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Flow of Energy & Charge in Porphyrin Nanostructures

H. L. Anderson[1]

[1]Department of Chemistry, Oxford University, Chemistry Research Laboratory, Oxford OX1 3TA, United Kingdom - harry.anderson@chem.ox.ac.uk

Template-directed synthesis can be used to create π-conjugated nanostructures with sizes extending into the domain of proteins [1,2]. Do these systems mimic the light harvesting behavior of photosynthetic chlorophyll arrays [3]? Can electrons delocalize coherently around such large macrocycles? Do they display aromaticity [4]? Can tunneling through these nanorings result in quantum interference? This lecture will present progress towards answering these questions, including computational studies, such as the calculated map of nucleus independent chemical shift shown in Figure 1.

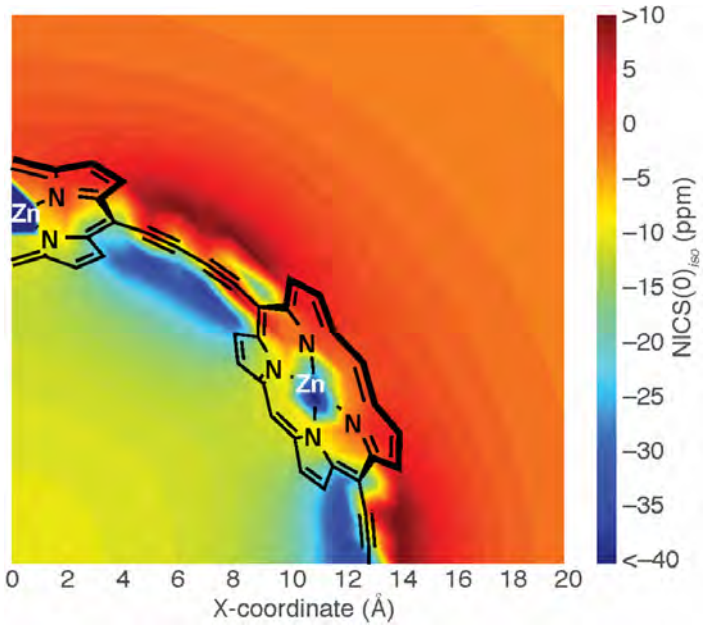

Figure 1. $NICS(0)_{iso}$ (B3LYP/def2-SV(P)) in the *xy* plane of a six-porphyrin nanoring in its 6+ oxidation state [4].

[1] M. C. O'Sullivan, J. K. Sprafke, D. V. Kondratuk, C. Rinfray, T. D. W. Claridge, A. Saywell, M. O. Blunt, J. N. O'Shea, P. H. Beton, M. Malfois, H. L. Anderson, *Nature*, **2011**, *469*, 72-75.
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Nanomaterials for Imaging and Therapy

L. De Cola[1]

[1]Institute de Science et d'Ingénierie Supramoléculaires (I.S.I.S.), University of Strasbourg, France and KIT, Germany - decola@unistra.fr

Nanoparticles, porous materials and capsules are interesting nano/micro system able to entrap desired molecules and act as delivery or imaging species. They can be created using soft species such as gels or polymers or inorganic precursor to obtain microporous and mesoporous silica based nanoparticles. In this talk I will focus on the use of ultrasmall (<5 nm) silicon nanoparticles, SiNPs, for *in vitro* and *in vivo* imaging and on breakable silica materials for an easy and rapid clearance after therapy. Indeed, the concern about the elimination of any type of artificial material from the body of animals can be solved using both approach: small size particles or fragments after destruction allows the elimination via renal patway. Indeed, the issue related to the use of materials for therapy in living organism, is their accumulation in vital organs that often prevent their use in clinical applications. The SiNPS can be decorated with different imaging labels allowing a multiple detection and even a recognition when sugars are covalently anchored on their surfaces.[1,2]

However the small particles cannot be efficiently employed for therapy and therefore we have recently developed a new generation of breakable hybrid nanoparticles, able to response and degrade upon external stimuli (*e.g.* reductive agents, pH, *etc.*).[3,4] The insertion of responsive linkers in the framework of these particles, results not only in the destruction and safe excretion of the nanoparticles from the cells, but also in a faster and better delivery of the payloads. Moreover, to expand the breakability properties of this material for other purpose, the possibility to entrap proteins into a breakable silica shell has also been realized in our laboratory.[5]

Experiments *in vivo* on the use of these materials for the treatment of hepatocarcinoma will be discussed.

