Abstract Book

Young Researchers Symposium

ESOR2023
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Table of Contents

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Welcome to ESOR2023

On behalf of the Organizing Committee, it is a pleasure to welcome you at the 19th European Symposium on Organic Reactivity (**ESOR2023**), which takes place on 19–22 September 2023 at the O|2 Building on the campus of the Vrije Universiteit Amsterdam.

The European Symposium on Organic Reactivity is a biennial conference series and has a long tradition with meetings being held across Europe.

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The series gathers scientists working in the field of physical and theoretical organic chemistry.

We wish you a wonderful stay in the beautiful city of Amsterdam and a pleasant and inspiring conference, with many interesting discussions, at Vrije Universiteit Amsterdam.

F. Matthias Bickelhaupt, Célia Fonseca Guerra, and Chris Slootweg

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Leonard Prins (Padova, Italy)

Program

Monday 18 September

10:00 – 10:50	**Registration + coffee and tea**
10:50 - 11:00	Opening by Celine Nieuwland and F. Matthias Bickelhaupt
	Chair: Eveline Tiekink
11:00 - 11:15	**Maxime Ferrer**
11:15 - 11:30	**Steven Beutick**
11:30 – 11:45	**Sachin Ramesh**
11:45 – 12:00	**Jelle Hofman**
12:00 – 12:15	**Andrea Madabeni**
12:15 – 12:30	**Kieran Redpath**
12:30 - 13:30	**Lunch**
	Chair: Lars van der Zee
13:30 - 13:45	**Pau Besalú**
13:45 - 14.00	**Maike Vahl**
14:00 - 14:15	**David Ryan**
14:15 - 14:30	**Andrew Hsieh**
14:30 – 14:45	**Eveline Tiekink**
14:45 – 15:00	**Gabrijel Zubčić**
15:00 – 15:30	**Coffee Break**
	Chair: Jelle Hofman
15:30 - 15:45	**Ricardo Meyrelles**
15:45 - 16:00	**Lars van der Zee**
16:00 - 16:15	**Daniela Rodrigues Silva**
16:15 - 16:30	**Yuri Damen**
16:30 – 16:45	**Pawel Wieczorkiewicz**
16:45 – 17:00	**Alicia Evans**
17:00 – 17:10	Closing by Celine Nieuwland
17:10 – 18.10	**Drinks**

Abstracts

1. **Maxime Ferrer I** Frustrated Lewis Pairs: An efficient and controllable carbon dioxide capture and activation
2. **Steven Beutick I** Understanding the Retro-Cope Reaction of Linear Alkynes
3. **Sachin Ramesh I** Complexation Behavior of Phosphoryl Ligands with Actinides and Lanthanides
4. **Jelle Hofman I** Synthesis and characterization of P-ligand stabilized Pd(I) complexes using Single Electron Transfer processes
5. **Andrea Madabeni I** Mechanistic Insight into the Selenium Catalysed Oxidation of Aniline to Nitrobenzene: The Role of the Chalcogen Oxidation State
6. **Kieran Redpath I** Utilising Model Phosphine-Ligated Nickel Complexes to Understand sp2-sp2 Cross-Coupling
7. **Pau Besalú I** Electric field-induced reactivity and selectivity: Insights from chemical bonding analysis
8. **Maike Vahl I** Quantitative structure–reactivity relationships for synthesis planning: The benzhydrylium case
9. **David Ryan I** PREDiCT: The Reaction Dynamics of the Nitrite Anion
10. **Andrew Hsieh I** Nucleofugality in ionic liquids
11. **Eveline Tiekink I** Regioselectivity in Cycloaddition Reactions with Tropone
12. **Gabrijel Zubčić I** EPR and NMR Investigation of Hofmann–Löffler–Freytag Reaction: Detection of N-centered Radical
13. **Ricardo Meyrelles I** Protonated Cyclopropane: The Key Intermediate Towards Cationic Cyclopropanation to Form 6,8-Cycloeudesmanes
14. **Lars van der Zee I** A Quinone-Amine Radical-Ion-Pair for Homolytic Bond Activation
15. **Daniela Rodrigues Silva I** Revisiting Rotational Isomerism of Organic Compounds
16. **Yuri Damen I** Kinetic and mechanistic insights into SPOCQ click chemistry
17. **Pawel Wieczorkiewicz I** Description of the substituent effect in polyenes, polyynes and acenes
18. **Alicia Evans I** Surprising insights into electronic effects on rearrangement reactions

