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Hetero Cycloadditions and Cycloreversions Mediated *via* Electron Transfer

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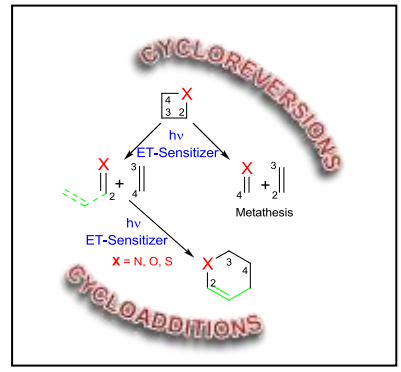

The Diels-Alder cycloaddition was discovered more than eight decades ago; however, it still remains one of the most versatile tools in synthetic organic chemistry, and its mechanism continues to attract considerable interest, both from the experimental and theoretical points of view. Specifically, hetero-Diels Alder processes are among the most powerful methods for the synthesis of densely functionalized six-membered heterocycles, which are ubiquitous substructures found in natural products and bioactive compounds. Azadienes and oxadienes are the most frequently employed synthons for this purpose, whereas only a limited number of Diels Alder processes with thiadienes have been reported.

Radical ionic hetero cycloadditions and cycloreversions have been far less developed than their corresponding neutral (thermal or photochemical) counterparts; however, they are emerging as an active research field in the last decade. Cycloadditions have been mainly used for synthetic purposes. They are limited to [4+2] processes, the vast majority of which involve oxidative electron transfer and occur via radical cations. Most of the reported examples correspond to imino-Diels-Alder reactions.

As regards cycloreversions, they have attracted considerable interest from a photobiological point of view, in connection with repair of pyrimidine(6-4)pyrimidone photolesions in DNA by photolyases and, to a lesser extent, with excess electron transport in DNA. Both the oxidative and reductive versions of the process have been widely illustrated. They have only been explored with four-membered heterocycles, with oxetanes as the most thoroughly investigated systems.

Activation of the hetero cycloadditions or cycloreversions by ionization of the reactants provides a new (and complementary) synthetic strategy, which remains largely unexplored, in spite of its potential to produce new chemistry. Thus, cycloadditions may afford a wide variety of heterocyclic compounds, whereas cycloreversions can in principle be exploited for achieving C=X/olefin metathesis.

This account deals with electron transfer-mediated hetero cycloaddition and cycloreversion reactions. The attention has been focused on the ionization of oxadienes, azadienes and thiadienes, to give six-membered heterocycles, as well as on the oxidative and reductive electron transfer splitting of oxetanes, azetidines and thietanes.

Hetero Cycloadditions and Cycloreversions mediated *via* Electron Transfer

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1. Introduction

The Diels-Alder (DA) cycloaddition (CA) was discovered more than eight decades ago; however, it still remains one of the most versatile tools in synthetic organic chemistry. Hetero-DA processes are powerful methods for the synthesis of densely functionalized six-membered heterocycles, which are ubiquitous substructures found in natural products and bioactive compounds.[1] Azadienes and oxadienes are the most frequently employed synthons for this purpose, whereas only a limited number of DA processes with thiadienes have been reported.[2,3,4] The electron transfer (ET) version of the DA reaction, has been much less investigated, although it is emerging as a subject of increasing interest, and many of its synthetic and mechanistic aspects still remain to be explored.[5,6,7]

Cycloreversion (CR) of four-membered heterocycles *via* radical ions has attracted considerable interest in connection with its possible role in the photoenzymatic repair of DNA by photolyases. [8] Both the anionic and the cationic pathways have been

investigated, in order to gain mechanistic insight. Ring splitting can occur through cleavage of the X-C2/C3-C4 or C2-C3/C4-X bonds, leading to the starting materials of the formal photocycloaddition or, more interestingly, to the metathesis products.

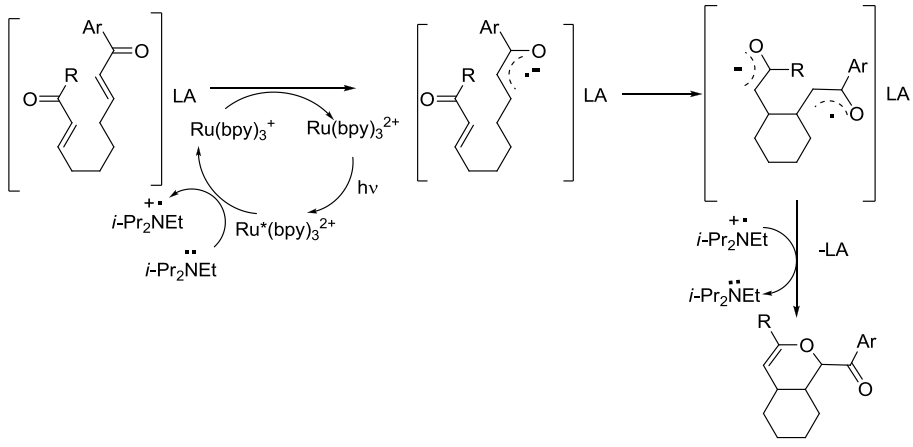
This account deals with ET-mediated hetero CA and CR reactions. The attention has been focused on the ionization of oxadienes, azadienes and thiadienes, to give six-membered heterocycles, and on the oxidative and reductive ET splitting of oxetanes, azetidines and thietanes.

2. Electron Transfer-Mediated Hetero Cycloadditions

2.1. Oxadienes

Irradiation of tethered bis(enones) with visible light in the presence of catalytic amounts of Lewis acid (LA) leads to [4+2] intramolecular CA.[9] The tether length is determinant for minimizing side processes such as [2+2] intramolecular CA. The proposed mechanism (Scheme 1) is similar to that previously discussed for all-carbon radical anion CA.[10]

SCHEME 1. Intramolecular Cycloaddition of Bis(enones) *via* Radical Anions

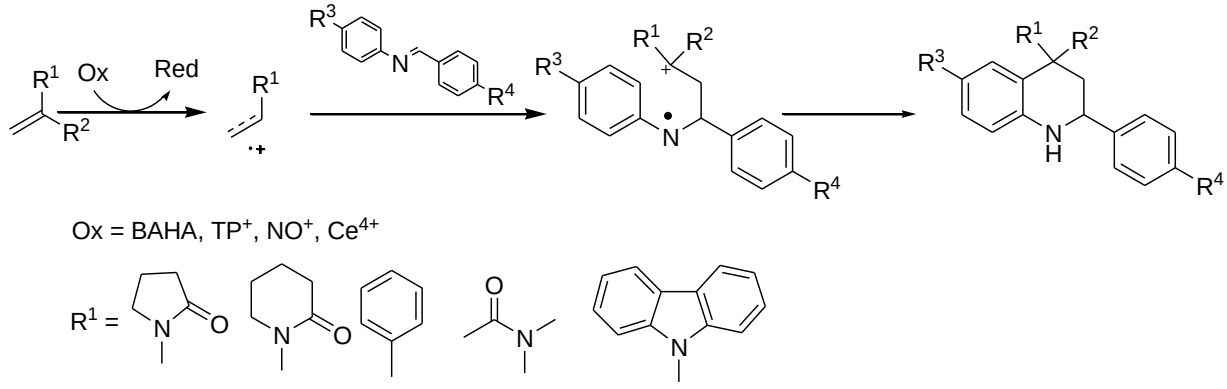


2.2. Azadienes

The imino Diels-Alder (IDA) reaction between *N*-arylimines and alkenes has been achieved under assumed ET-conditions, employing different strategies for the generation of alkene radical cations.[11-16] Chemical activation with cerium ammonium nitrate (CAN) affords stereoselectively *cis*-2,4-disubstituted tetrahydroquinolines from *N*-arylimines and *N*-vinylpyrrolidin-2-one or *N*-methyl-*N*-vinylacetamide.[11] Concomitant reduction of Ce^{4+} to Ce^{3+} supports ET catalysis. Nitrosonium tetrafluoroborate has also been used as radical cation initiator.[12] Likewise, the reaction works with tris(4-bromophenyl)aminium hexachloroantimonate (BAHA) as ET-oxidizing reagent.[13]

