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EDITORIAL

President's Letter

Dear EPA members
During the past months we have worked in order to increase the appealing of our association. In this field we have good news but also the emergence of new concerns. First of all we assigned the award to the best PhD Thesis in Photochemistry, and the award to the scientist that contributed to the success of our community. I'm very glad to announce that the first award on this theme has been assigned to Silvia Braslavsky. In this contest, in the next year we will announce the 2020 award to the young investigator and the first edition of the award for a teacher.

Furthermore, now we have an agreement with the organizers of the next IUPAC congress on Photochemistry for a reduced fee for the EPA members. An important result was the agreement reached with HRSMC Group for a reduced fee for EPA members to participate to the EPA-HRSMC Advanced School in photochemistry that will be organized in Amsterdam in 2020. This is an important issue. I think that the diffusion of introductory schools on photochemistry together with the presence of an advanced school has to become the main mission of our association. I think that all spontaneous schools have to be reorganized in a systematic scheme that has to economically sustain by EPA. EPA is not the direct organizer of meetings, events, schools. EPA supports the efforts of national organizers to do it in a national scale. However, we have not initiatives at the European scale with the exception of the HRSMC Advanced School. I think that all the efforts of the national groups have to be canalized in order to have an organized system of European schools in Photochemistry.

Finally, the Brexit adventure can modify our perspectives, and we have to consider the possible effect of Brexit on our organization. First of all, I think that we have to increase the presence (now absent) of Great Britain in the Executive Committee in order to give a signal on the presence of this country in our European Association. However, we have to consider the possible negative effects of Brexit, for example on the editorial policy of the Royal Society of Chemistry.

Maurizio D'Auria
Università della Basilicata

PUBLICATIONS

Two Versatile Experiments for Teaching Photochemistry: Photon Upconversion by TTA and All Optical INHIBIT Logical Gate

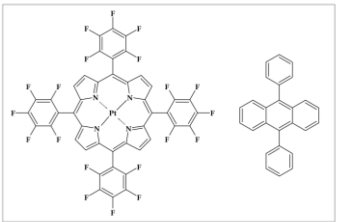
Nico Meuter, Sebastian Spinnen, Michael W. Tausch
Bergische Universität Wuppertal, Germany

The two new experiments reported below address students and teachers at the tertiary educational level, that is students and teachers from colleges and universities. Experimental approaches at the secondary educational level in high schools have already been published. Appropriate introductory experiments concerning photoluminescence, photochromism, solvatochromism and molecular switches are available as follows:

- M. W. Tausch, N. Meuter, S. Spinnen: "Photoprocesses in Chemical Education - Key Experiments for Core Concepts" **(2018)**, *Education Quimica*, DOI: 10.1016/j.eq.2017.03.003
- M. W. Tausch, R. Brunnert, C. Bohrmann-Linde, N. Meuter; N. Pereira Vaz, S. Spinnen, Y. Yurdanur: „Photons and Molecules - Basic Concepts of Photochemistry in Video Tutorials" EPA (European Photochemistry Association) Newsletter, Volume 96, p. 70-77 **(2019)**;
- M. W. Tausch et al. „Chemistry with Light - Innovative Didactics for Study and Teaching" Internet Platform **(2019)** https://chemiemitlicht.uni-wuppertal.de/

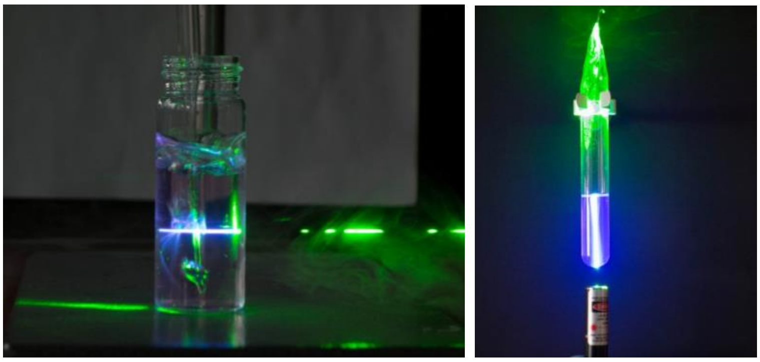
Upconversion by TTA

Experimental procedure: 0,5 mg of Diphenylanthracene DPA and 0,2 mg of 5,10,15,20-Tetrakis-(2,3,4,5,6-pentafluorophenyl) porphyrine-Pt(II) TPFPP-Pt(II) are dissolved in 15 mL of acetone. The solution shows a slight pink color and generates a weak red fluorescent trace if irradiated with the beam of a green laser pointer (power: about 10



mW). In order to make the upconversion effect visible, oxygen has to be removed from the solution. This is easily achieved by flushing the solution with nitrongen. During this process the fluorescent trace insidet the solution changes from a weak red to strong blue color within one or two minutes. If the purging with nitrogen is stopped, the blue fluorescence stays for a maximum of roughly 2 to 3 minutes until sufficient oxygen has diffused back into the solution.

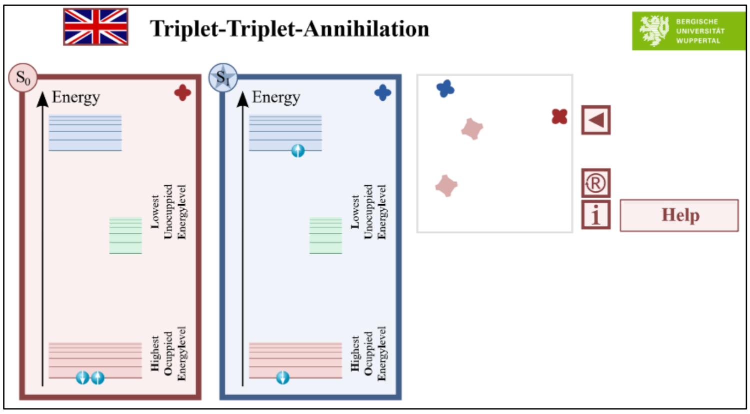
In order to get a long-lasting upconverting solution, the vial has to be hermetically sealed immediately after flushing the solution with nitrogen gas. The solution can then be stored for years within the sealed vial. It is suitable for hands-on demonstrations of the photon upconversion effect.



A green laser beam triggers a blue fluorescent trace in the TTA solution

Teaching recommendations: In photoluminescence processes photons are commonly down converted. The energy of incident photons is partially dissipated as heat by vibrational relaxations within molecules. As a consequence, the color of the light emitted by fluorescence is red shifted compared to the color of the exciting radiation (*Stokes* shift). This can be explained convincingly by means of the concept of electronically excited states of molecules including their vibrational levels. While teaching photoluminescence, it's recommended to introduce this theoretical concept by first investigating the photon down conversion via fluorescence and phosphorescence (see experiments in online publications mentioned above).

Doing so, students will be surprised when seeing that green light is converted into blue light by fluorescence. In fact, the observation from the TTA-experiment disagrees with the established theoretical concept. Therefore, the logical contradiction between the theoretical prediction and the experimental observation requires a credible explanation for the anti-*Stokes* behavior of the setup in our TTA experiment. In order to facilitate this explanation, we provide a model animation.



Screenshot from the model animation available at https://chemiemitlicht.uni-wuppertal.de/en/models-animations/triplet-triplet-annihilation.html

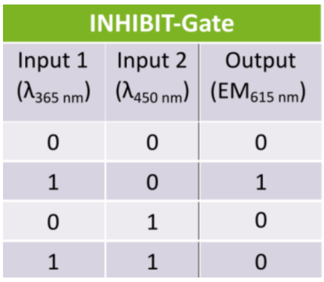
The interactive animation shows and describes step by step the TTA mechanism from the absorption of a “green” photon by the platinum complex (the triplet sensitizer) until the emission of an upconverted “blue” photon by diphenylanthracene (the fluorophore).

Corresponding key terminology: photoluminescence, fluorescence, phosphorescence, upconversion, triplet-triplet-annihilation, energy transfer, Stokes shift, model animation

All Optical INHIBIT Logical Gate

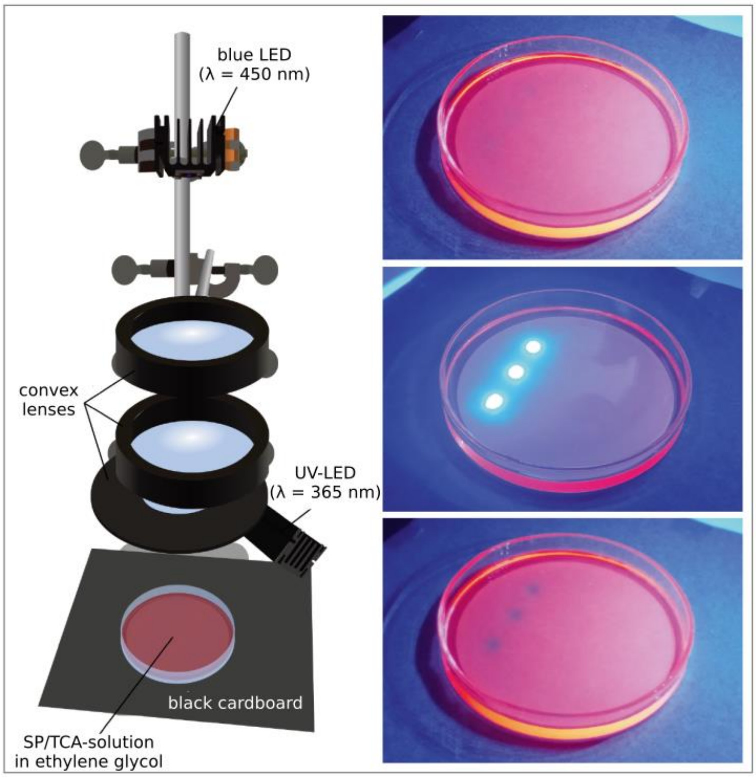
Experimental procedure a): A solution of spiropyrane SP in ethylene glycol, acidified with trichloroacetic acid TCA, [c(SP) = 10^{-3} mol/L, c(TCE) = $5 \cdot 10^{-2}$ mol/L] is placed in a Petri dish and irradiated on the whole surface with a strong LED-UV-light-source (λ = 365 nm). The solution exhibits a fairly strong red fluorescence. This emission at λ = 615 nm is generated by the protonated species of merocyanine MCH^+, and represents the ON signal (input 1) of the INHIBIT gate.

It persists during the whole experiment.



INHIBIT-Gate

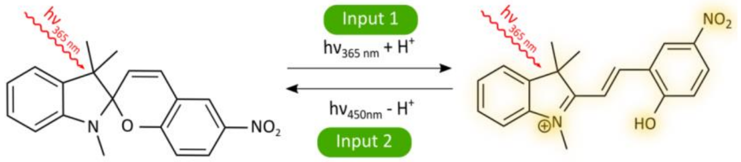
Input 1 ($\lambda_{365\ nm}$)	Input 2 ($\lambda_{450\ nm}$)	Output ($EM_{615\ nm}$)
0	0	0
1	0	1
0	1	0
1	1	0



In ethylene glycol solution the red fluorescence of MCH$^+$ *is switched ON by irradiation at 365 nm, and the fluorescence is locally switched OFF by irradiation at 450 nm*

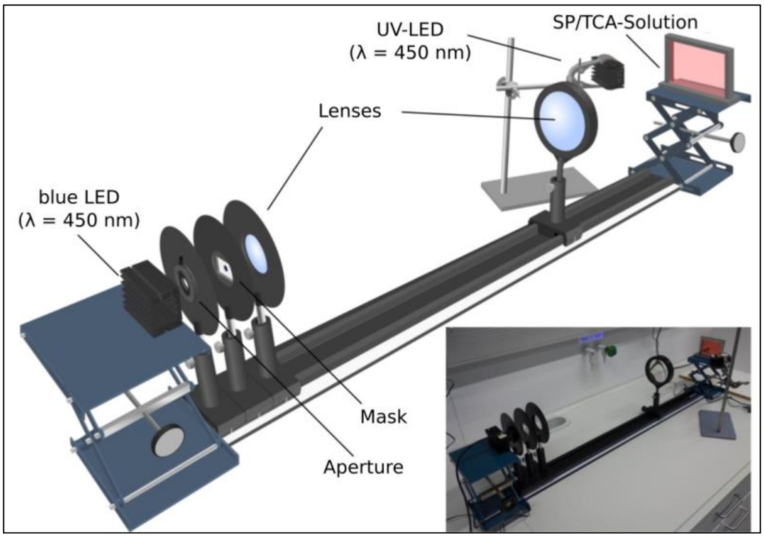
The OFF signal (input 2) consists of irradiation with blue light (λ = 450 nm). It is focused on three small circular points using a vertically arranged device made of three LEDs and a system of lenses as seen above. Irradiation with blue light for four seconds leads to a complete quenching of the fluorescence. This can be convincingly observed immediately after switching off the 450 nm LEDs. It takes approx. 10 seconds until the whole surface in the Petri dish fluoresces again.

The reversible processes are summarized in the following scheme:



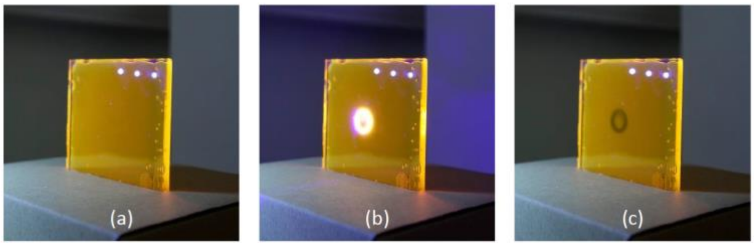
Spiropyrane SP *Protonated Merocyanine MCH*

Experimental procedure b): Using samples of spiropyrane SP and trichloroacetic acid TCA in a matrix of polymethylmethacryate PMMA, applied as thin film on a plate of glass, the all optical INHIBIT experiment can be carried out using the following horizontal set up.



Horizontal setup for demonstration of an all optical INHIBIT logical gate

In this case the ON signal (input 1, irradiation at λ = 365 nm) induces a yellow-orange fluorescence, and the OFF signal (input 2, irradiation at λ = 450 nm) quenches the fluorescence. Operating similarly as in procedure a), the following pictures have been obtained.



In a PMMA matrix the yellow fluorescence of MCH^+ is switched ON by irradiation at 365 nm, and the fluorescence is locally switched OFF by irradiation at 450 nm

Teaching comments: The non-fluorescent region on the sample (c) brings to mind the doughnut-like non-fluorescent region applied in the STED nanoscopy method invented and developed by Stefan Hell [S. W. Hell, "Nanoscopy with Focused Light", Nobel Lecture, *Angew. Chem. Int. Ed. 2015*, 54,8054 –8066]. Due to the fact, that the fluorescence of different molecular species (SP and MCH^+) is remotely switched ON and OFF using focused light, our experiment can be considered as a model for the STED-related RESOLFT concept. With reference to *Z/E (cis-trans)* isomers, S. Hell justifies the denotation RESOLFT in the cited paper above as follows:

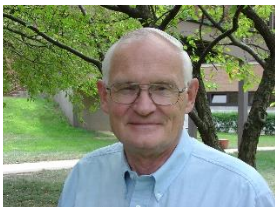
"I called it RESOLFT, for 'reversible saturable/switchable optically linear (fluorescence) transitions' simply because I could not have called it STED anymore. There is no stimulated emission in there, which is why I had to give it a different name. The strength is not only that one can obtain high resolution at low light levels. Notably, one can use inexpensive lasers, continuous-wave (CW) lasers, and/or spread out the light over a large field of view, because one does not need such intense light to switch the molecules."

Actually, in our all optical INHIBIT gate continuous waves from inexpensive LEDs (< 1 W/cm^2) are used for switching the fluorescence ON and OFF. But like any other model experiment it is far away from the real super resolution micro- and nanoscopy. However, it is suitable for teaching applications of molecular switches and for demonstrating the principle of the RESOLFT method used in nanoscopy.

Corresponding key terminology: molecular switch, all optical INHIBIT logical gate, model experiment, RESOLFT concept, nanoscopy

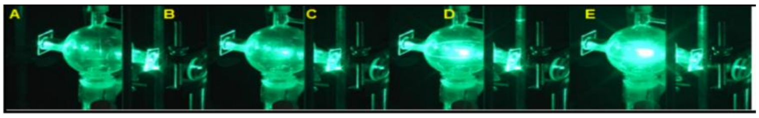
Photomasking Groups to DNA Photo-manipulation, 50+ Years of Light Chemistry *I-APS 2019* (part 2)

R. Marshall Wilson
Center for Pure and Applied Photosciences, Bowling Green State University, Bowling Green, Ohio, USA

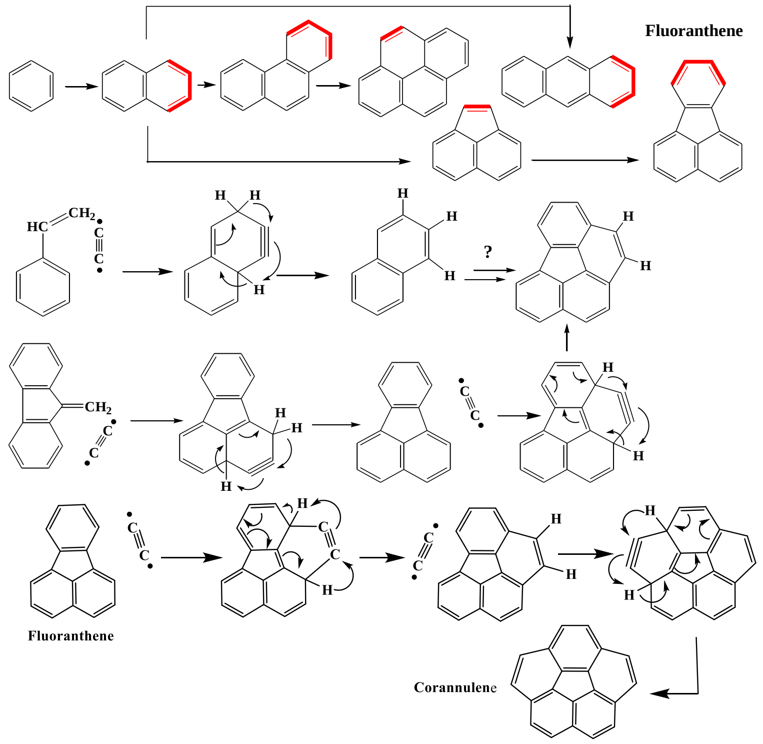


This document continues the presentation begun in the June issue of this journal and summarizes my presentation at the 2019 Inter-American Photochemical Society meeting in Sarasota, Florida where I was inducted as a Fellow of the Society.

The previously described laser microjet apparatus has another unique application. If a solid object such as the microjet nozzle is briefly inserted into the focal point of the laser, a plasma is initiated and persists after the solid object is removed from the focal region. CW-Ar laser atmospheric pressure apparatus utilizing benzene vapors – argon plasma: A) a trigger is inserted from the top into the benzene-saturated focal point of the laser beam; B) plasma is triggered; C) trigger is removed; D) plasma is sustained in the focal point of the laser; E) CCD in the camera becomes saturated by the high plasma-light intensity. The snapshots were taken in 0.25 s intervals.