Frustrated Lewis Pairs: An efficient and controllable carbon dioxide capture and activation

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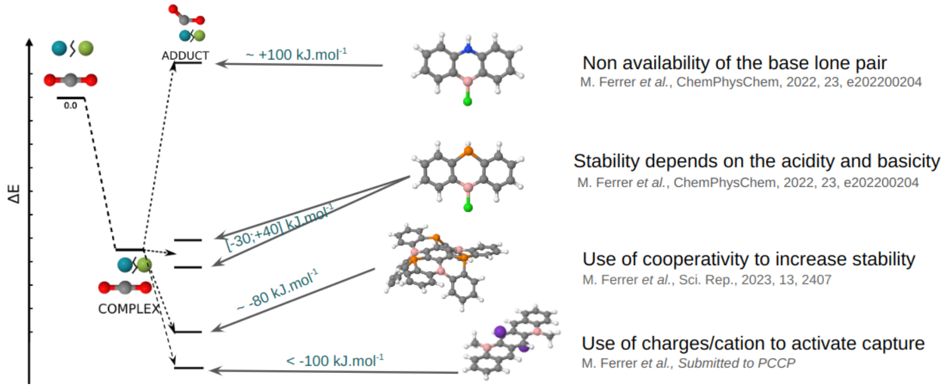
Since their discovery in 2006 by Stefan et al. [1], Frustrated Lewis Pairs (FLP) gained a lot of interest in the scientific community due to their large range of applications. The main property that gives a bright future to those systems is their metal-free character that integrates them in the "green chemistry" tendency. Due to the constant growing of CO_2 concentration in the atmosphere one possible application of the FLP is the capture and activation of CO_2 molecules. FLP can be used as a possible storage supply, as well as a catalyst that enables to capture CO_2 and to activate it, making its transformation easier [2]. In the literature, there is a plethora of FLP. From the original $P(^tBu)_3/B(C_6F_5)_3$ [1], to the 5,10-Disubstituted dibenzophosphaborines [3], passing by the $R_3P\text{-}CH_2CH_2\text{-}BR_2$ linked FLP [4], the boron Lewis acid seems to be a very interesting candidate. During the study of several FLP reacting with CO_2 [3-5], it was shown that the capture of carbon dioxide molecules by FLP can be controlled by playing with the acidity and basicity of the Lewis acid and base or by imposing an internal or external electric field. One can pass from a non-favorable, to a thermodynamically favorable reaction.



Non availability of the base lone pair
M. Ferrer *et al.*, ChemPhysChem, 2022, 23, e202200204

Stability depends on the acidity and basicity
M. Ferrer *et al.*, ChemPhysChem, 2022, 23, e202200204

Use of cooperativity to increase stability
M. Ferrer *et al.*, Sci. Rep., 2023, 13, 2407

Use of charges/cation to activate capture
M. Ferrer *et al.*, *Submitted to PCCP*

Figure 1. Factors influencing the stability of the adduct formed by an FLP.

[1] G. C. Welch *et al.*, *Science*, **2006**, *314*, 1124.
[2] Y. Zhang, T. Zhang, S. Das, *Green Chem.*, **2020**, *22,* 1800.
[3] M. Ferrer *et al.*, *ChemPhysChem,* **2022**, e2022002.
[4] D. Stephan, *Acc. Chem. Res.*, **2015**, *48*, 306.
[5] M. Ferrer *et al.*, *Sci. Rep.,* **2023,** *13*, 2407.