[1] K. Zarschler, L. De Cola et al. *Nanomedicine: Nanotechnology, Biology, and Medicine* **2016**, *12*, 1663–1701.
[2] P. Seeberger, L. De Cola et al. *Nano Lett.*, **2016**, *16*, 807-811.
[3] L. Maggini, L. De Cola et al. *Nanoscale,* **2016**, *8*, 7240-7247.
[4] L. Maggini, L. De Cola et al*. Chem. Eu. J.*, **2016**, *22*, 3697-3703.
[5] E.A. Prasetyanto, L. De Cola et al. *Angew. Chem. Int. Ed.*, **2016**, *55*, 3323-3327

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SISF-SCS Senior Investigator Award Lecture 2017/I: Highlights from a 20 year-journey of Medicinal Chemistry at Roche

E. Pinard[1]

[1]F. Hoffmann-La Roche Ltd., Pharma Research & Early Development, Roche Innovation Center Basel, Basel, Switzerland - emmanuel.pinard@roche.com

My presentation will discuss drug discovery and clinical development results obtained in two different program targeting disorders with high unmet need: GlyT1 inhibitor program for the treatment of schizophrenia that reached phase III studies [1] with bitopertin [2] and SMN2 splicing modifier program that led to the identification of RG7800 for the treatment of SMA (Spinal Muscular Atrophy) [3],[4].

[1] *Biol. Psychiatry*, **2017**, *82*, 8-16
[2] *J. Med. Chem*., **2010**, *53*, 4603-4614
[3] *J. Med. Chem*., **2016**, *59*, 6086-6100
[4] *J. Med. Chem*., **2017**, *60*, 4444-4457

The KGF-SCS Senior Industrial Science Award is given to Dr. Emmanuel Pinard, F. Hoffmann-La Roche Ltd, Basel, for his very successful research on several therapeutic targets as enzymes (Bace1, COMT), ion channels (NMDA), GPCRs (Orexin, Vasopressin) and transporters (GlyT1) that address high unmet central nervous system disorders such as Parkinson’s Disease, Stroke, Schizophrenia, Depression, Autism and Spinal Motor Atrophy.

Grammaticakis-Neumann Award Lecture 2017: Excited State Proton-Coupled Electron Transfer in Organic Synthesis

R. R. Knowles[1]

[1]Department of Chemistry, Princeton University, Princeton, USA - rknowles@princeton.edu

Proton-coupled electron transfers (PCETs) are unconventional redox processes in which an electron and proton are exchanged together in a concerted elementary step. While PCET is now recognized to play a central a role in biological redox catalysis and inorganic solar energy conversion technologies, its applications in organic chemistry remain largely unexplored. This talk will highlight our group's efforts to use photo-initiated PCET as a means to address significant and long-standing synthetic challenges in the areas of free radical chemistry and asymmetric catalysis. In particular we are interested in the ability of excited state PCET to enable catalytic and chemoselective generation of synthetically useful radical intermediates via the direct homolytic activation of common organic functional groups that are energetically inaccessible using conventional H-atom transfer catalysts. Our approach makes use of a simple thermodynamic formalism to rationally identify combinations of proton and electron donors that can formally transfer hydrogen to form very weak bonds (BDFEs <25 kcal/mol) and combinations of proton and electron acceptors that are competent to homolyze strong bonds (BDFEs >105 kcal/mol). Application of these concepts in the development of new synthetic methods will be presented.

SISF-SCS Investigator Award Lecture 2017: The COP9 Signalosome (CSN): Tackling a Complex Target

R. Sedrani[1]

[1]Novartis Institutes for BioMedical Research, Global Discovery Chemistry, CH-4002 Basel

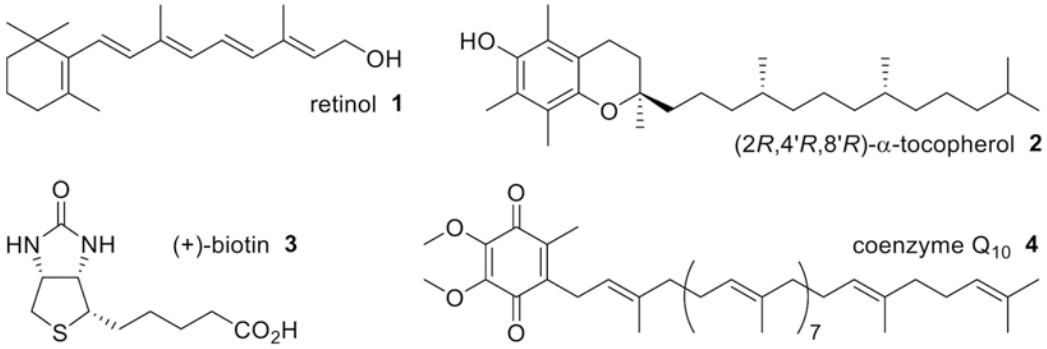
The KGF-SCS Industrial Science Award is given to Dr. Richard Sedrani, Novartis Pharma AG, Basel, for his achievements in many important projects as research chemists, team leader, project leader and unit head that resulted in the discovery and development of the mTOR inhibitor Everolimus, which is the active ingredient of several successfully marketed drugs: Certican® / Zortress®; Afinitor®, Xience™.