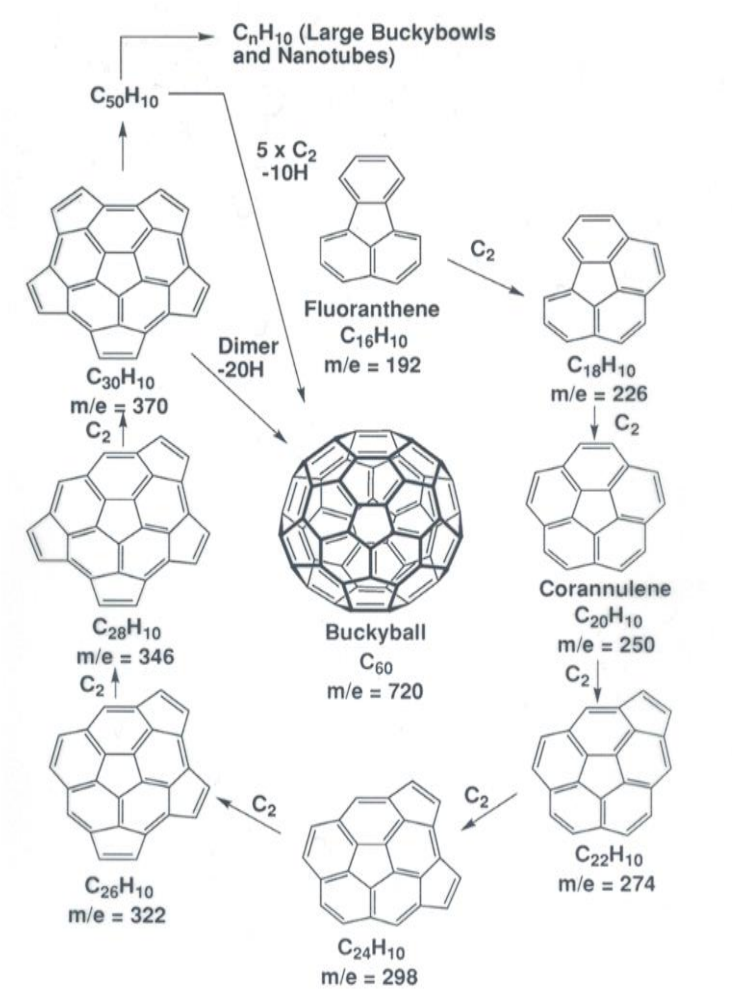


This plasma was generated in a microjet of benzene and apparently forms a plasma of C_2 fragments which add to the benzene solvent molecules as outlined below ultimately forming fluoranthene and corannulene.

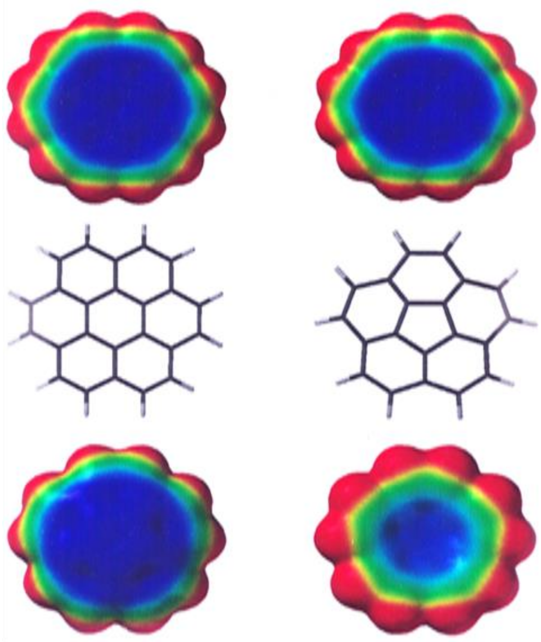


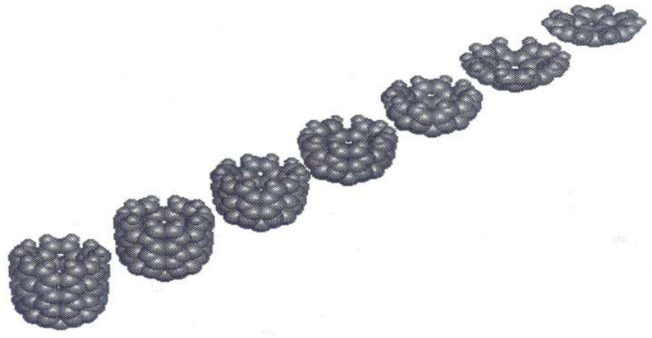
These C_2 fragments can continue adding to carbon molecules until bucky balls and carbon nanotubes are completed and will continue plasma generation until the laser is turned off. The result is that large quantities of carbon materials can be formed by this plasma method.

A very interesting aspect of corannulene is that it is not a planar hydrocarbon. If the central ring is six-membered, the hydrocarbon is flat and both sides have identical electron density. However, when the central ring is five-membered the hydrocarbon is bowl-shaped with the inner surface being electron-poor and the outer surface being electron-rich as shown below. As can be seen, buckyballs and carbon nanotubes fall into this latter category and thus, form curved hydrocarbon surfaces that have different electronic properties. It should be noted that the formation of buckyballs can be enhanced by adding fluoranthene as a template to the benzene solution irradiated in the microjet. Furthermore, it should be noted that the synthetic potential of this method of forming graphene carbon molecules has not been thoroughly explored and much work remains to be done in the development of this photochemical method.



Charge Distribution (+10 (red) to -13 (blue))





In the early 1980's, I coauthored a book, "The Vocabulary of Organic Chemistry" along with my colleagues, Milton Orchin, Fred Kaplan, Roger S. Macomber, and Hans Zimmer.[1] I wrote the chapters entitled "Name Reactions, Type Reactions and Their Mechanistic

Pathways" and "Natural Products and Biosynthesis". These were two of the most frequently read chapters in the book. One could make this determination by looking at the closed book of students and noting the most discolored pages and opening the book to those chapters. In 2005, we decided to write a second edition of this text. This volume was entitled "The Vocabulary and Concepts of Organic Chemistry" and was coauthored by Milton Orchin, Roger S. Macomber, Allan R. Pinhas and myself.[2] The chapters that I had written in the first edition were going to be included in a second volume of an extended series. In the first volume of the second edition, I wrote chapters entitles "Reactive Intermediates (Ions, Radials, Radical Ions, Electron-Deficient Species, Arynes)", "Types of Organic Reaction Mechanisms", and "Electronic Spectroscopy and Photochemistry". The anticipated second volume in this series was never written and therefore, the chapters omitted from this second volume were never published.

Another extremely useful area of photochemistry is photoaffinity labeling. Many biological molecule loosely associate via hydrogen bonding or other types of weak associative bonding that is essential for their biological function. So when one attempts to characterize the structural details of how these molecular associate, they fall apart in the isolation processes. One method for dealing with this type of problem is to slightly modify one of the biological components in such a way that it still bonds to its biological partners in the usual way, but that it is photochemically reactive and upon exposure to light will become covalently bonded to these partners. These light sensitive analogs are called photoaffinity labels.

During the early 1990's, I took a sabbatical leave from the University of Cincinnati to visit The Ohio State University in the laboratory of Professor Matthew S. Platz where I also worked with Professor Christopher M. Hadad. This was my first exposure to both nucleic acid chemistry and transient absorption spectroscopy. Work on ultrahigh resolution transient spectroscopy was later done in the laboratory of Professor Alexander N. Tarnovsky at Bowling Green State Univeristy.[3]

Professor
Christopher M. Hadad

Professor
Alexander N. Tarnovsky

Professor
Matthew S. Platz

The first of these affinity labels studied was with the *p*-amino-*o*-nitrobenzoazide molecule which can be incorporated into many protein molecules via their amino groups and photochemically forms very reactive basic nitrenes intermediates that will react with many proton sources as shown below. The lifetime of many of the intermediates of these processes were determined by transient absorption spectroscopy. This new technique allowed us to directly observe mechanistic steps that we had previously only speculated upon their existence.

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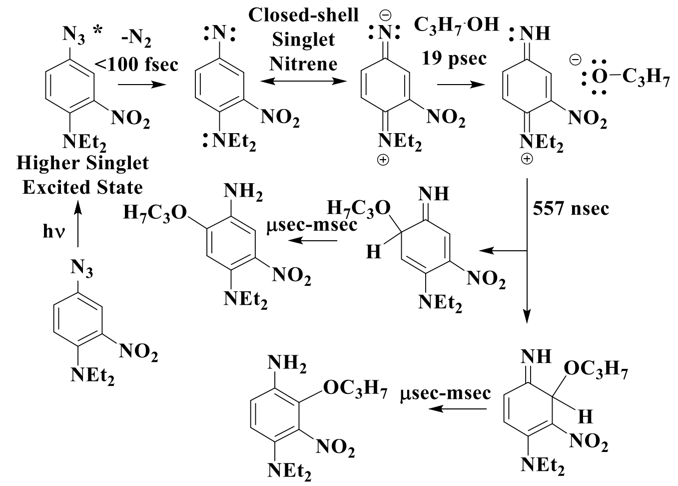
This technique was extended to the nucleic acid 8-azidoadenonsine. Irradiation of this nucleic acid produced a very electrophilic purine intermediate that reacted with many nucleophiles, thus constituting a very effective photoaffinity label in the nucleic acid family. This work was done primarily in the Ohio State laboratory of Professor Matthew S. Platz[4] and the mechanism of action of its photochemistry was determined by ultrafast transient absorption spectroscopy in the laboratory of Professor Alexander N. Tarnovsky at Bowling Green State University[5] as shown below.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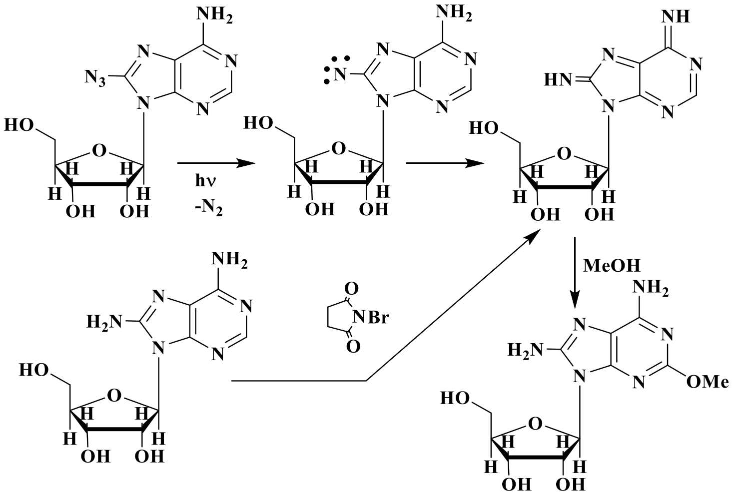
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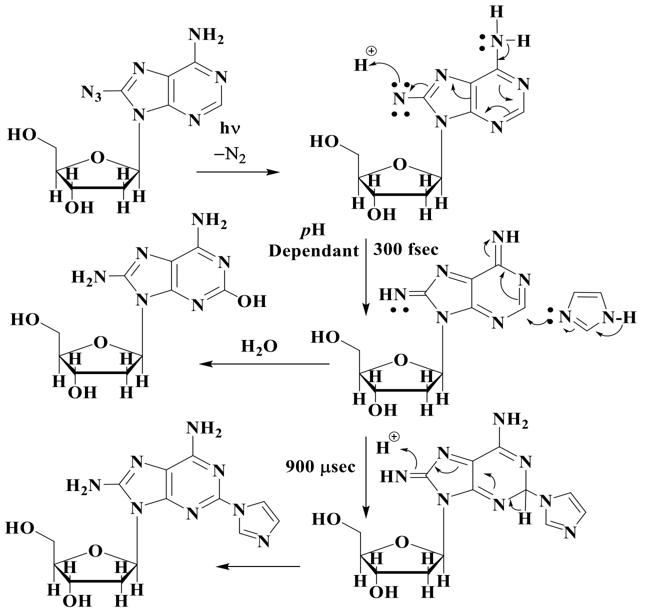


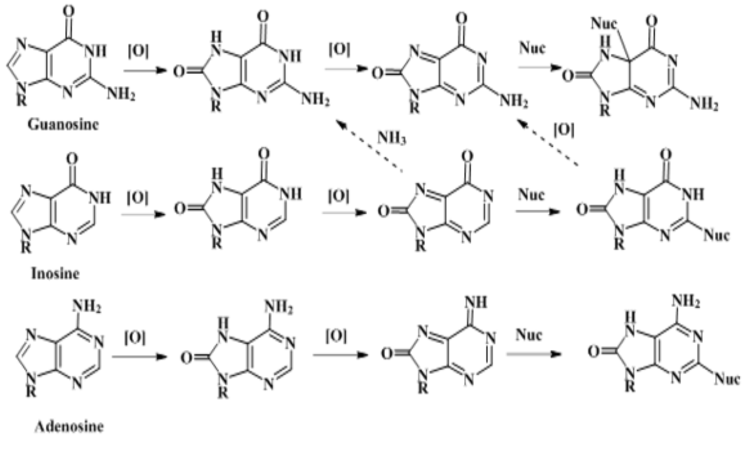
An incident occurred during my stay in Professor Platz's laboratory that might be useful to describe since several people have died from similar accidents. While drying several liters of 2-methyltetrahydrofuran (2-MTHF) over sodium-potassium allory, the flask became overheated and the 2-MTHF was not boiling smoothly, but flashing. As I was trying to disconnect the heating mantle, the liquid flashed violently, blew out the condenser, sprayed me all over and exploded. The explosion blew out the windows in the laboratory and cracked to the stone base of the hood. The students said the building lifted off the ground, "Wilson fell to the ground, his face and arms aflame and rolled on the floor until a student, Atnaf Admasuu, smothered the flames with a jacket." "Wilson then jumped to his feet and tried to extinguish the flames at his lab station, but the student grabbed the extinguisher and doused the fire. "Everything happen in a fraction of a second, Admasu said" (Ohio State Lantern, Thursday, Jan. 17, 1991). Nevertheless, I sustained second degree burns over 20% of my body. My observations as a person in the middle of an explosion was that I did not hear the explosion, but found myself five feet away from the hood with my body on fire and the flames reaching the celling. My hands were cracking up the sides. So I closed my eyes, stopped breathing and rolled on the floor. While aflame I had a warm cozy feeling, but one hour later the pain was so great that I had to leave my body. However, the most embarrassing aspect of this incident was having to walk out of the building to the ambulance past all of the people in the department with much of my clothing burned from my body! I recovered in several months with the help of the burn doctors in Cincinnati. Since I do not scar, my body parts returned to normal. Professor Platz most kindly accepted me back into his repaired laboratory and we continued a very productive collaboration.

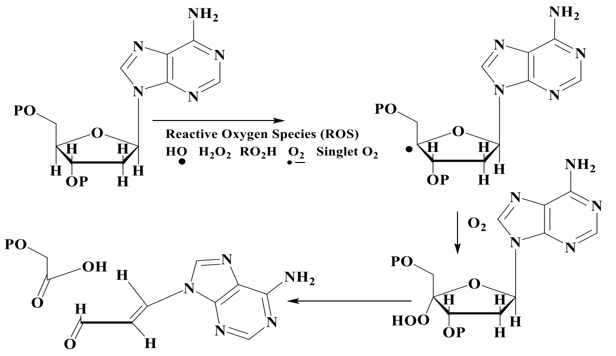
In 2005, after many unsuccessful attempts by the dean of the College of Arts and Sciences to take Chemistry Department endowment funds, which had been donated to the Department by very successful faculty members, including Ralph E. Oesper, Hans W. and Marlies Zimmer, and Edward K. Deutsch, the Dean fired me as Head of the Department of Chemistry of which I had been Head for eight years. The justification was that I had been uncooperative with her effort to hire more than 18 staff personnel for her office since she needed them more than the Chemistry Department needed them to run their NMR's, Mass Spectrometers, computers, and X-ray crystalographic instruments. Since the chemistry faculty at the University of Cincinnati was no longer suitable for me, I secured a position on the faculty of the Center for Photochemical Sciences with the help of Douglas C. Neckers, the center's director and moved from the University of Cincinnati to Bowling Green State University (BGsu). At BGsu, I used my personal financial company established over the years to fund my research and a named faculty position. This arrangement made it possible for me to devote all of my time to research and teaching and not have to spend enormous amounts of time applying of external funding in the deteriorating scientific environment of the United States.

Professor Douglas C. Neckers

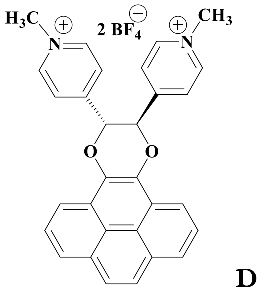
While at Bowling Green State University, I began to conduct DNA research as a serious effort with the investigation of the oxidation of purine nucleic acids. It was found that the oxidation of purines led to 8-oxopurine which are in turn much more easily oxidized than the parent purine and lead to quinone-like purines that are very susceptible to nucleophilic attack and cross-linking with proteins and other nucleic acids as shown below. These nucleic acid oxidations are frequently initiated by Reactive Oxygen Species (ROS), which include singlet oxygen, super oxide ($O_2^{\cdot -}$), hydroxyl radical, hydrogen peroxide, etc. As indicated below, many of these species add to the 8-positions of the purine rings, but they may also react with the ribose sugar ring and break one of the DNA strands.[6] Breaking a single strand is not a major problem since the damage can be repaired because the complementary strand is intact and clearly templates the base sequence of the broken strand. However, breaking both strands in close proximity to each other can make repair difficult to impossible.

Another mechanism by which ROS might damage nucleic acids is shown below in the ribose cleavage mechanism describe by Professor J. Stubbe.[6]

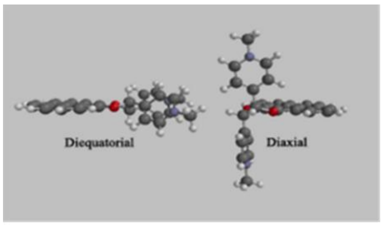


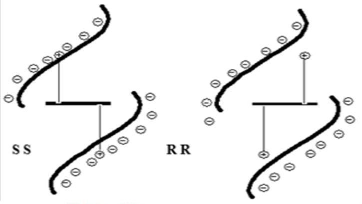


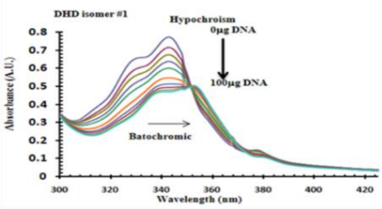
In my later years at the University of Cincinnati, my group developed dihydrodioxins that bind to and cleave DNA strands photochemically. A particularly effective variation on this type if DNA cleaving agent was the the dipyridinium salt dihydrodioxin (**PDHD**) shown below. This molecule might exist in either a diequatorial or diaxial conformation. In the diaxial conformation, the pyrene ring is ideally situated to intercalate between two bases in the nucleic acid duplex while the pyridinium salts are ideally positioned to electrostatically bind to the phosphate back bones of the duplex.[7] This work was done in collaboration with both Professors Alex N. Tarnovsky and Neocles N. Leontes of Bowling Green State University and demonstrated that the dihydrodioxin was bound to the nucleic acid as shown below and that it did not matter much if the dioxin had the RR or SS stereo chemistry.