Photoinduced electron transfer (PET) between *N*-arylimines and alkenes, using 2,4,6-triphenylpyrylium (TP^+) tetrafluoroborate as sensitizer (E^*_{RED} = 2.0 V *vs* SCE)[14], has also been reported.[15,16] Under these conditions, styrene derivatives (E_{OX} = 1.7-1.9 V *vs* SCE), affords substituted tetrahydroquinolines (stereoisomeric mixtures), together with aromatized quinolines. The proposed mechanism is shown in Scheme 2.

SCHEME 2. Imino-Diels-Alder Reaction between Azadienes and Alkenes Mediated *via* Oxidative ET



The involvement of an ET-IDA reaction pathway for the [4+2] CA between *N*-benzylideneaniline and arylalkenes has been convincingly demonstrated by combining product studies, laser flash photolysis (LFP), and density functional theory (DFT) calculations.[17] Irradiation of *N*-benzylideneaniline and *trans*-anethole in the presence of TP^+ leads to *cis*- and *trans*-tetrahydroquinolines. The free energy change estimated using the Rehm-Weller equation[18] (ΔG_{ET}= -19 kcal/mol), is compatible with initial generation of the alkene radical cation. The involvement of such intermediate in the photocyclization process has been demonstrated by LFP, where quenching of the $^3TP^{+}$* absorption (λ = 460 nm) in the presence of increasing amounts of *trans*-anethole is observed (Figure 1A); the rate constant (k_q= 1.6 ×10^{10} M^{-1} s^{-1}) indicates a diffusion controlled process. Concomitantly, two new bands appear at 550 and 610 nm, ascribed to the pyranyl radical (TP•) and to *trans*-anethole radical cation, respectively (Figure 1B).

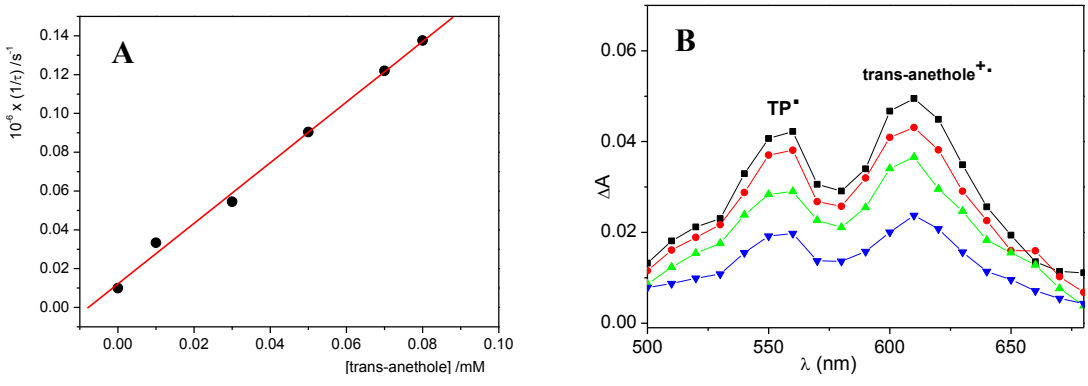
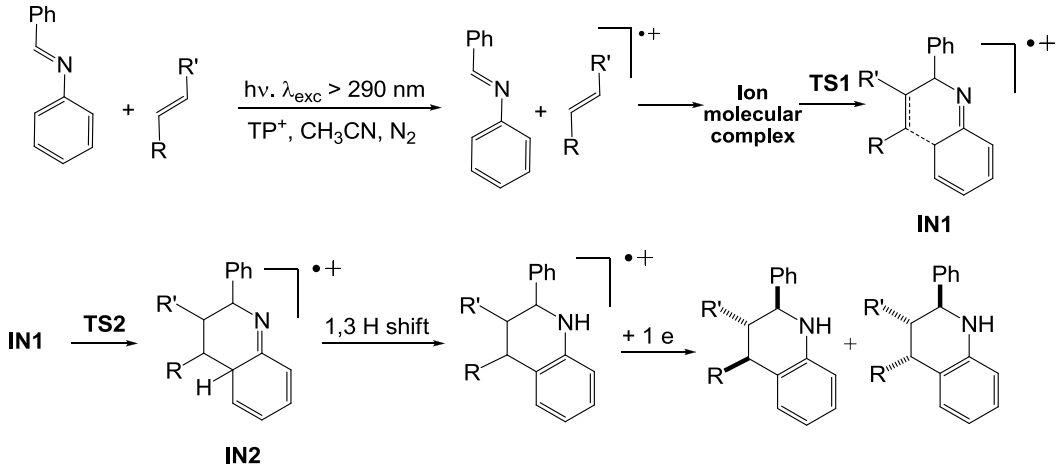


FIGURE 1. A: Stern-Volmer plot of the triplet quenching of TP^+ by *trans*-anethole. **B:** LFP (λ_{exc} = 355 nm, MeCN/N_2) of TP^+ (0.03 mM) and *trans*-anethole (0.30 mM). Spectra recorded 1µs (black), 3 µs (red), 10 µs (green) and 30 µs (blue) after the laser pulse.

The mechanism is confirmed by a shortening of the *trans*-anethole radical cation lifetime as a consequence of its reaction with *N*-benzylideneaniline. Theoretical (DFT) calculations at the (U)B3LYP/6-31G* level indicate that the geometries and the relative energies of the stationary points involved in the reaction (ion molecular complex, transition states TS1 and TS2, as well as intermediates IN1 and IN2) are consistent with an asynchronous formation of the two new C-C bonds, as summarized in Scheme 3.

SCHEME 3. Mechanism for PET Imino-Diels-Alder CA Based on Experimental Evidence and Theoretical Calculations



2.3. Thiadienes

The feasibility of ET-mediated [4+2] CA between thiobenzophenone and arylalkenes (*trans*-1-propenylbenzene, *trans*-anethole and 4-chloro-*trans*-1-propenylbenzene) has been proven.[19] Based on transient absorption spectroscopic evidence, quenching of the triplet excited state of 2,4,6- triphenylthiapyrylium cation

(TTP^+) by both thiobenzophenone and the arylakenes is observed, and the radical cations of the latter are effectively detected. Thus, the spectrum obtained after LFP of TTP^+ exhibits the characteristic band of the triplet excited state, while in the presence of *trans*-anethole the alkene radical cation is clearly observed; its intensity decreases upon addition of thiobenzophenone (Figure 2). The estimated ΔG_{ET} values (between -10.3 and -7.9 kcal/mol) indicate that ET from the three arylalkenes to $^3TTP^+$* is exergonic.

