WG4/WG1 Meeting COST Action CM1201

Biomimetic Radical Chemistry

WG1: Radical Enzymes

WG4: Bio-Inspired Synthetic Strategies

Puerto de la Cruz, Tenerife (Spain)

1-3 October 2014

REGISTRATION DESK/VENUE

Beatriz Hotel (Atlantis & Spa), Puerto de la Cruz, Tenerife
Avenida Venezuela nº15, 38400 Puerto de la Cruz - Tenerife - Spain
Telephone: +34 922 37 45 45 - email: *reservas.tenerife@beatrizhoteles.com*

HOW TO ARRIVE

Airports

There is no choice, if you want to arrive on time, you must get into the island by plane. There are two airports; one located in the south of the island and the other, which is nearer to Puerto de la Cruz, is in the north.

Tenerife North Airport (TFN, Los Rodeos): 26 km to Puerto de la Cruz
Tenerife South Airport (TFS, Reina Sofía): 91 km to Puerto de la Cruz

Transport

Once you have landed at the airport of choice you could take the public transport, a shuttle service, a taxi or rent a car.

B**us TFN Airport-Puerto de la Cruz:**
Line 102 (Sta. Cruz de Tenerife-TFN-Puerto de la Cruz), 4.75€.
Line 343 (Los Cristianos-Puerto de la Cruz, stopping at both airports), 4.75€.
B**us TFS Airport-Puerto de la Cruz:**
Line 343 (Los Cristianos-Puerto de la Cruz stopping at both airports), 13.55€.

CONTACT

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Timetable

	Wednesday 1/10	Thursday 2/10	Friday 3/10
8:00-8:45	Registration		
8:45-9:00	IntroductoryRemarks		
9:00-9:30	H. Zipse	B. Golding	U. Jahn
9:30-10:00	L. Engman	M. Seemann	G. Speier
10:00-10:30	C. Ollivier	S. Barata	T. Gimisis
10:30-11:00	M. Rodríguez	A. Studer	C. Chatgilialoglu
11:00-11:30	Coffee	Coffee	Coffee
11:30-12:00	J. L. Gebicki	A. Montes/D. Sosa	A. Croft
12:00-12:30	M. Boll	M. C. Jiménez	M. Surducan
12:30-13:00	M. Drozdowska	S. Abazi	M. Sibi
13:00-14:30	Lunch	Lunch	Lunch
14:30-15:00	P. Renaud	A. Boto	Discussion around COST, Collaboration, STSM, etc. Final remarks
15:00-15:30	F. Dénès	A. Kellett	
15:30-16:00	E. León	M. Salamone	
16:00-16:30	Coffee	Coffee	
16:30-17:00	C. Ferreri	A. J. Herrera	
17:00-17:30	M. Díaz	J. Kaiser	
17:30			Teide Dinner

Program

Tuesday, September 30th

Arrival and Hotel registration

Wednesday, October 1st

8.00-8.45	Registration
8.45-9.00	Welcome Introduction **Chryssostomos Chatgilialoglu** (Chair of the Action)
9.00-9.30	The Stability of Nitrogen-Centered Radicals **Hendrik Zipse** (WG4 member)
9.30-10.00	Improving on Nature – Introduction of Chalcogen Substituents into Tocopherols **Lars Engman** (WG4 member)
10.00-10.30	Visible Light Photoredox Catalysis for Radical Synthesis **Cyril Ollivier** (WG4 member)
10.30-11.00	Fragmentation of Carbohydrate Anomeric Alkoxyl Radicals. Synthesis of Organophosphorus Compounds Highly Functionalized **Marisol Rodríguez** (from local WG4 member group)
11.00-11.30	**Coffee Break**
11.30-12.00	Spectral properties and kinetic studies of heme proteins in microheterogeneous environment **Jerzy L. Gebicki** (WG1 member)
12.00-12.30	Radical enzymes involved in the anaerobic degradation of aromatic compounds **Matthias Boll** (WG1 member)
12.30-13.00	Investigations into the mechanism of the coenzyme B12-dependent rearrangement catalyzed by glutamate mutase from Clostridium cochlearium **Marta P. Drozdowska** (WG1 member)
13.00-14.30	**Lunch**

14.30-15.00 Memory of Chirality in Radical Addition-Translocation-Cyclization Cascade Reactions
Philippe Renaud (Vice-Chair and WG4 member)

15.00-15.30 Biologically active natural products as a source of inspiration for the development of new synthetic methods in radical chemistry: The use of intramolecular hydrogen shifts in vinyl radicals
Fabrice Dénès (WG4 member)

15.30-16.00 Ring Contraction of nono-2,3-Diulose Derivatives Photochemically Promoted
Elisa I. León (from local WG4 member group)

16.00-16.30 **Coffee Break**

16.30-17.00 Metal-sulfur free radical reactivity
Carla Ferreri (WG3 leader)

17.00-17.30 Docosahexaenoic acid (DHA) activates glutathione and thioredoxin antioxidant systems in murine hippocampal HT22 cells: potential implications in neuroprotection
Mario Díaz (Local invited lecture)

Thursday, October 2nd

9.00-9.30 Were Radicals Participants in Darwin's 'Warm Pond'?
Bernard T. Golding (MC and WG1 leader)

9.30-10.00 Mechanistic investigations of LytB, an iron sulfur enzyme
Myriam Seemann (WG1 member)

10.00-10.30 Radical Fluoroalkylation of Organic Substrates in Aqueous Media
Sebastian Barata Vallejo (WG4 member)

10.30-11.00 Oxidative N-Heterocyclic Carbene (NHC) Catalysis
Armido Studer (WG4 member)

11.00-11.30 **Coffee Break**

11.30-11.45 *N*-Halo Sulfonamides, Sulfamates and Sulfamides as Nitrogen-Centered Radical Precursors and its Applications in the Selective Functionalizations of Unactivated Methyl Groups and Oxidations.
Dionisio Rodríguez-Sosa (from local WG4 member group, young investigator)

11.45-12.00 Intramolecular 1,5-Hydrogen Atom Transfer Reactions under reductive conditions in Monosaccharide Systems
Adrián S. Montes (from local WG4 member group, young investigator)

12.00-12.30 Free Radicals in Photosensitization by Drugs
María C. Jiménez (WG4 member)

12.30-13.00 Radical Mediated Modifications of Natural Products
Sokol Abazi (WG4 member)

13.00-14.30 **Lunch**

14.30-15.00 Creating Diversity by Site-Selective peptide Modification: towards new bioactive peptides
Alicia Boto (Local invited lecture)

15.00-15.30 NCI-60 chemotherapeutic action of copper metallointercalators bear apoptotic hallmarks of hydroxyl radical induced death
Andrew Kellett (WG2 member)

15.30-16.00 Reactions of the cumyloxyl radical with alkanamides. The influence of structural and medium effects on the hydrogen atom transfer selectivity.
Michela Salamone (from WG2 member group)

16.00-16.30 **Coffee Break**

16.30-17.00 Iodine and Bromine Redox Systems Induce the Formation of Nitrogen Centered Radicals. Searching for a possible Role of Iodine, Bromine and Sulfamates in Biological Radical Processes.
Antonio J. Herrera (WG4 member)

17.00-17.30 Functional ribonucleotide reductase enzyme models
József Kaizer (WG4 member)

Friday, October 3rd

9.00-9.30 New Radical Avenues to Antiviral Carbo- and Heterocyclic Compounds
Ullrich Jahn (WG4 leader)

9.30-10.00 Oxygenation and oxidation of PPh_3 and phenols by $^3O_2$ catalyzed by a 1,3,2-oxazaphosphole as organic cofactor mimic
Gábor Speier (WG4 member)

10.00-10.30 Development of a General Synthetic Methodology for Isotopically Enriching Pyrimidine Nucleosides and their Oxidation Products
Thanasis Gimisis (WG4 member)

10.30-11.00 Cyclopurine modification as radiation-induced lesions in DNA
Chryssostomos Chatgilialoglu (Chair and WG2 member)

11.00-11.30	**Coffee Break**
11.30-12.00	QueE – Influencing the Mechanistic Outcome of Radical Reactions in the Biosynthesis of Queosine **Anna K. Croft** (WG1 member)
12.00-12.30	Computational and experimental investigations of bond activation in structures similar to ferric-peroxide species known in hemoproteins and hemoenzymes **Mihai Surducan** (from WG1 member group)
12.30-13.00	Light Mediated Organic Reactions: Asymmetric Synthesis and Polymer Degradation **Mukund Sibi** (Invited lecture)
13.00-14.30	**Lunch**
14.30-16.30	Discussions and planning of collaborations. Final remarks. Coordinators: **Bernard T. Golding** (WG1 Group Leader) **Ullrich Jahn** (WG4 Group Leader)
17:30	**Teide Dinner** (A bus will pick us up at the hotel to go to El Parador de las Cañadas del Teide. It will take about one hour drive)

Saturday, October 4th

Departure

Abstract book

Texts of abstracts have not undergone any linguistic correction.
Talks are presented by time order.

The Stability of Nitrogen-Centered Radicals

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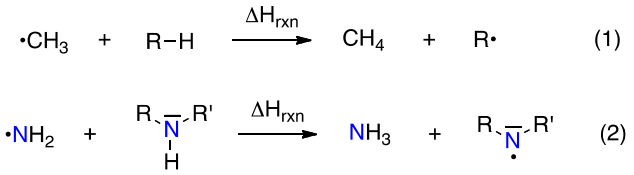
Radical stabilization energies (RSEs) for carbon-centered radicals can be calculated as reaction enthalpies of eq. (1) and, with this definition, are identical to differences in bond dissociation energies (BDEs) between the C-H bond in methane and in the parent hydrocarbon (R-H). Based on the same logic the stability of nitrogen-centered radicals can be calculated using the definition in eq. (2) as the difference in BDE(N-H) values of ammonia and the parent amines.



Using the reference systems H_2O, NH_3, and CH_4 the RSE data for oxygen-, nitrogen-, and carbon-centered radicals can be combined in a global scale of BDE values (Figure 1).[1-3] Using this type of presentation the reaction enthalpy of hydrogen transfer steps between amines and C- or O-centered radicals can be predicted in a straight forward manner. Using recently calculated data for a variety of nitrogen-centered radicals, substituent and environmental effects on N-radical stability will be discussed.

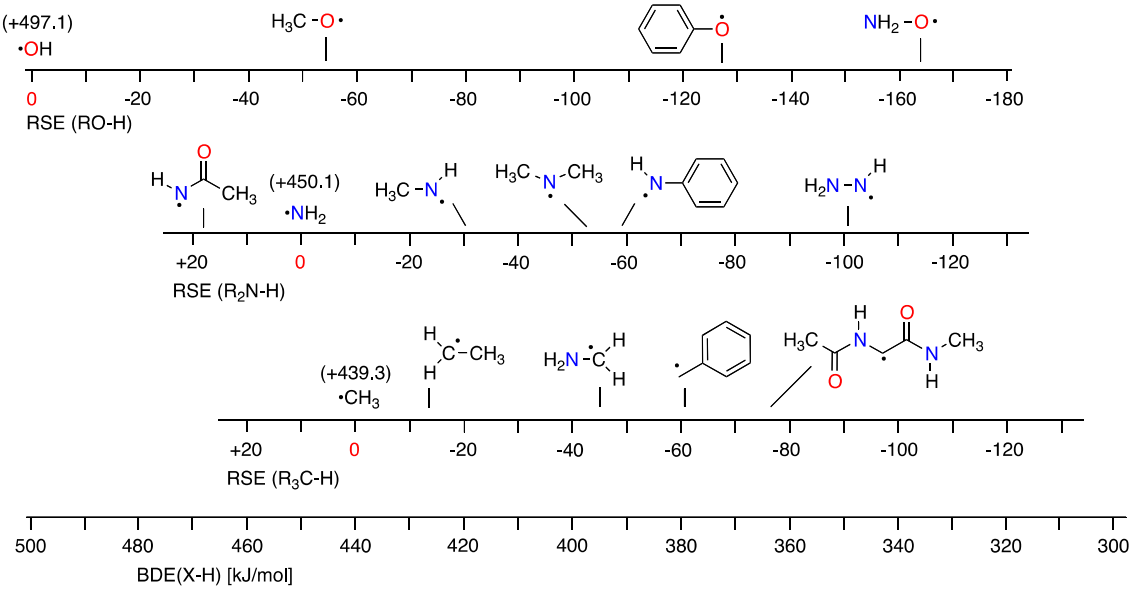


Figure 1. Radical stabilization energies (RSEs) of selected open shell systems (in kJ/mol).