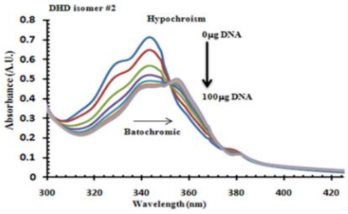


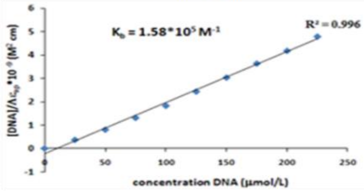
Dipyridinium Dihydrodioxin (PDHD)

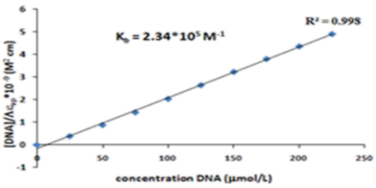




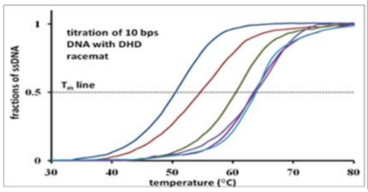


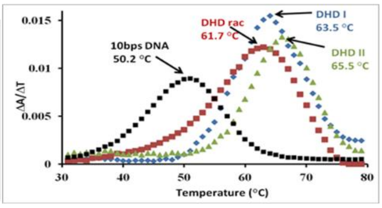






The dihydrodioxins not only bind to the nucleic acids, but bind the two strands together more strongly than they would be in the absence of the pyridinium clamps as indicated by the duplex melting point curves shown below.

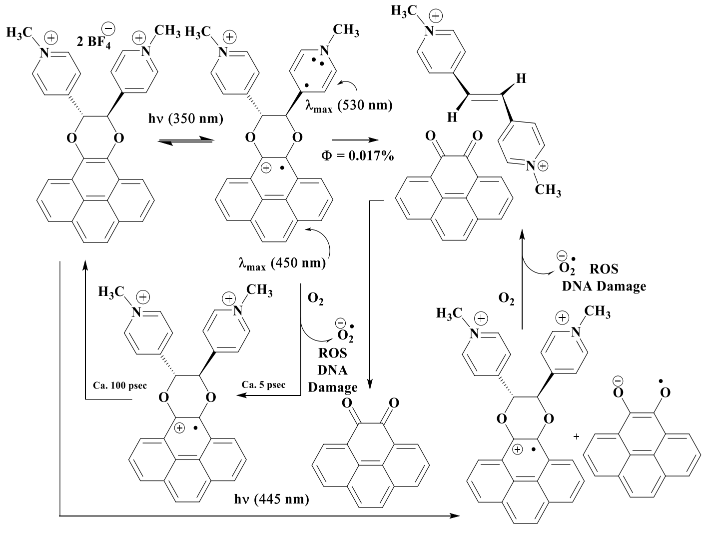


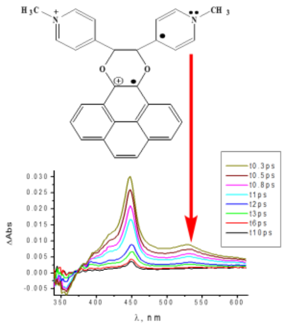


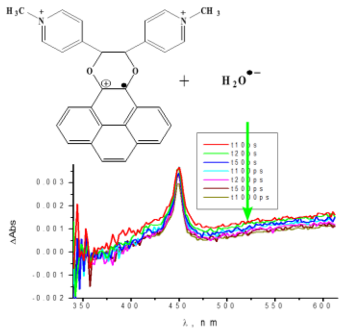
Professor Neocles Leontis

Detailed ultrafast transient spectroscopy absorption studies showed that the dihydrodioxin releases pyrene quinone as shown below when irradiated with long wavelength UV light. The pyrene quinone, which cannot be directly intercalated into duplex nucleic acids in a aqueous environment since it is not water soluble, is then trapped in an intercalative environment in the duplex nucleic acid where it is not released into the aqueous environment and can do extensive damage to the nucleic acids upon irradiation with visible light. Furthermore, upon oxidation of the DNA, the quinone becomes reduced to the hydroquinone and within a few minutes is spontaneously oxidized back to the quinone by atmospheric oxygen. At which point it can continue to photo-oxidatively damage the DNA. Thus, a single pyrene quinone molecule can do extensive damage to a nucleic acid into which it is introduced.[7]

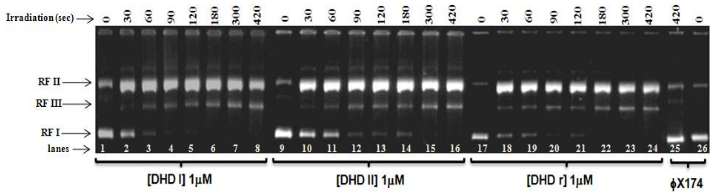
The initial pyrene quinone release is triggered by the photochemical electron transfer from the pyrene moiety to a pyridinium salt. This electron transfer reaction becomes very obvious by ultrafast transient spectroscopy as indicated by the conspicuous pyrene radical cation absorption at 440 nm that is shown below.[7]



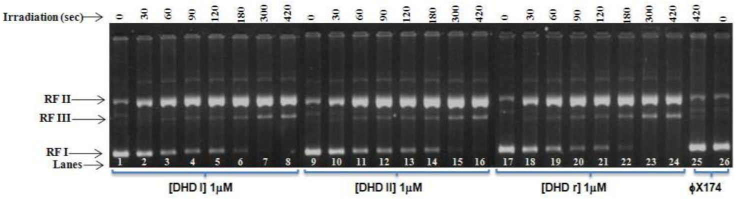




The effect of oxygen is best shown by the damage to the ΦX174 plasmid that has 5386 base pairs requiring 653 random cuts to linearize the system. Yet, in these experiments it required far less than 653 cuts to cut both chains of the ΦX174 and linearize the DNA. We attribute this to the entrapment of the pyrene quinone within a single intercalative space in the DNA and the localization of the damage to that space.



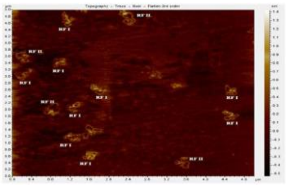
Photochemical cleavage of supercoiled ΦX174 plasmid DNA (0.033 μg/μl) with PDHD enantiomers and racemic mixture (1μM of each) in cacodylate buffer (10 mM sodium cacodylate, 100 mM NaCl, 0.5 mM EDTA, pH 7.1). Each sample was irradiated with the 442 nm He/Cd CW laser light at 18° C in the **presence of oxygen**. Samples were then analyzed on a 1% agarose gel. Lanes 1–8, are DNA-PDHD RR complex with an increasing irradiation time of 0 – 420 s; lanes 9–16 are DNA-PDHD SS complex with an increasing irradiation time of 0–420 s; lanes 17–24 are DNA-PDHD rac., lane 25 is DNA alone irradiated for 420 s., and lane 26 is DNA alone with no irradiation. Photochemical cleavage of supercoiled ΦX 174 plasmid DNA (0.033 μg/μl) with PDHD enantiomers and racemic mixture (1 μM of each) in cacodylate buffer (10 mM sodium cacodylate, 100 mM NaCl, 0.5 mM EDTA, pH 7.1) in **absence of oxygen**. Each sample was irradiated with the 442 nm He/Cd CW laser light while maintaining



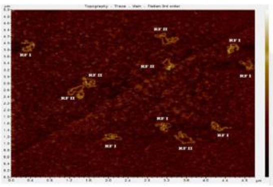
temperature at 18° C in the **absence of oxygen**. Then samples were analyzed on a 1% agarose gel. Lanes 1–8, are DNA-PDHD RR complex with an increasing irradiation time from 0 – 420 s; lanes 9–16 are DNA-PDHD SS complex with an increasing irradiation time from 0–420 s; lanes 17–24 are DNA- PDHD rac with an increasing irradiation time from 0–420 s; lane 25 is DNA alone irradiated for 420 s, and lane 26 is DNA alone with no irradiation.

One type of DNA damage that has been suspected for many years, but never demonstrated is aggregation of the DNA strands which might occur via strand radical dimerization. Since these aggregates would be very large, they would not be conspicuous via electrophoresis or detected by mass spectrometric analyses. Therefore, we collaborated with Professor Emil Khisamutdinov of Ball State University in an atomic force microscopy study of pyrene dihydrodioxin photochemical damage to ΦX174 plasmid photochemistry.[8] In the first two photos, one can see the relaxation of the super coiled plasmid (tight knots to open loops), and in the lower three photos, one can see the DNA strands becoming thicker as they aggregate.

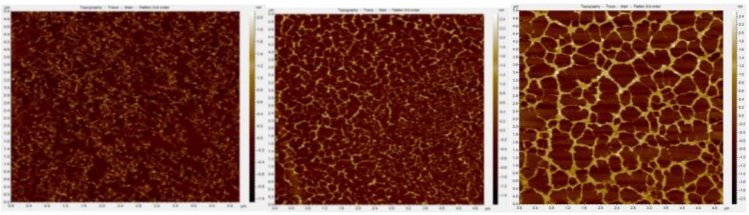
Professor Emil F. Khisamutdinov



ΦX 174 + hν

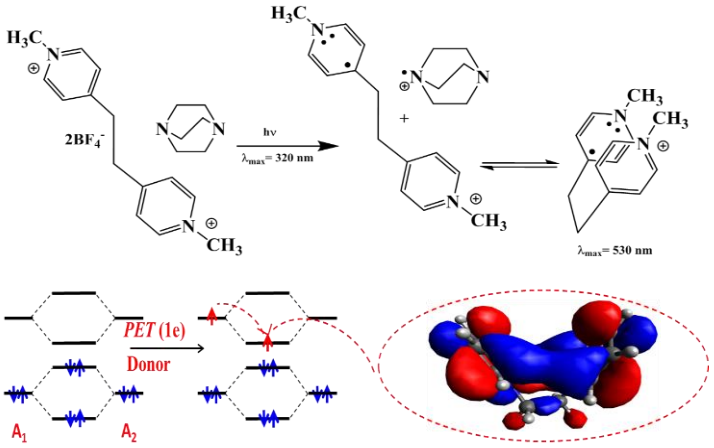


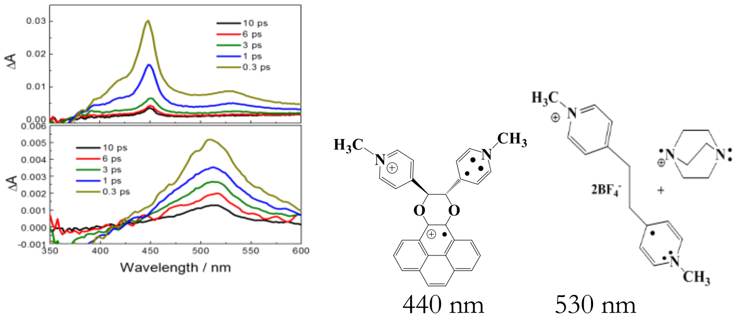
ΦX 174 + PDHD + hν



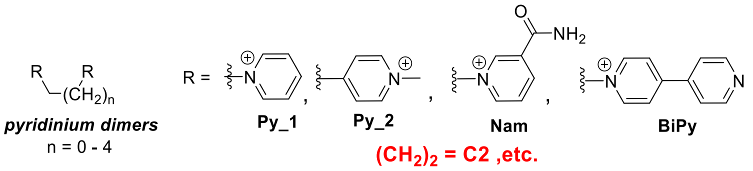
ΦX 174 plasmid DNA **ΦX 174 plasmid DNA + hν** **ΦX 174 plasmid DNA + hν + PDHD**

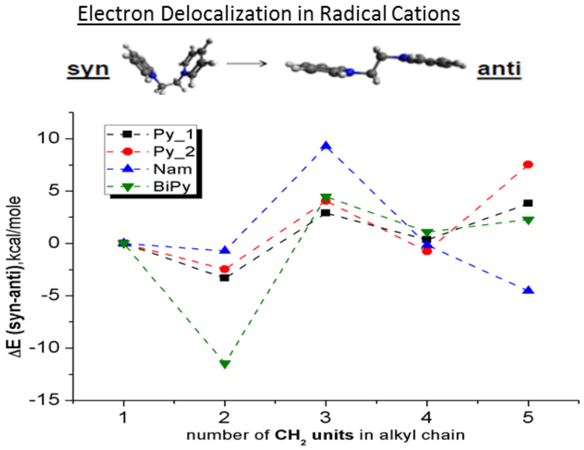
We were intriqued by the much more efficient release of the pyrene quinone by the irradiation of the Dipyridinium pyrene dihydrodioxin. The ultrafast transient absorption spectroscopic results shown above were obtained in the absence of DNA. Therefore, the two Pyridinium rings would be most stable in the diequatorial configuratiton. In this configuratation, they would be ideally situated to collaborate in the binding of the electrons ejected by the pyrene excited state as shown below. This novel type of electron clamp of two pyridinium salts attached as shown below with two carbon atoms does serve as a good electron acceptor in electron transfer photoreactions. In fact, the 540 nm absorption of the dipyridinium pyrene dihydrodioxin charge transfer transient displays a weak absorption at 540 nm in close proximity to the 530 nm transient of the dipyridinium radical cation shown below.

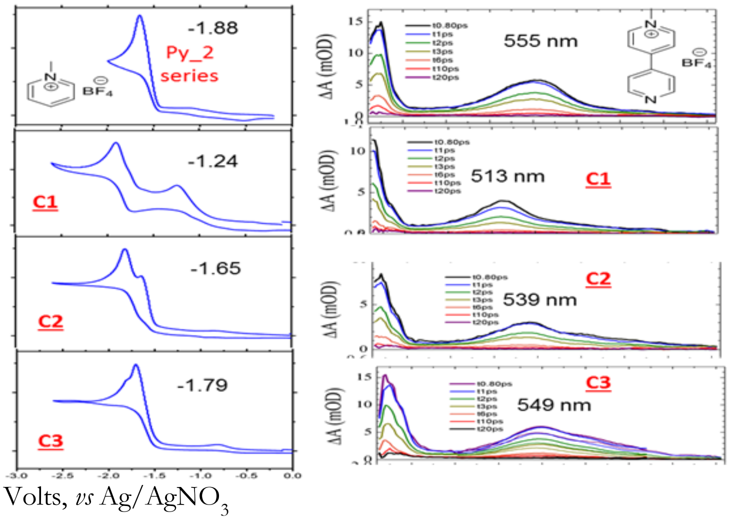




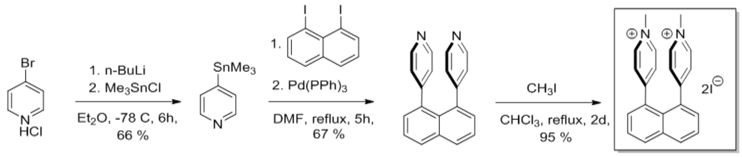
The stabilization of a number of pyridinium electron traps were examined and the syn Py-2 found to be one of the most stable as shown below.



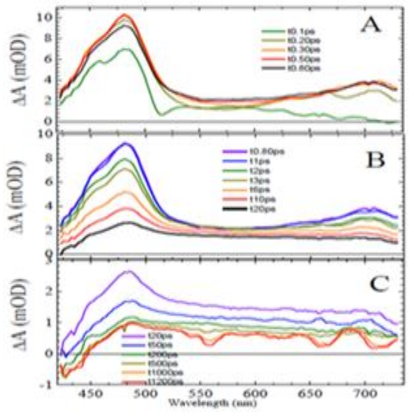


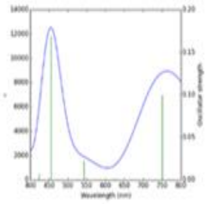


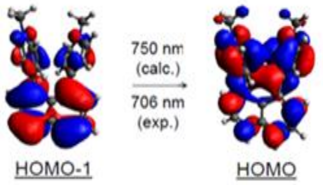
Professor Ksenija Klusac of the University of Illinois at Chicago kindly measured the electron entrapment of the rigidly syn 9,10-dipyridinium naphthalene salt.



Rigid System (Py rings "fixed" face-to-face)

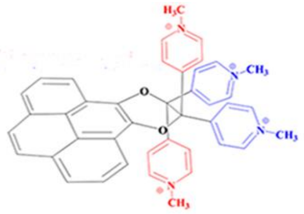




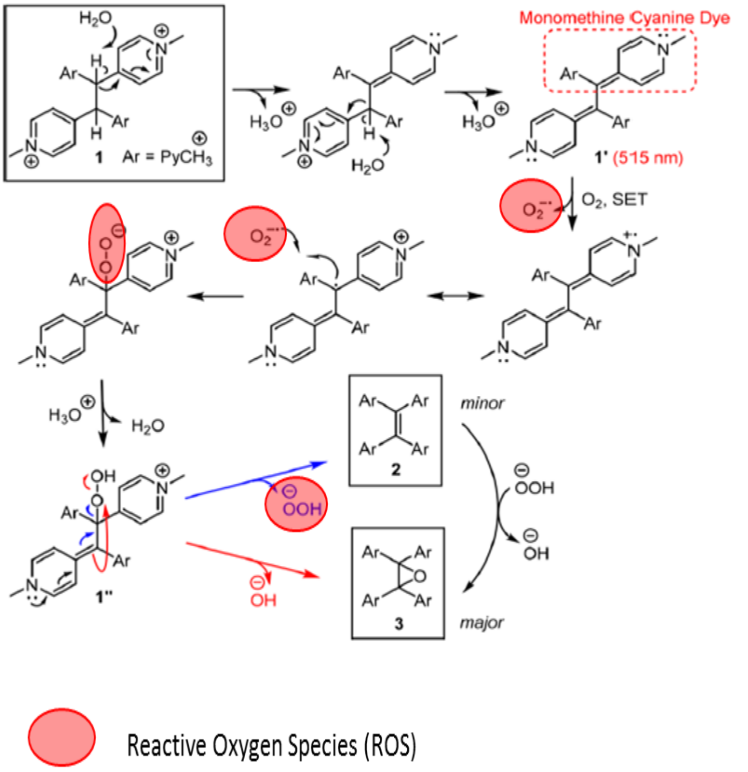


TDDFT provides good prediction of TA spectra. Other functionals (wB97XD) and SMD model were tested as well. Prediction of UV-Vis absorption for flexible systems was not successful due to the conformational complexity of such systems.

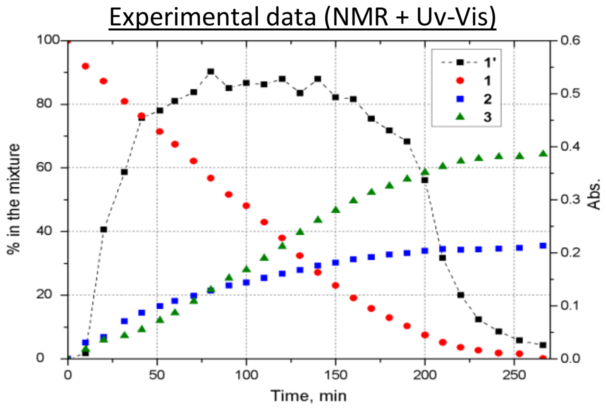
These experiments clearly show the benefits of having two pyridinium arms to entrap the electron ejected by the dihydrodioxin moiety. However, as indicated earlier, these same two pyridinium arms are also necessary to bind to the phosphate strands of the nucleic acid and they are most effective in this capacity when in the diaxial configuration which is not the best configuration for electron entrapment. Therefore, we have set as one of our research goals the synthesis of the *tetra*-pyridinium dihydrodioxin shown below that contain both types of pyridinium arms.