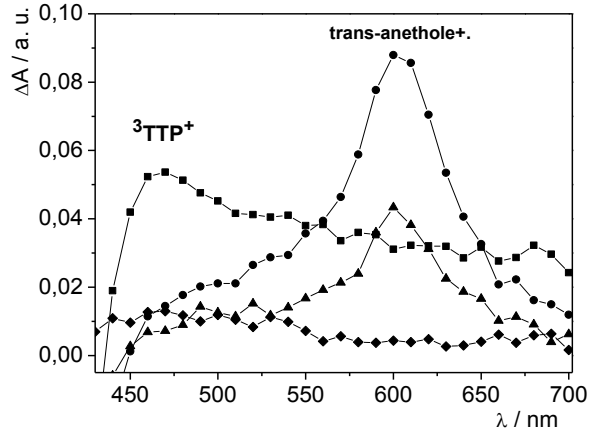
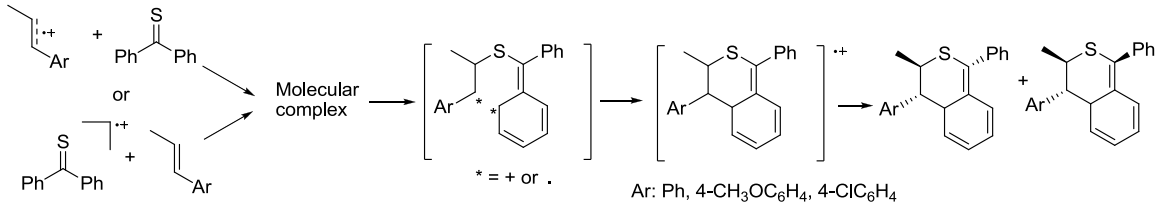


FIGURE 2. Transient absorption spectra obtained 1 μs after LFP (λ = 355 nm, MeCN, Ar) of TTP^+ (0.06 mM) in the absence of *trans*-anethole (■) and in the presence of: 1 mM *trans*-anethole (●), 1 mM *trans*-anethole and 0.05 mM thiobenzophenone (▲), 0.05 mM thiobenzophenone (♦).

The mechanistic aspects of the process have been analyzed using DFT methods at the UB3LYP/6-31G* level.[20] After generation of the radical cations, formation of a molecular complex (MC) initiates a stepwise mechanism, where ring closure is the rate-

determining step. The reaction mechanism for this novel ET CA reaction is outlined in Scheme 4.

SCHEME 4. Radical Cationic Cycloaddition between Thiobenzophenone and Arylalkenes



A related [4+2] CA with sulfur derivatives as dienophiles has been reported between bis(trifluoromethy1)sulfene and anthracenes, where the key ET-step is assumed to generate an anthracene radical cation/sulfene radical anion pair.[21]

3. Electron Transfer-Mediated Hetero Cycloreversions

Photorepair of the (6-4) DNA lesions by photolyases is thought to involve PET from a catalytic flavin-adenosine cofactor to the dimeric lesion; however, a critical and controversial issue is whether (photo)chemical conversion of the (6-4) photoproducts to oxetanes is actually a necessary step.[22,23,24,25,26,27]

The idea that (6–4) photoproducts are converted to oxetanes (or azetidines) upon binding to the enzyme in the dark has been questioned based on the crystal structure of a model (6–4) photoproduct in the binding pocket.[28,29] In general, experimental and theoretical studies assume that (6–4) photoproducts are repaired upon absorption of a single photon by the enzyme. However, the possibility of a two-photon process has

been recently proposed, whereby a first PET converts the (6–4) lesion into the oxetane and a second one splits the oxetane ring leading to the repaired thymines.[30,31,32]

In addition to photorepair studies, the PET CR of four-membered ring heterocycles has attracted considerable interest from the mechanistic point of view and also as a tool to reveal the transfer of excess electrons in biomolecules by charge trapping.[33]

3.1. Oxetanes

The PET CR of oxetanes arising from the Paternò-Büchi reaction between thymine or uracil and different carbonyl compounds has been achieved with either electron donating or accepting photosensitizers (Figure 3).[34,35,36,37] In the reductive version, formation of the radical anion of the carbonyl fragment can be monitored by LFP. A lower limit for the rate constant of the splitting reaction has been estimated at 5×10^7 s^{-1}.

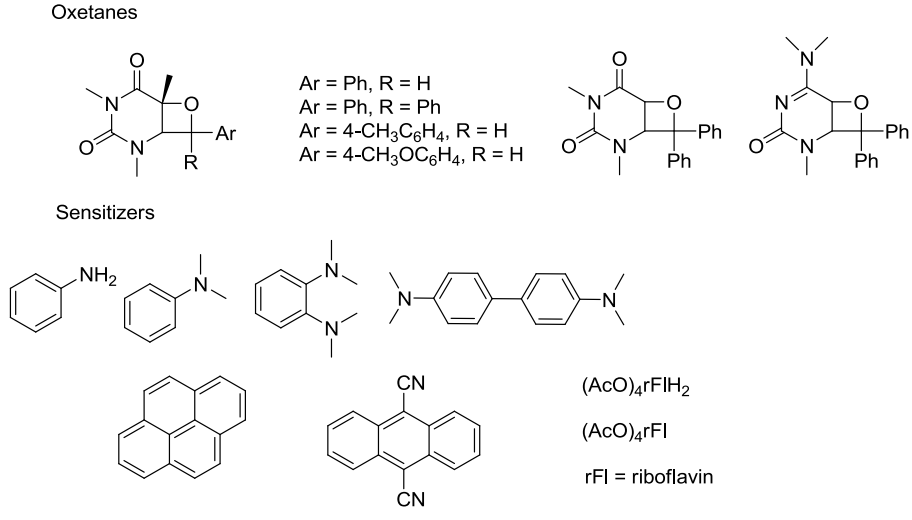


FIGURE 3. Chemical structures of oxetanes and sensitizers used for the study of PET CR

Intramolecular PET CR has been investigated in a system containing the oxetane obtained from thymine and benzophenone, covalently linked to a flavin subunit (Figure 4A).[28] Ring splitting occurs through the radical anionic pathway and requires that flavin acts in the reduced and deprotonated state. Related DNA hairpin model compounds (Figure 4B) have been used to prove that excess electrons move through the duplex even over distances as long as 17 A.[38]

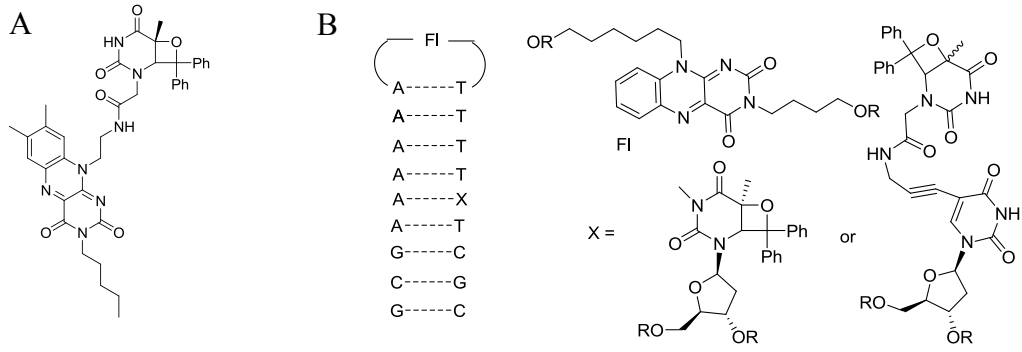


FIGURE 4. A: Chemical structure of a covalently linked flavin-oxetane system for model studies on DNA repair. **B**: Chemical structures of hairpins for the investigation of excess electron transport in DNA.