References
1) J. Hioe, H. Zipse, *RSC Advances* **2013**, *3*, 12403 - 12408.
2) D. Sakic, F. Achrainer, V. Vrcek, H. Zipse, *Org. Biomol. Chem.* **2013**, *11*, 4232 - 4239.
3) J. Hioe, H. Zipse, *Chem. Eur. J.* **2012**, *18*, 16463 - 16472.

Notes

Improving on Nature – Introduction of Chalcogen Substituents into Tocopherols

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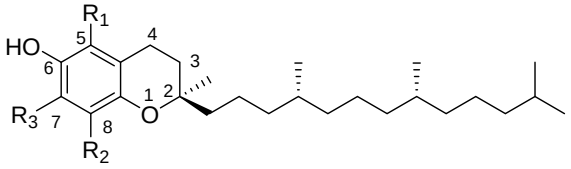
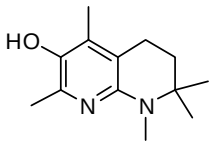
α-Tocopherol (**1**) is generally recognized as the most significant lipophilic, chain-breaking antioxidant *in vivo*. It has an important role in biological membranes to minimize polyunsaturated fatty acid



1 α-Tocopherol $R_1 = R_2 = R_3 = Me$
2 β-Tocopherol $R_1 = R_2 = Me$; $R_3 = H$
3 γ-Tocopherol $R_1 = H$; $R_2 = R_3 = Me$
4 δ-Tocopherol $R_1 = R_3 = H$; $R_2 = Me$

oxidation and keep membrane fluids in the highest possible quality. In order to improve on the radical-trapping capacity, the tocopherol structure has been subjected to many variations. For example, contraction of the ring-size in the heterocyclic ring from six- to five-membered was found early on to cause an almost two-fold increase in reactivity. Another strategy, pioneered by Pratt and co-workers, involves incorporation of nitrogen atoms both into the phenolic and heterocyclic rings. Tetrahydro-naphthyridinol **5** is an example of such a compound. It was found to react with peroxyl radicals some 15 times more rapidly than α-tocopherol. The nature of the chalcogen in the



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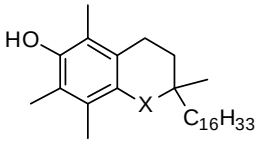
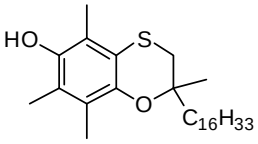


6a X=S
6b X=Se



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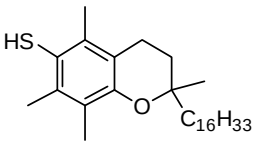

8

heterocyclic ring has been another target for variation. Both the 1-thio- (**6a**) and 1-seleno-α-tocopherol (**6b**) have been prepared and evaluated for their antioxidant capacity. None of the compounds turned out to be a better quencher of peroxyl radicals than the parent. This was also true for 4-thia-α-tocopherol (**7**) where an additional sulfur atom had been incorporated in position 4. The thiol analogue **8** of α-tocopherol is a known compound since more than fifty years.

We have now developed methodology for introduction of chalcogen substituents RX (where X=S, Se or Te and R=butyl or octyl) into all posible vacant aromatic positions in compounds **2**-**4**.[1] Evaluation in a water/chlorobenzene two-phase lipid peroxidation model showed that the tellurium analogues could quench peroxyl radicals >10 times more rapidly than α-tocoperol. Furthermore, in the presence of *N*-acetylcysteine as a reducing agent in the aqueous phase they were highly regenerable. Under conditions where α-tocopherol could inhibit peroxidation for 100 min, the inhibition time for 7-octyltelluro-β-tocopherol was almost 600 min.

References

[1] For a communication of this work, see: Singh, V. P.; Poon, J.; Engman, L. *Org. Lett*. **2013**, *15*, 6274.

Notes

Visible Light Photoredox Catalysis for Radical Synthesis

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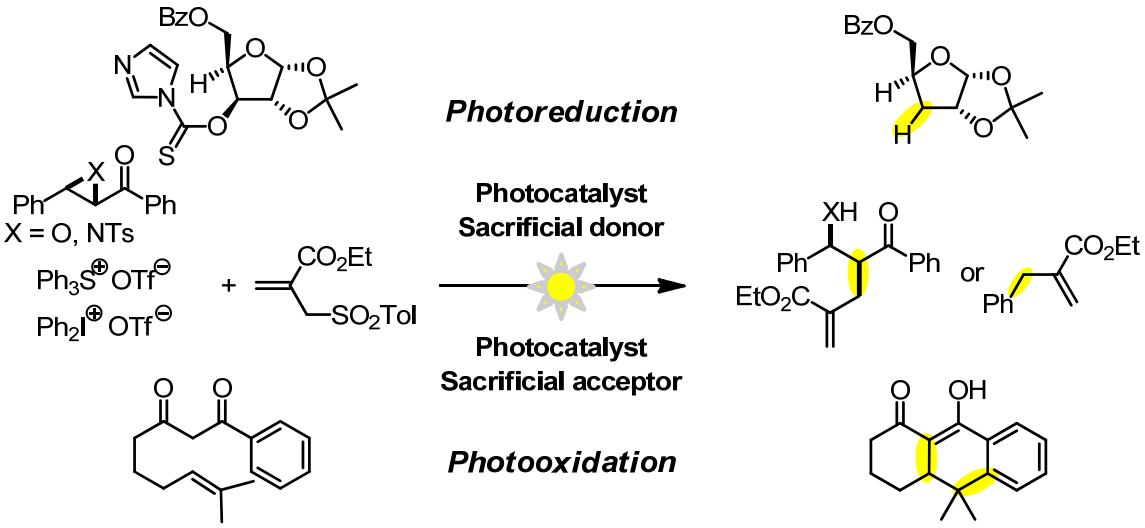
Radical chemistry has witnessed an explosive growth over the last three decades. But the development of mild and sustainable preparative redox processes limiting the utilization of stoichiometric toxic metal complexes is still needed. Recently, visible-light photoredox catalysis has emerged as a valuable and a greener alternative to generate radicals by single electron transfer reactions from an appropriate photocatalyst - which can be a polypyridine complex of transition metal - that absorbs light in the visible region. Since the pioneering studies of Kellogg and Deronzier, important contributions have been reported for synthetic purposes.[1] In this context, we investigated various radical transformations involving photoreduction of ketoepoxides, ketoaziridines,[2] onium salts[3,4] and O-thiocarbamates[5] and photooxidation of 1,3-dicarbonyl compounds.[6] Then, we took advantage of the reactivity of the photogenerated radicals to create new carbon-carbon bonds. Finally, related mechanistic studies were performed.



References
[1] For general reviews on photoredox catalysis in organic synthesis, see: (a) Narayanam, M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*,102. (b) Teplý, F. *Collect*. *Czech*. *Chem*. *Commun*. **2011**, *76*, *859.* (c) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (d) Xuan, J.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2012**, *51*, 6828. (e) Prier, C.K.; Rankic, D. A.; MacMillan D. W. C. *Chem. Rev.* **2013**, *113*, 5322.
[2]. Larraufie, M.-L.; Pellet, R.; Fensterbank, L.; Goddard, J.-P.; Lacôte, E.; Malacria, M.; Ollivier, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 4463.
[3] Donck, S.; Baroudi, A.; Fensterbank, L.; Goddard, J.-P.; Ollivier, C. *Adv. Synth. Catal.* **2013**, *355*, 1477.
[4] Baralle, A.; Fensterbank, L.; Goddard, J.-P.; Ollivier, C. *Chem. Eur. J.* **2013**, *19*, 10809.
[5] Chenneberg, L.; Baralle, A.; Daniel, M.; Fensterbank, L.; Goddard, J.-P.; Ollivier, C. *Adv. Synth. Catal.* **2014**, *356*, in press.
[6] Daniel, M.; Fensterbank, L.; Goddard, J.-P.; Ollivier, C. *Org. Chem. Front.* **2014**, *1*, 551.

Notes

Fragmentation of Carbohydrate Anomeric Alkoxyl Radicals. Synthesis of Organophosphorus Compounds Highly Functionalized

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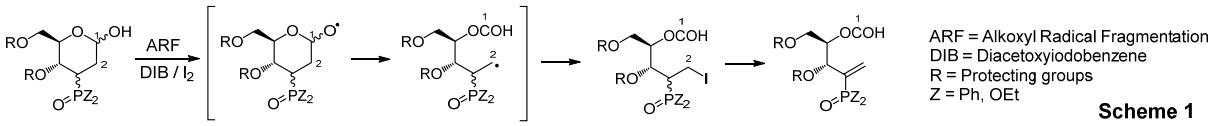
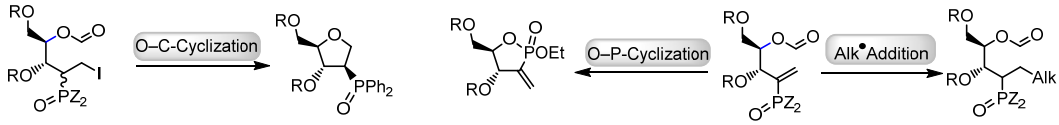
The alkoxyl radical fragmentation (ARF) reaction of carbohydrate anomeric alcohols with hypervalent iodine reagents in the presence of iodine has been described by this laboratory.[1] The synthesis of chiral vinylphosphonate and vinylphosphine oxide[2] carbohydrate derivatives has been developed using this protocol. The synthetic sequence proceeded via β-iodophosphonate and β-iodophosphine oxide intermediates, which may be interesting synthons for the introduction of phosphorus into complex organic molecules (Scheme 1).



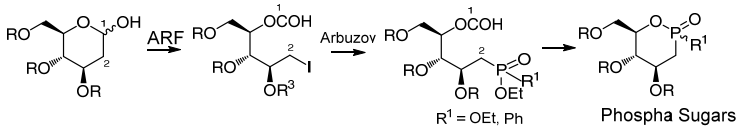
Scheme 1

These vinylphosphonates could be easily transformed into α-methylene-γ-phostones (O–P-cyclization) and β-aminophosphonates, isosteres of biologically active α-methylene-γ-lactones and β-amino acids, respectively. β-Iodophosphine oxides were easily converted into cyclic 1,4-anhydro-2-deoxy-2-phosphoryl-alditol derivatives (O–C-cyclization). We have also used these conjugated vinylphosphorus compounds as radical acceptors in photostimulated alkyl radical addition reactions (Scheme 2).[3]



Scheme 2

Using the ARF reaction as key step, we have developed a new general methodology for the synthesis of phostones[4] and phostines (Scheme 3). The organophosphorus were obtained by Arbuzov reaction that finally produced 1-phospha-sugars in good yields.



Scheme 3

The talk will focus on this research and recent advances on the synthesis of new organophosphorus compunds.

References

[1] Suárez, E.; Rodríguez, M. S. *β-Fragmentation of Alkoxyl Radicals: Synthetic Applications*; Renaud, P.; Sibi, M. P., Eds.; Radicals in Organic Synthesis; Wiley-VCH: Weinheim, 2001.
[2] (a) Gaumont, A. C.; Gulea, M. In *Science of Synthesis, Houben Weyl Methods of Molecular Transformations*; Georg Thieme Verlag KG: Stuttgart, 2007; Vol. 33, pp 701–710. (b) Janecki, T.; Kedzia, J.; Wasek, T. *Synthesis* **2009**, 1227.
[3] Hernández-Guerra, D.; Rodríguez, M. S.; Suárez, E. *Org. Lett*. **2013**, *15*, 250; *E. J. Org. Chem*, **2014**, 5033.
[4] Thiem, J.; Günther, M.; Paulsen, H.; Kopf, *J. Chem. Ber*. **1977**, *110*, 3190.

