted, two-step mechanisms have been proposed for the splitting of oxetane radical cations based on the loss of stereochemistry of the products obtained under PET conditions.[5] Although a concerted route cannot be ruled out from these results, the stepwise mechanism appears more likely due to the presence of a heteroatom (Scheme 1).[6]

Theoretical calculations on the cationic ET cycloreversion of oxetanes point to an initial C−C bond breaking (Scheme 1, pathway b_1) according to free energy changes estimated for the gas-phase reaction.[4,6] By contrast, the anionic ET cycloreversion of (6−4) photoproducts of DNA dipyrimidine sites appears to start with C−O cleavage.[6] This possibility (Scheme 1, pathway a_1) should also be considered in the cationic CR.

Formation of the neutral carbonyl/olefin units requires a back electron transfer (BET) step. In nonconcerted mechanisms, BET could take place either prior to (Scheme 1, pathways a_2 and b_2) or after the second bond breaking process (Scheme 1, pathway d). Time-resolved studies have provided no direct evidence for the concerted versus stepwise nature of ring splitting.[7]

Thus, the mechanism of PET cycloreversion of oxetanes is still unclear. In particular, the following points have to be clarified: (a) the involvement of a concerted or stepwise mechanism, (b) the nature of the first bond breaking, and (c) the location of spin and charge in the intermediates.

Intramolecular nucleophilic trapping of the carbocationic site has been reported as an elegant tool for elucidating the intermediates involved in several PET reactions, such as the photooxygenation of diphenylalkenes[8] or the denitrogenation of bicyclic azoalkanes.[9] In the present work, a similar strategy has been employed to gain conclusive mechanistic insight into the CR of oxetane radical cations. Thus, the hydroxymethyl-substituted oxetane **1** has been submitted to steady-state and time-resolved photolysis studies, using triaryl(thia)pyrylium salts **2a**−**c**[10] as electron-transfer sensitizers (Chart 1). The results clearly show that the process occurs through a nonconcerted mechanism involving initial cleavage of the C−O bond (Scheme 1, pathway $a_1 + a_3 +$ d).

Scheme 1

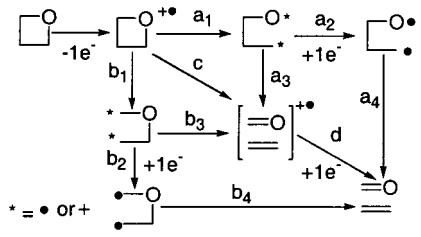
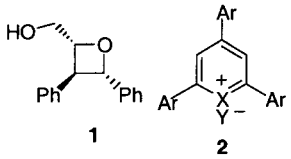


Chart 1



sensitizer	X	Y	Ar
2a	O	BF_4	Ph
2b	S	ClO_4	Ph
2c	O	BF_4	*p*-Br-C_6H_4

Compound **1** was prepared by Paterno−Büchi photoaddition of cinnamyl alcohol to benzaldehyde.[11] Irradiation of **1** in the presence of **2a**−**c** produced stilbene **3,** 2,5-dihydroxy-1,4-dioxane (the dimer of hydroxyacetaldehyde), and a new product whose structure was safely assigned as **4a,** based on NMR and MS data.[12] As expected from involvement of the triplet sensitizer,[7] the highest conversion was achieved with **2b** (Table 1), where intersystem crossing is most efficient.

From the ^{1}H and ^{13}C NMR data of **4a** (including coupling constants and NOE effects) it is clear that the initial *trans*-diphenyl arrangement of **1** is also present in the photoproduct; thus isomerization to **4b** via C_2-C_3 rotation (Scheme 2) does not take place to a significant extent.

Isolation of **3** indicates that CR involves cleavage of the $O-C_2$ and C_3-C_4 bonds. Not even traces of cinnamyl alcohol or benzaldehyde (arising from C_2-C_3/C_4-O splitting) were detected. Formation of **4a** is explained as outlined in Scheme 2. Initial cleavage along pathway a_1 gives rise to a distonic radical cation, where spin and charge are located in the oxygen and the C_2 atoms, respectively. This intermediate can undergo either further C−C scission (pathway a_3), to give **3**, or intramolecular nucleophilic attack leading to **4a**. The latter process must occur somewhat slower, as indicated by the **3**/**4a** product ratio (see Table 1), which is consistently about 2.7:1. At the present stage, it is not possible to exclude the possibility that cleavage of the $O-C_2$ and C_3-C_4 bonds takes place to some extent via a concerted mechanism (Scheme 1, pathway c), which might compete with the nonconcerted one.

In principle, ring splitting of $\mathbf{1}^{+\bullet}$ to give **3** might also have occurred via initial C_3-C_4 bond cleavage. However, in this case, intramolecular nucleophilic trapping should lead to **5** (Scheme 2).

* Corresponding author. E-mail: mmiranda@qim.upv.es.