Understanding the Retro-Cope Reaction of Linear Alkynes

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[c] Radboud University, Nijmegen, The Netherlands
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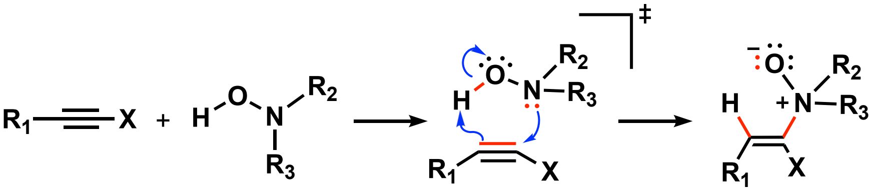
Steveneelco.beutick@phd.unipd.it

We have quantum chemically investigated the bioorthogonal retro-Cope reaction of linear alkynes R3C–C≡C–X (R3 = combinations of H, MeO, F; X = H, F, Cl, Br, I) with and N,N-dimethylhydroxylamine using relativistic density functional theory at ZORA-BP86/TZ2P. This novel reaction can be tuned through judicious substitution of the alkyne at both the terminal and propargylic position to render second-order kinetics that rival and out-compete strain-promoted variants.[i] Using our activation strain and quantitative MO analyses, we are the first to tease apart the physical factors at the root of this reactivity enhancement upon terminal or propargylic substitution of propyne.



[1] a) D. Kang, J. Kim, *J. Am. Chem. Soc.* **2021**, *143*, 5616–5621; b) D. Kang, S. T. Cheung, J. Kim, *Angew. Chem.* **2021**, *133*, 17084–17089; c) D. Kang, S. T. Cheung, A. Wong-Rolle, J. Kim, *ACS Cent. Sci.* **2021**, *7*, 631–640; d) D. Kang, S. Lee, J. Kim, *Chem.* **2022**, *8*, 2260–2277.

Complexation Behavior of Phosphoryl Ligands with Actinides and Lanthanides

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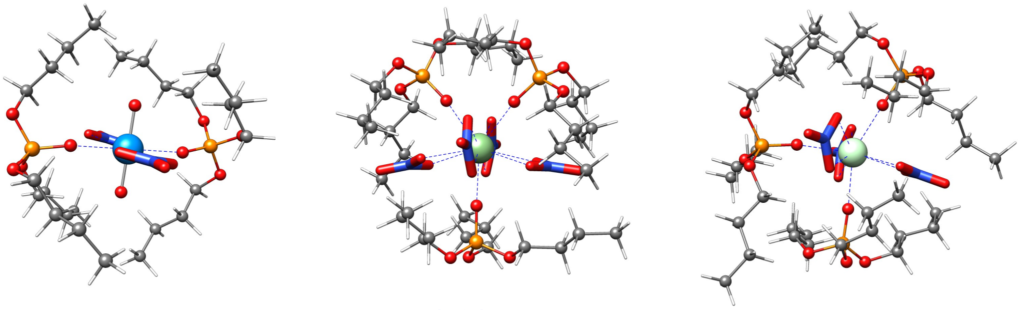
Actinide separation and recovery are important at various stages of the nuclear fuel cycle. The recovery of uranium and plutonium from the spent fuel is a vital step in the nuclear fuel cycle, where the major actinides are recycled. The most preferred method for this task is solvent extraction, where tri-*n*-butyl phosphate (TBP) has been used as an extractant for more than seven decades.[1] In this context, developing new molecules (ligands) for actinide separation and recovery is an active field of research. The development of ligands finds its application in removing actinides from lean solutions, separating actinides and lanthanides, and developing better ligands for fast reactor fuel reprocessing, etc. Experimental studies in the past were dedicated to synthesizing and studying a large number of molecules for various applications. On the other hand, understanding the behavior of actinide extraction from a theoretical point of view and insights derived over time will help us tailor making an extractant for a specific application. In this regard, quantum chemical calculations are performed using ADF 2016[2] and ORCA version 4.2.1[3] and 5.0.3,[4] to understand the electronic structure and complexation behavior of various ligands containing phosphoryl groups with lanthanides and actinides (Figure 1). The talk will summarize the results of the work carried out at IGCAR, Kalpakkam.



$UO_2(NO_3)_2.2TBP$ **$Th(NO_3)_4.3TBP$** **$Nd(NO_3)_3.3TBP$**

Figure 1. The complexes of TBP ligand with U(VI), Th(IV) and Nd(III). Color code: Blue sphere is uranium, dark green sphere is thorium, white sphere is neodymium, red is oxygen, orange is phosphorous, blue is nitrogen, grey is carbon and white sticks are hydrogen.

[1] Healy, T. V., Mckay, H. A. C., Trans. Faraday. Soc. **1956**, 52, 633.

[2] SCM. ADF 2016; Theoretical Chemistry, V. U. A., The Netherlands, **2016**; http://www.scm.com/.