Notes

Spectral properties and kinetic studies of heme proteins in microheterogeneous environment

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Conventional spectrophotometry, stopped-flow spectrofluorometry, circular dichroism and pulse radiolysis were applied to study the influence of aqueous and reverse micelles stabilized by anionic surfactants on the heme proteins, catalase, peroxidases, and cytochrome c. Catalase and peroxidases catalytically scavenge hydrogen peroxide with the formation of heme radical intermediate, Compound I (Cpd I). Cytochrome c has two physiological roles. It transfers electrons in the respiratory chain and serves as the apoptosis-triggering agent. In the latter case, cytochrome c is released from mitochondria into the cytosol, where it undergoes conformational transition. In this new conformation cytochrome c exhibits peroxidase-like activity. It has been suggested that similar changes in the cytochrome c molecule can be induced by anionic surfactants.

Reverse micelles which are formed by certain surfactants in apolar solvents can entrap water and hydrophilic molecules, including proteins, within their hydrophilic core. The entrapment of horseradish peroxidase (HRP) into sodium bis(2-ethylhexyl)sulfosuccinate (AOT)/n-heptane reverse micelles favors the intramolecular electron transfer to the heme iron, while the yield of cytochrome c reduction in reverse micelles is lower in comparison with that observed in water. Heme iron of catalase is neither reduced by the hydrated electron in an aqueous solution nor in reverse micellar systems. The rates of formation of catalase and HRP Cpds I in AOT reverse micelles are significantly higher than in water and depend on the size of reverse micelles. On the other hand, catalase in aqueous micellar solution of AOT or sodium n-dodecyl sulphate (SDS) completely loses its activity.

Peroxidase-like activity of cytochrome c encapsulated into AOT reverse micelles is approximately two orders of magnitude higher than that measured in water. The enhancement is due to the higher reaction rate of cytochrome c with hydrogen peroxide, which, contrary to true peroxidases, is the rate determining step in the peroxidase cycle of cytochrome c. Similar behavior of cytochrome c is observed in aqueous micellar solutions of AOT or SDS. It should be noted that cytochrome c in micellar solution is much more sensitive to oxidative damage than the native protein.

In the talk some other examples of the behavior of heme enzymes in the presence of surfactants will also be given and possible consequences, both biological and practical, will be discussed.

Notes

Radical enzymes involved in the anaerobic degradation of aromatic compounds

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The aromatic ring is next to the glycosyl functionality the second most abundant structure in nature. The complete degradation of aromatic compounds can only be accomplished by microorganisms. In the presence of molecular oxygen, aerobic fungi and bacteria use mono- or dioxygenases for hydroxylation and ring cleavage of aromatic structures. At anaerobic sites, e.g. in contaminated aquifers, in soil frequently flooded with water, in sediments of rivers, lakes or seas, anaerobic bacteria use rather reductive than oxidative processes for using aromatic compounds as carbon and energy source. The enzymology involved in the anaerobic catabolism of aromatic compounds involves a completely different inventory of enzymes/pathways than under aerobic conditions. Many enzymes involved follow unprecedented mechanisms, and many involve catalysis via substrate/enzyme radicals[1]. The diversity and function of verified or proposed radical enzymes that are involved in the degradation of numerous aromatic compounds including toluene, xylenes, cresols, phthalates, benzene and others will be presented. Enzymes involved in anaerobic C-H-bond activations belong to the glycyl radical family that add methyl group containing aromatics to fumarate[2]. The best studied enzyme is benzylsuccinate synthase that adds toluene to fumarate yielding benzylsuccinate. Enzymes involved in aromatic ring dearomatization belong to the BCR/HAD radical enzyme families[3]. These enzymes catalyse a Birch-like reduction of aromatic rings to a conjugated dienoyl-CoA but are also involved in dehalogenation reactions probably by a non-radical nucleophilic substitution reaction. The involvement of radical catalysis by carboxylation reactions of non-substituted aromatic compounds such as benzene or polycyclic aromatic hydrocarbons is hypothesized[3].

References

[1] Boll, M; Löffler, C; Morris, BE; Kung, JW. *Environ Microbiol* **2014**, *16*, 612.
[2] Heider, J. *Curr Opin Chem Bio* **2007***, 11,* 188.
[3] Buckel, W; Kung, JW; Boll, M. ChemBioChem **2014**, *in press*.

Notes

Investigations into the mechanism of the coenzyme B_{12}-dependent rearrangement catalyzed by glutamate mutase from *Clostridium cochlearium*

Marta P.Drozdowska,[a,b] **Bernard T.Golding**[b] **and Wolfgang Buckel**[a]
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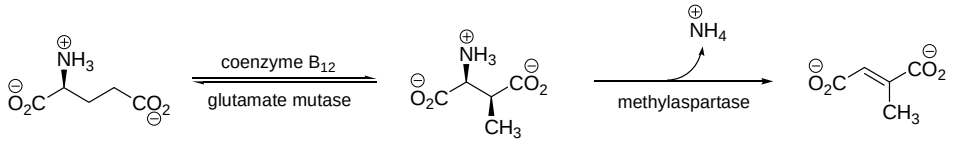
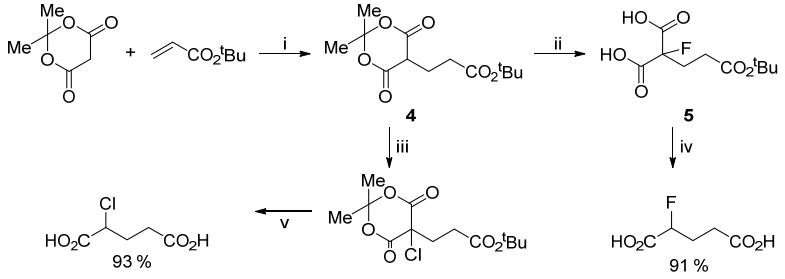
Coenzyme B_{12} (adenosylcobalamin)-dependent reactions proceed *via* the reversible homolytic cleavage of the Co-C-bond to form cob(II)alamin and the 5'-deoxyadenosyl radical. This radical initiates the subsequent rearrangement or elimination *via* substrate-derived and product related radicals. The coenzyme B_{12}-dependent glutamate mutase reversibly converts (*S*)-glutamate **1**to (2*S*,3*S*)-3-methylasparate **2**during the fermentation of glutamate to butyrate in *Clostridium cochlearium*:[1]



1 **2** **3**

This reaction is proposed to involve a fragmentation-recombination mechanism with radical intermediates.[2] (2*S*,3*S*)-3-Methylasparate**2** is further converted to mesaconate **3**catalyzed by methylaspartase.To enhance the understanding of the glutamate mutase mechanism, we would like to establish whether 2-fluoroglutarate (or 2-chloroglutarate) could act as substrates and/or inhibitors of this enzyme and provide EPR characterisation of the radical intermediates involved. Possible products of the rearrangement, 2-fluoro- and 2-chloro-3-methylsuccinate, may serve as substrates for methylaspartase to produce mesaconate**3**.



4 **5** **6** **7** **8**

Reagents and conditions:**i)** K_2CO_3, $BnEt_3N^+Cl^-$, CH_3CN, 60 °C, 90 %; **ii)** Selectfluor, DBU, MeCN, -15 °C→ r.t, 4 h, 90 %; **iii)** NCS,DBU, DCM, -15 °C→ r.t., 3 h, 94 %; **iv)** TFE, microwave heating at 150 °C, 2 h, 91 %; **v)** TFA, 140 °C, 1 h, 93 %;

Synthesis of both 2-fluoroglutaric acid**6**and 2-chloroglutaric acid **8**proceeded through halogenation of the Meldrum's acid derivative **4** followed by acid catalysed hydrolysis and decarboxylation.[4].The proposed intermediate 2-fluoro-3-methylsuccinate has also been synthesizedthrough a Meldrum's acid derivative (not shown above). We have started to investigate the potential of these compounds as substrates for glutamate mutase and potential inhibitors of the downstream enzyme-methylaspartase. Initial experiments indicate that 2-fluoroglutarate is not a substrate for glutamate mutase;2-fluoro-3-methylsuccinate is not a substrate for methylaspartase;andboth 2-fluoroglutarate and 2-fluoro-3-methylsuccinate areinhibitors of methylaspartase. The type of inhibition is to be established in future experiments.

References

[1] Buckel, W.; Barker, H. A. *J. Bacteriol* **1974**, *117*, 1248.
[2] Bothe, H. *et al*. *Biochemistry* **1998**, *24*, 4105.
[3] Buckel, W.; Golding, B. T. *Radical Enzymes*; Chatgilialoglu, C.,Studer, A. Eds.; Encyclopedia of Radicals in Chemistry, Biology and Materials; Wiley: 2012.
[4] Drozdowska, M. P. *PhD Thesis*; Newcastle University: Newcastle upon Tyne, 2012.

Notes

Memory of Chirality in Radical Addition-Translocation-Cyclization Cascade Reactions

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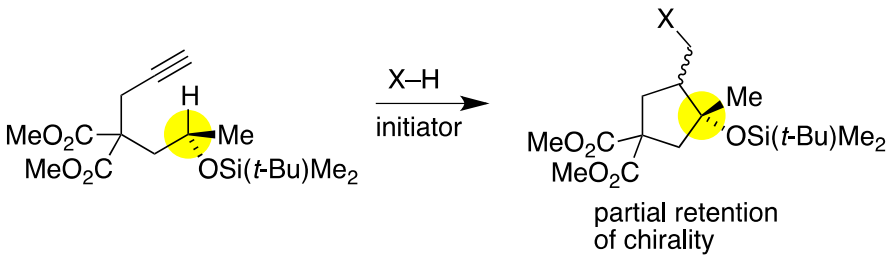
Radical reactions involving memory of chirality are quite rare processes and are usually based on systems undergoing slow conformation changes or on extremely fast radical recombination processes. In an early work, Heiba and Dessau reported that the formation of a lactone via a radical translocation-cyclization process was occurring with some unknown level of retention of the absolute configuration.[1] Recently, Curran and coworkers reexamined this reaction and found that translocation-cyclisation of related α-amide radicals leading to amides were taking place with partial retention of chirality.[2, 3]

A few years ago, we reported a radical cascade reaction involving phosphonyl and thiyl radicals to access cyclopentane derivatives.[4] We report here that this reaction involving intermediates with high conformational lability is proceeding with substancial levels of retention of chirality.



X–H = PhSH or $(EtO)_2P(O)$–H

References

[1] Heiba, E.; Dessau, R. *J. Am. Chem. Soc.* **1967**, *89*, 2238.
[2] Sassmal, A.; Taniguchi, T.; Wipf, P.; Curran, D. P. *Can. J. Chem.*, **2013**, *91*, 1
[3] For a review on memory of chirality see: Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis*, **2005**, 1
[4] Beaufils, F.; Dénès, F., Renaud, P. *Angew. Chem. Int. Ed.*, **2005**, *44*, 5273. Beaufils, F.; Dénès, F., Renaud, P. *Org. Lett.*, **2004**, *6*, 2563.

Notes

Biologically active natural products as a source of inspiration for the development of new synthetic methods in radical chemistry: The use of intramolecular hydrogen shifts in vinyl radicals

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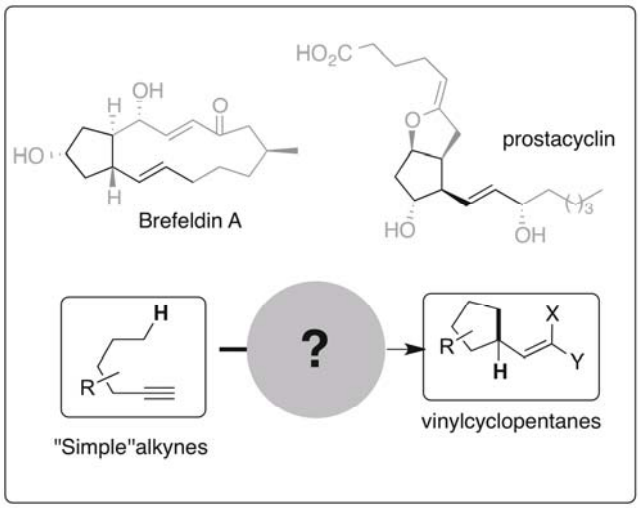
The synthesis of complex molecules represents a challenge for organic chemists. Efficient strategies have to be planned to access the desired molecule in a limited number of steps. The retrosynthetic analysis is driven by the knowledge of reaction conditions to achieve carbon-carbon and carbon-heteroatom bonds formation. The need for milder reaction conditions, new reagents or new catalysts to achieve more selective chemical transformations stimulates the development of new synthetic methods and in this context, the structural complexity of natural products is a fantastic source of inspiration.