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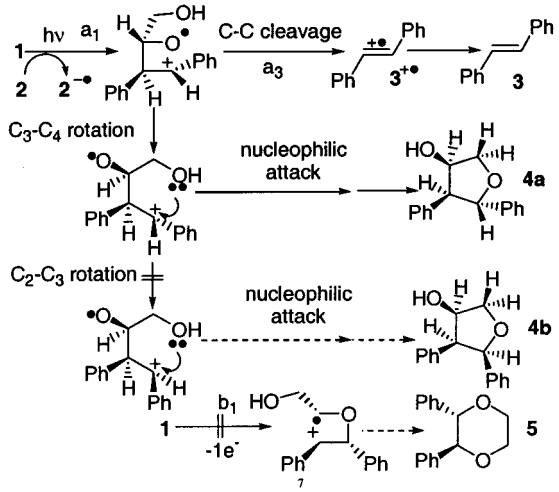
Table 1. Product Yields in the PET CR of **1** Sensitized by **2a**−**c**[a]

sensitizer[b]	unreacted **1**[c]	**3**[c]	4a[c]
2a	35	48	17
2b		73	27
2c	52	32	16

[a] Oxetane **1**, 6×10^{-2} M; sensitizer, 10^{-3} M; $CDCl_3$; argon; Luzchem multilamp photoreactor, 8W lamps (4×) with emission maximum at 350 nm; irradiation time 20 min. [b] Control samples without sensitizer were irradiated in parallel to ensure that reaction occurs only in the presence of sensitizer. [c] Reaction followed by ^{1}H NMR.

Scheme 2



As this product was not detected in the reaction mixture, C_3-C_4 cleavage of the oxetane radical cation (pathway b_1) can be safely ruled out.

Previously, we have shown[7] that laser flash photolysis (LFP) of 2,3-diphenyl-4-methyloxetane (**1′**) at 355 nm, in the presence of pyrylium salts, leads to $\mathbf{3}^{+\bullet}$ (absorption maxima at 470 nm).[13] This indicates that BET, under the employed reaction conditions, must occur in the last step (Scheme 1, pathway d); hence biradicals are not direct precursors of the neutral carbonyl/olefin pair. We have now applied the time-resolved LFP techniques to the PET cycloreversion of **1**, in order gain further insight into the reaction mechanism.

Thus, LFP (355 nm) of **1** in the presence of **2a**−**c** gave rise to an intense signal centered around 470 nm assigned to $\mathbf{3}^{+\bullet}$. This is shown in Figure 1 for the case of **2b**. Besides, some contribution of the (thia)pyrylium triplet absorption is also present in the transient spectra between 470 and 560 nm. Another band peaking at 550 nm was also clearly observed in the LFP experiments performed with **2a** and **2c** as photosensitizers. This band was safely assigned to the pyranyl radical resulting from reduction of **2a**,**c**.[14] As the thiapyranyl radical does not absorb in the range 500−600 nm,[15] it does not appear in Figure 1. It was remarkable that formation of $\mathbf{3}^{+\bullet}$ was not "instantaneous". The inset of Figure 1 shows a growth of the 470 nm band in the submicrosecond time scale, corresponding to generation of $\mathbf{3}^{+\bullet}$ from its undetectable precursor, the radical cation from cleavage of the $O-C_2$ bond. The rate constant estimated for this growth was 10^7 s^{-1}. These data, together with the **3**/**4a** product ratio, allow a rough estimation of the rate constant of the intramolecular nucleophilic attack, which must be about 2.7×10^6 s^{-1}.

Summarizing, the results obtained here in the steady-state and time-resolved experiments support stepwise CR of $\mathbf{1}^{+\bullet}$ via initial $O-C_2$ cleavage. Current studies are aimed at disclosing the generality of this finding.

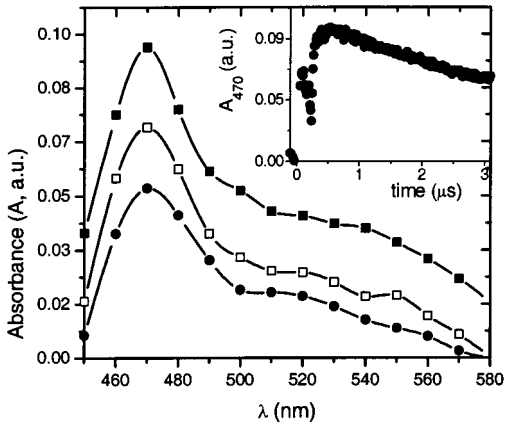


Figure 1. Transient spectrum obtained from LFP ($\lambda = 355$ nm) of **1** (1.25×10^{-3} M) and **2b** (1.2×10^{-4} M) in acetonitrile under nitrogen. Spectra recorded 1, 2, and 3.5 μs after the laser pulse. Inset: Growth and decay of the 470 nm band.

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Supporting Information Available: Table with relevant NMR data of **4a**; detailed reaction mechanism; ^{1}H NMR monitoring of the reaction of **1** photosensitized by **2b**; transient absorption spectra obtained after LFP of **1** + **2b**, **1′** + **2b**, and **1** + **2a**; and growth and decay of the relevant bands at 470, 550, and 580 nm (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Molecular ion: *m*/*z* 240. Important fragment ions: *m*/*z* 180, 134, 107, 92.

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