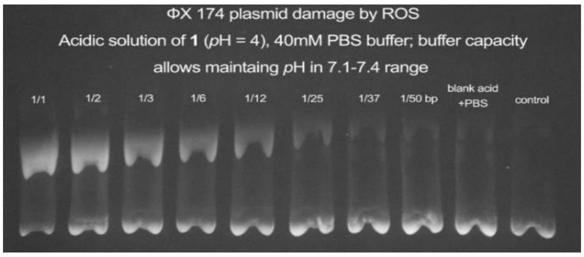


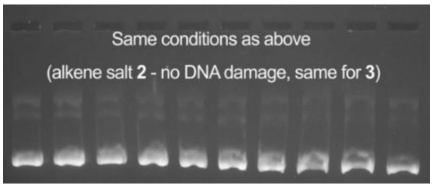
Towards this goal, we have set out to synthesize the tetrapyridinium ethylene necessary to prepare this *tetra*-pyridinium dihydrodioxin. In the process of this synthesis, the tetrapyridinium ethane was prepared and observed to be very unstable to atmospheric oxygen. This unusual ethane formed the corresponding epoxide and ethane upon simple exposure to oxygen in only a few hours as shown below.[9]



As one can see, in the course of this oxidation many Reactive Oxygen Species (ROS) seem to be generated (red circled molecules) and no photochemical trigger is necessary. In order to test the generation of ROS in this reaction, the alkane **1** was mixed with plasmid ΦX174 under atmospheric conditions and the DNA found to undergo conversion from supercoiled to relaxed configurations (see below). Interestingly, while the supercoiled form was readily converted to the relaxed form, little if any linear form was produced and the tetrapyridinium ethylene did not have a similar effect on the DNA (see below). This failure to linearize the DNA may be due to the extreme mobility of the ROS which will cut the DNA chains at random remote locations instead of localized sites as is the case for the intercalated *ortho*-quinones generated photochemically from the DHDs. These results are of further interest since single strand DNA damage is often easily repaired since the template strand remains intact. Whereas, double strand damage is not repairable and causes the cell to commit apoptosis. These considerations and observations raise the most interesting question of whether the controlled generation of ROS could be used to regulate genetic processes. Work in this fascinating field will continue so long as my age and health permit.







Finally, I would like to thank The National Institutes of Health who supported my Ph.D. and postdoctoral research, the National Science Foundation and University of Cincinnati who supported many years of research while at UC and Bowling Green State University and my wife, Antonia, who consented to using family finances for research support at BGsu.

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Continuous-flow photochemistry made easy with Vapourtec's photoreactor series.

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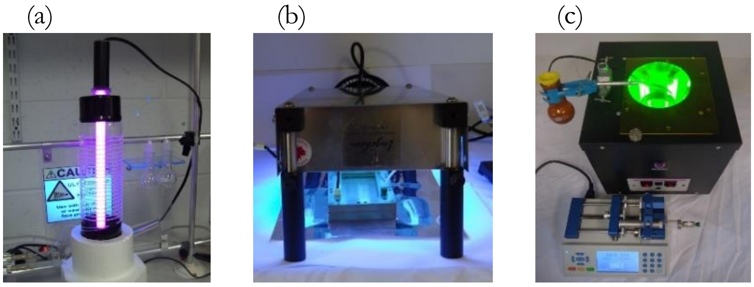
Recently, continuous-flow operation has emerged as a new technology trend in synthetic organic photochemistry, especially on laboratory scales [1]. Compared to traditional batch systems such as immersion-well or chamber reactors, flow photoreactors offer a range of advantages:

- effective light penetration through the reaction medium,
- removal of (light-sensitive) products from the irradiated zone,
- greater heat and mass transfer within the small reactor dimensions,
- safer operations under higher temperatures and pressures, and
- easy reaction scalability from process optimization to demonstration-scale production.

These representative benefits make continuous flow an attractive option with the potential to implement preparative photochemistry for pharmaceutical applications and fine chemical productions.

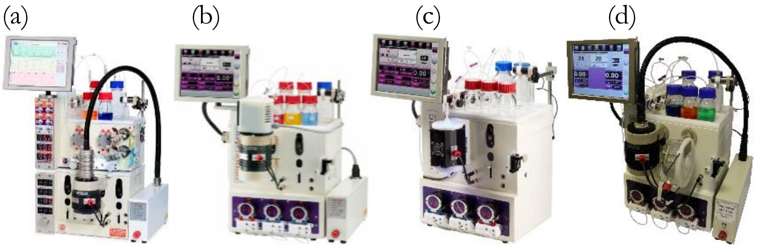
Many flow photoreactors are largely improvised devices with components taken from conventional flow and photochemical technologies (**Figures 1**). Commercial flow devices in combination with self-fabricated light-sources are also common. These systems generally suffer from compromised designs, incomplete descriptions and inadequate characterizations. This has led to a generally poor reproducibility of the reactors themselves as well as the experimental results achieved within these devices [2].

With the growing importance and acceptance of flow photochemistry in the industrial community [3], a reliable and purpose designed flow reactor with optimal component matching, easy control over reaction conditions (e.g. temperature, pressure, exposure time, & wavelength of emitted light) and scale-up potential is undeniably essential.



Figures 1. Examples of improvised flow photoreactors: (a) dual-capillary reactor with internal fluorescent tube, (b) block reactor under UV-panel and (c) capillary tower inserted into chamber photoreactor.

In March 2014, Vapourtec launched its UV-150 photochemical reactor [4]. Since its introduction, additional accessories and features have been continuously released (**Figures 2**), which have made this device family suitable for a wide range of photochemical applications. Subsequently, the systems have been rapidly adopted by the academic and industrial communities and have been featured in over 75 publications [5].

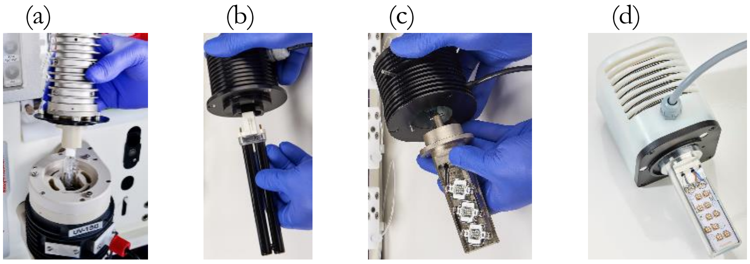


Figures 2. (a) UV-150 reactor R-series, (b) high power LED reactor E-series, (c) immobilized photocatalyst reactor E-series and (d) UV-150 reactor E-series in tandem configuration.

Each photochemical module can be easily plugged into either the E-Series (peristaltic pump) or the R-Series (piston pump) platform. The entire installation of these compact and space-efficient modules and their power supplies takes less than 5 minutes. In tandem configuration (**Figure 2d**), each reactor can be equipped with an additional thermal loop that allows flow photochemical and thermal reactions to be performed in series with precise control over reaction conditions, all from an intuitive touch screen user interface [6].

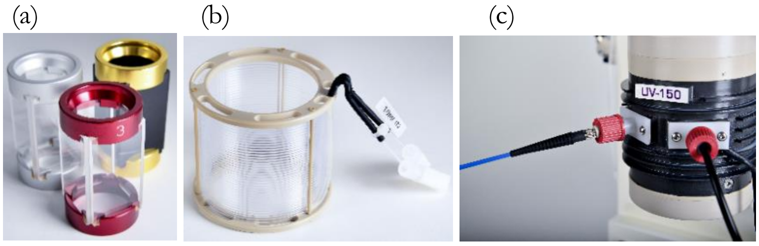
The UV-150 photochemical reactor chamber can be fitted with three different light sources (**Figures 3**) that cover the entire photochemically important range of 220-650 nm. Each lamp can be changed rapidly by hand within a minute. The available light sources comprise of:

- a dimmable polychromatic (75-150W) medium-pressure mercury lamp,
- low-pressure mercury lamps (9 W) that emit in the UVA, UVB or UVC range, and
- narrowly emitting medium- (60 W) or high-power (150 W) LED panels ranging from 365-525 nm.



Figures 3. (a) 150 W medium-pressure lamp, (b) UVA 9 W low-pressure lamp, (c) 60 W LED-array and (d) 150 W high-power LED array.

The medium-pressure mercury lamp can be equipped with a range of easily exchangeable band-pass or cut-off filters (**Figure 4a**) that are placed between the bulb and the reactor coil for a selective wavelength region, and thus permit selective photochemical activation. The reactor cartridge itself consists of a replaceable 2, 5 or 10 mL fluorinated ethylene propylene (FEP) coil with a wall thickness of 0.15 mm and an internal diameter (ID) of 1.30 mm (**Figure 4b**). The coil material is (photo)chemically inert and shows excellent transparency at wavelengths >240 nm. An optional spectrometer can be attached to the reactor housing via a fiber-optic probe (**Figure 4c**), thus allowing real-time monitoring of the transmission spectra. The photoreactor chamber is designed to give safe and accurate heat management. Reactor cartridge and lamp are housed in separate, sealed quartz chambers and air is circulated within each chamber at high flow rates to dissipate heat. An optional external cooling module utilizes a dry-ice filled Dewar that delivers chilled gas (N_2 or compressed air) to the irradiation unit. The reactor temperature can thus be varied with ±1°C precision between -5 and +80°C for the medium-pressure mercury lamp or between -40°C and +80°C for the low-pressure mercury lamps and LED arrays. The temperature is measured directly at the reactor wall for most accurate representation.



Figures 4. (a) Selection of glass-filter inserts, (b) 10 mL-FEP reactor coil and (c) fiber-optic probe and temperature sensor attachments.

The alternative packed-bed photoreactor system (**Figure 2c**) has been developed for illuminations involving immobilized or solid photocatalysts [7]. It consists of a glass column that allows adjustable packed bed volumes of 0.3-3 mL. The column is surrounded by three LED arrays (60 W) with variable wavelengths of 365-700 nm.

The photoreactor series developed by Vapourtec Ltd has been successfully applied to a wide range of homogeneous and heterogeneous (gas-liquid, solid-liquid or gas-liquid-solid) photoreactions. Optimization of reaction conditions (e.g. concentrations, wavelengths, light power or temperature) is rapidly achieved using small reagent volumes. Scale-up is then simply conducted by continuous operation over longer periods of time using larger stock solutions of reagents. In contrast to other commercial flow devices that are based entirely on LED light-sources, the UV-150 module allows photochemical investigations in the important UVC- and UVB-ranges. The simple interlock design of the individual components also permits an easy modification of the reactor system based on experimental requirements. Likewise, the unique tandem option readily facilitates in-series photochemical-thermal operations in the same continuous-flow in a single compact device ('telescoping') [8].

For more information, application notes and references, please visit https://www.vapourtec.com (last accessed December 20th 2019).

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Artificial Photosynthesis - Photochemical energy conversion based on Nature's model

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Based on the model of natural photosynthesis, the 2018 established Transregional Collaborative Research Center (CRC) "CataLight" (Light-driven Molecular Catalysts in Hierarchically Structured Materials - Synthesis and Mechanistic Studies) develops innovative photocatalytic systems for the production of hydrogen and oxygen from water. In perspective, the materials' concept research within CataLight shall be developed also towards other industrially relevant photooxidation and photoreduction reactions.

The central theme of CataLight research is to integrate molecular photocatalysts into stimuli-responsive soft matter matrices and to understand the molecule-matrix interactions towards optimized photocatalytic performance. The soft matter - heterogeneous matrices offer vast opportunities to synergistically control charge transfer processes, photochemical reaction pathways and degradation resistance. Though, the underlying mechanisms which control component interactions, photochemical and -physical properties and overall catalytic activity are not fully understand, yet.

CataLight develops suitable model systems to gain molecular-level insights into key processes, which govern reactivity and stability in photocatalysis. Specifically designed molecular light-driven catalysts are developed based on organic or metal complex chromophores linked to metal complex or molecular metal oxide/sulfide catalysts. As stimuli-responsive soft matter matrices CataLight resorts to polymers and block copolymers, nanostructured carbon / carbon nitride or DNA architectures.

Molecule-matrix interactions are studied both experimentally and theoretically on the multiple scale starting from molecular level and ultrafast processed bridging to materials and long term stability, giving fundamental mechanistic understanding of structure-activity relationship. This will allow to stabilise molecular photocatalysts, tune the molecule-matrix interplay and catalytic activity as well as development of molecular repair strategies.

Two recent results are highlighted in the following. A group centered around Radim Beranek reports about water-soluble polymeric carbon nitrides (PCN) as easily operable quasi-homogeneous photocatalysts for light-driven redox transformations.[1] Pristine and modified PCN are well-known photocatalysts for partial photooxidation of organic molecules,[2,3] and methoxy-substituted aromatic alcohols in particular.[4] They open the route for synthesis of high-value chemicals from low-value feedstock using only sunlight or cost-effective light sources (*e.g.*, LED arrays) and easily available oxidizing agents such as aerial oxygen. Due to their small specific reaction surface and few catalytically active centres, the efficiency of PCN is not particularly high. In this work, colloidal PCN is prepared in a bottom-up approach affording water-soluble photocatalysts with superior performance. This is demonstrated by photocatalytic H_2O_2 production *via* reduction of oxygen accompanied by highly selective (up to 100%) photooxidation of 4-methoxybenzyl alcohol (4MBA) and benzyl alcohol or other lignocellulose-derived feedstock (ethanol, glycerol, glucose) (**Figure 1**).

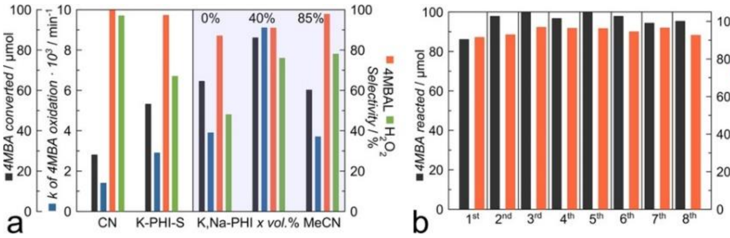

Figure 1. a) Photocatalytic oxidation of 4MBA with simultaneous H_2O_2 formation in H_2O (20 mL, 4MBA 0.1 mmol, pH 6.5-7.0, LED 365 nm, 4 h) and in H_2O/acetonitrile mixture in the presence of a heptazine-based PCN (K,Na-PHI) (20 mL, x vol % of acetonitrile, 4MBA 0.1mmol, LED 365 nm, 4 h); CN: bulk melamine-derived PCN; K-PHI-S solid heptazine-based PCN; b) recyclability test of K,Na-PHI samples for 4MBA oxidation (20 mL, H_2O/ acetonitrile (40 vol %), 4MBA 0.1 mmol, pH 6.5-7.0, LED 365 nm, 4 h, 0.125 g NaCl is added for the photocatalyst recovery).

In a combined, experimental, theoretical and spectroscopic study, the groups of Rau, Gräfe and Dietzek unraveled complex light-activated multi-step reaction mechanisms in a molecular catalyst for artificial photosynthesis.[5] Since water splitting is an inherent multielectron process, elucidation of the properties of the redox-activated, partially reduced or oxidized intermediates is of paramount importance to understanding the overall catalytic activity. However, identification and spectroscopic characterization of those highly reactive intermediates and their excited-state dynamics is very challenging due to their short lifetimes. In the presented approach, spectroelectrochemical methods (UV/Vis absorption and resonance-Raman spectroscopy) are combined with quantum-chemical simulations and time-resolved transient absorption spectroscopy are used to investigated the photoinduced electron transfer in the catalytically competent, doubly reduced intermediate $[(tbbpy)_2Ru^{II}(tpphz)Rh^{I}Cp^*]$ on femto-to-nanosecond timescales. The intermediate is generated by electrochemical and chemical reduction of $[(tbbpy)_2Ru(tpphz)Rh(Cp^*)Cl]Cl(PF_6)_2$ (Ru(tpphz)RhCp*), a photocatalyst for the hydrogenation of nicotinamide (NAD-analogue) and proton reduction. The *in-situ* photophysical and theoretical studies showed that photoinduced electronic transitions shift electron density from the activated catalytic center to the bridging tpphz ligand, which significantly reduces the catalytic activity upon visible-light irradiation. Applying an adapted irradiation sequence of bright and dark phases re-established overall photocatalytic activity.

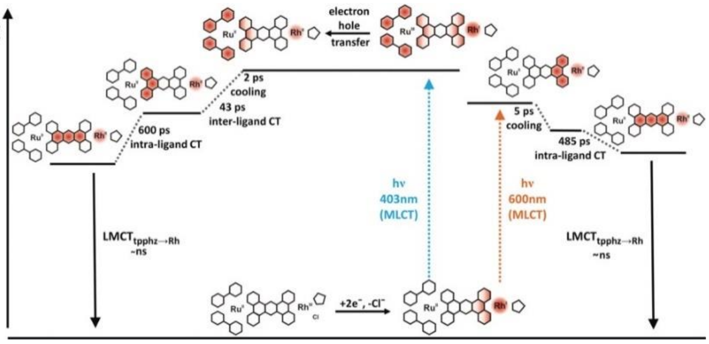

Figure 2. Schematic representation of the proposed photophysical pathways for the doubly reduced photocatalyst Ru(tpphz)RhCp* upon photoexcitation at 403 nm and 600 nm.

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Tailored Molecules for Advanced Nanomaterials and Devices: Blue & NIR-Emission, Light Absorption and Surface Protection

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Optoelectronics and nanoscience take great advantage from the ability of organic, organometallic and hybrid compounds to fulfill specific needs and requirements.

Organic and organometallic frameworks can be easily and judiciously engineered in order to tune the optical absorption and emission features, the electronic energy levels, the sterical hindrances and the solid state aggregation. Once a molecular framework is identified as the suitable candidate for a given application, different techniques would enable its exploitation in the form of thin/ultrathin film nanomaterial. Physical vapor deposition (PVD) is an extremely versatile technique which allows for the epitaxial growth of hybrid thin films. PVD benefits from the precise control on the deposition parameters (temperature, rate, thickness control down to few Angstrom) and contaminant-free environment (suiting *high-end* optoelectronics), likewise comensurate nanostructures can be prepared on given templating substrates.

The reaserch team from the CNR istitute SCITEC, the Politecnico di Milano and the Università degli Studi di Milano – Bicocca, are applying their multidiscipinary expertise in the challanging areas where the design, synthesis and growth of molecular materials and substrates closely interplay with optical and morphological characterizations and fabrication of layered devices (Figure 1). In this contest three main activities are concerted focusing on two class of molecules: iridium complexes, which represent the emitters of choice in organic light emitting diodes (OLEDs), and porphyrins, chromophores for organic solar cells (OPVs&DSSCs) and organic 2D systems for thin anti-corrosion coating of electrodes.

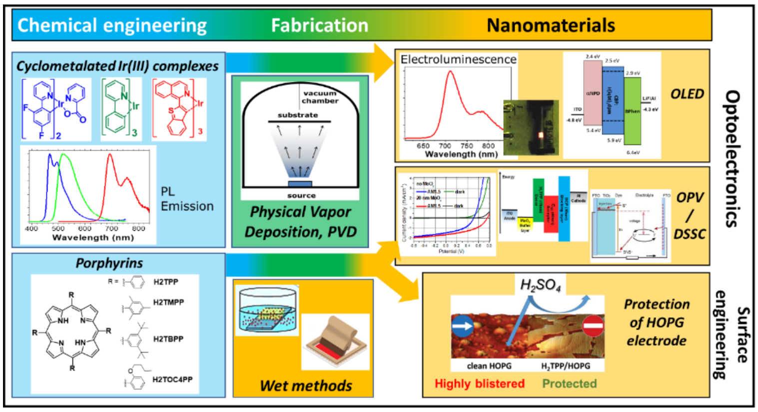

Figure 1. Selected examples of molecularly engineered organics and their applications

1- <u>Organic light emitting diodes</u> (OLEDs) are the reference technology employed in *energy-saving* flat panel displays and are likely alternative to develop *solid-state lighting*. Although market-ready, two big challenges still affect the technology, i) the instability and the degradation of blue-emissive materials and ii) the lack of efficient emitters to extend the OLED applications into the nearIR region ($\lambda_{NIR} > 700$ nm) for automotive, surveillance and phototherapy.