Sulfur and phosphorous-centred radicals proved to be efficient mediator to access carbocyclic and heterocyclic 5-membered rings from linear alkynes.[1-3] The thioether moiety can be further exploited to generate carbon-centred radicals,[4] or to introduce further functionalization under ionic conditions. Similarly, the thiophosphonate moiety can be useful to introduce an alkenyl side chain by the mean of olefination reaction.[5] However, these transformations required additional steps, including protection-deprotection sequences. In order to develop new tools for the ''disconnection approach'', we decided to investigate a new strategy for the formation of functionalized vinylcyclopentanes (and related heterocycles) based on a radical cascade involving a hydrogen atom abstraction to generate in a regioselective manner a carbon–centred radical. Our recent efforts in this field will be discussed.



References
[1] Beaufils, F.; Dénès; F. Renaud, P. *Org. Lett*. **2004**, 2563.
[2] Beaufils, F.; Dénès, F.; Renaud, P. *Angew. Chem. Int. Ed*. **2005**, 5273.
[3] Lamarque, C; Beaufils, F.; Dénès, F.; Schenk, K.; Renaud, P. *Adv. Synth. Catal.* **2011**, *353*, 1353-1358.
[4] Dénès, F.; Schiesser, C. H.; Renaud, P. *Chem. Soc. Rev.* **2013**, *42*, 7900.
[5] Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. J. *Eur. J. Org. Chem.* **2006**, 1547

Notes

Ring Contraction of nono-2,3-Diulose Derivatives Photochemically Promoted

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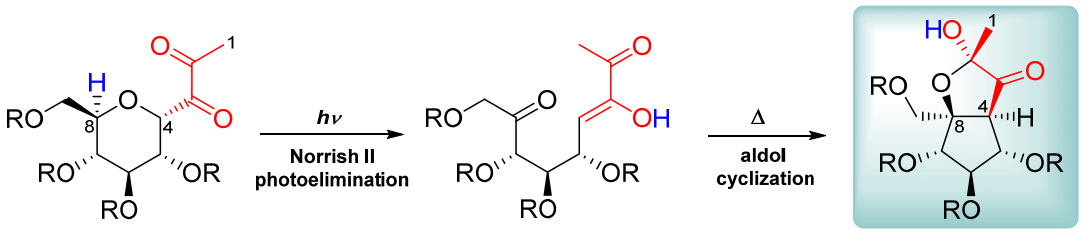
The ring contraction of pyranoside carbohydrate derivatives which require a single synthetic process represents a highly efficient biomimetic approach to the synthesis of cyclopentanols.[1]
The photochemical excitation of nono-2,3-diulose derivatives triggers a sequential Norrish type II photoelimination and aldol cyclization process that promotes a pyranosyl ring contraction and the formation of a new type of cyclopentitol derivatives with high diastereoselectivity.[2]



R = acyl, alkyl, silyl group

In contrast with other ring contraction methodologies[3] no transition-metal reagents are needed and this sequential rearrangement occurs simply by using visible light irradiation and moderate heating (0 to 60 °C).
Different aspects of the photoelimination mechanism, the stereochemical course of the aldol cyclization reaction and the scope of this rearrangement will be discussed in this lecture.

References

[1] a) Dalko, P. I.; Sinaÿ, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 773–777. b) Redlich, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1345–1347.
[2] a) Alvarez-Dorta, D.; León, E. I.; Kennedy, A. R.; Martín, A.; Pérez-Martín, I.; Riesco-Fagundo, C.; Suárez, E. *Chem. Eur. J.* **2014**, *20*, 2663–2671. b) Alvarez-Dorta, D.; León, E. I.; Kennedy, A. R.; Martín, A.; Pérez-Martín, I.; Riesco-Fagundo, C.; Suárez, E. *Chem. Eur. J.* **2013**, *19*, 10312–10333. c) Alvarez-Dorta, D.; León, E. I.; Kennedy, A. R.; Riesco-Fagundo, C.; Suárez, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 8917–8919.
[3] a) Aurrecoechea, J. M. ; Lopez, B.; Arrate, M. *J. Org. Chem.* **2000**, *65*, 6493–6501. b) Kan, T.; Nara, S.; Ozawa, T.; Shirahama, H.; Matsuda, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 355–357. c) Chiara, J. L.; Martínez, S.; Bernabé, M. *J. Org. Chem.* **1996**, *61*, 6488–6489. d) Chénedé, A.; Pothier, P.; Sollogoub, M.; Fairbanks, A. J.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1995**, 1373–1374. e) Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835–8836.

Notes

Metal-sulfur free radical reactivity

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Biomimetic chemistry can be successfully applied to the discovery of new free radical reaction pathways, either for understanding the biological transformations during cellular stress and for mimicking the selectivity and efficiency of the enzymatic processes. The cis-trans lipid isomerisation was discovered using liposomes as models of cell membrane and several sulfur-containing biomolecules as potential generators of thiyl radicals, the efficient isomerisation catalyst.[1]
Metallothioneins were used as proteins containing Zn- or Cd-sulfur bonds involved in the stress response of animals and plants.[2] Under irradiation conditions the formation of diffusible thiyl radicals occurred, as indicated by the reaction with the unsaturated double bonds and formation of trans phospholipid isomers. Proteoliposomes were proposed as a first screening model of the protein/peptide potential of "stress-absorber", either by reactivity the cystein-derived sulfur moieties and the "inorganic" sulfur connected by the metal bridges. Proteomic analysis afforded a punctual characterization of the reactions occurring on the protein primary structure.
Recently, we examined metal-sulfur reactivity using the complex formed by iron salts and 2-mercaptoethanol, incubated under aerobic and anaerobic conditions with unsaturated liposomes containing MUFA and PUFA residues. These biomimetic systems showed that thiyl radicals can be formed and catalyse lipid isomerisation. In the presence of polyunsaturated fatty acids in the vesicles both peroxidation and isomerisation can compete, depending on the reaction conditions. Interesting insights on this reactivity can be also useful for extrapolation to enzymatic catalysis and pharmacological effects.

References

[1] Chatgilialoglu, C.; Ferreri, C.; Melchiorre, M.; Sansone, A.; Torreggiani A. *Chem. Rev.* **2014**, *114*, 255.
[2] Torreggiani, A.; Domènech, J.; Orihuela, R; Ferreri, C.; Atrian, S.; Capdevila, M.; Chatgilialoglu, C. *Chem. Eur. J.*, **2009**, *15*, 6015.

Notes

Docosahexaenoic acid (DHA) activates glutathione and thioredoxin antioxidant systems in murine hippocampal HT22 cells: potential implications in neuroprotection

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Docosahexaenoic acid (DHA, 22:6n-3) is a major constituent of nerve cell membrane phospholipids. Besides a role in membrane architecture, DHA is a pleiotropic molecule involved in multiple facets of neuronal biology and also in neuroprotection. We show here that DHA supplementation to mouse hippocampal HT22 cells modulates the expression of genes encoding for antioxidant proteins associated with thioredoxin/peroxiredoxin and glutathione/glutaredoxin systems. Thus, within the thioredoxin system, DHA increased *Txn1-2, Trxrd1-2, Prdx3* and *Srxn1* gene expression and reduced that of *Prdx4*. Paralleling these changes, DHA increased thioredoxin reductase activity, the main enzyme involved in thioredoxin regeneration. For the glutathione system, the most important change triggered by DHA was the upregulation of *Gpx4* gene, encoding for the nuclear, cytosolic and mitochondrial isoforms of phospholipid-hydroperoxide glutathione peroxidase (PH-GPx/GPx4, the main enzyme protecting cell membranes against lipid peroxidation), which was followed by a significant increase in total glutathione peroxidase and GPx4 activities. Noticeably, DHA also upregulated a new *Gpx4* splicing variant that retained part of the first intronic region. DHA treatment was initially followed by a significant increase in cellular levels of thiobarbituric acid-reactive substances and oxidized glutathione, which are likely secondary to increased products of lipid peroxidation from DHA, and part of the signaling pathway modulating antioxidant systems gene expression. Finally, we demonstrate that DHA treatment, under the same time-course, protects HT22 cells from the oxytocic exposure to amyloid beta (Aβ25-35) peptide. Altogether, our data pinpoint to a central role of DHA as *Indirect Antioxidant* that modulates neuronal defenses in neuroprotection.

Supported by grants SAF2010-22114-C02-01/02 from Ministerio de Economía y Competitividad (Spain). VCS and CF hold fellowships from Gobierno de Canarias (Spain). We are grateful to CEI-Canarias, Campus Atlántico Tricontinental (Universidad de La Laguna) and to Biosearch Life-Puleva Biotech for continuous support to the project at the Laboratory of Membrane Physiology and Biophysics.

Notes

Were Radicals Participants in Darwin's 'Warm Pond'?

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Darwin imagined 'some warm little pond' in which a cocktail of chemicals would be exposed to 'light, heat, electricity' and generate a 'protein compound …. ready to undergo still more complex changes'. In the same vein Albert Eschenmoser asked 'What happens when excessive energy hammers on basic chemicals under conditions that may have existed on the primordial earth?' Most, if not all, discussions of life's origin focus on heterolytic chemistry even though today we recognize an increasing number of radical processes in biology. What can we perceive if we take today's biology and extrapolate back: can we identify prebiotic radical chemistry? This lecture speculates about the formation of some of the molecules of life for which radical chemistry is an intimate part of their known biology today. Can we model, in a 'warm pond', i.e. reaction flask, the formation of the polyamine spermidine, DNA nucleotides and porphobilinogen, the building block for porphyrins, chlorophylls and corrins? The biochemistry of polyamines and nucleic acids are intimately linked. Polyamines have a central role in eukaryotic cell growth and function and act as free radical scavengers that can protect DNA from radical damage by reactive oxygen species. If polyamines like spermidine are so important to DNA today, did they evolve at the same time? The proposed prebiotic routes to DNA bases and porphobilinogen starting from HCN, and which are experimentally supported, can be diverted towards polyamines, although such a process is presently hypothetical. The formation of porphobilinogen from two molecules of δ-aminolevulinic acid is problematical with a putative cyclisation of an imine precursor being stereoelectronically difficult.

Notes

Mechanistic investigations of LytB, an iron sulfur enzyme

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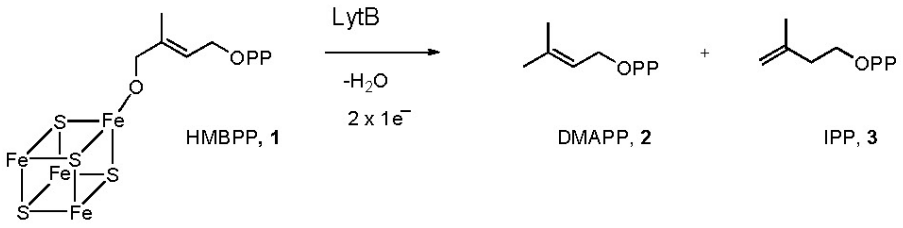
Disease-causing microbes have become rapidly resistant to antibiotic drug therapies and diseases that were thought to be eradicated, are re-emerging. Tuberculosis for example is reappearing even in the developed world causing more than 1.1 million deaths a year worldwide. The methylerythritol phosphate (MEP) pathway an alternative to the mevalonate pathway is used for the biosynthesis of essential terpenoids in most pathogenic bacteria (including *Mycobacterium tuberculosis*) and in plant plastids. Therefore the MEP pathway is a target for the development of new antimicrobial agents as it is essential for some microorganisms, and absent in humans. In the last step of this biosynthetic route, (*E*)-4-hydroxy-2-methylbut-2-enyl 1-diphosphate (HMBPP, **1)** is converted into a mixture of isopentenyl diphosphate (IPP, **3**) and dimethylallyl diphosphate (DMAPP, **2**), which are both precursors of isoprenoids (Scheme 1).