[3] Neese, F. Software update: the ORCA program system, version 4.0 *Wiley Interdisciplinary Reviews: Computational Molecular Science*, **2017**, Vol. 8, Issue 1, p. e1327.

[4] Neese, F. Software update: The ORCA program system—Version 5.0. *WIREs Comput Mol Sci.* **2022**; 12:e1606. https://doi.org/10.1002/wcms.1606

Generation of Radical Ion Pairs using Frustrated Lewis Pairs to provide insights into homolytic substrate activation

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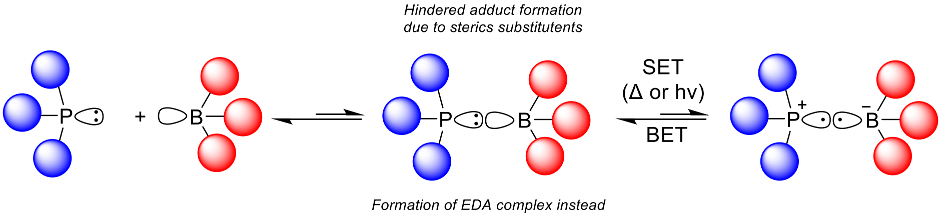
Frustrated Lewis Pairs (FLPs) have been investigated over the years as promising metal-free catalytic systems for small molecule activation.[1][2] By polarizing the bond of the substrate in its binding pocket, FLP systems have proven to activate molecules, such as H_2 and CO_2, in a heterolytic fashion. However, the activation of more inert substrates (e.g. CH_4, Ph3P=O) via this mechanism remains elusive. In our group, homolytic pathways are explored via the generation of Radical Ion Pairs (RIPs).[3][4] These RIPs are generated via Single Electron Transfer (SET) processes in FLP systems, either via a photoinduced or a thermal mechanism. Comparing the difference in ionization energy of the donor and the electron affinity of the acceptor using DFT calculations provides insight into the mechanism of SET, aiding the design of suitable FLP systems for RIP formation. This presentation will explain the methodology used to generate these RIP systems and elaborate on the envisioned homolytic substrate activation.


Hindered adduct formation due to sterics substitutents

Formation of EDA complex instead

Figure 1. The generic formation of a RIP out of a FLP system.

[1] G.C. Welch, R. R. S. Juan, J.D. Masuda, D. W. Stephan, *Science* **2006**, 314 (5802), 1124–1126.
[2] D. W. Stephan, *Science* **2016**, 354 (6317).
[3] F. Holtrop, A. R. Jupp, B. J. Kooij, N. P. van Leest, B. de Bruin, J. C. Slootweg, *Angew. Chem. Int. Ed.* **2020**, *59*, 22210.
[4] F. Holtrop, A. R. Jupp, N. P. van Leest, M. Paradiz Dominguez, R. M. Williams, A. M. Brouwer, B. de Bruin, A. W. Ehlers, J. C. Slootweg, *Chem. Eur. J.* **2020**, *26*, 9005.

Mechanistic Insight into the Selenium Catalysed Oxidation of Aniline to Nitrobenzene: The Role of the Chalcogen Oxidation State

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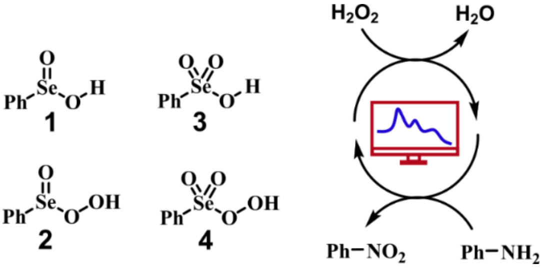

Seleninic acid (1) is recognized as an oxygen-transfer catalyst, capable of mediating oxidations by H_2O_2 under green conditions.[1] The only plausible active oxidant was long thought to be the Se(IV) species peroxyseleninic acid (2), until very recently, when the involvement of the Se(VI) selenonic and peroxyselenonic acids (3 and 4) in epoxidation reactions was disclosed.[2] The extent of the generality of such evidence is still to be understood. In fact, the participation of the conventional Se(IV) peroxyseleninic acid (2) was found consistent with experiments carried out on another selenium catalyzed reaction i.e., aniline oxidation to nitrobenzene.[3] In this contribution, we investigate the whole catalytic mechanism leading to the oxidation of aniline to nitrobenzene by H_2O_2, comparing the performance of 1 and 3 as catalysts. *Via* a benchmarked Density Functional Theory (DFT) protocol, different mechanistic hypotheses are compared and the turnover frequency (TOF) of each cycle is evaluated to gain quantitative insight into the role of the oxidation state of the selenium catalyst in the process. The impact of the Se(IV) and Se(VI) oxidation states in different parts of the mechanism is pinpointed, thus obtaining physico-chemical insight into advantages and disadvantages of both.