The study of the degradation pathway leading to OLED failure is essential to meet the device lifetime and efficiency requirements. We recently tackle this issue combining: i) chemical, photophysical and thermal studies of the molecular emitters; ii) fabrication of multilayered engineered devices and chemical analysis of degradation fragments at the interface; iii) theoretical investigation of exciton induced molecular instabilities.[1,2] We were able to define the boundary conditions for the suppression of degradation in a model blue OLED based on the archetypal FIrpic complex (Fig. 2a).

NIR emission is in by far a recent *hot-topic* in the field. We undertook a rational structure-property engineering of Ir(III) emitters with isoquinoline-benzothiophene ligand (Fig. 1b) and identified Ir(iqbt)2dpm as the leading system with a high NIR quantum efficiency of 16% and a short radiative lifetime. Phosphorescent OLEDs were fabricated by solution processes and vacuum thermal evaporation showing state-of-the-art efficiencies exceeding 3% (Fig. 2b).[3-5]

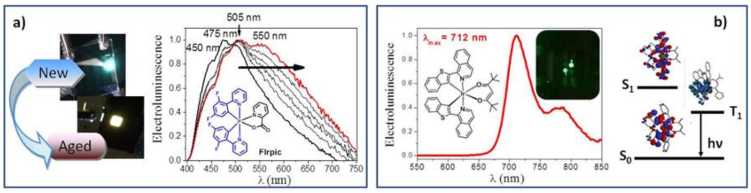

Figure 2. (a) Aging on blue-OLED: color and spectral alteration, FIrpic structures. (b) NIR emissive Ir(III) complex and its OLED application under IR camera.

2- In third generation photovoltaics, namely organic photovolaics (OPVs) and hybrid organic-inorganic photovoltaics (dye-sensitized solar cells, DSSCs), porphyrins have emerged in the last years as promising active materials due to their interesting optical and electrochemical properties. In particular, zinc porphyrins have been reported to yield record photoconversion efficiencies when exploited as sensitizers in DSSCs taking advantage fromrational design strategies adopted introducing substituents at *meso-* or *β-* positions. Such chemical modifications result in a fine tuning of the energy levels and a control of the molecular packaging to best match the working devices' requirements. [6] The current aims of our researches are focusing on the investigation of porphyrin films as active materials in evaporated multilayers devices where different electronics, bulkiness and solid state packing of the molecules can tune OPV responce.

3- **Graphite electrodes,** that are traditionally employed in batteries and graphene production, suffer from stability issues due to the severe working conditions. In this context, the ongoing investigations on the chemistry of porphyrins and their supramolecolar nanorganization led us to the succesful study of these systems as promising and unexplored class of organic molecules suitable to be developed as non-insulating, sacrificial, protective coating layer against surface corrosion. Our recent works reported the growth by PVD of ultra-thin (below 1 Å) and thin (within 1 and 10 Å) films of porphyrins on highly oriented pyrolytic graphite (HOPG), the latter used as model electrode-surface. Herein, the films start growing as 2D wetting-layer with the presence of 3D-structure as a function of the thickness. Electrochemical-AFM investigations highlight the protective effect of porphyrin when HOPG undergoes oxidative stress.[7,8] We move from a simple case study (metal-free tetra-phenyl-porphyrin, H_2TPP) and explored the role of different peripheral groups on the porphyrin core. The groups are chosen to tune the electronic properties and the sterical hindrance of the molecules and their orientation on the graphite surface. The current informations are pointing to the interest of the fluorination as an effective method to realize stable coatings.[9] In this contest, we also demonstrate the epytaxyal growt of H_2TPP film on chiral organic crystals. [10]

In our laboratories, chemical and physical expertise together with complementary technologies are available for the characterization (by optical absorption and emissions -steady state and time resolved modes- and scanning probe microscopy AFM), and the processing of active optoelectronic materials.

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When Photochemistry meets Biology

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The project "Logic Lab - Molecular logic lab-on-a-vesicle for intracellular diagnostics" investigates how fluorescent molecules can be assembled to form new molecular logic gates. The aim of the interdisciplinary research team is to stepwise adapt the concept of molecular logic sensing for applications in biological environments and living cells.

Molecular logic gates are mostly organic molecules that react to physical and/or chemical inputs by generating a distinct output - for example fluorescence. Important medical applications include e.g. photodynamic therapy (PDT)[1,2] and point-of-care biomedical diagnostics.[3,4] Whereas these examples show the potential of molecular logic sensing for medical diagnostics, molecular logic gates are still rarely used in biomedical research or for diagnostic applications. The major obstacle, which is the transfer of this sensing concept from solution to a complex biological environment such as the living cell, has not been tackled to date. Another reason is that molecular logic gates are only available for a few specific inputs, e.g. for pH and sodium ions, although, the questions in medical diagnostics are more complex. The synthetic routes to design molecules that react to multiple analytical inputs are limited as well as the reaction sites for subsequent functionalization (e.g. for targeting specific cells).

LogicLab's objective is to adapt the concept of molecular logic sensing for applications in biological environments and cells. In a holistic approach, we combine the synthesis of novel fluorescent probes[5] and innovative triplet-triplet annihilation upconversion (TTA-UC) systems[6] with modern quantum theoretical experiments, ultrafast time-resolved (micro)-spectroscopy[7] and Raman imaging to develop and characterize the systems in solution, membrane models and finally in a biological environment. The results are used by experts in cell biology, metabolomics, toxicology and microfluidics, who investigate the molecular logic gates in cell cultures, artificial vessels (artery-on-a-chip)[8] and ex-vivo tissue. Iterative research based on feedback between the different disciplines allows to bring the concept of molecular logic gates to biological applications.

The specific approach followed in LogicLab envisages to integrate several molecular switches for different analytical inputs in a supramolecular structure, i.e. a liposome or polymersome. This supramolecular logic gate, constituting a lab-on-a-vesicle, creates a distinct fluorescent output upon reaction with the analytes and thus allows us to detect different biological signaling and physiologically relevant messenger substances in parallel. In this way LogicLab aims at detecting cellular dysfunctions and diagnosing the onset of diseases such as arteriosclerosis earlier than the current state-of-the-art. As the supramolecular labs-on-a-vesicle are assembled in a modular fashion, various applications can be targeted based on the same platform. Further, the design of the vesicle allows for subsequent functionalization, e.g. in order to target specific cell compartments or tissues.

The LogicLab project is an EU-funded Innovative Training Network (ITN, www.logiclab-itn.eu), in which 14 international doctoral students conduct their research projects at different universities, research institutions and companies in Germany, Ireland, the Netherlands, Poland and Slovakia. The project, coordinated by Leibniz IPHT Jena / Germany, has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 813920. www.logiclab-itn.eu

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PILLS OF HISTORY

Chirality in photochemical reactions. A case of fake?

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In the life of an experimental researcher like me it has often happened to be faced with apparently disconcerting results, with experiments that cannot be reproduced. This could have happened essentially for two different reasons: either because the experimental description of the experiment was summary and therefore did not put the reader in a position to repeat the experiment successfully, or because it was a false experiment. Fakes exist in science and sometimes they also lurk inside things that we believe are well established. In recent times, for me who are now "old", the cases of studies on the memory of water have been emblematic, a study commissioned by a homeopathic products company, and which wanted to demonstrate how a certain biological message continued to be transmitted also in very high dilution situations, typical of that pseudoscience which is homeopathy, and that study which demonstrated an effect of magnetic fields on the stereoselectivity of a chemical reaction. In this case, when it was shown that the reported data was totally false, the professor in charge of the article was unable to do anything else than to blame on doctoral student.

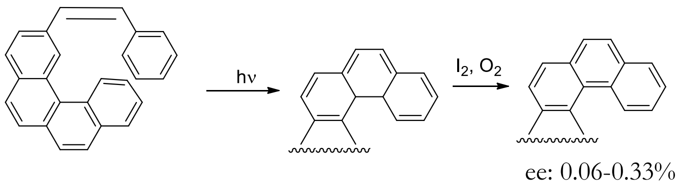
The publication of false data can have various reasons: in a highly competitive environment, such as the scientific world, it is easy to fall into the shortcut of publishing an altered data compared to the real one, but such as to make the result much more palatable, read , quoted. Despite the many experiences that each of us has had in his life, I never expected to be faced with something that looks so much like a fake by examining the history of photochemistry in Italy.

We describe the facts. First, though, I must make a few considerations. Organic photochemistry developed in the world and in Italy in the late nineteenth century. The Italian researchers, Cannizzaro, Ciamician, Paternò, have obtained, by exploiting the interaction of light with organic substances, important results, which have made it possible to take important steps in this discipline (1). In all cases, the use of light has made it possible to "highlight" new methods for forming carbon-carbon bonds that could not be formed using "thermal" methodologies. However, the most modern research in organic synthesis is no longer satisfied with having new reactions to form even very complex molecular skeletons, but wants the reactions to be stereoselective, that is, that the arrangement of the bonds in space is well defined.

The nature of this problem was also known to the photochemists of the early twentieth century. Although Ciamician had expressed doubts about the tetrahedral nature of the carbon atom (2), one of his assistants, Maurizio Leone Padoa, attempted to create a chiral photochemical reaction using a chiral light. One of the most used strategies still today to obtain a stereoselective reaction is to make the reaction take place in a chiral environment, introducing chiral objects that act as catalysts in the reaction environment. These catalysts normally form transient aggregates with one of the reaction reactants, forming a chiral complex which exposes only one of the two enantiotopic faces of the complex to the second reaction reactant. Light can also be made chiral by using circularly polarized light.

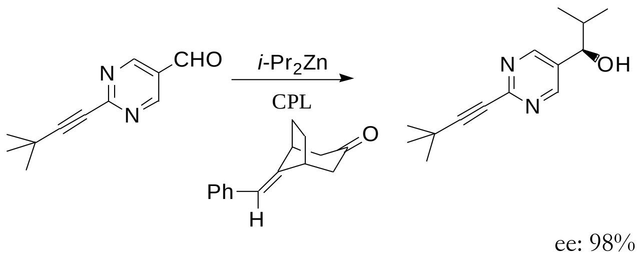
The possibility of using a chiral light source to obtain stereoselective photochemical reactions had been highlighted immediately. Le Bel in 1874 had hypothesized that circularly polarized light, being chiral, could induce chirality in photochemical reactions, creating a chiral environment in which to make the reaction take place (3). This hypothesis has been used to justify the birth of chirality in primordial molecules (4). However, it did not bring results with great success. Only in 1929 is a first positive result described (5). In this experiment, a racemic mixture of ethyl 2-bromopropionate, subjected to irradiation, shows that one enantiomer is destroyed more quickly than the other. In fact, the residue of the reaction shows an excess of one of the enantiomers of the molecule.

Subsequently, attempts to use this method for synthetic purposes did not yield striking results, except for one case. For example, the reaction described in Scheme 1, which leads to the formation of a helicene, occurs if it is carried out in the presence of circularly polarized light, but the enantiomeric excesses reported are extremely low (6).



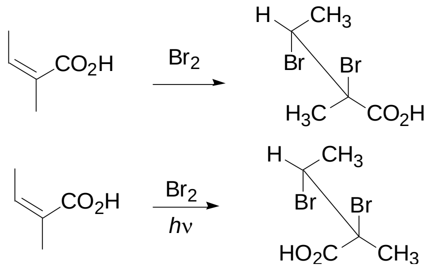
Scheme 1. Chiral synthesis of helicenes.

On the contrary, the reaction of a dialkyl zinc with a photocatalyzed aldehyde, gives an unexpectedly positive result. At the time, the authors proposed the existence of an autocatalytic process in which the chiral product acts as a catalyst for the reaction itself (Scheme 2) (7).



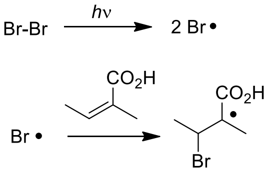
Scheme 2. Reaction of dialkylzinc with an aldehyde.

Well, Maurizio Padoa in Bologna in 1911 attempted to perform an asymmetric synthesis using circularly polarized light (8). The reaction studied by Padoa was the bromination of angelic acid and was unsuccessful (Scheme 3). Padoa carried out this last reaction in the presence of light but the product of the reaction in no way showed an excess of one enantiometer compared to the other. In fact, the product of the reaction is chiral. In the product of the photochemical reaction there are two asymmetric carbon atoms. In theory, two pairs of enantiomers could form between them diastereoisomers. Thus, the prevailing product derives from a single diastereoisomer, but has been found as a mixture of two enantiomers.



Scheme 3. The reactions performed by Padoa.

The reason for this behavior is very simple: light does not intervene in the bromine addition reaction to the double bond, in which a chiral light could play a role, but in a previous reaction, which Padoa could not know, that is, in the cleavage of bromine molecular in two bromine radicals. It is then this radical that is added to the double bond giving a radical that will react with another bromine molecule to give the thermodynamically more stable product, the one actually observed. The attack of radical bromine on the double bond cannot follow a preferential path of attack (Scheme 4).



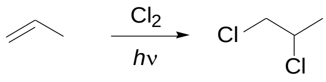
Scheme 4. The reaction performed by Padoa.

The failure was due to the fact that light intervened in the process only to generate the bromine atom by homolytic cleavage of bromine, but then it had no role in the subsequent addition of bromine to angelic acid.

In this case it is a question of the honest admission of a failure. Which does not happen easily in science. Some time ago, however, I find a bibliographical reference that leaves me perplexed. It is a work by Mario Betti.

Mario Betti is an important chemist of the early twentieth century. Born in Bagni di Lucca in 1875, he graduated in chemistry and pharmacy in Pisa and was assistant to U. Schiff in Pisa and then in Florence. He became professor of general chemistry in Cagliari and then of pharmaceutical chemistry in Siena and Genoa. In 1923, he took over the chair of organic chemistry in Bologna after Ciamician's death. Betti is responsible for important contributions in the chemistry of heterocyclic compounds and precisely in the field of stereoisomerism. In 1939 he was appointed senator of the Kingdom. Mario Betti certainly represents one of the most important figures in the Italian scientific panorama between the two wars. Particularly important results were due to him, such as the study of the correlation between the rotary power and the nature of the groups linked to the stereogenic center. For these and other considerations, please refer to the article written by Naso in 2017 (9).

In 1938 at the 10th International Congress of Chemistry held in Rome, Betti and a collaborator, Elio Lucchi, made a communication announcing that they had obtained a certain enantiomeric excess in the reaction between propene and chlorine in the presence of circularly polarized light (Scheme 5) (10). The same results, put in full form, were then published in the documents of the Academy of Sciences of the Institute of Bologna in 1942, close to his death (11).



Scheme 5. The reaction reported by Betti.

Also in this case the addition of chlorine to the double bond leads to the formation of a chiral molecule, given that the central carbon is replaced by four different substituents. Betti observes discrete enantiomeric excesses (prevalence of one enantiomer over the other). Betti claims to find a certain asymmetry. It comes to determine values of α up to 0.22. If we consider that the liquid (-) - 1,2-dichloropropane shows an optical rotation of -4.33, the result indicates a relatively good (excellent for the time) asymmetric induction.

The problem in this case is the same as that encountered by Padoa. In this case, the light has the only function of exciting the chlorine molecule allowing the homolytic cleavage of the chlorine-chlorine bond and the formation of two chlorine atoms. These atoms are very reactive and react immediately with propene giving an intermediate radical. This radical then reacts with another chlorine molecule giving the final product. In all these passages the light no longer has any role and it is not clear why it should induce an asymmetric attack on propene.

Goffredo Rosini also realizes that this is the problem in his article (12). Citing the works that took over Betti's article in the following years, he cites an article published in Chemische Berichte from 1971 in which the authors attempted to reproduce Betti's results without any apparent result (13). So it was clear in the literature that those experiments were not reproducible.

At this point we are almost certain that the data reported by Betti are a fake. It remains to be understood what might have happened: there are two hypotheses that I feel I can make: the first possibility is that Betti's collaborator, Lucchi, has produced results in which "domesticated" results were present. The second, which I hope most likely, is that the synthesis procedure showed a flaw. The reaction product had to form at the meeting point of the two reacting gases, become a liquid and then accumulate in a separate container, leaving the reaction environment. Is it conceivable, however, that the liquid remained on the glass walls of the reactor, undergoing an enantioselective photodestruction reaction, such as those described above, such as to allow the results described to be obtained? It could be a plausible explanation, although it does not justify the fact that nobody was able to reproduce the experiment.

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ABSTRACT OF THESIS ON PHOTOCHEMISTRY

Novel Photo- and Electro-responsive Supramolecular Systems and Molecular Machines

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Molecular and supramolecular machines[1,2] belong to a fascinating and flourishing field of chemistry. Indeed, the research endeavours in this area not only allow the comprehension of many mechanisms that lie at the basis of the natural processes, but they can also lead to artificial nanoscaled devices and materials, that can eventually be used in everyday life.[3] In this regard, a thorough investigation on the properties of the molecular building blocks, and on how they change from the molecule to the supramolecular assembly, is of cardinal importance.
The work presented here deals with the study of new prototypes of light- and electro-activated supermolecules and molecular machines. The discussion will be divided in two main parts: part A deals with the exploration of single- and multi-component structures or supramolecular complexes involving light-responsive units, whereas part B deals with the investigation of electro-responsive pseudorotaxanes and rotaxanes.

Part A: (Supra)molecular structures involving photochromic units

The major part of the research activity was devoted to the study of new prototypes of molecular pumps, *i.e.*, nanometric motors able to move one component with respect to the other(s) in a unidirectional fashion.[2] An interesting example of light-activated supramolecular pump, based on a pseudorotaxane, has been reported by Credi *et al.* in 2015.[4] The axle is an ammonium salt functionalized with a photoswitchable azobenzene and a cyclopentyl units, while the macrocycle is either a dibenzo[24]crown-8 (**DB24C8**) or a dinaphtho[24]crown-8 (**DN24C8**). The *Z* isomer of the azobenzene possesses a larger steric hindrance with respect to the *E*, and acts as a stopper. On the other hand, the threading through the cyclopentyl extremity occurs with a kinetic rate between those of the *E* and *Z* isomers of the azobenzene, thus it behaves as a *pseudostopper*. As *E*-*Z* isomerization destabilizes the complex, under continuous light irradiation this system works out of equilibrium, by unidirectionally threading on the *E*-azobenzene and dethreading from the pseudostopper after *E*-*Z* photoisomerization (figure 1, top).

In order to improve the efficiency of this device and allow its possible implementation in more complex smart architectures, new molecular axles were studied (figure 1, bottom), bearing either a different derivatization on the azobenzene (**1**H$^+$), a different pseudostopper (**2**H$^+$) or a relocation of the linker between the ammonium site and the azobenzene (**3**H$^+$ and **4**H$^+$).