Steady state photolysis, LFP and fluorescence experiments have provided support for cleavage of oxetane radical anions formally resulting from photocycloaddition between benzophenone and 1,3-dimethylthymine or 2'-deoxyuridine, upon photosensitization by methyl 2-(carbazol-2-yl)-propanoate (Figure 5). [39] An interesting feature of this photosensitizer is that it plays the role of a double-edged sword: while it may induce formation of cyclobutane pyrimidine dimers, it can also achieve CR of oxetanes.

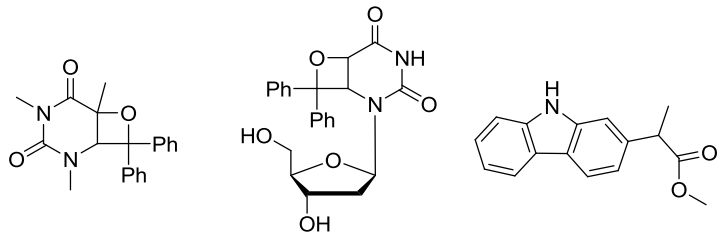
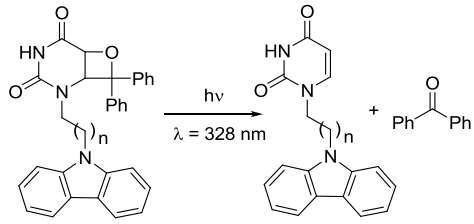


FIGURE 5. Chemical structures of thymine-derived oxetanes and a carbazole photosensitizer.

The intramolecular version of this process has been investigated with the carbazole chromophore covalently linked to an oxetane unit (Scheme 5).[40] As expected for an ET reaction, a strong medium dependence is observed. In nonpolar solvents no splitting occurs, charge separation is disfavored, and fluorescence quenching of the carbazole moiety is not observed.

SCHEME 5. Intramolecular PET CR in a Carbazole-Oxetane Linked System



A related oxetane has been covalently linked to *β*-cyclodextrin, and electron-rich fluorophores such as *N,N*-dimethylaniline or indole have been encapsulated within the cavity (Figure 6).[41] Upon irradiation, CR to thymine and benzophenone is confirmed by NMR measurements. In addition, fluorescence quenching occurs in all the investigated systems. The ET mechanism of the splitting reaction is supported by the negative ΔG_{ET} values, estimated in terms of the Rehm-Weller equation. The quantum yields are

concentration and solvent-dependent; they are much higher for the oxetane-indole supramolecular systems than for the equivalent covalently-linked models (Figure 6).[42]

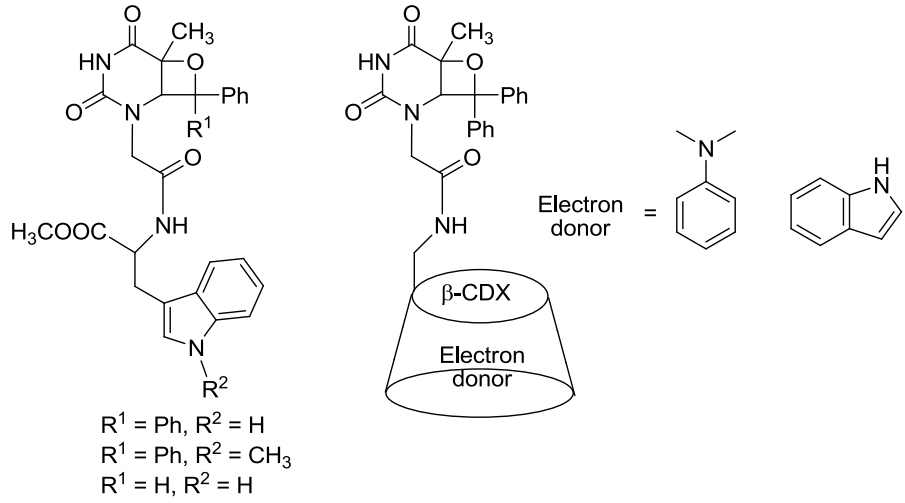
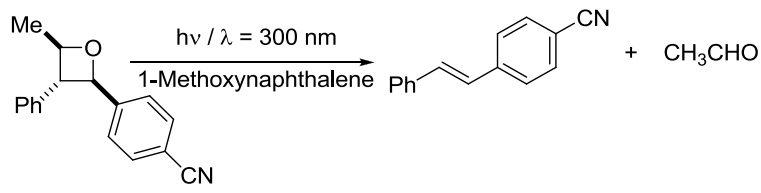


FIGURE 6. Chemical structures of a thymine-derived oxetane covalently linked to tryptophan and to a cyclodextrin. Structures of encapsulated electron donors.

The CR of 2-(*p*-cyanophenyl)-4-methyl-3-phenyloxetane has been achieved using 1-methoxynaphthalene as ET photosensitizer.[43] Splitting of the radical anion through cleavage of the O-C2 and C3-C4 bonds leads to acetaldehyde and *p*-cyanostilbene (Scheme 6), whereas construction of the oxetane ring from its precursors by the Paterno-Büchi reaction involves formation of the C2-C3 and O-C4 bonds.

SCHEME 6. Reductive PET CR of a Cyanophenyl-Substituted Oxetane



Fluorescence of the sensitizer is quenched by the oxetane ($k_q = 7.4 \times 10^9\ M^{-1}s^{-1}$), in agreement with ET from the singlet excited state of the former (Figure 7A). In addition, the radical anion of *trans*-*p*-cyanostilbene, peaking at *ca.* 500 nm, is detected upon LFP of the mixed reaction partners (Figure 7B).

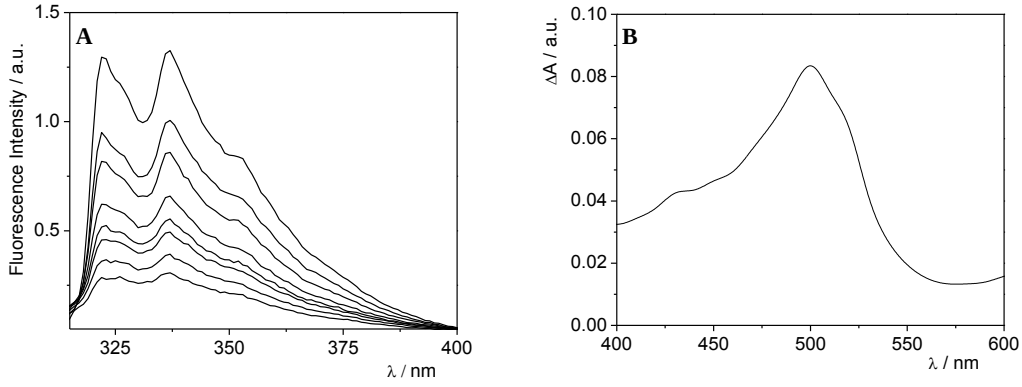


FIGURE 7. A: Fluorescence quenching of 1-methoxynaphthalene by increasing amounts of 2-(*p*-cyanophenyl)-4-methyl-3-phenyloxetane. **B:** Spectrum obtained 1 μs after LFP (λ_{exc} = 308 nm, MeCN/Ar) of 1-methoxynaphthalene in the presence of 2-(*p*-cyanophenyl)-4-methyl-3-phenyloxetane.