Scheme 1: The reaction catalyzed by LytB

This reaction is catalyzed by a peculiar [4Fe-4S] center of LytB,1 an oxygen sensitive enzyme. The structures of LytB containing the [4Fe-4S]-cluster bound to (*E*)-4-mercapto-3-methylbut-2-en-1-yl diphosphate or (*E*)-4-amino-3-methylbut-2-en-1-yl diphosphate, two analogues of HMBPP which act as potent inhibitors 2,3 of the enzyme, were solved. These structures and our first results of site-directed mutagenesis of LytB will be presented.

References

[1] Seemann, M., Janthawornpong, K.; Schweizer,J.; Böttger, L.H.; Janoschka, A.; Ahrens-Botzong, A.; Ngouamegne Tambou, E.; Rotthaus, O.; Trautwein, A.X.; Rohmer, M.; Schünemann, V. *J. Am. Chem. Soc.* **2009**, *131*, 13184
[2] Ahrens-Botzong, A.; Janthawornpong, K.: Wolny, J. A.; Ngouamegne Tambou, E.; Rohmer, M.;Krasutsky, S.; Poulter, C.D.; Schünemann, V.; Seemann, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11976.
[3] Janthawornpong, K.; Krasutsky, S., Chaignon, P.; Rohmer, M.; Poulter, C.D.; Seemann, M. *J. Am. Chem. Soc.* **2013**, *135*, 1816.

Notes

Radical Fluoroalkylation of Organic Substrates in Aqueous Media

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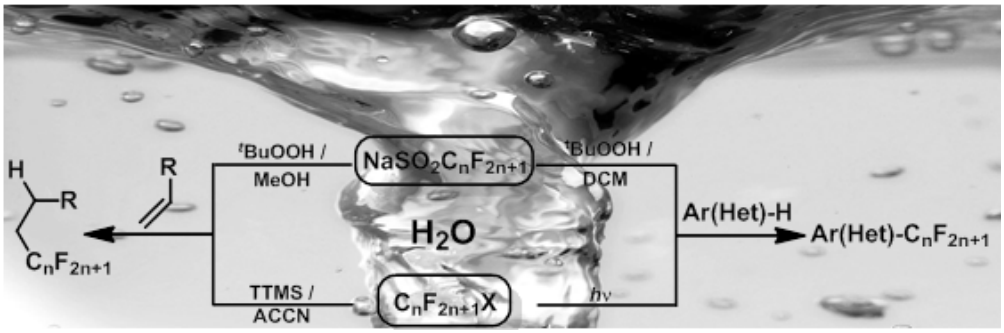
Recently, the introduction of trifluoromethyl and perfluoroalkyl groups into organic substrates has been reinvigorated, as evidenced by the large volume of papers published in the last five years.[1,2]
In this presentation, different radical-based strategies for the fluoroalkylation of both aliphatic and aromatic substrates in aqueous media obtained in our research group shall be discussed. These methodologies do not employ metals or organocatalysts, and make use of diverse fluoroalkyl radical sources/precursors, generated either through thermal or photochemical methods.[3]



References

[1] Studer, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 2.
[2] Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2014**, DOI: 10.1021/cr500223h.
[3] Barata-Vallejo, S.; Martin Flesia, M.; Lantaño, B.; Argüello, J.; Peñeñory, A.; Postigo, A. *Eur. J. Org. Chem.* **2013**, *2013*, 998.

Notes

Oxidative N-Heterocyclic Carbene (NHC) Catalysis

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In the presentation applications of TEMPO[1] and diquinones as environmentally benign oxidants in combination with NHC catalysis will be discussed. We will first focus on the use of these organic SET reagents as mild oxidants in biomimetic aldehyde oxidations.[2] Oxidative esterifications and amidations will be discussed.[3] Reactions occur via acylazolium ions which show unusual chemoselectivities in the reaction with amines and alcohols.[4] α,β-Unsaturated acylazolium ions can also be used as formal Michael acceptors.[5] Finally, an application of this chemistry for the formation of β-lactones will be presented.[6]

References
[1] Tebben, L.; Studer, A. *Angew. Chem. Int. Ed.* **2011***, 50,* 5034.
[2] Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8727.
[3] De Sarkar, S.; Studer, A. *Org. Lett.* **2010**, *12*, 1992; Zhao, J.; Mück-Lichtenfeld, C.; Studer, A. *Adv. Synth. Catal.* **2013**, *355*, 1098; Samanta, R. C.; Studer, A. *Org. Chem. Front.* **2014**, *in press*.
[4] De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190; Samanta, R. C.; De Sarkar, S.; Fröhlich, R.; Grimme, S.; Studer, A, *Chem. Sci.* **2013**, *4*, 2177.
[5] De Sarkar, S.; Studer, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 9266; Biswas, A.; De Sarkar, S.; Fröhlich, R.; Studer, A. *Org. Lett.* **2011**, *13*, 4966. Biswas, A.; De Sarkar, S.; Tebben, L.; Studer, A. *Chem. Commun.* **2012**, *48*, 5190; Samanta, R. C.; Maji, B.; De Sarkar, S.; Bergander, K.; Fröhlich, R.; Mück-Lichtenfeld, C.; Mayr, H.; Studer, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 5234; De Sarkar, S.; Biswas, A.; Samanta, R. C.; Studer, A. *Chem. Eur. J.* **2013**, *19*, 4664.
[6] Bera, S.; Samanta, R. C.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2014**, *53*, *early view*.

Notes

N–Halo Sulfonamides, Sulfamates and Sulfamides as Nitrogen-Centered Radicals Precursors and its Applications in the Selective Functionalizations of Unactivated Methyl Groups and Oxidations

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Among all the functionalizations of unactivated C(sp^3)–H bonds described in the literature to date, the functionalization of methyl groups in conformational non-restricted molecules remains challenging.[1]

In this communication, we focused on the reactivity of these methyl groups, to convert a C–H bond in a C–N or C–X (X = Halogen) bond with high chemoselectivity.[2] These functionalizations are achieved in an intramolecular way, with Nitrogen-centered radicals generated from different precursors using the redox systems [$I^0 \leftrightarrow I^+ \leftrightarrow I^{3+}$] and [$Br^0 \leftrightarrow Br^+$]. The key for the chemoselectivity between mono- and polyoxidation of the methyl moiety, via Single Hydrogen Atom Transference (SHAT) or Multiple Hydrogen Atom Transferences (MHAT), respectively, is also discussed.[3] In addition, the use of sulfamates and sulfamides as *N*–radical precursors also allows the oxidation to synthetically versatile aldi- or ketimines.

References

[1] For selected reviews on C(sp^3)–H functionalization in organic synthesis, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (c) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991.

[2] For selected reviews on catalytic C–H amination reactions, see: (a) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Soc. Rev.* **2009**, *38*, 5061–5074. (b) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083.

[3] Herrera, A. J.; Melián, D.; Marticorena, R.; Copano, M. B.; Paz, N. R.; Valdés, H.; Rodríguez-Sosa, D.; González, C. C. *J. Am. Chem. Soc.* submitted for publication.

Notes

Intramolecular 1,5-Hydrogen Atom Transfer Reactions under reductive conditions in Monosaccharide Systems

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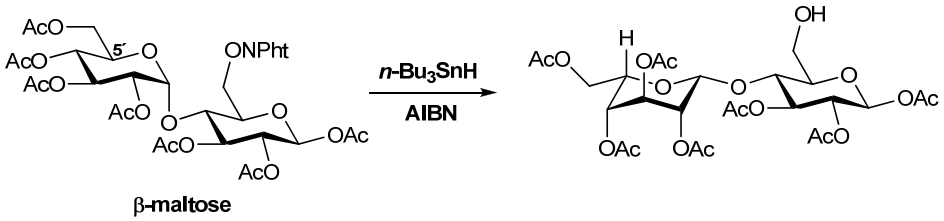
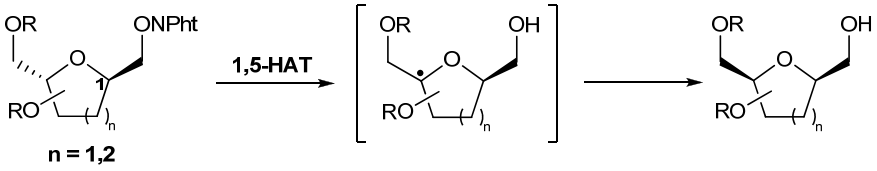
L-Sugars play important roles because they are constituents of antibiotics[1] and clinically functional nucleosides.[2] However, besides their usefulness, L-sugars are rare in nature and in consequence, expensive. Thus, it becomes necessary to develop efficient methods for their synthesis and some synthetic routes have been reported a few years ago.[3]
Recently in our group, the intramolecular 1,8-hydrogen atom transfer (1,8-HAT) reaction under reductive conditions has been studied in disaccharide derivatives observing that in well-disposed substrates, an inversion at C-5' takes place with excellent diastereoselectivity, as it ocurrs in β-maltose.[4]



β-maltose

Considering these previous results, herein, the 1,5-HAT reaction under reductive conditions in monosaccharide systems is described, studying the stereoselective reduction of the C-4 and C-5 radical intermediates in furanoses and pyranoses, respectively. As observed in previous work, the reaction strongly depends on steric and stereoelectronic effects of the substituents in the carbohydrate ring. A proper choice of the configuration and the electronic nature of these substituents could be very efficient in our task to generate inversion of the configuration at C-4 or C-5.



n = 1,2

References
[1] Wang, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4389−4393.
[2] Chen, X.; Zhou, W.; Scinazi, R. F.; Chu, C. K. *J. Org. Chem.* **2004**, *69*, 6034−6041.
[3] a) Boulineau, F. P.; Wei, A. *J. Org. Chem.* **2004**, *69*, 3391−3399; b) Ermolenko, L.; Sasak, N. A. *J. Org. Chem.* **2006**, *71*, 693−703.
[4] Martin, A.; Pérez-Martín, I.; Quintanal, L. M; Suárez, E. *J. Org. Chem.* **2008**, *73*, 7710−7720.

Notes

Free Radicals in Photosensitization by Drugs

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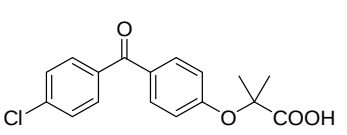
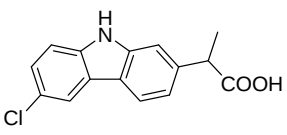
A number of drugs can elicit photosensitivity disorders, which are undesired skin reactions resulting from sunlight exposure of treated patients. These side effects are becoming increasingly important, due to the modern lifestyle with frequent outdoor activities. Among drug-induced photosensitivity disorders, phototoxicity, photoallergy and photocarcinogenicity are well characterized. Phototoxicity is more general and can appear in any patient, provided that the drug and light doses are sufficient. By contrast, photoallergy is idiosyncratic and involves the immunological system. As regards drug-mediated photocarcinogenicity, only a few cases have been demonstrated *in vivo*, although photosensitized damage to DNA (photogenotoxicity) is well established.

The initial event in photosensitization by drugs is light absorption by the key chromophore, to produce an excited state. Most frequently, only the triplet manifold is relevant; however, the role of excited singlets is not negligible and cannot be ruled out. Subsequently, reactive species are formed, which are the immediate mediators of biological damage. These chemical entities include the well-known reactive oxygen species (ROS), for instance single oxygen, but also carbon-centered free radicals. The present contribution is focused on the latter.