[1] D. M. Freudendahl, S. Santoro, S. A. Shahzad, C. Santi, T. Wirth, *Angew. Chemie - Int. Ed.* **2009**, *48*, 8409–8411.
[2] K. N. Sands, E. Mendoza Rengifo, G. N. George, I. J. Pickering, B. S. Gelfand, T. G. Back, *Angew. Chemie - Int. Ed.* **2020**, *59*, 4283–4287.
[3] D. Tanini, C. Dalia, A. Capperucci, *Green Chem.* **2021**, *23*, 5680–5686.

Utilising Model Phosphine-Ligated Nickel Complexes to Understand sp^2-sp^2 Cross-Coupling

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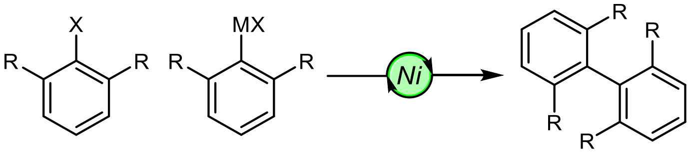
Catalysis has underpinned modern synthetic chemistry since the 1970s, driving down energetic requirements of reactions, decreasing cost and environmental impact, and opening up new synthetic targets. Its importance cannot be overstated, culminating in the 2010 Nobel Prize for Chemistry being awarded for the development of palladium-catalysed cross-coupling methods in organic synthesis. These methods often utilise platinum-group metals, with palladium-catalysed methods being the most common. These metals have a considerable environmental impact due to their low crustal abundance and the emissions resulting from their mining and processing.[1] An alternative metal for these catalytic reactions is nickel; it shares enough similarities in its properties to allow it to undertake these reactions.

Nickel has been the subject of much research into catalytic reactions, particularly in C-C and C-X bond forming reactions.[2 - 4] Our area of interest is the C-C cross-coupling of sterically hindered aryl moieties: current homogeneous nickel-catalysed methods achieve only moderate yields under forcing conditions. Our aim is to investigate the steps in the catalytic cycle, utilising model phosphine-ligated complexes to determine preferable ligand properties for some C-C cross-coupling types and understand any pitfalls within these cycles. Determination of preferred properties will enable for informed ligand use/design in future cross-couplings.



[1] Nuss, P., Eckelman, M.J., *PLoS ONE,* **2014***, 9*, e101298
[2] Ananikov, V.P., *ACS Catal.*, **2015**, *5*, 1964
[3] Tasker, S.Z., Standley, E.A., Jamison, T.F., *Nature*, **2014**, *509*, 299
[4] Chernyshev, V.M., Ananikov, V.P., ACS Catal., 2022, 12, 1180

Electric field-induced reactivity and selectivity: Insights from chemical bonding analysis

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Electric fields (EF) can induce substantial changes in reaction rates, the selectivity towards a particular product, or in general to reaction mechanisms, even for the simplest transformations. This bears tremendous potential impact on various areas of catalysis, ranging from heterogeneous to enzymatic catalysis. The analysis and understanding of such effects at the molecular level is crucial for the design of novel processes and optimization of the existing ones.[1,2] To this end, the activation strain model and the energy decomposition analysis (EDA) are suitable computational techniques, however they are computationally demanding.[2,3] Herein, we present a fast and efficient methodology to decompose energy differences (kinetics and thermodynamics) into physically meaningful energy terms in the presence of an EF in any direction of the space: the Field-Dependent Barrier Activation Strain Model (FDB-ASM) and Field-Dependent Barrier Energy Decomposition Analysis (FDB-EDA).[3] Analysis and visual representations of the electric-field effects on reactivity and selectivity will be presented.