The intramolecular version of this PET CR process has been investigated using covalently linked dyads (Figure 8), both in acetonitrile and in chloroform.[44] The photoreactivity is higher in the former solvent, where stereodifferentiation is less marked. The (*S,R,R*) isomer reacts faster, due to the predominancy of its folded conformation, with the naphthalene ring directed toward the oxetane region.

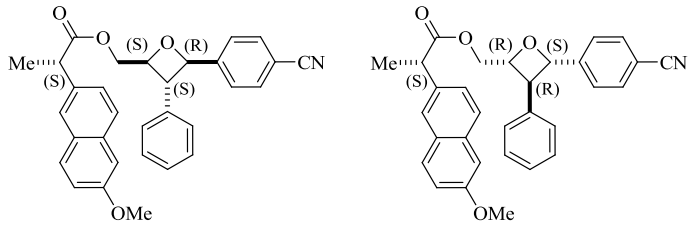


FIGURE 8. Chemical structures of stereoisomeric dyads constructed by linking methoxynaphthalene and oxetane moieties

Accordingly, intramolecular fluorescence quenching is more efficient in acetonitrile, but it reveals higher stereodifferentiation in chloroform (Figure 9).

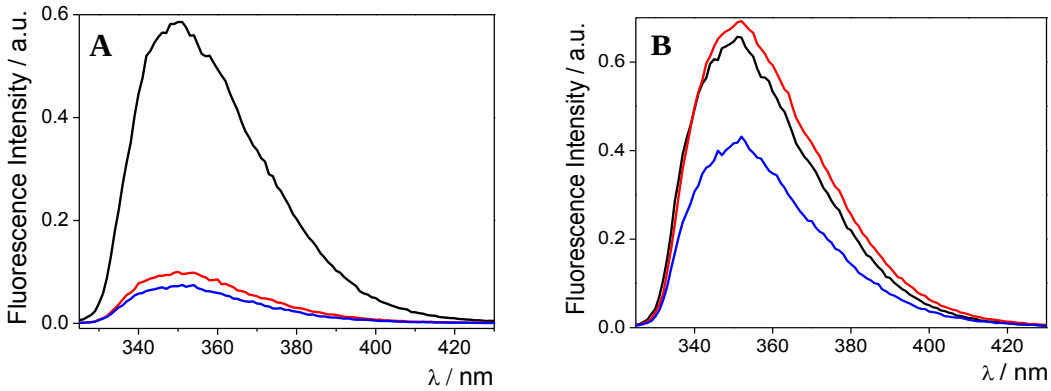


FIGURE 9. Fluorescence spectra of methoxynaphthalene (black) and methoxynaphthalene-oxetane dyads with *(R,S,S)* (red) or *(S,R,R)* (blue) stereochemistry, recorded after excitation at 320 nm under nitrogen in acetonitrile (**A**) and in chloroform (**B**).

From the synthetic point of view, the metathesis of oxetanes constitutes an attractive tool to obtain carbonyl-olefin pairs. In this context, the behavior of bicyclic oxetanes resulting from photocycloaddition of aromatic aldehydes to 2,3-dihydrofuran has been investigated using 1-methoxy and 2,7-dimethoxynaphthalene as PET-donors.[45] Under

these conditions, ring splitting ensues with photo-metathesis (Figure 10). The rate constants for quenching of the photosensitizer fluorescence show a marked dependence on aromatic substitution and are in the order of 10^9 $M^{-1}s^{-1}$. The same trend is observed for triplet quenching, although the values are one order of magnitude lower. According to Rehm-Weller, the ET process is only exergonic from the singlet excited state.

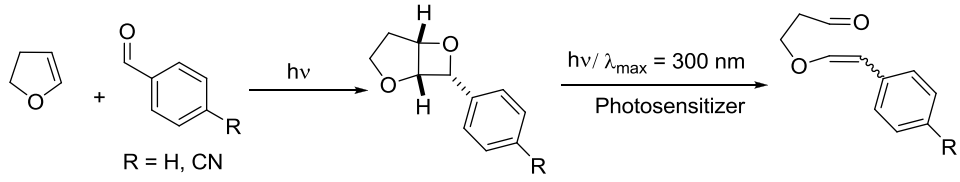
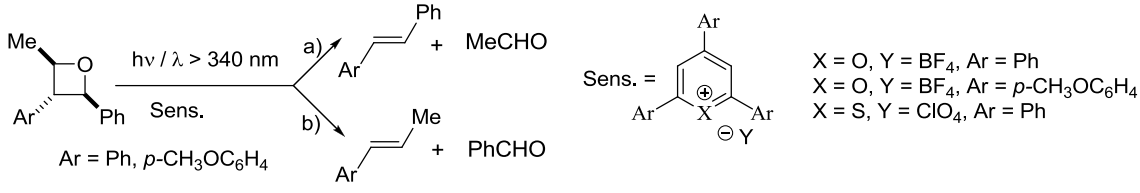


FIGURE 10. Photo-metathesis in the PET-CR of a dihydrofuran-derived oxetane

Although photooxidative cleavage of oxetanes can in principle be used for DNA repair, [46] the reported studies are mainly focused on the interesting mechanistic aspects of this process. In this context, early studies on PET sensitization with cyanonaphthalenes point to involvement of the singlet excited state, in a stepwise CR mechanism involving initial C–C bond breaking. [34,47]

In the case of *trans,trans*-2,3-diphenyl-4-methyloxetane (obtained from β-methylstyrene and benzaldehyde), photosensitization by TTP^+ leads to *trans*-stilbene and acetaldehyde (Scheme 7, path a).[48,49]

SCHEME 7. (Thia)pyrylium-sensitized Photoreaction of *trans,trans*-2,3-Diaryl-4-methyloxetanes



In principle, both the singlet or triplet excited states of TTP^+ can be involved, and indeed they are effectively quenched by the oxetane. In addition, LFP of TTP^+ in the presence of the oxetane leads to *trans*-stilbene radical cation, detected at $\lambda_{max} = 470$ nm (Figure 11A). The facts that TTP^+ (with a very high intersystem crossing quantum yield) is an efficient sensitizer and that the reaction does not occur in the presence of oxygen point clearly to triplet involvement. The molecular mechanism for this CR has been studied at the UB3LYP/6-31G* level.[50] Calculations are in agreement with an asynchronous process, which allows a favorable rearrangement of the spin electron density from the oxygen atom of the oxetane radical cation to the π system of the alkene radical cation.

The reaction regioselectivity switches when chloranil is used instead of TTP^+, leading to products arising from trapping of t*rans*-β-methylstyrene radical cation. The regioselectivity of the ET-mediated CR process can also be controlled by changing the substituents attached to the aryl groups.[51,52] Thus, replacement of phenyl with *p*-methoxyphenyl results in *trans*-anethole and benzaldehyde (Scheme 7, path b). In agreement, *trans*-anethole radical cation is detected upon LFP (Figure 11B).