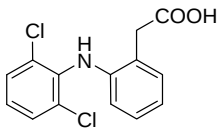
Thus, three examples are presented here to illustrate how photogeneration of free radicals can result in chemical modifications of biomolecules, which can ultimately lead to photobiological effects. The first one is fenofibric acid (**FA**), the active metabolite of the antilipidemic agent fenofibrate. It contains a benzophenone chromophore, whose triplet excited state can abstract hydrogen atoms from suitable donors. This is in the origin of photodynamic lipid peroxidation, demonstrated by the formation of dienic hydroperoxides from linoleic acid by means of a radical chain mechanism.[1] The second example is carprofen (**CP**), a nonsteroidal anti-inflammatory drug (NSAID) containing a chlorocarbazole moiety. Its photodehalogenation occurs from the triplet excited state, through self-quenching, leading to highly reactive aryl radicals. These species are involved in covalent photobinding to proteins, to give a photoantigen that is in the origin of the observed photoallergic reactions.[2] The last case study deals with diclofenac (**DC**), another NSAID with a dichloro diphenylamine structure whose photolysis also leads to reactive aryl radicals.[3] During the phase I metabolism, diclofenac is hydroxylated in either of the two rings, a chemical change that is accompanied by an increased light absorption in the UVB- and UVA-regions. Interestingly, depending on the site of hydroxylation, the capability to produce DNA damage (as revealed by the single strand break electrophoresis assay) is enhanced or reduced.



FA



CP



DC

Overall, the above results show that formation of carbon-centered radicals upon photolysis of certain drugs may lead to chemical modification of biomolecules and hence to unwanted photobiological side effects.

References

[1] Boscá, F.; Miranda, M.A. *J. Photochem. Photobiol.* **1998**, *43*, 1.
[2] Lhiaubet-Vallet, V.; Hurtado, Z., Boscá, F., Miranda, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 9538.
[3] Encinas, S.; Boscá, F.; Miranda, M. A. *Chem. Res. Toxicol.* **1998**, *11*, 946.

Notes

Radical Mediated Modifications of Natural Products

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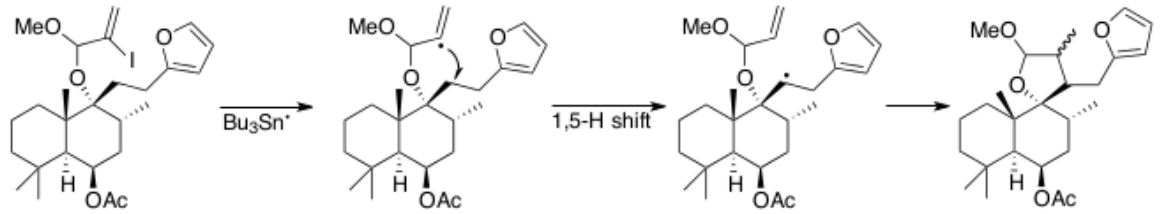
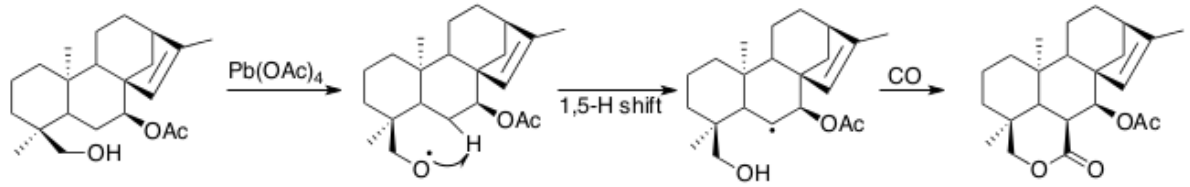
One of the main challenges that synthetic chemists have to face is to achieve selective chemical modifications of complex natural structures, in which several functional groups of similar reactivity are often present. Several diterpenes, isolated from medicinal plants, have been chosen to be modified using radical chemistry. A new technique of isolation of these diterpenes using soxhlet like extration with subcritical CO_2, has shown to be very selective and therefore allowing isolation of hundreds milligrams of pure compounds[1]. In our project, the radical modifications of the selected substances will be based on the activation of unreactive C-H bonds via hydrogen abstraction (template assisted, oxygen mediated and intermolecular version). As Renaud has shown after iodine abstraction or thiyl radical addition, translocation of the vinyl radical occurs to furnish an alkyl radical, which can further react to afford the cyclized compounds.[2]



Interestingly, natural products like siderol could be directly reacted following Ryu's protocol. In this case, the formation of the oxygen-centered radical will be promoted by lead tetraacetate. Working under an atmosphere of carbon monoxide, and after 1,5-radical translocation, a new lactone ring will be formed



References
[1] Mele, A.; Feizlmayr, E.; Abazi, S.; Bauer, R. Planta Med. **2010**, *76*, 300.
[2]Renaud, P.; Beaufils, F.; Feray, L.; Schenk, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 4230.

Notes

Creating Diversity by Site-Selective peptide Modification: towards new bioactive peptides

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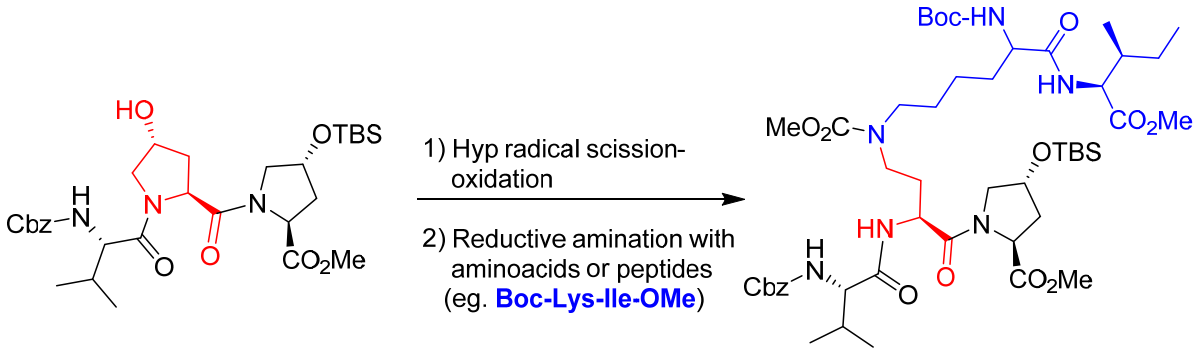
Peptide modification is an area eliciting much interest both in medicinal chemistry (discovery of new peptide or peptidomimetic drugs) and in synthetic chemistry (new catalytic peptides and foldamers, etc).[1] In the conventional approach to prepare peptides, each compound is synthesized *de novo*, representing a considerable investment in time and materials. An alternative strategy is site-selective peptide modification, where a single unit is manipulated while the others remain unchanged. In this way, a library of modified peptides can be created from from a single (or a few) peptide precursors. However, this strategy poses an important challenge due to the similar reactivity of the residues, particularly if several convertible units are present.[2] Recently, we introduced natural, commercial hydroxyproline as a customizable unit, which can be introduced in peptides and then readily converted into a variety of amino acids while retaining its optical purity.[3] Orthogonal protection of its lateral chain allows differentiation of the Hyp units. The progress in this work will be commented, including the formation of small branched peptides, with a view to developing new antimicrobial peptides.



References

[1] a) Takaoka, Y.; Ojida, A.; Hamachi, I. *Angew. Chem. Int. Ed.***2013**, *52*, 4088; b) Chalker, J. M.; Bernardes, G. J. L.; Davis, B. G. *Acc. Chem. Res*. **2011**, *44*, 730; c) Waldmann, H.; Janning, P. *Chemical Biology*, Wiley-VCH, Weinheim, 2004; d) Johannesen, S. A.; Karaffa, J.; Lindsay, K. B.; Taaning, R.; Skrydstrup, T. *Org. Biomol. Chem.***2006**, *4*, 3553; e) Antos, J. M.; Francis, M. B. *Curr.Opin.Chem. Biol.* 2006, *10*, 253; f) Qi, D.; Tann, C. M.; Distefano, M. D. *Chem. Rev.* 2001, *101*, 3081.

[2] Saavedra, C. J.; Boto, A.; Hernández, R. *Org. Lett.*, **2012**, *14,* 3788 and references cited therein.

[3] Romero-Estudillo, I.; Boto, A. *Org. Lett.***2013**, *15*, 5778.

Notes

NCI-60 chemotherapeutic action of copper metallointercalators bear apoptotic hallmarks of hydroxyl radical induced death

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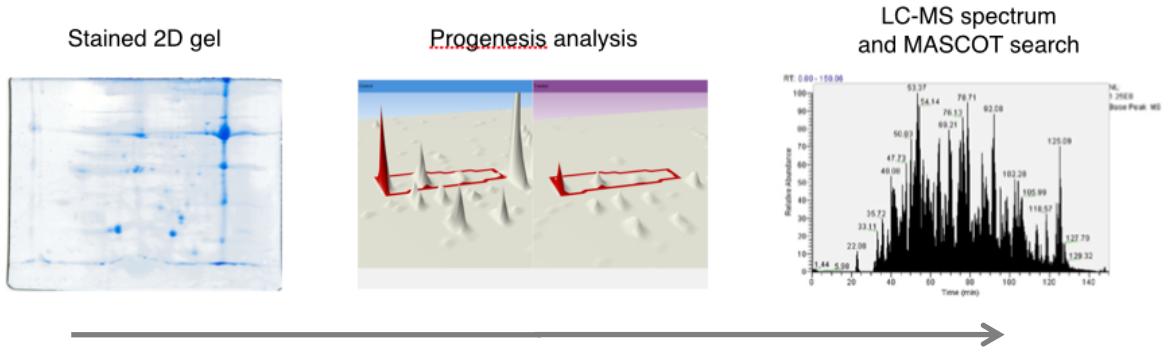
The advent of coordinating phenanthrene-based intercalators to transition metal cations has unveiled a new frontier for DNA-targeted metallodrug development. Here we describe the National Cancer Institute (NCI) 60 Human Tumor Cell Line Screen results for mono-nuclear and di-nuclear copper(II) metallointercalators[1-4] under development at our laboratory. Mechanistic evidence generated via the COMPARE algorithm, flow cytometry, immunohistochemistry, and confocal microscopy points toward a unique cytotoxic profile bearing the apoptotic hallmarks of hydroxyl radical induced cell death. We also describe the development of second-generation metallointercalators[4] bearing phenazine ligands and the application of *Galleria mellonella* larvae as models for *in vivo* proteomic drug tolerance screening.



References
[1] A. Prisecaru; A. Kellett *et al.*, *Chem. Comm.* **2012**, *48*, 6906.
[2] A. Prisecaru; A. Kellett *et al.*, *J. Med. Chem.* **2013**, *56*, 8599.
[3] A. Kellett; M. Devereux *et al.*, *Med. Chem. Comm.*, **2011**, *2*, 579.
[4] Z. Molphy; A. Kellett *et al.*, *Inorg. Chem.*, **2014**, *53*, 5391.

Notes

Reactions of the cumyloxyl radical with alkanamides. The influence of structural and medium effects on the hydrogen atom transfer selectivity.

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The amide functional group is recurrent in chemistry as it occurs in natural products, biomolecules, pharmaceuticals and agrochemicals. In particular simple amides are widely used as solvents for a variety of purposes and are often taken as models for peptide bonds in proteins and polypeptides.

In the last years our research interest has been focused on the study of the role of structural and medium effects on hydrogen atom transfer (HAT) reactions from hydrogen atom donor substrates to alkoxyl radicals[1]. Among the substrates investigated, attention has been devoted to the reactions of a representative alkoxyl radical such as cumyloxyl ($PhC(CH_3)_2O^{\bullet}$, $CumO^{\bullet}$) with a variety of alkanamides, taking in particular into account the HAT selectivity[2,3] in view of the wide number of recently described synthetically useful C–H functionalization procedures based on HAT reactions from amides to alkoxyl radicals[4].

Following these lines, the HAT reactivity and selectivity obtained through detailed time-resolved kinetic studies on the reactions of the cumyloxyl radical with *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA) and with a variety of tertiary and secondary amides will be discussed.