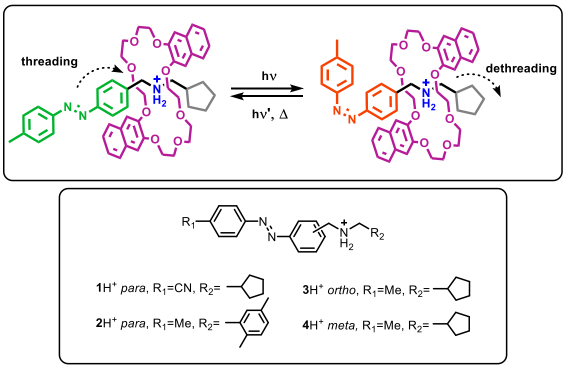

Figure 1. Top: unidirectional threading-dethreading of the supramolecular pump by Credi et al;[4] bottom: structures of the studied compounds **1**H$^+$, **2**H$^+$, **3**H$^+$ and **4**H$^+$.

The supramolecular pump based on **1**H$^+$ and **DN24C8** showed a high selectivity and operation efficiency, but an erratic photochemical behaviour of the free axle that would preclude the correct working of the pump.[5] In the case of the complexes **2**H$^+$ - **DN24C8** and **3**H$^+$ -

DB24C8 the threading is not unidirectional, thus these systems cannot be properly considered motors. Conversely, the prototype based on $4H^+$ and **DB24C8** possesses the right kinetic features and appears to be the most promising candidate for the new generation of light-activated molecular pumps.

Parallel studies focused on elucidating how the photochromism can be tuned upon the effect of the solvent or of a molecular or supramolecular interaction. A first investigation was conducted on photochromic terarylenes,[6] whose bridging unit is an imidazolium, able to give pseudorotaxanes with either **24C8** or **DB24C8** crown ethers (figure 2, left).[7,8] The closed form of the free axles, obtained upon UV-irradiation, is short-lived, and reverts to the open isomer within tens of seconds, following, in some cases, an unusual zero-order profile. Nevertheless, the pseudorotaxanes showed large stability constants (up to 10^6 M^{-1}) and a photochromic behaviour improved with respect to the isolated axles. Indeed, the thermal isomerization kinetics were affected in terms of reaction order, lifetime elongation or both. In summary, this study showed that the photochromic properties of a molecule can be tuned and enhanced by means of supramolecular chemistry.[8]

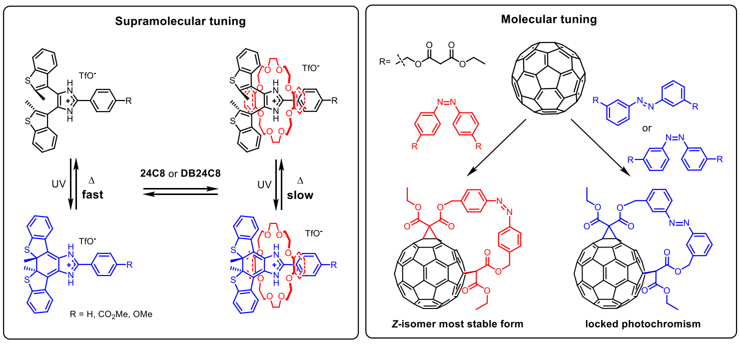

Figure 2. Schematic representation of the supramolecular (left) and molecular (right) tuning of photochromism.

To elucidate if and how photochromism can be tuned also by means of covalent chemistry, a second research line was devoted to the study of two azobenzene bis(malonate) derivatives, able to react with fullerene to give cyclopropanated bisadducts (figure 2, right).[9] Reaction of the *para*-substituted azobenzene with $\mathbf{C_{60}}$ yields an equatorial bisadduct where the *Z* configuration of the azo bond becomes the thermodynamically favoured isomer. On the contrary, when the *meta*-derivative is anchored to the $\mathbf{C_{60}}$, the azo-bond is locked in the *E* configuration, regardless of the reactant isomer. Since both reactions yield almost exclusively the equatorial regioisomer, it can be stated that the azobenzene configuration changes accordingly, thus these bisadducts represent a novel example of how the photochromism can be successfully inverted or locked by means of covalent chemistry.

The third research line, conducted during a research stay at the ENS-Paris-Saclay, in the group of Dr. R. Métivier and Prof. J. Xie, has been focused on a photochromic and fluorophoric compound based on the dicyanomethylenepyran unit, known as DCM.[10] From a thorough photophysical and photochemical characterization, it was found out that this molecule shows a solvent- and photochromically-gated fluorescence.

Part B: Electro-responsive supramolecular devices

The second part of the research activity deals with the characterization of new pseudorotaxanes and rotaxanes based on the calix[6]arene-bipyridinium (viologen) recognition pattern.[11,12] In particular, derivatives bearing either only two phenylureido groups on the upper rim of the calix[6]arene[13] or a scorptionate motif, *i.e.*, with the axle covalently linked and threaded in the macrocycle, were studied.

UV-vis spectroscopic measurements evidenced that the systems based on the diphenylureido derivative are less stable with respect to parent compounds bearing three phenylureido groups.[12] Moreover, electrochemical experiments showed that in all the rotaxanes the two reduction processes of the viologen unit are shifted to more negative potentials, on account of the charge transfer interaction between the host and the guest, and that the pseudorotaxanes disassemble upon mono-reduction of the viologen and re-assemble upon re-oxidation.[12]

The systems shown above can be considered as electro-responsive supramolecular devices that can form the basis for new supramolecular architectures with a tubular structure or behaving as electro-activated molecular muscles.

In conclusion, the whole research reported above explored new frontiers of functional molecular devices and increased the knowledge on the chemical and energetic requirements of their molecular components.

Funding

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Investigating Photoinduced Charge-Transfer Products using Ultrafast Spectroscopy

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PhD Thesis

Charge-transfer products and their generation are at the heart of a huge amount of chemistry, from solar cells to enzyme function. In this PhD thesis, photoinduced charge-transfer products and charge-transfer reactions have been studied. A schematic overview of the projects undertaken during this PhD thesis, undertaken in the group of Prof. Eric Vauthey at the University of Geneva, are shown in Figure 1.

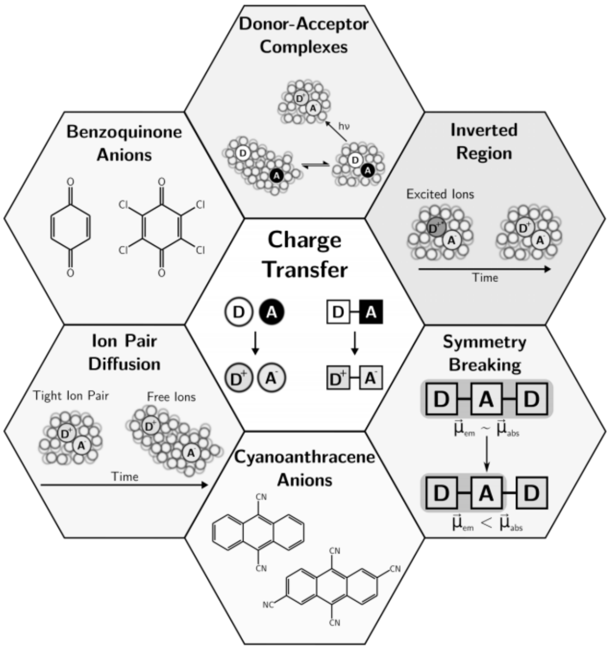

Figure 1: A schematic overview of the topics investigated during this thesis, with the unifying theme (Charge-Transfer) highlighted in the centre.

In a study of the products of photoinduced electron transfer, the radical ion excited states of di-, tri- and tetra-cyanoanthracene, highly used molecules in electron-transfer experiments, were studied using transient absorption spectroscopy. The excited-state dynamics of dicyanoanthracene were found to differ from tri- and tetra-cynaonanthracene in an unexpected fashion, with the excited-state lifetime appearing ~3 times longer than the similar tri- and tetra-cyanoanthracene derivatives – thus making it a potentially useful anion excited state with which to do highly exergonic electron transfer chemistry. Quinone derivatives were also investigated, with their excited-states appearing to be unexpectedly long-lived, in line with a previous report from the late 1990s[1] but appearing to contradict more recent reports.[2] This also points to their potential use as anions with which one could do highly exergonic electron transfer chemistry, and implies these excited states could have relevance to their biological function.

To study if such ion excited states are relevant to highly exergonic charge-transfer, highly exergonic bimolecular charge separation reactions were studied using broadband fluorescence upconversion techniques. For the first time, fluorescence from radical ion products was observed at early times of the reaction. This observation was made possible by the new high temporal and spectral resolution of the newly developed broadband fluorescence upconversion techniques.[3] This represents the first *direct* confirmation of a nearly 5 decades old hypothesis,[4] recently also suggested to be relevant using transient IR techniques,[5] as to why the Marcus inverted region went unobserved in such a reaction.

A new method to track excited-state symmetry breaking in molecules lacking IR marker modes is presented,[6] along with a refutation of the literature view[7] that excited-state symmetry breaking may be tracked using the fluorescence peak position. This method uses the broadband fluorescence upconversion technique to directly track the instantaneous transition dipole moment, and shows that this is a sensitive indicator of a change of the charge distribution of a molecule. This is thus a general technique that may be applied to a variety of problems, and has indeed already found use in the literature in tracking partial charge-transfer.

An investigation of ion-pair dynamics using both pump-probe and pump-pump-probe techniques reveals that the excited-state of the radical anion may be used as a probe of the distance distribution between it and its corresponding radical counterion - raising the prospect that the excited-state dynamics of ions may be used as a sensitive ``molecular ruler''.[8] Using this method, a charge recombination from an excited ion to an excited-state neutral is also observed, an extremely rare reaction.

Finally, a variety of donor-acceptor complexes have been studied using multiple spectroscopies, with the investigations finding a rich excited-state dynamics involving structural, vibrational and solvent relaxation in what is likely a conformationally heterogeneous system.

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Porphycenes in photodynamic therapy of cancer cells and photodynamic inactivation of bacteria

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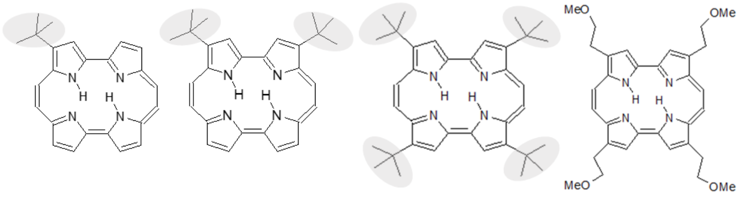
Photodynamic therapy (PDT) is an approved method of treatment for a variety of malignances including cancer. The method requires simultaneous application of light and photosensitizer to the targeted cell or tissue. Phototherapeutic action is based either on the energy transfer from the excited state of the photosensitizer directly to molecular oxygen present in the targeted cells or it is directed via intermediate radical forms to reactive oxygen species (ROS). In both cases the species created in situ is a powerful drug leading to the cell death. Starting from the beginning of 21st century substantial interest has been drawn to antimicrobial applications of PDT, as the potential weapon against multidrug resistant strains. [1]

The aim of the present PhD thesis was the evaluation of the PDT and photodynamic inactivation (PDI) applicability of selected porphycene-core compounds. The studies included evaluation of photophysical properties of the chromophores and selection of the delivery system for *in vitro* applications against cancer cells and bacteria, considering the high hydrophobicity of the porphycene compounds and the requirement of biocompatibility. The following parts included also evaluation of the efficiency of the proposed compounds in photodynamic inactivation of Gram-positive bacteria and photodynamic therapy of cancer, performed on HeLa cell line. Moreover, the investigations included measurements of quantum yields of singlet oxygen generation (Φ_Δ) and simple analysis of structure – activity relationship of different porphycenes.

The porphycenes (Figure 1) selected for the studies were uncharged and highly hydrophobic. Selection and optimization of the carrier media for chromophores delivery to the bacteria and cancer cells covered the investigation of three different kinds of delivery systems: cyclodextrins, liposomes, and micelles. Finally, the micelles consisting of Pluronic F-127 polymer were selected, due to the best effective concentration of chromophores and the best stability that they provided. They also turned out to be better than phosphatidylcholine liposomes in the in vitro trials against HeLa cells, meaning that the same concentration of photosensitizer (PS) delivered in the pluronic micelle was providing a stronger photodynamic effect than the same concentration of PS delivered in liposomes. The most convenient range of concentrations is 1 – 10 μM of porphycene per 2.5 – 3.5 mM of pluronic. [2]



1 2 3 4

Figure 3. Structures of studied porphycenes (t-butyl moieties highlighted).

The second part of the studies was devoted to the biological application of porphycenes. Photodynamic inactivation studies were performed on three different strains of Gram-positive bacteria: E. faecalis, S. epidermidis and S. aureus, which are common causes of multidrug resistant nosocomial infections. The comparative bactericidal studies were conducted with **1**, since it exhibited the highest activity in the preliminary experiments. Comparatively low concentration of 7 μM of Pc was used for PDI studies and it was sufficient to obtain over 6 log eradication of all used bacterial strains (Figure 2). It is worth noting that low doses of light in the range 6 – 30 J/cm^2 were used. The structure-activity relationship studies were also conducted, resulting in the conclusion that the *tert*-butyl substituents, contrary to apparently similar methoxyethyl moieties, lower the bactericidal activity of porphycenes and can eventually block it completely. The steric hindrance affecting bacterial cell wall penetration is the postulated reason. [3]

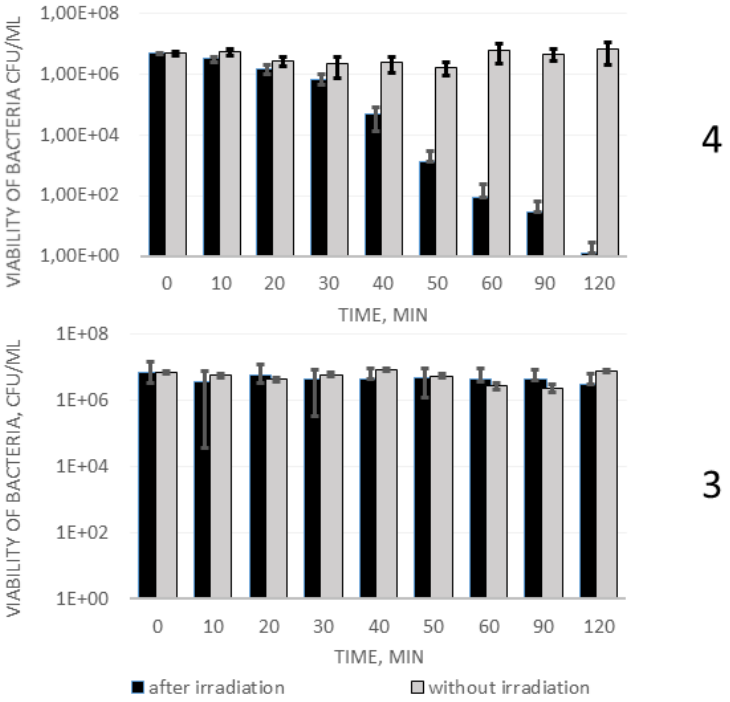


Figure 4. Dependence of the viability of E. faecalis bacteria on the time of irradiation of pluronic solution samples containing 4 and 3 in the concentration of 7 μM. Light dose: 0.6 J/ (cm^2 min).

The photosensitizing potential measured with singlet oxygen generation quantum yield was similar for all the studied porphycenes. In toluene, Φ_Δ determined for the compounds was in the range between 0.30 to 0.38 and in deuterated water pluronic solution, which resembled the biological environment the best, the values ranged from 0.21 to 0.28. The results obtained during PDT studies of HeLa cells were matching the conclusions from bacteria inactivation. Also in this case the photosensitizing effect recorded for **1** and **4** was very pronounced, whereas **3** seemed to be inert in *in vitro* studies. The co-localization studies in the HeLa cells confirmed that porphycenes are usually located in the cellular membrane and cytoplasm, whereas **3** is an exception and it accumulates in lysosomes. Lysosomes are most probably used by the cell to excrete unwanted compounds and this is the reason of the unusual inactivity of **3** in PDT studies.

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Design of new systems for photoprotection and solar energy storage

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Skin cancer incidence has been increasing in the last decades, but most of the commercial formulations used as sunscreens were designed to protect only against solar burn. Majority of those sunscreens are structurally similar, for that, all present common critical weaknesses, such as low stability and toxicity. Thus, the development of more efficient ingredients is an urgent health necessity and an attractive industrial target.

Inspired on natural compounds, Mycosporine-like amino acids (MAA), a new family of molecules was studied under the framework of CASSCF/CASPT2 strategy to unveil the minimal structure which retains photoprotective capabilities. Through the different studied core structures, two different behaviors are found depending on the studied system.[1] In general, when high energy S1/S0 CIs (> 80 kcal/mol) are found usually a minimum in excited state appears. This is not ideal because it increases the chances of photoreaction and radiative emission (arrow from Min S1). While with low energy S1/S0 CIs (<70 kcal/mol) a barrierless pathway to the ground state is observed.(Fig. 1)

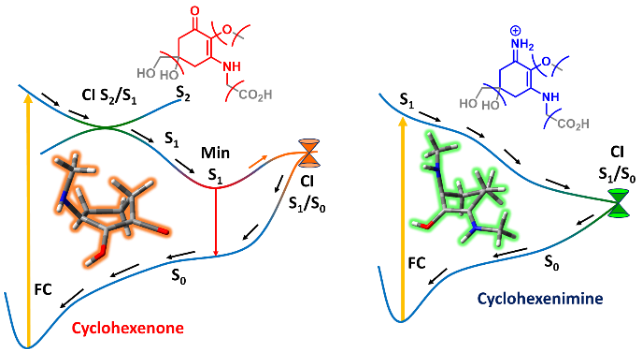

Figure 1. General MAA cores with marked parts to remove and a schematic representation of the typical PES in each case.

This novel photoprotection mechanism, which seems to be general in this type of compounds, opens a challenging opportunity for the development of a new generation of sunscreen candidates. Based on that, a series of cyclohexenimine compounds with tunable properties suitable for their use in sunscreens have been synthesized,(Fig.2) presenting enhanced properties in terms of stability, light energy dissipation,[2] and toxicity.

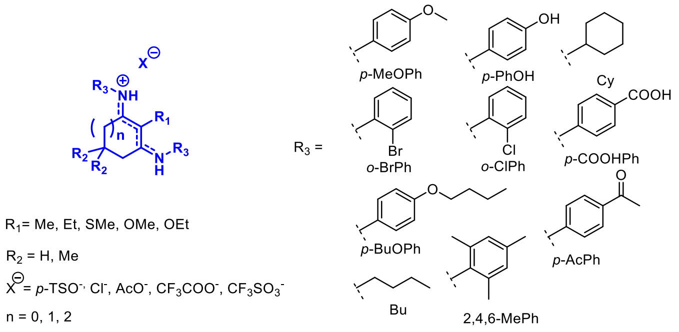

Figure 2. Prepared MAA analogues, yielding in more than one hundred possibilities.

In combination, a time-resolved spectroscopic study[2] was done for some of the prepared compounds, (Fig. 2) confirming an ultra-fast relaxation to ground state in a few hundred of femtoseconds. Interestingly, the presence of aromatic substituents opens a new relaxation pathway rarely observed in natural MAAs. Here, the orbital overlapping with a phenyl π orbital stabilizes the isomerization process. This feature was observed along the minimum energy path in a higher level CASSCF/CASPT2 study of the system. However, the isomerization quantum yield seems to be negligible due to the sloped and single product conical intersection found. This is in agreement with experimental data, where the photoisomer was not detectable.