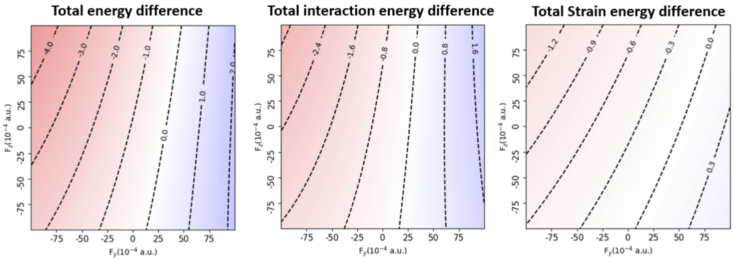

Figure 1. FDB-ASM analysis of the *endo* vs *exo* selectivity of a simple Diels-Alder reaction.

[1] S. Shaik, R. Ramanan, D. Danovich, D. Mandal, *Chem. Soc. Rev.*, **2018**, *47*, 5125.
[2] S. Yu, P. Vermeeren, T. A. Hamlin, F. M. Bickelhaupt, *Chem. Eur. J.*, **2021**, *27*, 5683.
[3] P. Besalú-Sala, M. Solà, J. M. Luis, M. Torrent-Sucarrat, *ACS Catal.*, **2021**, *11*, 14467.

Quantitative structure–reactivity relationships for synthesis planning: The benzhydrylium case

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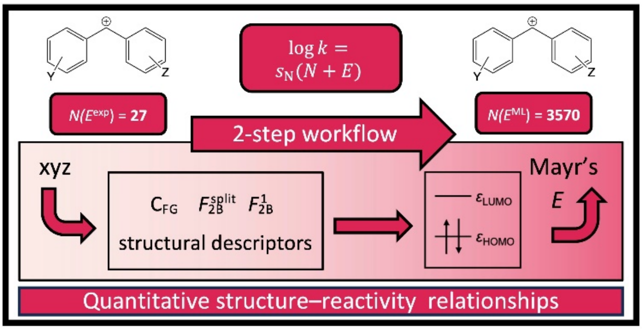
Selective and feasible reactions are top targets in synthesis planning, both of which depend on the reactivity of the molecules involved. Mayr's approach to quantifying reactivity[1] has greatly facilitated the planning process, but reactivity parameters for new compounds require time-consuming experiments. In the past decade, data-driven modeling has been gaining momentum in the field as it shows promise in terms of efficient reactivity prediction.[2] However, state-of-the-art models use quantum chemical data as input, which prevents access to real-time planning in organic synthesis.

We present a novel data-driven workflow for predicting reactivity parameters of molecules that takes only structural information as input, enabling *de facto* real-time reactivity predictions.[3] We use the well-understood chemical space of benzhydrylium ions as an example to demonstrate the functionality of the approach and the performance of the resulting quantitative structure–reactivity relationships (QSRRs). The results suggest that it is straightforward to build low-cost QSRRs that are accurate, interpretable, and transferable to yet unexplored systems within a given scope of application.



[1] H. Mayr, M. Patz, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938.
[2] M. Vahl, J. Proppe, *Phys. Chem. Chem. Phys.* **2023**, *25*, 2717.
[3] M. Vahl, J. V. Diedrich, M. Mücke, J. Proppe, *10.26434/chemrxiv-2023-dx1qv,* **2023**.

PREDiCT: The Reaction Dynamics of the Nitrite Anion

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[a] *Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland*
[b] *School of Chemistry, University College Dublin, Dublin, Ireland*
[c] *Department of Chemistry, Technische Universität Chemnitz, Chemnitz, Germany*
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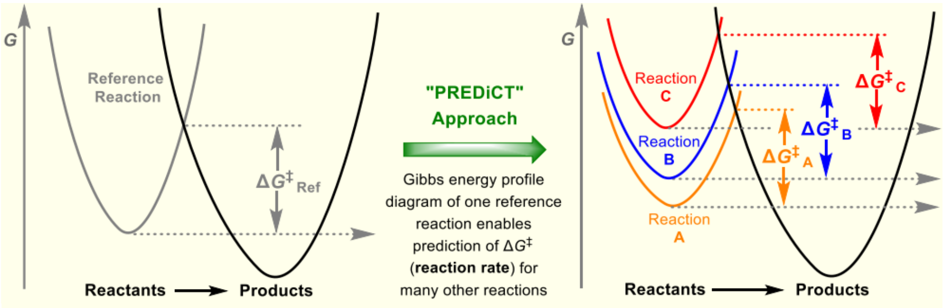