References

[1] Salamone, M.; Bietti, M. *Synlett.* **2014**, *25*, 1803.
[2] Salamone, M.; Milan, M.; DiLabio, G. A.; Bietti, M. *J. Org. Chem.* **2013**, *78*, 5909.
[3] Salamone, M.; Milan, M.; DiLabio, G. A.; Bietti, M. *J. Org. Chem.* **2014**, *79*, 7179.
[4] Feng, J.-B.; Wei, D.; Gong, J.-L.; Qi, X.; Wu, X.-F. *Tetrahedron Lett.* **2014**, *55*, 5082. Wang, R.; Liu, H.; Yue, L.; Zhang, X.-K.; Tan, Q.-Y.; Pan, R.-L. *Tetrahedron Lett.* **2014**, *55*, 2233. Sathish Kumar, G.; Arun Kumar, R.; Santhosh Kumar, P.; Veera Reddy, N.; Vijaya Kumar, K.; Lakshmi Kantam, M.; Prabhakar, S.; Rajender Reddy, K. *Chem. Commun.* **2013**, *49*, 6686. Li, D.; Liu, J.; Zhao, Q.; Wang, L. *Chem. Commun.* **2013**, *49*, 3640. Ding, S.; Jiao, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 9226. Yan, Y.; Zhang, Y.; Feng, C.; Zha, Z.; Wang, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 8077.

Notes

Iodine and Bromine Redox Systems Induce the Formation of Nitrogen Centered Radicals. Searching for a possible Role of Iodine, Bromine and Sulfamates in Biological Radical Processes.

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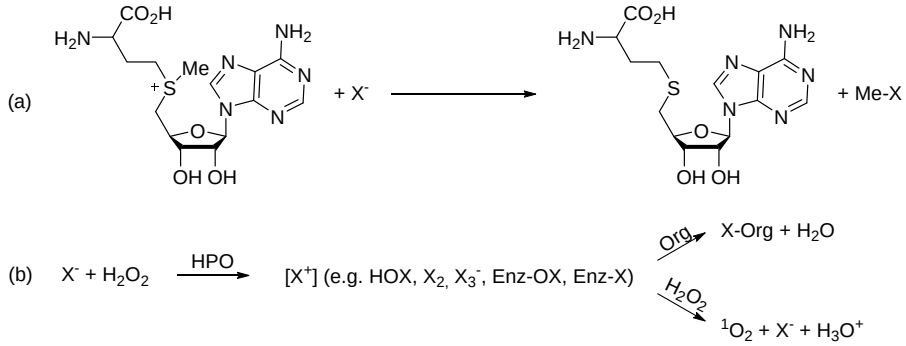
In the last years, we have been focused in the development of new synthetic strategies to perform the selective functionalization of unactivated aliphatic C(sp^3)–H bond mainly employing nitrogen centered radicals as activating specie.[1] For this purpose, various *N*-halo sulfamates have been used as *N*-radicals precursors and therewith, promote selective transformations of C–H bonds into new C–Halogen, C–N, and C–O bonds. Within the mechanistic studies involved in such processes, we have faced a very complex reactive medium characterized by the interaction of halogenated species in different oxidation states with sulfamates. This complex medium is extremely reactive but however, remarkably selective and moldable due to its high sensitivity to modifications in the reaction conditions.

Iodine and bromine are trace elements that exist in natural water, earth, atmosphere and most of living organisms, being biologically essential nutrients for all mammals including humans, and, indeed, most organisms seem to have the ability to produce halogenated organic compounds.[2] In general, it is accepted that halogenated alkanes are formed either by mediated nucleophilic attack of corresponding halides (Br^- or I^-) (equation a), or by reactions of I^+ and Br^+ species (e.g. HOX, X_2, X_3^+, etc.), generated by haloperoxidases (HPO), with electron-rich substrates (equation b); however no radical processes induced by X^+ species appear in the literature.[3] Herein, we will discuss about the possibility to perform apparently direct transformations of alkyl C–H bonds into C–N or C–O bonds via a transient C–X bond formation (X = Br or I) using an initial radical pathway followed by an oxidative dehalogenation step. Is it not a possible metabolic pathway to perform selective oxidation in biological systems?, Is it possible to export our mechanistic findings (in vitro) into possible biological radical processes?... These and other questions will be posed to the audience.



References

[1] Herrera, A. J.; Melián, D.; Marticorena, R.; Copano, M. B.; Paz, N. R.; Valdés, H.; Rodríguez-Sosa, D.; González, C. C. submitted for publication.

[2] La Barre, Stéphane; Potin, P.; Leblanc, C.; Delage, L. *Mar. Drugs* **2010**, *8*, 988.

[3] Wagner, C.; El Omari, M.; König, G. M. *J. Nat. Prod.* **2009**, *72*, 540.

Notes

Functional ribonucleotide reductase enzyme models

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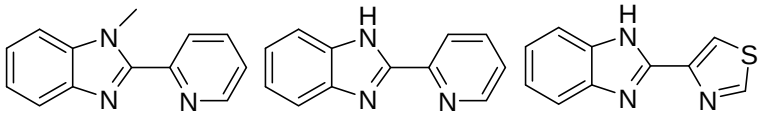
Investigation of enzymatic processes via their model compounds gives a new opportunity for science. The aim of using functional and structural models is to have a better understanding on biochemical mechanisms. This area is called bioinorganic chemistry and it has a strong impact on the developments in medical sciences.

Dioxygen activation by non-hem diiron enzymes occurs in a number of metabolically important transformations including the conversion of ribonucleotides to deoxyribonucleotides by ribonucleotide reductase (RNR)[1], the formation of unsaturated fatty acids by fatty acid desaturases, the biosynthesis of antibiotics (CmlA, CmlI). In general, O_2 activation is thought to be initiated by the binding of O_2 to the diiron(II) center to form a peroxidodiiron(III) intermediate that in turn converts to the oxidizing species. Peroxidodiiron(III) intermediates with visible features between 600-750 nm have been identified for RNR R2[2].

The complexes have been isolated from the reaction of different non-symmetric bidentate N-donor ligands and Fe^{II} salts in acetonitrile, and have been characterized by X-ray crystallography and several spectroscopic techniques[3] (Scheme 1). They are suitable catalyst for oxidation of 2,6-di-tert-butylphenol and 2,4-di-tert-butylphenol with H_2O_2 as the oxidant, where the *in situ* formed peroxidodiiron(III) intermediates were isolated as key species, as found for RNR R2. The peroxidodiiron(III) intermediate undergoes O-O bond scission to generate a high-valent oxidant capable of X-H bond cleavage.



(L^1) (L^2) (L^3)

1 $[Fe^{II}(L^1)_3](CF_3SO_3)_2\ 3H_2O$
2 $[Fe^{II}(L^2)_3](CF_3SO_3)_2\ 2H_2O$
3 $[Fe^{II}(L^3)_3](CF_3SO_3)_2\ 2H_2O$

Scheme. 1

References

[1] P. Nordlund, P. Reichard, Annu. *Rev. Biochem.,* **2006,** *75*, 681-706.
[2] J. S. Pap, M. A. CransWick, É. Balogh-Hergovich, G. Baráth, M. Giorgi, G. T. Rohde, J. Kaizer, G. Speier, L. Que Jr., *Eur. J. Inorg. Chem.*, **2013,** *22-23*, 3858-3866
[3] J. S. Pap, A. Draksharapu, M. Giorgi, -W. R. Browne, J. Kaizer, G. Speier, *Chem. Commun.,* **2014,** *50*, 326-1329.

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Notes

New Radical Avenues to Antiviral Carbo- and Heterocyclic Compounds

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Methodologies, which couple polar with radical reaction steps - either sequential or in tandem, are a straightforward tool to approach complex target molecules in an economic manner from very cheap commodity precursors.

We report here oxidative reactions, which enable the synthesis of complex carbo- and heterocyclic compounds via very short approaches. Potential approaches to the total synthesis of natural products and analogs are outlined and antiviral activities are reported.

References

[1] P. R. Jagtap, L. Ford, E. Deister, R. Pohl, I. Císařová, J. Hodek, J. Weber, Richard Mackman, G. Bahador, U. Jahn *Chem. Eur. J.* **2014**, *20*, 10298-10306.

[2] F. Kafka, M. Holan, D. Hidasová, R. Pohl, I. Císařová, B. Klepetářová, U. Jahn, *Angew. Chem. Int. Ed*. **2014**, *53*, DOI: 10.1002/anie.201403776.

Notes

Oxygenation and oxidation of PPh_3 and phenols by $^3O_2$ catalyzed by a 1,3,2-oxazaphosphole as organic cofactor mimic

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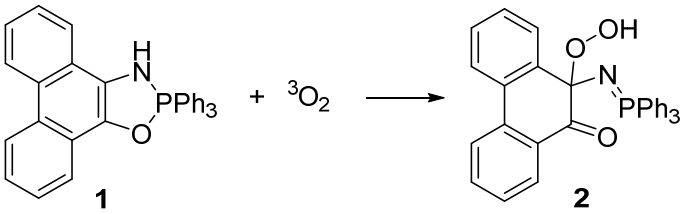
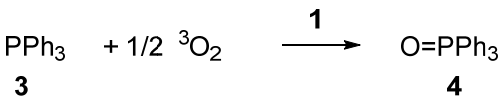
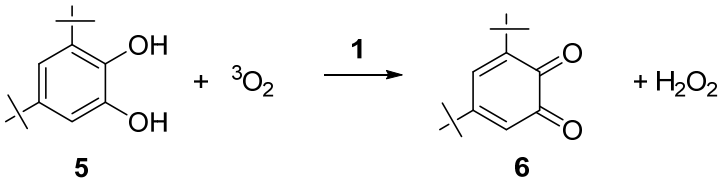
1,3,2-Oxazaphosphole (**1**) picks up triplet dioxygen in a 1:1 ratio at ambient condition and hydroperoxide (**2**) is formed.[1] It catalyzes the oxygenation of triphenylphosphine (**3**) to triphenylphosphine oxide (**4**) and the oxidation of 3,5-di-*tert*-butylcatechol (**5**) to the corresponding *o*-quinone (**6**), and 2-aminophenol (**7**) to 2-aminophenoxazine-3-one (**8**). In the oxidation reactions hydrogen peroxide and water are formed.



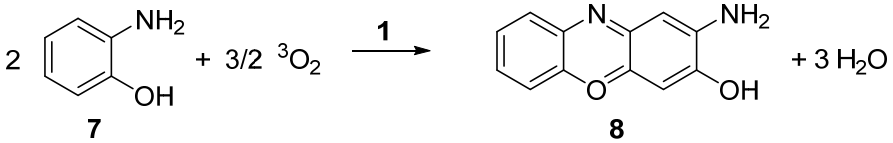
1 **2** (1)



3 **4** (2)



5 **6** (3)



7 **8** (4)

Kinetic and labeling studies have shown that all three reactions obey an overall third order rate equation. On the basis of kinetic measurements and spectroscopic studies a general radical mechanism is proposed.

References

[1] Bors, I.; Kaizer, J.; Speier, G. *RSC Adv*. **2014**, *4*, 16928.