SISF-SCS Senior Investigator Award Lecture 2017/II: Vitamins and Nutraceuticals from the Perspective of Process Research

T. Netscher[1]

[1]Research and Development, DSM Nutritional Products, P.O. Box 2676, 4002 Basel, Switzerland - thomas.netscher@dsm.com

The development of efficient, sustainable low-cost processes is the basis for providing high-quality products for daily life applications in human and animal nutrition1. The importance of chemical process research towards ecologically benign and competitively advantageous processes for the large-scale preparation of various vitamins, nutraceuticals and fine chemicals is highlighted.



Representative examples from the field of naturally occurring food supplements such as vitamin A (retinol, **1**), vitamin E (tocopherols, e.g. **2**)[2-4], vitamin K_1 (phylloquinone), d-(+)-biotin (vitamin H, **3**)[5], or ubiquinones (e.g. coenzyme Q_{10}, **4**) will be given, including contributions from collaborations with external partners. General trends include the shift from stoichiometric to catalytic protocols and from batch to continuous processes. In addition, the use of renewable (bio-based) raw materials as key building blocks for the production of vitamins is of growing importance.

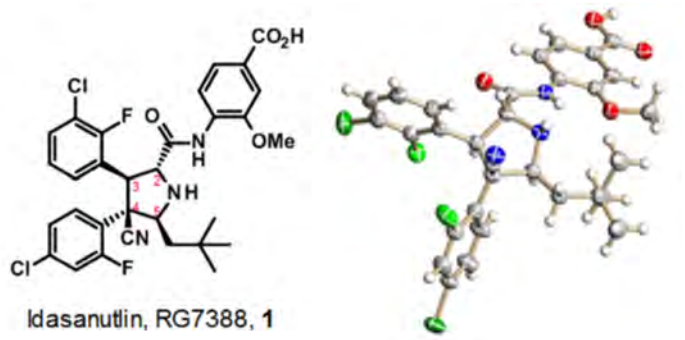
[1] M. Eggersdorfer, D. Laudert, U. Létinois, T. McClymont, J. Medlock, T. Netscher, W. Bonrath, *Angew. Chem. Int. Ed.* **2012**, *51*, 12960-12990; B. Wüstenberg, R.T. Stemmler, U. Létinois, W. Bonrath, M. Hugentobler, T. Netscher, *Chimia* **2011**, *65*, 420-428.
[2] T. Netscher, *Vitamins and Hormones* **2007**, *76*, 155-202; T. Netscher, *Synthesis and production of vitamin E*, in: *Lipid Synthesis and Manufacture,* F.D. Gunstone (Ed.), Sheffield Academic Press Ltd, Sheffield, UK, **1999**, pp. 250-267.
[3] T. Netscher, *Angew. Chem. Int. Ed.* **2014**, *53*, 14313-14315, and cit. literature.
[4] S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642-644; T. Netscher, M. Scalone, R. Schmid, in *Asymmetric Catalysis on Industrial Scale*, Eds. H.-U. Blaser, E. Schmidt (Eds.), Wiley-VCH, Weinheim, **2004**, pp. 71-89.
[5] W. Bonrath, R. Karge, T. Netscher, F. Roessler, F. Spindler, in *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches, and Solutions* (2nd Ed.), H.-U. Blaser, H.-J. Federsel (Eds.), Wiley-VCH, Weinheim, **2010**, pp. 27-39; W. Bonrath, R. Karge, T. Netscher, F. Roessler, F. Spindler, *Chimia* **2009**, *63*, 265-269.

Efficient Industrial Synthesis of Idasanutlin via a Cu(I)-catalyzed [3+2] Asymmetric Cycloaddition

D. Fishlock[1,2], G. Rimmler[1], R. Diodone[1], S. Hildbrand[1], C. Moessner[1], C. Peters[1], P. D. Rege[1], M. Schantz[1]

[1]Small Molecule Technical Development, F. Hoffmann-La Roche, 4070 Basel, Switzerland, [2] Daniel.fishlock@roche.com

A concise asymmetric synthesis has been developed to prepare idasanutlin (1), a small molecule MDM2 antagonist currently being investigated as a potential treatment for various solid tumors and hematologic malignancies. The highly congested pyrrolidine core, containing four contiguous stereocenters, was constructed via a Cu(I)/BINAP catalyzed [3+2]-cycloaddition reaction. This optimized copper(I) catalyzed process has been used to produce more than 1500 kg of idasanutlin.



Idasanutlin, RG7388, **1**

The evolution of this synthetic route from the laboratory to commercial-scale manufacturing will be described, highlighting the exceptionally selective and consistent cycloaddition/isomerization/ hydrolysis sequence. The excellent yields, short cycle times and reduction in waste streams result in a sustainable production process with low environmental impact.

[1] Rimmler, G. Alker, A. Bosco, M. Diodone, R. Fishlock, D. Hildbrand, S. Kuhn, B. Moessner, C. Peters, C. Rege, P.D. Schantz, M. *Org. Process Res. Dev.* **2016**, *20*, 2057-2066.