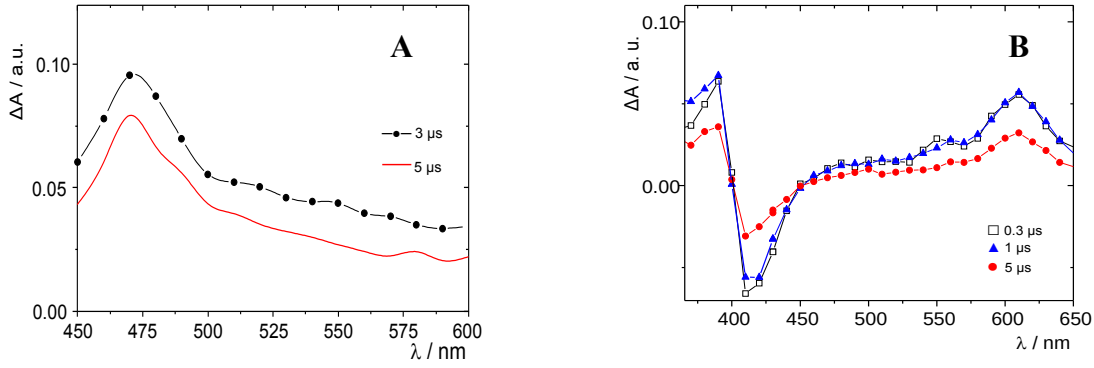
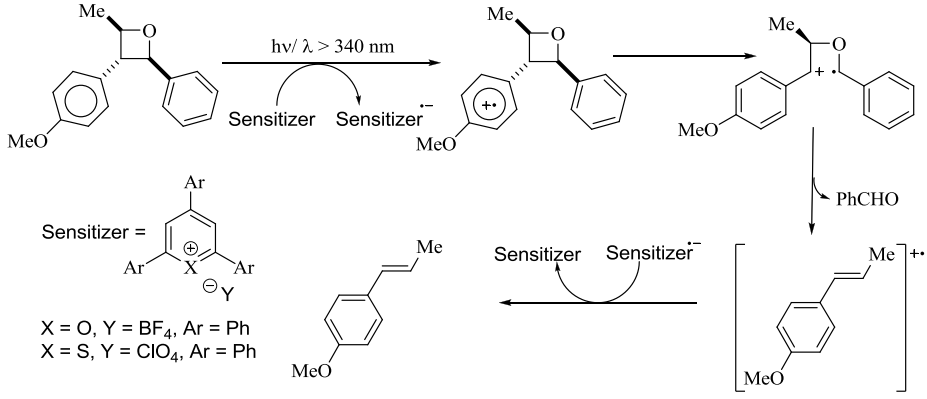


FIGURE 11. Transient absorption spectra obtained at the indicated delays after LFP (λ_{exc} = 355 nm, MeCN, Ar) of oxetanes in the presence of TTP^+. **A:** *trans, trans*-2,3-diphenyl-4-methyloxetane. **B:** *trans, trans*-3-(4-methoxyphenyl)-2-phenyl-4-methyloxetane

Initial ionization occurs at the methoxy-substituted aromatic ring. Subsequent C2-C3 bond cleavage generates a 1,4-radical cation, and the observed intermediate is formed after subsequent O-C4 bond splitting (Scheme 8).

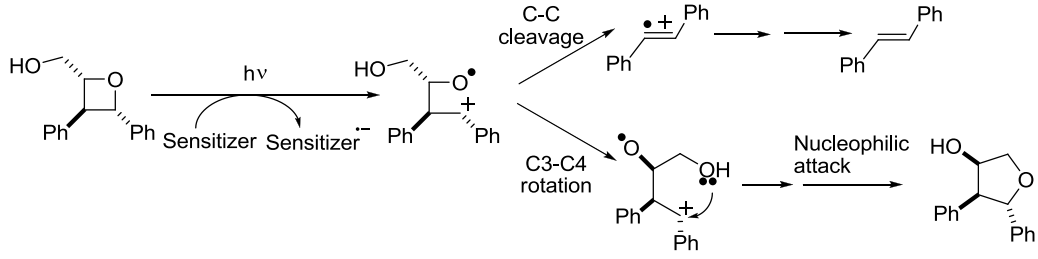
SCHEME 8. Photosensitized ET Ring Splitting of *trans, trans*-3-(4-Methoxyphenyl)-2-phenyl-4-methyloxetane



Intramolecular nucleophilic trapping of the cationic center has further proven the stepwise mechanism involved in the PET CR of oxetane radical cations. Thus, *trans, trans*-2,3-diphenyl-4-hydroxymethyloxetane has been submitted to steady-state and time-resolved photolysis, using (thia)pyrylium salts as ET sensitizers.[53] The isolated photoproducts are stilbene, 2,5-dihydroxy-1,4-dioxane (the dimer of hydroxyacetaldehyde), and 2,3-diphenyl-4-hydroxytetrahydrofuran (Scheme 9). Initial

O-C2 cleavage gives rise to a distonic radical cation, where spin and charge are located in the oxygen and the C2 atoms, respectively. This intermediate follows two competing pathways, namely C-C cleavage and intramolecular nucleophilic attack. After LFP excitation of a sensitizer/oxetane mixture, a transient band is observed centered at *ca*. 470 nm, corresponding to stilbene radical cation. Its formation is not "instantaneous" and occurs in the submicrosecond timescale. The estimated rate constant of intramolecular nucleophilic attack is 2.7×10^6 s^{-1}.

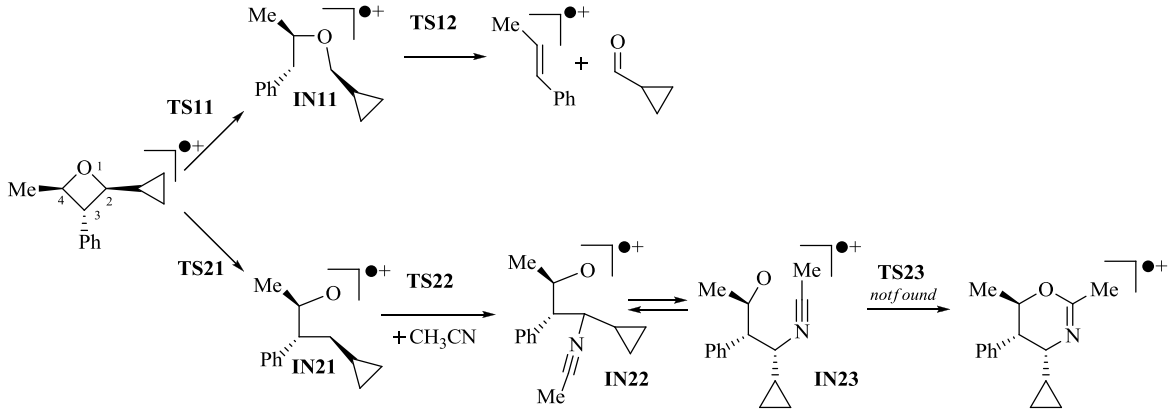
SCHEME 9. Intramolecular Trapping in the PET Reaction of *trans, trans*-2,3-Diphenyl-4-hydroxymethyloxetane



Intermolecular trapping of a similar 1,4-radical cation intermediate has been achieved in the ET oxidation of *trans,trans*-2-cyclopropyl-4-methyl-3-phenyloxetane.[54] Its TP^+ sensitized photolysis in acetonitrile leads to *trans*-1-propenylbenzene, cyclopropanecarboxaldehyde and the solvent adduct *cis,trans*-4-cyclopropyl-2,6-dimethyl-5-phenyl-4H-5,6-dihydro-1,3-oxazine. Combined fluorescence and LFP results indicate that the reaction takes place from the singlet excited state of the photosensitizer, which agrees well with the estimation of the free energy changes

associated with ET from this excited state. The operating mechanism is summarized in Scheme 10.