Notes

Development of a General Synthetic Methodology for Isotopically Enriching Pyrimidine Nucleosides and their Oxidation Products

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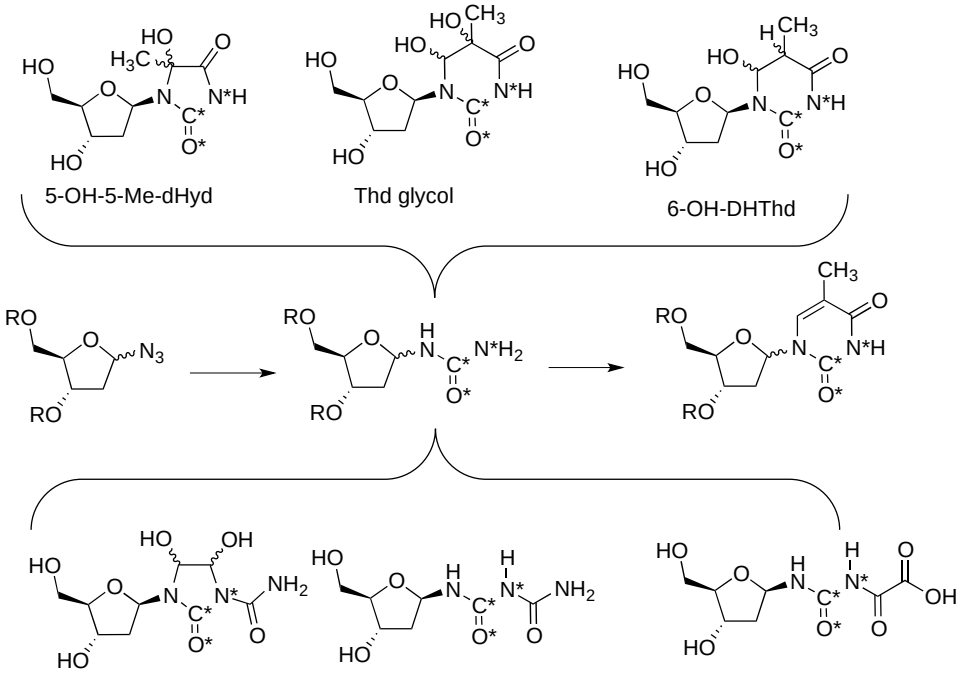
The isotope dilution technique, coupled with liquid chromatography – tandem mass spectrometry has been used extensively in the quantification of DNA damage *in vitro* and *in vivo*.[1] It provides precise quantitative data regarding the generation of certain DNA lesions when cellular DNA is exposed to a number of endogenous or exogenous oxidants. In order for the methodology to be applied, access to isotopically enriched natural nucleosides and oxidized DNA lesions is required. The cost of the enriched nucleosides is formidable and many DNA lesions are not yet accessible.
The purpose of this work is the development of a general synthetic methodology that provides, through a common intermediate, easy and low cost access to isotopically enriched pyrimidine nucleosides as well as a number of known lesions. The common intermediate corresponds to a urea nucleoside (Scheme), itself a known DNA lesion, readily prepared from a precursor azide and easily enriched with the use of low cost, stable isotopes of ammonia and carbon dioxide. We have been interested, in particular, in well-known oxidation products of thymidine[2] and cytidine[3] and the results of our recent synthetic efforts will be reported.



References

[1] Dedon, P. C. & coworkers *Nature Prot.* **2008**, *3*, 1287.
[2] Wagner, J. R.; van Lier, J. E.; Berger, M.; Cadet, J. *J. Am. Chem. Soc.* **1994**, *116*, 2235.
[3] Wagner, J. R.; Decarroz, C.; Berger M. and Cadet, J. *J. Am. Chem. Soc.*, **1999**, *121*, 4101.

Notes

Cyclopurine modification as radiation-induced lesions in DNA

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Radiation-induced modification of biomolecules is a multidisciplinary subject of research, aiming at addressing the mechanisms, products and biological significance involved in these structural transformations. In this context DNA has attracted a lot of attention for discovering the mutagenic consequences of the produced lesions and for the different capability of repair response by the enzymatic protective systems.

Chemical biology studies carried out by our group were addressed to the role of cyclopurine lesions, produced by the attack of $HO^{\bullet}$ radicals to the C5′ position of the sugar moiety of purine nucleotide units (adenine and guanine), thus creating a new covalent bond between C5′and the C8 position of the base moiety [1]. The mechanism of C5′formationunder radiation conditions, intramolecular cyclization and formation of the diastereoisomeric forms (5′*R* and 5′*S*) of 5′,8-cyclo-2′-deoxyguanosine and 5′,8-cyclo-2′-deoxyadenosine have been fully understood.

The study has been also conducted in oligonucleotide sequences mimicking the radiation effect in DNA, arranged in differentmacromolecular structures (double strands and G-quadruplexes), useful also for biochemical/biophysical studies related to specific diseases and impairment of enzymatic repair [2,3].

The scenario of DNA reactivity emerging from this work indicated the relevance of cyclopurine lesions as direct and unequivocal marker of free radical damage, with promising application to biological assays of DNA damage.

References

[1] Chatgilialoglu C, Ferreri C, Terzidis MA, *Chem. Soc. Rev*. **2011**, *40*, 1368–1382.
[2] Belmadoui N, Boussicault F, Guerra M, Ravanat JL, Chatgilialoglu C, Cadet J, *Org. Biomol. Chem*. **2010**, *8*, 3211–3219.
[3] Kropachev, K.; Ding, S.; Terzidis, M. A.; Masi, A.; Liu, Z.; Cai, Y.; Kolbanovskiy, M.; Chatgilialoglu, C.; Broyde, S.; Geancitov, N. E.; Shafirovich, V. *Nucl. Acids Res.* **2014**, *42*, 5020–5032.

Notes

QueE – Influencing the Mechanistic Outcome of Radical Reactions in the Biosynthesis of Queosine

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Radical reactions are notoriously difficult to control because of the high reactivity of free radical species. Nature is able to harness the transformative power of free radicals through strict control in enzyme active sites. Identifying how this is achieved can aid the design of new catalysts, and identify the scope for protein engineering in these enzymes to generate novel products through the remarkable chemistry that they catalyse.

The class of radical S-adenosylmethionine (rSAM) mediated reactions in enzymes has attracted much interest because of the diversity of substrates/products and broad range of key biological processes that these enzymes are involved in. In particular, the enzyme 7-carboxy-7-deazaguanine (CDG) synthase (QueE) catalysis the rearrangement of 6-carboxy-5,6,7,8-tetrahydropterin (CPH4) into CDG as a key step in queosine biosynthesis. This intermediate is a precursor to a number of interesting *Streptomyces* antibiotics, and molecules with anti-viral and anti-cancer properties.[1]

Mechanistically, the activity of QueE has been shown to have a clear dependence on the presence of Mg^{2+},[2] confirmed by recent X-ray crystallography to be substrate bound.[3] Our recent results regarding role of Mg^{2+} in directing the radical rearrangement will be discussed.

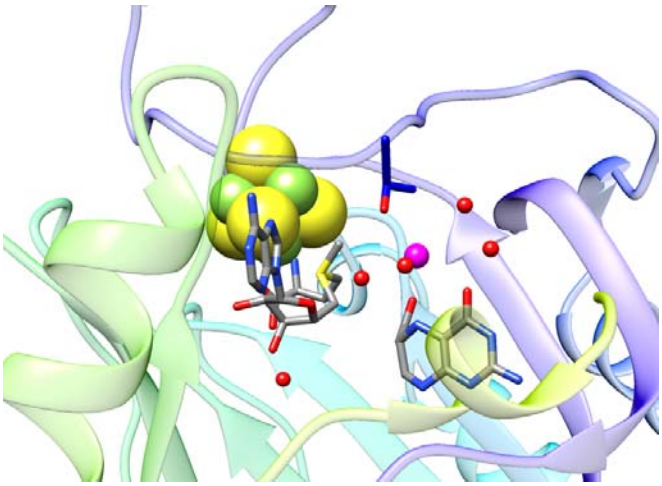

Figure 1. The active site of the rSAM enzyme QueE, as determined by X-ray crystallography,[3] depicting both the Mg^{2+} (in pink) and substrate binding.

References

[1] McCarty, R. M.; Bandarian, V. *Bioorganic Chemistry* **2012**, *43*, 15.
[2] McCarty, R. M.; Krebs, C.; Bandarian, V. *Biochemistry* **2013**, *52*, 188.
[3] Dowling, D. P.; Bruender, N. A.; Young, A. P.; McCarty, R. M.; Bandarian, V.; Drennan, C. L. *Nat. Chem. Biol.* **2014**, *10*, 106.

Notes

Computational and experimental investigations of bond activation in structures similar to ferric-peroxide species known in hemoproteins and hemoenzymes

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Investigated here using DFT is the interaction of H_2S with Fe(V)O structures known in hemoproteins and the interaction of peroxide-like H_2OS systems with ferric heme. The data are relevant for sulfheme formation in globins and for the catalytic cycle of sulfite reductases. Heme FeOS systems (and protonated versions) feature relatively accessible potential energy surfaces for OS bond formation and cleavage, and for insertion of the S at the meso position of the heme; O-S bond cleavage is favorable thermodynamically only in the diprotonated versions of the FeOS unit – Fe(V)O+H2S version or the ferric-HOSH isomer. The meso-insertion reaction is reminiscent of heme oxygenase meso-hydroxylation via a ferric-hydroperoxo intermediate. In addition to these, bond activation in FeSO and FeOI/FeIO systems in presented and commented. Separately, also reported are stopped-flow UV-vis data allowing the direct and first time spectroscopic detection of a ferryl species during the reaction of met myoglobin with chlorite, inferring a pathway involving prior formation of a Fe-O-O-Cl-O2 adduct analogous to that detected in the isoelectronic reaction of nitrite with oxy myoglobin. The reaction of ferric myoglobin with hypochlorite additionally allows for a Compound X – like (ferric-hypochlorite) adduct to be detected. Lower amounts of ferryl also appear to accumulate early in the reaction of oxy myoglobin with chlorite or hypochlorite; for the latter, a short-lived species identifiable as Fe-O-O-Cl-O is detected in the reaction with hemoglobin.

Notes

Light Mediated Organic Reactions: Asymmetric Synthesis and Polymer Degradation

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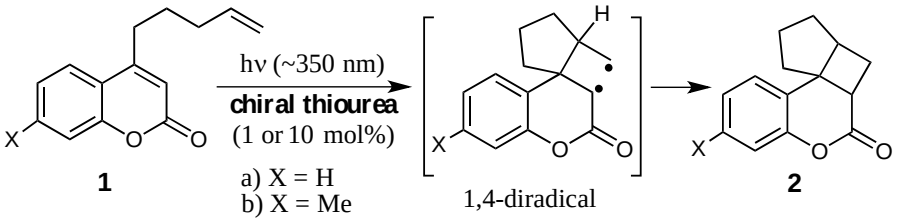
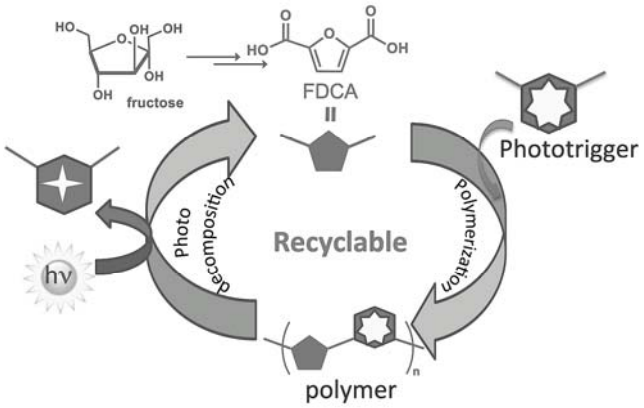
We have recently evaluated novel chiral thiourea mediated catalysis of [2+2] photocycloaddition of coumarins. These reactions proceed with very high selectivity under low catalyst loading. A new mechanism of 'energy sharing' has been introduced to explain the results of the catalyzed cycloaddition.[1,2] Results from these studies will be presented.



We have also developed a novel strategy to degrade polymers using light. In this process, a phototrigger is incorporated into a polymer. Degradation of the polymer to the monomers can be carried out using a light mediated process.[3] Results from this novel programmed degradation study will also be presented.



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References

[1] Vallavoju, N.; Sermadurai, S.; Jocksuch, S.; Sibi, M. P.; Jayaraman, S. *Angew. Chem. Int. Ed,* **2014***, 53*, 5604

[2] Vallavoju, N.; Sermadurai, S.; Jocksuch, S.; Prabhakaran, M. T.; Sibi, M. P.; Jayaraman, S. *Adv. Synth. Catal. In press.*

[3] Rajendran, S.; Raghunathan, R.; Hevus, I.; Ugrinov, A.; Sibi, M. P.; Webster, D. C.; Jayaraman, S. *Angew. Chem. Int. Ed.*, Submitted for publication.

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