The prepared compounds are being tested including them in sunscreen formulations and for other applications as coatings for different surfaces, presenting in all cases promising results.

Nowadays, availability of energy sources, like fossil fuels, are becoming a problem due to the high demand in industries and transports. In contrast, solar energy is an inexhaustible and renewable power source that actually is majorly missed. One of the newest approaches to exploit it is to store solar energy in molecules. Those systems, commonly known as molecular solar thermal systems (MOST), are characterized to present two stable isomers, one with a higher stability respect to the other (Fig. 3). With that bi-stable system, we can store the energy of the absorbed radiation in a molecular transformation, like a chemical bond or a molecular isomerization, which can be released using a catalyst as trigger.

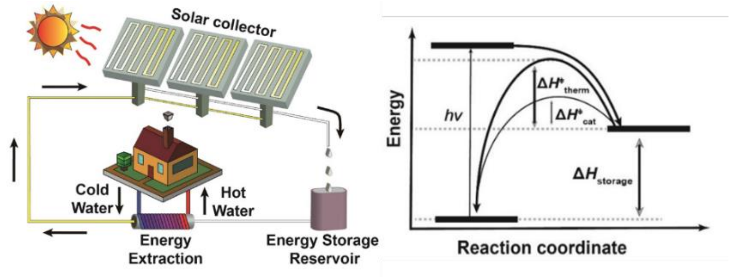

Figure 3. Macroscopic (left) and energy profile (right) of MOST system.

According to this, norbornadiene,[3] azobenzene,[4] and other well-known photoswitchers are being investigated in computational and experimental terms to be used in MOST devices, involving a design challenge.

One of this challenging processes is the catalytic back conversion reaction, in this step the photoisomer interacts with a substance which triggers the backreaction. To study this process, computational chemistry provides a powerful tool to study and understand the interactions between photoisomer and catalyst, independently of the system used. In this case, the interaction of quadricyclane with cobalt phthalocyanine and azobenzene with a copper salt were studied offering very different backreaction mechanisms.(Fig. 4)

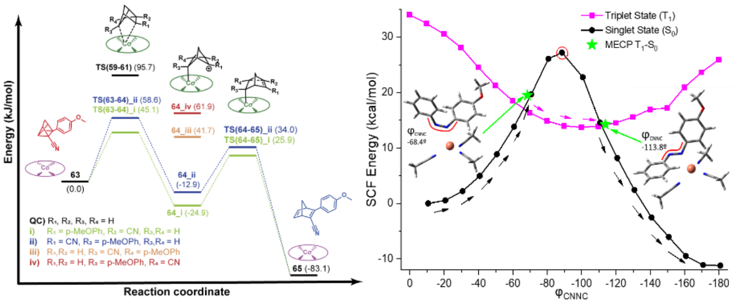

Figure 4. Quadricyclane and cobalt phthalocyanine (left) and azobenzene with Cu(ACN)$_4$PF$_6$ backreaction mechanisms.[3, 4]

In both cases the effect of catalyst is clear in the reaction rate, speeding up the reaction allowing in case of quadricyclane, the measurement of a temperature gradient of 63ºC in the sample, being the record temperature obtained in MOST devices.[3]

In contrast, for azobenzene with this computational approach we could evaluate the influence of different ligands in the reaction energy barrier without the bigger synthetic effort needed to do it experimentally.

With that, a series of useful keys and tools to improve the design of MOST systems were proposed yielding in good experimental results and promising perspectives for future developments.

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Photoinduced intramolecular radical cyclization with imines via hydrogen atom transfer (HAT)

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HAT induced by light – a sustainable and green alternative to thermic reactions in organic synthesis

This abstract deals with the part of my thesis on imines photochemistry. The majority of classical organic chemistry reactions can be classified as 'thermic' reactions due to their intrinsic relations with **temperature** in thermodynamic and kinetic equations. Indeed, heating a reaction mixture results generally in a faster transformation and leads the equilibrium constant reaction to the formation of products from reactants. Although temperature is only a parameter among others, it is possible to determine the importance of photochemistry in the homolytic dissociation of a C—H bond. If we consider a bond dissociation energy (BDE) of 410 kJ.mol^{-1} for a C—H bond, what is the necessary temperature to dissociate 1 % of a population of C—H bonds? That is considering the following transformation:

$$\text{C-H} \xrightarrow{\Delta} (\text{C-C})^{\ddagger} \equiv \text{C}^{\bullet} + \text{H}^{\bullet}$$

Boltzmann equation allows for knowing this latter. In this way we can determine a necessary temperature around 10000°C to homolitycally dissociate 1 % of a C—H bonds population which is almost two times the solar surface temperature! The process cannot be obviously used in our common organic chemistry laboratories… What about photochemistry? Using Einstein relation we can figure out the necessary wavelength to dissociate our C—H bond. Thus, Figure 1, showing the link between energy brought by a considered wavelength mole of photons and BDE can be drawn.

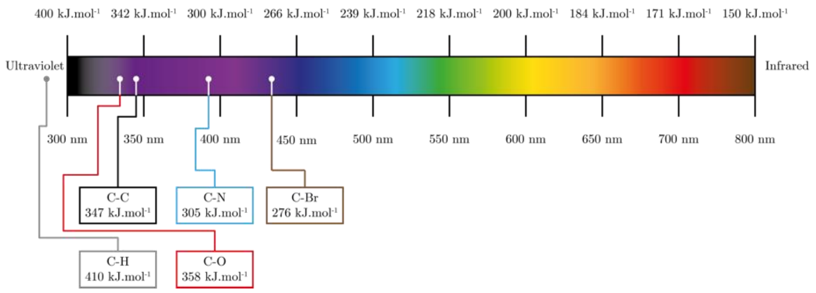


Figure 1. Link between energy brought by a considered wavelength mole of photons and BDE of classical bonds encountered in organic chemistry.

Technology of light sources and their accessibility enables the easy dissociation of C—H bond via direct absorption of photons. Furthermore, lamps can deliver more than a mole of photons depending on their intensity, offering a sustainable alternative to its thermic counterpart. Hydrogen atom can then be transferred and trigger a chemical reaction. The way of transmitting this atom has a big influence on the obtained products through the photochemical reaction and the regioselectivity of this latter. Photochemical hydrogen atom transfer can henceforth be a key-step in complex molecules formation.

HAT induced by light – influence of the way of transferring and applications

HAT is a subcategory of a wider type of reaction: **proton-coupled electron** transfer (PCET). In this former, hydrogen-atom comes from a same site or a same molecule of a donor **D** after irradiation. Two types of mechanism can be considered in the present context.

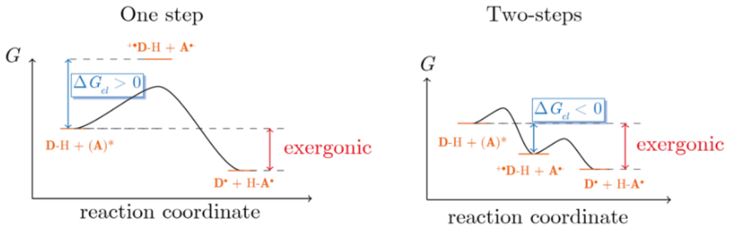
- First, electron and proton can be transferred in the same time from a donor **D** to an excited acceptor **A**. The mechanism is in one-step.

$$\mathbf{D}-\mathrm{H}+(\mathbf{A})^{*} \longrightarrow \left[\begin{array}{c}\text{Simultaneous electron}\\ \text{and proton transfer}\end{array}\right] \longrightarrow \mathbf{D}^{\bullet}+\mathrm{H}-\mathbf{A}^{\bullet}$$

- Secondly, electron can be transferred, followed by the proton. The mechanism is in two steps.

$$\mathbf{D}-\mathrm{H}+(\mathbf{A})^{*} \longrightarrow {}^{\bullet+}\mathbf{D}-\mathrm{H}+\mathbf{A}^{\bullet-} \longrightarrow \mathbf{D}^{\bullet}+\mathrm{H}-\mathbf{A}^{\bullet}$$

From an energy point of view, these two mechanisms are exergonic. But, in the case of a one-step mechanism, electron transfer is endergonic (Figure 2).



(a) (b)

Figure 2. Two possible mechanisms for HAT. (a) one-step mechanism. (b) two-steps mechanisms.

In the case of a two-steps mechanism, $\Delta S^{\ddagger}$term of $\Delta G_{el} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$ is generally close to 0 : there is no need for the transition state to get structured. However, for a one-step mechanism, transition-state must be well-structured to host the electron and the proton in the same time : $\Delta S^{\ddagger}$ is negative, resulting in an endergonic electron transfer.[1,2] ΔG_{el} can be calculated from Rehm-Weller equation (eq.1).

$$\Delta G_{el} = \mathcal{N}_A \left\{ e(E^\circ_{\mathrm{D}^{\bullet+}/\mathrm{D}} - E^\circ_{\mathrm{A}/\mathrm{A}^{\bullet-}}) + w_{\mathrm{D}^{\bullet+}/\mathrm{A}^{\bullet-}} - w_{\mathrm{D}/\mathrm{A}} \right\} - \Delta E_{0-0} \qquad \text{(eq.1)}$$

With $\mathcal{N}_A$ the Avogadro constant, *e*, the elementary charge, $E°$ the redox potential, *w* coulombic interaction (eq.2) and $E_{0\text{-}0}$ excitation energy.

$$w_{\mathrm{D}^{\bullet+}/\mathrm{A}^{\bullet-}} = \frac{z_{\mathrm{A}^{\bullet-}} z_{\mathrm{D}^{\bullet+}} e^2}{4\pi\varepsilon_0\varepsilon_s r} \qquad \text{(eq.2)}$$

With *z* the respective charge of **A** and **D**, ε_0, the vacuum permittivity, ε_s, the solvent permittivity and *r* the distance between the charges. eq.2 shows that exergonicity of electron transfer is a function of solvent polarity ; that means we can access to one or the other type of mechanism by changing the polarity of solvent used during the photoreaction. Recently, we showed the choice of solvent is dramatically important to the products obtained after irradiation of a phenyl (methyl-tetrazolyl) ketone.[3] Numerous examples of influence of HAT on reactions selectivity are present in the literature.[4] One concrete example was developed by Hoffmann group in 2010 concerning furanone moiety like **1** (Figure 3).[5]

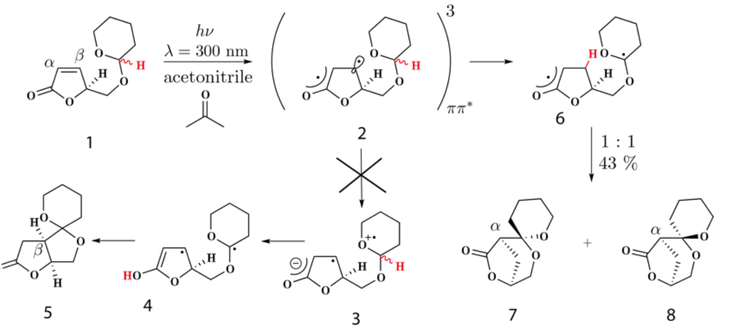


Figure 3. Photochemical intramolecular radical cyclization with furanone **1**. Importance of HAT mechanism.

After irradiation of **1** in acetonitrile with acetone as a sensitizer, $(\pi\pi^*)^3$ excited-state **2** is obtained. If we consider a mechanism in two-steps, an electron from the lone pair of oxygen is transferred to the furanone. Due to the basicity of enolate **3**, proton is transferred onto the oxygen to give **4**. After radical recombination on β, product **5** must be obtained. But, this is not what occurred during the photoreaction. Indeed, it is very difficult if not impossible, to oxidize an acetal.[6,7] HAT must proceed via a one-step mechanism. Hydrogen is transferred to the β position and cyclization is carried out in α position; product **7** and **8** are obtained so.

One of the work of my thesis was to replace the C—H in β position of this furanone **1** to study the feasibility of HAT with imines and to access new nitrogen-containing polyheterocycles (Figure 4).

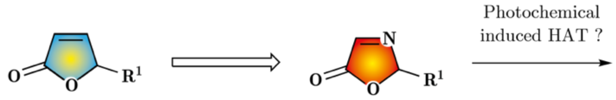


Figure 4. Replacing C—H in β position: photochemical induced HAT with imines.

Photoinduced intramolecular radical cyclization with imines via HAT

Nitrogen atom is placed between Carbon and Oxygen in the periodic table. Even though C=C and C=O bonds photochemistry has been intensively studied, C=N bond photochemistry has been elusively considered.[8,9] The position of Nitrogen atom conferred to this latter a hybrid photoreactivity. With taking account of prevalence of isomerization as the major reaction with imines, we decided to study a cyclic imine **9** from pseudo-oxazolone family. After a Michael addition on acrolein and acetalisation, products **11a** and **11b** were obtained (Figure 5).

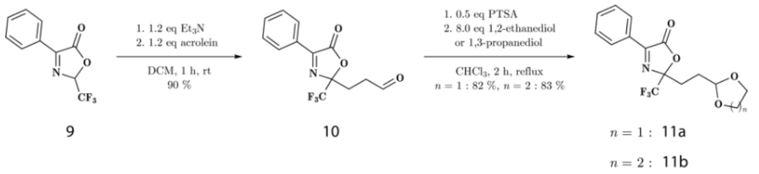


Figure 5. Synthesis of **11a** and **11b** for upcoming photoreactions.

After irradiation of **11a** and **11b** in acetonitrile, two types of products were obtained: a C—N formation adduct **12a** and a C—C formation adduct **13b**. Thermic decarboxylation was also performed to provide compound **14b**, whereas this latter is fast and occurs during irradiation in the case of dioxolane (*n* = 1, Figure 6).[10]

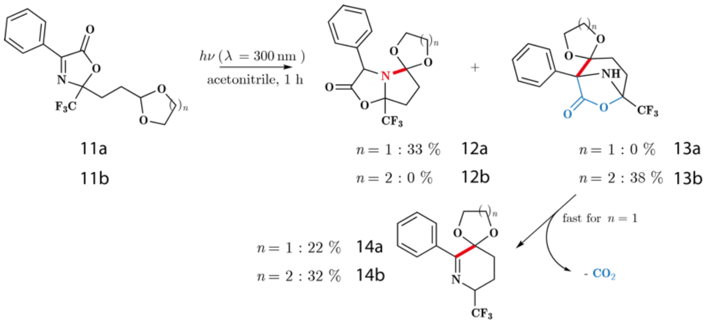


Figure 6. Photoreaction of compounds **11a** and **11b**.

In contrary of the case of furanones as described in Figure 3, cyclization occurs both in α and in β position despite a one-step mechanism as it is not possible to oxidize an acetal. After passing through a $(n\pi^*)^3$ excited state, favourable for HAT in analogy with carbonyl photochemistry, we need to know which atom abstracts the Hydrogen. To elucidate the mechanism, we cooperated with Prof. M. Abe from Hiroshima University, Japan which carried out theoretical calculations to describe the path of HAT. As presented in Figure 7, the only thermodynamically and kineticatilly favourable pathway for HAT is the abstraction of Hydrogen by Nitrogen atom.

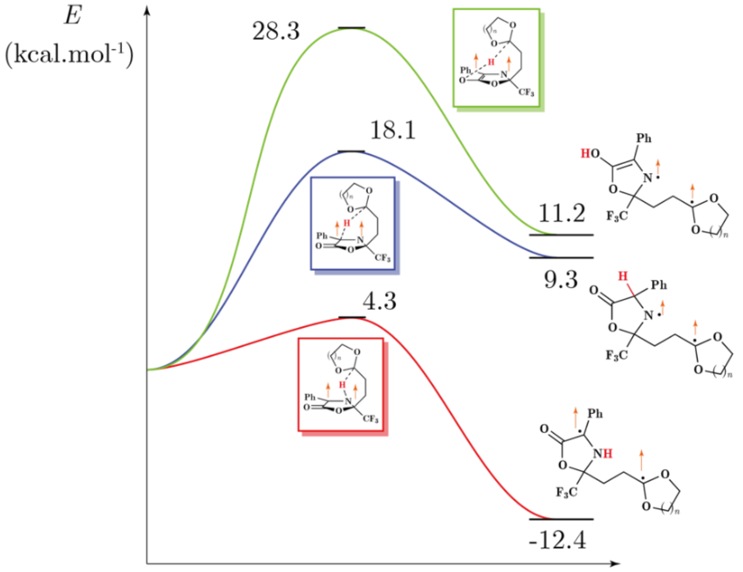


Figure 7. Different reaction paths for HAT in the case of compound **11a**. Hydrogen atom is kindly abstracted by Nitrogen atom. A similar diagram could be drawn for compound **11b**. Level of theory: UB3LYP 6-31G(d).

The question remains how we can obtain two different products. We suppose after HAT we have a reverse intersystem crossing (risc), providing a singlet biradical specie **11a-3** or **11b-3** from a triplet biradical specie **11a-2** or **11b-2**. This singlet biradical specie owns a zwitterionic character revealing an ambivalent nucleophile: a secondary amine and a carbanion **11a-4** or **11b-4** which are in competition for cyclization (Figure 8).

It is important to underline that in contrary of furanones, regioselectivity of the reaction for imines is not based on HAT mechanism since Hydrogen would be always abstracted by Nitrogen atom, but based on the cyclization due to the appearing of an ambivalent nucleophile.

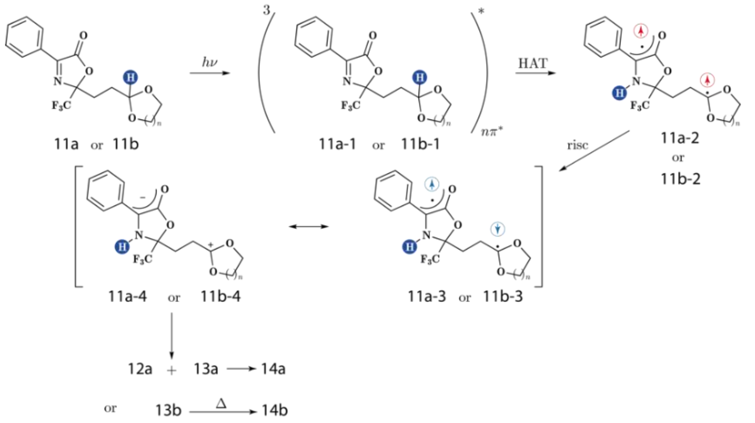


Figure 8. Proposed mechanism for **11a** and **11b** photoreaction.

In conclusion, we succeed in making HAT with imines and proved this reaction is possible for conceiving nitrogen-containing polyheterocycles in one-step. Photoinduced PCET and HAT are powerful and versatile reactions that can be applied in organic synthesis and in natural/bioactive products conception.[11,12]

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Irreversible Photobinding of Ligands to Serum Albumins

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Photoallergy (also known as haptenation)[1] is one of the main societies concern due to the use of topical drugs, cosmetics and nutraceutical in humans. This toxic effect regards as a delayed immune response to photosensitizer-bound proteins,[2] awaking great attention in both industry and regulatory agencies. Among cosmetics, several widely used pharmaceutical substances have been found to be associated with chemical photoallergy, including antibiotics, antifungals, antihistamines, cardiovascular drugs and non-stereoidal anti-inflammatory drugs. Either topical or systemic administration may cause photoallergic reactions with 24h-to-several days delay of the starting process so it requires a pre-sensitization process that implies a covalent binding of a light-activated photosensitizer or its reactive photoproduct (hapten) to a protein, generating an antigen hapten-protein complex which is the responsible of the inflammatory skin reaction. Therefore, this is viewed as a risk factor in drug development.