SCHEME 10. Reaction Pathways of *trans*,*trans*-2-Cyclopropyl-4-methyl-3-phenyloxetane in the Absence and in the Presence of Acetonitrile



In principle, C2-C3 or O-C2 cleavage can occur. The first pathway leads to a 1,4-radical cation, whose carbocationic site is stabilized by oxygen as an oxonium ion. Subsequent O-C4 bond cleavage affords *trans*-prop-1-enylbenzene radical cation and cyclopropanecarboxaldehyde. The alternative C2-C3 or O-C2 bond breaking pathway involves formation of a different 1,4- radical cation with spin and charge located at the oxygen and at C2, respectively. The higher degree of charge localization favors now nucleophilic attack by acetonitrile at C2, leading to a nitrilium derivative; ring closure and back-electron transfer affords the solvent 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. The absence of acetaldehyde and *trans*-2-cyclopropyl-1-phenylethene in the photomixture indicates that by acetonitrile occurs faster than C3-C4 cleavage.

Since the initial *trans* arrangement of phenyl and cyclopropyl groups in the oxetane is no longer maintained in the oxazine, bond rotation must occur along the reaction path. Theoretical calculations at the UMP2(FC)/6-31G(d) level support the mechanism assignment (see diagram showing the relative energies of the involved transition states and intermediates in Figure 12).

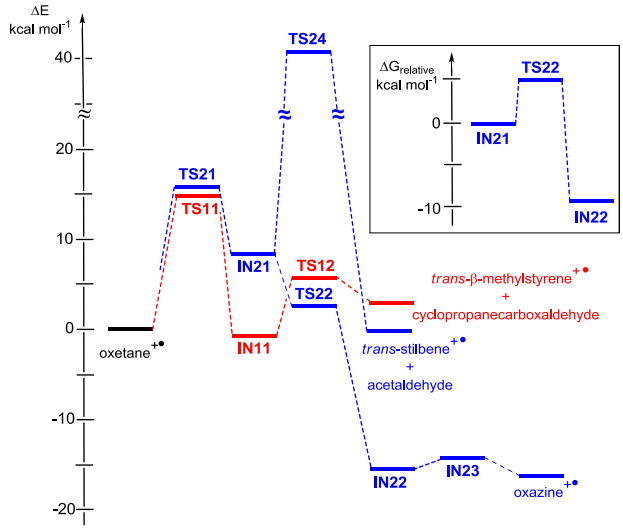


FIGURE 12. Diagram showing the relative energies of the transition states and intermediates involved in the PET CR of *trans*,*trans*-2-cyclopropyl-4-methyl-3 phenyloxetane

3.2 Azetidines

The azetidine ring is found in a variety of natural products and biologically active substances. In addition, it is a key substructure of synthetic intermediates and conformationally constrained amino acids used for the design of novel peptides. The PET CR of azetidines has also been the subject of experimental and theoretical work related to

UVB-induced DNA repair.[25,26] Moreover, the generation and fate of azetidine radical ions in the gas phase has been reported in the course of mass spectrometric studies.[55]

Reaction of *cis*- and *trans*-1,2,3-triphenylazetidine with BAHA as ET-oxidizing agent leads to *cis*- and *trans*-stilbene, together with *N*-benzylideneaniline.[56] In this context, LFP of neutral *tris*-(4-bromophenyl)amine leads to photoionization (Figure 13A), and the resulting aminium radical cation is quenched by both azetidine stereosisomers (Figure 13B), with a rate constant of 2×10^9 M^{-1} s^{-1}. This is assumed to occur by ET, on the basis of the favorable free energy changes associated with the process.

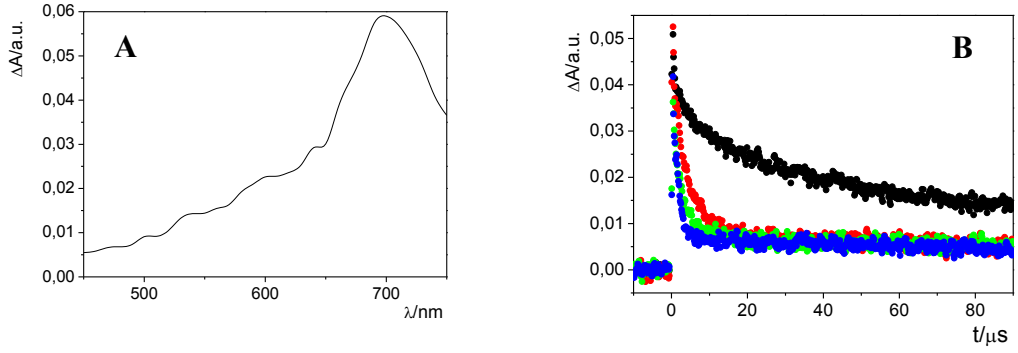
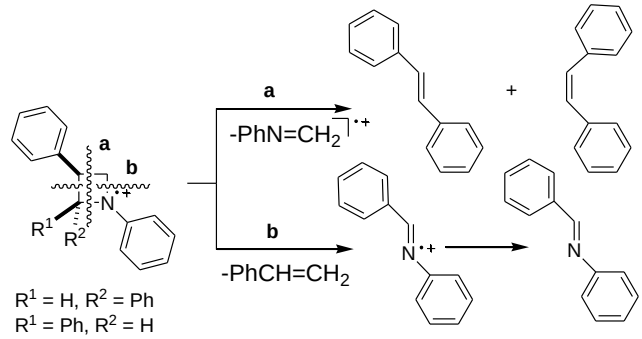


FIGURE 13. A. Spectrum obtained upon LFP of *tris*-(4-bromophenyl)amine (355 nm, MeCN/N_2). **B**. Quenching of the resulting radical cation by increasing amounts of *trans*-azetidine. Concentration of amine is 2.5×10^{-4} M in all cases. The decay traces correspond to amine/azetidine ratios equal to 1:0 (black), 1:0.5 (red), 1:1 (green), and 1:2 (blue).

By contrast, no quenching of the aminium radical cation is observed in the presence of *cis*- or *trans*-stilbenes. This supports that twisting around the C2-C3 bond occurs in the 1,4 intermediate, through a stepwise CR of the azetidine radical cation. Furthermore, no new transient absorption spectrum corresponding to *cis*- or *trans*-

stilbene radical cations is detected, indicating that CR of the azetidine along pathway a (Scheme 11), leads to spin and charge located at the more easily oxidizable imine fragment. The same is true for CR through pathway b in Scheme 11, which leads to the radical cation of *N*-benzylideneaniline. Overall, the results correlate well with the fragmentation routes observed in the gas phase, upon electron impact ionization.

SCHEME 11. Fragmentation of *cis*- and *trans*-1,2,3-Triphenylazetidine Radical Cations



3.3. Thietanes

Although bipyrimidine-derived oxetanes and azetidines are thought to be the primary intermediates leading to (6-4) photoproducts, they are not sufficiently stable at room temperature as to investigate the mechanism of DNA repair. However, the corresponding thietanes are much longer lived and can therefore be conveniently employed for model studies in the field.[57,58,59]

In this context, reductive CR of a thietane has been achieved by intramolecular PET from a covalently linked flavin moiety (Figure 14).[60] However, thietanes derived from

pyrimidine/thiopyrimidine dinucleotides are not enzymatically repaired,[61] which can be attributed to inefficient binding rather than to lack of ET-reactivity.