Predicting Reaction Rates – Energy Diagrams for Chemical Transformations

The primary aim of this project is to develop a novel method for predicting Gibbs energies of activation (the heights of activation barriers, $\Delta G^{\ddagger}$) and hence the rates of chemical reactions. The S_N2 alkylations of the nitrite anion were selected as one test case for the development of this model. A Gibbs energy profile diagram was constructed for one reference reaction by combining experimentally determined values of $\Delta G^{\ddagger}$, values of $\Delta_r G^{\circ}$ calculated at a high level of theory,[1] along with Intrinsic Reaction Coordinate (IRC) data.[3,4] For a given Series of alkylating agents (MeX, EtX) it is assumed that the Gibbs energy well of the product remains unchanged. Consequently, the values of $\Delta G^{\ddagger}$ for these related reactions can be predicted. Upon comparison with experimentally derived values, it is observed that the predictions closely reproduce activation barrier values. This work will ultimately form part of a model which aims for general predictive capability of the rates of chemical reactions. The potential impacts of such a model are far reaching and could allow for efficient synthetic planning, maximisation of yields and minimisation of contamination with impurities generated, in addition to reduction of waste generated and power consumption.

[1] Sheehy, K.J., Bateman, L.M., Flosbach, N.T., Breugst, M., Byrne, P.A., *Chem Sci.*, **2020**, 11, 9630
[2] Fukui, F., *J. Phys. Chem.*, **1970**, 74, 4161
[3] Maeda, S., Harabuchi, Y., Ono, Y., Taketsugu, T., Morokuma, K.., *Int. J. Quantum Chem.*, **2015**, 115, 258

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Nucleofugality in ionic liquids

Andrew Y. Hsieh,[a] Ronald S. Haines,[a] Jason B. Harper[a]
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Ionic liquids are promising alternatives to molecular solvents for preparative chemistry.[1] They have been shown to affect the reaction outcomes (*e.g.* rates of reaction) of a range of organic processes.[2] These effects are dependent on the proportion of ionic liquid in solution and the nature of the ions present, both of which determine the microscopic interactions between the solvent and species along the reaction coordinate.[3]

While a range of reaction outcomes might be qualitatively predicted, they remain difficult to quantify. To overcome this, we have been examining the nucleofugality, a quantitative reaction parameter evaluating the leaving group ability,[4] of a series nucleofuges in mixtures containing ionic liquids.

The work presented here investigates the effects of ionic liquids on the nucleofugality of bromide (Figure 1). These data will be compared to that of the chloride in the corresponding ionic liquids,[5] which have been shown to quantitatively predict reaction outcome[6] This work expands our understanding of solvent effects in ionic liquids and is integral to developing a quantitative predictive framework for the rational selection of ionic liquids in preparative chemistry.

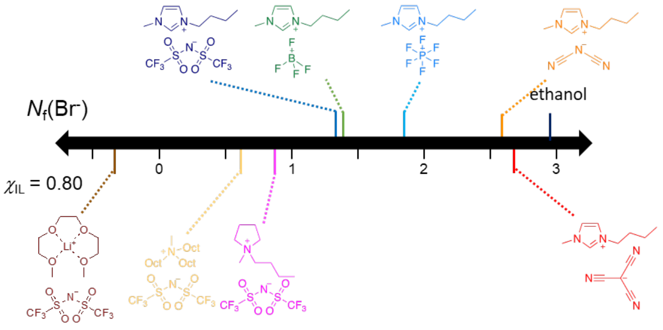

Figure 1. The nucleofugality of bromide in ethanol and each of a series of ionic liquids (χ_{IL} = 0.8).