On the other hand, the last decade has witnessed the renaissance of targeted covalent inhibition (TCI) in drug discovery.[3] Two pivotal steps are consecutively implied: 1) reversible binding of a high-affinity ligand (latent electrophiles) with a biological target (i. e. proteins), and 2) reaction between both species to form a covalent adduct. Hence, electrophiles that are unreactive unless activated upon protein binding (la-tent electrophiles, LEs) are of particular interest in drug development and this constitutes nowadays an active area of research.

In this thesis, relevant information either in photoallergy or TCI processes related to the formation of irreversible ligand-protein adducts has been successfully obtained following a multidisciplinary strategy including ligand/protein complexes irradiation together with fluorescence and/or laser flash photolysis, size-exclusion chromatography followed by absorption and/or fluorescence spectroscopy, proteomic analysis and modelling (docking and molecular dynamics simulations). Accordingly, three principal chapters have been obtained which are briefly described below:

I. Common recognition centre

In this part, we were interested in discovering the existence of a common recognition centre in serum albumin (SA) of different species. For this purpose, we used the (*S*)-carprofen (CPF), a non-steroidal anti-inflammatory drug, as photoactive probe since its photochemical reaction had been well-established (Fig. 1A). Thus, CPF/SA complexes were submitted to irradiation (λ_{max} = 320 nm) and the course of the reaction were followed by means of fluorescence spectroscopy (Fig. 1B), showing an emission enhancement due to dehalogenation forming the carbazole-based photoproduct (CBZ). After Sephadex filtration, the protein fraction still exhibited a fluorescence band from the ligand (Fig. 1C), demonstrating that CBZ-like species was covalently attached to the SAs. Proteomic analysis showed incorporation of the carbazole radical intermediate CBZ• in various positions in the different albumins. In all cases, modifications in the IB/IIIA interface ("V" cleft pocket) were observed (Tyr452 in human, rabbit and rat serum albumin and Tyr451 in bovine, porcine and sheep serum albumin). The existence of this common recognition centre was well supported by docking and Molecular Dynamics simulation studies which agreed with the experimentally observed covalent modifications.[4]

II. HTB, metabolite of Triflusal

It is well-known that the main active metabolite of Triflusal, a platelet antiaggregant, is the 2-hydroxy-4-trifluoromethylbenzoic acid (HTB). Herein, we investigated the photochemical binding of HTB to human serum albumin (HSA) following the abovementioned multidisciplinary strategy (Fig. 2A). Thus, after irradiation of the HTB/HSA solutions, proteomic analysis revealed the addition of HTB in the ε-amino groups of eight residues such as Lys137, Lys199, Lys205, Lys352, Lys432, Lys541, Lys545 and Lys525 of the HAS (Fig. 2B). The reaction mechanism agreed with the replacement of the CF_3 group at the HTB with a new amide function. Importantly, only Lys199 residue was found to be in an internal cavity of the protein whereas the rest of the modified residues were located on the outside. Further, the results obtained from the computational studies showed that supramolecular anchoring of HTB to HSA occurred in the "V-cleft" region. Therefore, based on these irreversible photobinding results, Triflusal may produce undesired photoallergic side effects in clinical studies.[5]

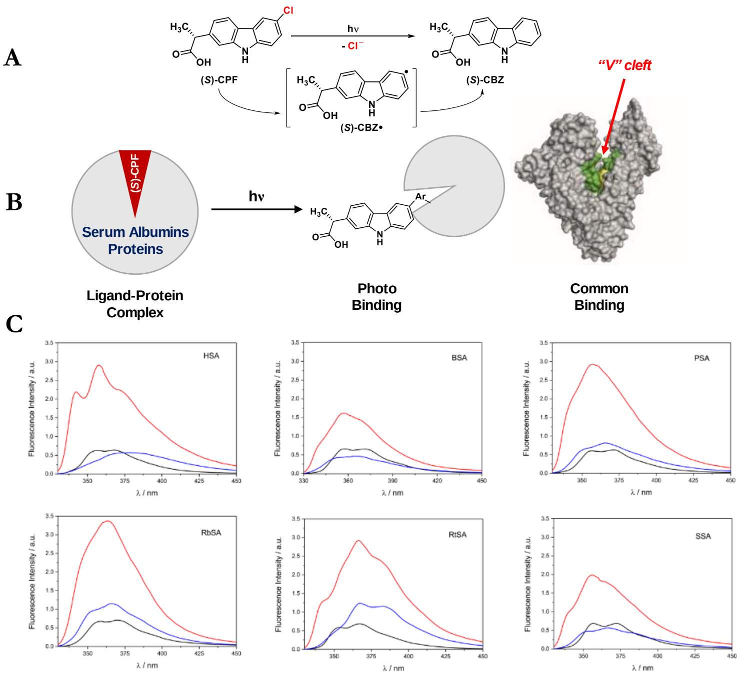
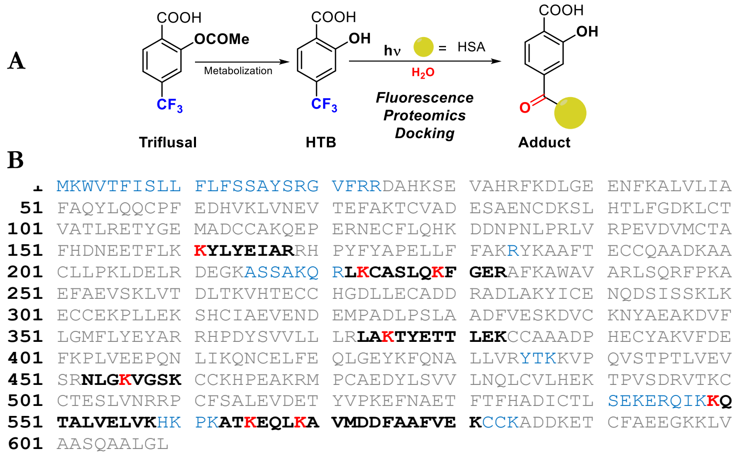


Fig. 1. **A**. Photochemical reaction of (*S*)-CPF to obtain (*S*)-CBZ via (*S*)-CBZ radical intermediate. **B**. Schematic illustration of the irreversible photobinding of (*S*)-CPF to SAs. **C**. Fluorescence spectra of CPF/SA mixtures at 1:1 drug/protein molar ratio: before irradiation (black trace), after 3 min of irradiation at λexc = 320 nm (red trace) and after Sephadex filtration of the photolyzate (blue trace).



1 MKWVTFISLL FLFSSAYSRG VFRRDAHKSE VAHRFKDLGE ENFKALVLIA
51 FAQYLQQCPF EDHVKLVNEV TEFAKTCVAD ESAENCDKSL HTLFGDKLCT
101 VATLRETYGE MADCCAKQEP ERNECFLQHK DDNPNLPRLV RPEVDVMCTA
151 FHDNEETFLK **KYLYEIAR**RH PYFYAPELLF FAKRYKAAFT ECCQAADKAA
201 CLLPKLDELR DEGKASSAKQ R**LKCASLQKF** **GER**AFKAWAV ARLSQRFPKA
251 EFAEVSKLVT DLTKVHTECC HGDLLECADD RADLAKYICE NQDSISSKLK
301 ECCEKPLLEK SHCIAEVEND EMPADLPSLA ADFVESKDVC KNYAEAKDVF
351 LGMFLYEYAR RHPDYSVVLL LR**LAKTYETT** **LEK**CCAAADP HECYAKVFDE
401 FKPLVEEPQN LIKQNCELFE QLGEYKFQNA LLVRYTKKVP QVSTPTLVEV
451 SR**NLGKVGSK** CCKHPEAKRM PCAEDYLSVV LNQLCVLHEK TPVSDRVTKC
501 CTESLVNRRP CFSALEVDET YVPKEFNAET FTFHADICTL SEKERQIK**KQ**
551 **TALVELVK**HK PK**ATKEQLKA** **VMDDFAAFVE** **K**CCKADDKET CFAEEGKKLV
601 AASQAALGL

Fig. 2. **A**. Approach for investigating the irreversible HTB photobinding to HSA. **B**. Amino acid sequence (92% coverage) obtained after irradiation of HTB in the presence of HSA, with the non-resolved amino acids in blue. The modified peptides are in black, and the altered amino acid residues are in red.

III. Latent electrophiles

The presence of an electrophilic functional group on the inhibitor is essential for the action mechanism and examples of inhibitors bearing such “selective and safe” electrophiles (latent electrophiles, LEs) are scarce. In this last chapter, an alternative strategy for addressing TCI was utilized where light was employed as an external factor to accomplish direct formation of latent electrophiles from the bound ligand without the catalytic activity of the protein (Fig. 3).

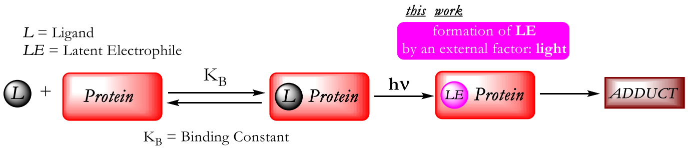
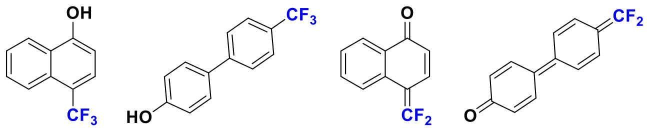


Fig. 3. General concept of this work: TCI approach using light as external factor.

Of particular interest was the utilization of inhibitors capable of generating reactive intermediates (LEs) upon light source, enabling them to form a stable adduct with the biological target. The viability of the method was proven by using trifluoromethyl substituted aromatic compounds (**1** or **2**) as appropriate candidates (Fig. 4).



1 **2** **I** **II**

Fig. 4. Chemical structures of 4-trifluoromethyl-1-naphthol (**1**), 4-(4-trifluoromethylphenyl)phenol (**2**) and their corresponding QM intermediates **I** and **II**.

These class of compounds (inhibitors) showed high-binding constants to HSA (biological target) in the ground sate. Upon irradiation, reactive QM-type intermediates (**I** or **II**) were generated which far exhibited chemoselective reactivity towards lysine residues leading to amide adducts. This fact was confirmed by proteomic analysis, revealing that derivative **1** modified the amino acids Lys106 and Lys414 located in sub-domains IA and IIIA, respectively, whereas Lys195 (placed in sub-domain IIA) was modified by **2**. Docking and molecular dynamics simulation studies provided an insight into the molecular basis of the selectivity of **1** and **2** for these HSA sub-domains and the covalent modification mechanism.

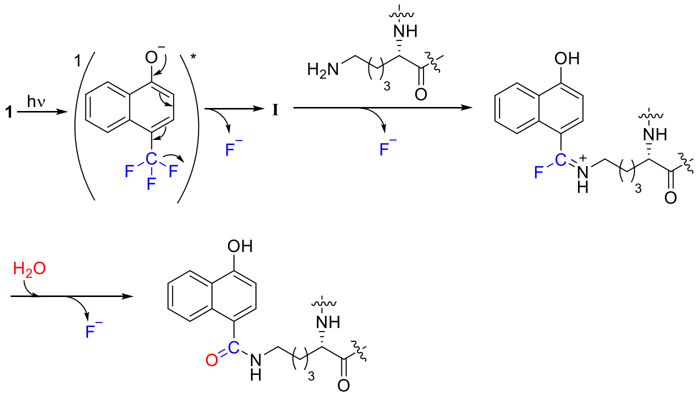


Fig. 5. Proposed covalent modification mechanism for **1**.

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CONFERENCE REPORT

Swiss Chemical Society Photochemistry Section Meeting – Fribourg, June 14, 2019

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On June 14, 2019, nearly 50 photochemists from all over Switzerland and beyond gathered together at the Haute Ecole d'Ingénierie et d'Architecture in Fribourg (HEIA-FR) for the annual Swiss Chemical Society (SCS) Photochemistry Section meeting to discuss their latest findings in the field. The organizing committee consisting of the board of the SCS Photochemistry Section put together a program consisting of 3 invited talks, 9 oral communications and a poster session with 24 posters to revive this event which, they hope, will take place annually. In addition, the general assembly of the Section was held at the premise during the day.

The morning started with the opening remarks from the Section President and conference chair, **Prof. Olivier Nicolet** during which he emphasized the importance of the financial support from the sponsors, namely the Swiss Chemical Society (SCS), the European Photochemistry Association (EPA), General Microtechnology and Photonics (GMP), Helvetica Chimica Acta (HCA), and HEIA-FR. The first session, chaired by Prof. Eric Vauthey, started with an invited lecture by **Prof. Steve Meech** from the University of East-Anglia (United Kingdom). Steve demonstrated how a combination of ultrafast spectroscopic techniques together with potential energy surfaces from computational chemistry provides a much richer picture on the excited-state dynamics of unidirectional molecular motors synthesized in the group of recent Nobel prize laureate Prof. Ben Feringa. Despite the inspiring lecture, it is safe to say that photon-fueled molecular motors are not going to replace the more conventional combustion engines in a foreseeable future. Steve's talk was followed by four presentations by younger researchers. First, **Alexander Aster** from the University of Geneva demonstrated how excitonic interactions in a perylene-based bichromophoric system are dictated by the overall geometry that can be controlled utilizing host-guest interactions. Second, **Rebecca Ingle** from EPFL showed how the broad and heavily convoluted transient absorption spectra of a platinum-based metal complex can be disentangled with the aid of anisotropy measurements and ab initio calculations. Subsequently, **Stephanie Remke** from Eawag discussed the role of short- and long-lived photo-oxidants in photochemical transformations of pollutants present in surface waters. Last, **Svenja Neumann** from the University of Basel showcased the role of light-induced charge recombination in donor-photosensitizer-acceptor triads using a double-pulse excitation scheme.

The second session, chaired by Dr. Silvio Canonica, was started with a lecture by **Prof. Natalie Banerji** from the University of Bern, Switzerland. Natalie explained how novel non-fullerene acceptor:polymer blend materials have led to significant increases in the efficiencies of organic solar cells during the past few years. Despite the complex dynamics observed in the blends, she demonstrated that both the charge and hole transfer in these materials is ultrafast, which is a prerequisite for efficient charge separation and transport. Furthermore, Natalie showed how THz spectroscopy can be utilized to get a detailed insight into the mobility of charge carriers in different structural domains of more conventional fullerene:polymer-based materials. The second session also featured two short presentations. **Dr. Nestor Guijarro** from EPFL discussed his novel in operando experiments on the semiconductor-liquid junctions of photoelectrochemical hydrogen-evolution catalysts. Next, **Dr. Andrea Pannwitz** from Leiden University (The Netherlands) demonstrated how precisely aligned chromophoric systems on phospholipid bilayers can be utilized to mimic natural photosynthetic and light harvesting complexes.

The last session, chaired by Dr. Alexandre Fürstenberg, featured **Prof. Katja Heinze** from the University of Mainz (Germany) as an invited speaker. Katja emphasized her general strategy to try to replace rare metals in photochemically active complexes and sensors by more abundant 3d elements. She showcased her recently developed molecular thermometer for contactless measurement using infrared light based on a water-soluble chromium complex ("molecular ruby"). Impressively, this molecular ruby can be further combined with a pH-sensitive fluorescein derivative, an inert reference dye, and a porphyrin into 100-nm sized silica-coated polystyrene nanoparticles to form a nanosensor for simultaneous measurement of the biologically relevant analytes temperature, oxygen, and pH at a single excitation wavelength. After Katja's lecture, three short presentations concluded the day. **Dr. Teresa Delgado** from the University of Geneva described how the optical characterization of a single crystal of an extraordinarily long-lasting phosphor containing Eu^{2+} and Dy^{3+} led to a better understanding of the effect of the co-dopants in the long-phosphorescence mechanism. **Prof. Christian Reber** from the University of Montréal (Canada) discussed his efforts to rationalize the effect of pressure on the luminescence properties of square-planar d^8 metal complexes. Finally, **Bahman Golesorkhi** from the University of Geneva explained how, for the first time, linear molecular light up-conversion from the near infrared to the visible could be achieved using a molecular erbium complex.

The poster session with 24 posters on display led to lively exchanges. **Fabian Brunner**, University of Basel, (winner) and **Yongpeng Liu**, EPFL, (runner-up) each received a poster award sponsored by the journal Helvetica Chemica Acta and **Patrick Herr**, University of Basel, won the iPad from the contest sponsored by GMP.

Given the success of this event and the very positive feedback provided by the participants, the meeting can be anticipated to take place again on a yearly basis. The next edition is already being planned for June 19, 2020, at the same location.

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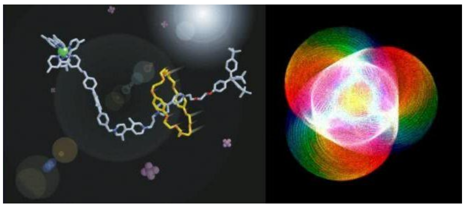

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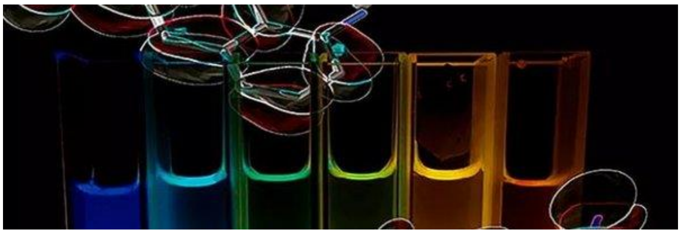

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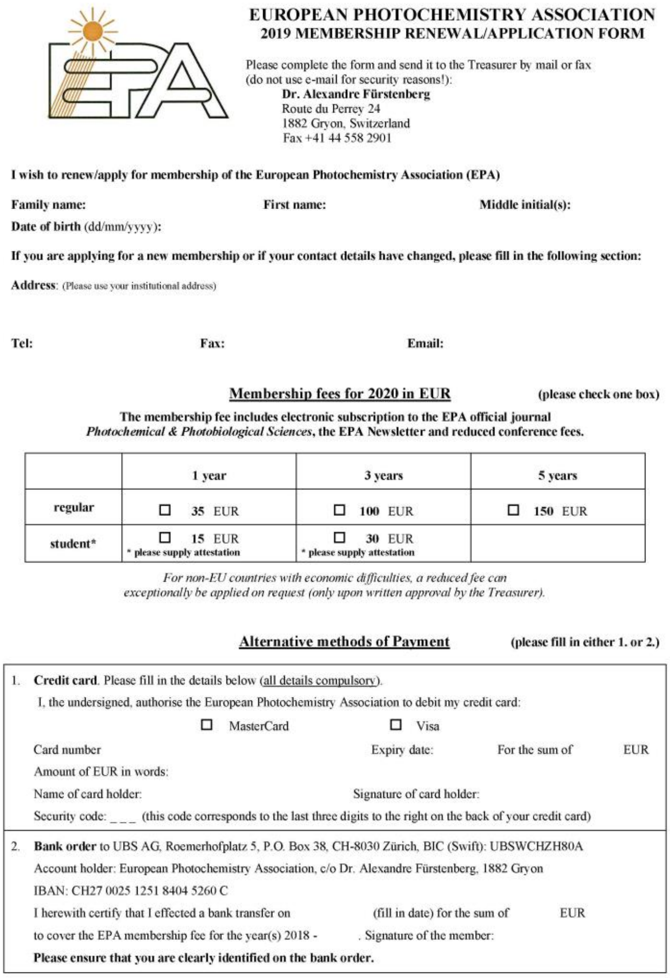

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