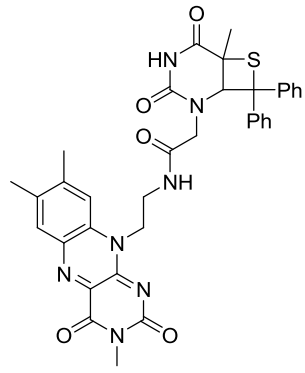


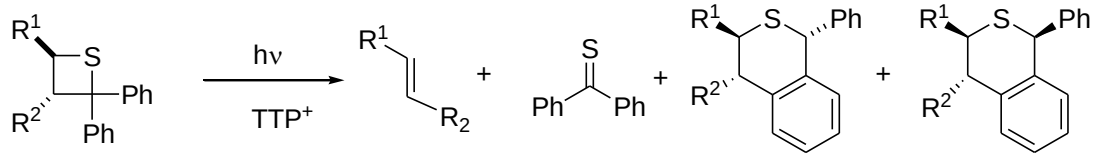
FIGURE 14. Thietane model containing a covalently linked flavin for intramolecular PET studies

As regards the oxidative version of thietane CR, photosensitization of 3-cyano or 3-ethoxy-2,2-diarylthietane by 9,10-dicyanoanthracene affords selectively 1,1-diarylethenes.[62] The reaction is thought to involve PET from the sulfur atom to the singlet excited state of the sensitizer, followed by S-C2 cleavage of the sulfide radical cation. This assumption is based on the observed quenching of dicyanoanthracene fluorescence by the thietanes.

A deeper mechanistic insight into the oxidative CR of thietanes has been gained by a combination of product studies, LFP and theoretical calculations at the UB3LYP/6-31G* level.[63,64] Photosensitization of 2,2,3-triarylthietanes by TTP^+ leads to thiobenzophenone and the corresponding alkenes, eventually followed by secondary [4+2] CA (Scheme 12). Crossover experiments are in agreement with formation of ion-

molecule complexes, and final product distribution depends on the escape ability of fragments.

SCHEME 12. Photosensitized Irradiation of 2,2,3-Triarylthietanes in the Presence of TTP^+



$R^1 = CH_3$, $R^2 = Ph$
$R^1 = CH_3$, $R^2 = 4\text{-}CH_3C_6H_4$
$R^1 = R^2 = Ph$

The triplet excited state of TTP^+ is quenched by thietanes at diffusion-controlled rate. In the case of the methyl-substituted derivatives, a new transient peaking at 500 nm appears concomitantly with the diminution of the T-T band (Figure 15A); this species is assigned to the isothiochromane radical cation. For the substrate bearing a methoxyphenyl substituent, the anethole radical cation is also observed at 600 nm. Excitation of TTP^+ at 355 nm in the presence of the tetraphenyl substituted analog gives rise to stilbene radical cation (centered at 470 nm), whose growth kinetics becomes faster in the presence of increasing thietane concentrations (Figure 15B). All these data unambiguously confirm the involvement of an ET process from the triplet excited state of the photosensitizer.

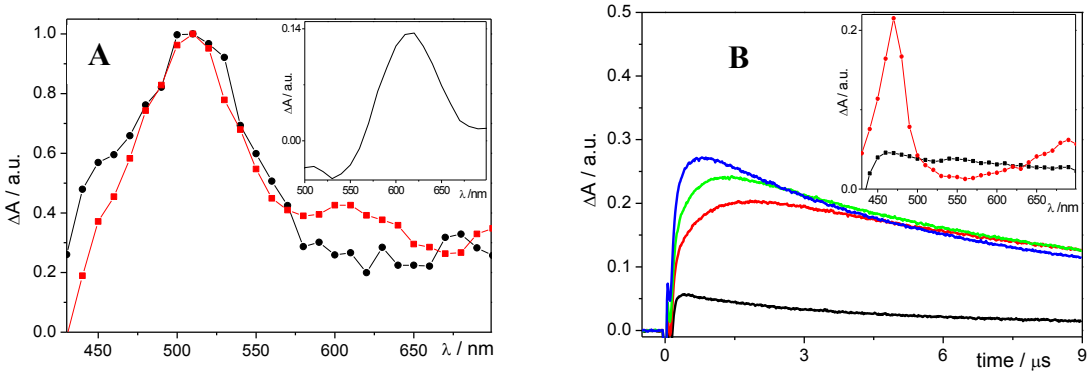


FIGURE 15. A: Normalized spectra obtained 0.4 μs after LFP (λ = 355 nm, MeCN, Ar) of TTP^+ (0.06 mM) in the presence of 1 mM 4-methyl-2,2,3-triphenylthietane (black) or 1 mM 2,2-diphenyl-3-(4-methoxyphenyl)-4-methylthietane (red).Inset: Difference spectrum of both traces (smooth fitting). **B**: Kinetics monitored at 470 nm after 355 nm LFP of TTP^+ (0.06 mM) in the presence of increasing amounts of 2,2,3,4-tetraphenylthietane: 0 M (black), 0.05 mM (red), 0.1 mM (green), and 0.2 mM (blue). Inset: Transient absorption obtained for TTP^+ (0.06 mM) in the absence (black) and in the presence of 2,2,3,4-tetraphenylthietane (1 mM) (red).

Overall, the results support formation of thietane radical cations through PET from their neutral precursors to the triplet excited state of TTP^+. Ring-splitting through C2-C3/C4-S bond scission is followed by formation of an ion-molecule complex. Escape of free radical ions from this complex constitutes a critical event. Back electron transfer leads to the alkenes plus thiobenzophenone. An alternative pathway is [4+2] cycloaddition, followed by rearrangement and back electron transfer, to give eventually the isothiochromanes. Competition between escape and [4+2] cycloaddition depends on the relative energy barriers: the former is clearly favored in the case of the tetraphenyl

derivative, whereas the latter largely predominates with the triphenyl analog as starting material. The situation for the methoxyphenyl substituted thietane is intermediate.

4. Conclusions and Remarks

Radical ionic hetero cycloadditions and cycloreversions have been far less developed than their corresponding neutral (thermal or photochemical) counterparts; however, they are emerging as an active research field in the last decade. Cycloadditions have been mainly used for synthetic purposes. They are limited to [4+2] processes, the vast majority of which involve oxidative electron transfer and occur *via* radical cations. Most of the reported examples correspond to imino-Diels-Alder reactions. As regards cycloreversions, they have attracted considerable interest from a photobiological point of view, in connection with repair of pyrimidine(6-4)pyrimidone photolesions in DNA by photolyases and, to a lesser extent, with excess electron transport in DNA. Both the oxidative and reductive versions of the process have been widely illustrated. They have only been explored with four-membered heterocycles, with oxetanes as the most thoroughly investigated systems. Activation of the hetero cycloadditions or cycloreversions by ionization of the reactants provides a new (and complementary) synthetic strategy, which remains largely unexplored, in spite of its potential to produce new chemistry. Thus, cycloadditions may afford a wide variety of six-membered heterocycles, whereas cycloreversions can in principle be exploited for achieving C=X/olefin metathesis.

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Miguel A. Miranda is Professor at the Technical University of Valencia and Head of the Institute of Chemical Technology UPV-CSIC. He was post-doc at the Universities of Saarland (H. Dürr) and Würzburg (W. Adam) and Associate Professor at the University of Valencia, before accepting his present position in 1990. He has received the Honda-Fujishima, the Spanish Organic Chemistry, and the Theodor Förster Awards.

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