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Regioselectivity in Cycloaddition Reactions with Tropone

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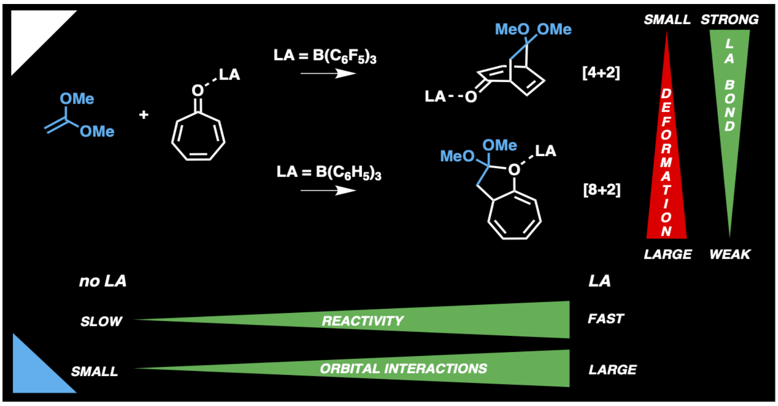
Higher-order cycloaddition reactions are efficient and powerful methods to synthesize bridged 3D molecular structures from simple 2D substrates. Tropone can engage in various competing higher-order cycloaddition reactions, for instance, [6+2], [6+3], [6+4], [6+6], [8+2], and [8+3] cycloaddition reactions.[1] Control of the regioselectivity is of paramount importance. Recently, Lewis acid catalysts were shown to impart total regiocontrol of the cycloaddition between tropone and 1,1-diethoxyethene: $B(C_6H_5)_3$ furnishes the [8+2] adduct while $B(C_6F_5)_3$ yields the [4+2] adduct.[2] We have studied the uncatalyzed and Lewis acid (LA)-catalyzed cycloaddition reaction between tropone and 1,1-dimethoxyethene using dispersion-corrected relativistic density functional theory.[3] The LA catalysts BF_3, $B(C_6H_5)_3$, and $B(C_6F_5)_3$ efficiently accelerate both the competing [4+2] and [8+2] cycloaddition reactions by lowering the activation barrier up to 12 kcal mol^{-1} compared to the uncatalyzed reaction. We discovered that the regioselectivity shift finds its origin in the ability of the LA to absorb distortion by adopting a trigonal pyramidal geometry around the boron atom.



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EPR and NMR Investigation of Hofmann–Löffler–Freytag Reaction: Detection of N-centered Radical

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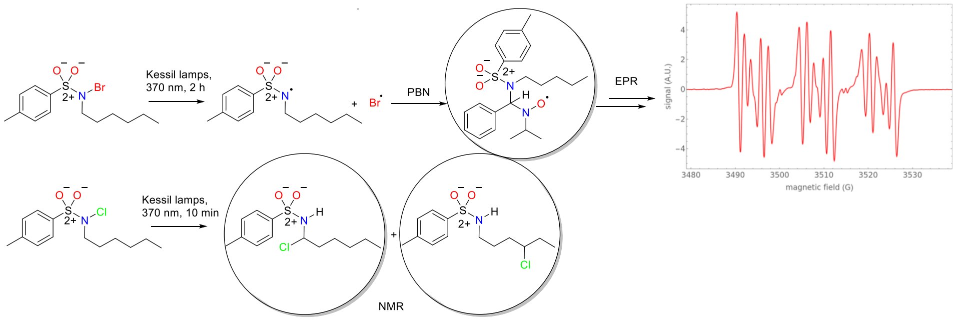
The Hofmann-Löffler-Freytag (HLF) reaction is a tool for functionalizing remote C-H bonds,[1] leading to the formation of pyrrolidine rings or C_5-substituted products. The mechanism of this reaction involves a rearrangement via 1,5-hydrogen atom transfer (HAT) from an N-centered radical. Studies by the Roizen[2] and Muñiz[3] groups have reported the formation of piperidine and C_6-halogenated products via 1,6-HAT.

We present the progress of an EPR and NMR study on *N*- and *C*-centered radical intermediates of the HLF reaction derived from N-halogen-N-alkyl-tosylamides. These radicals, produced by in situ UV light irradiation, are captured using a phenylbutylnitrone (PBN) spin trap, with the resultant adducts monitored via EPR. Our EPR measurements identified a Cl-PBN adduct produced by light in toluene experiments, substantiating that light effectively homolytically cleaves the N-Cl bond, leading to a chlorine radical that rapidly combines with PBN. Furthermore, we discerned EPR signals from spin adducts of light-induced N-centered radicals and rearrangement products, examining variations in N-halogen bonds (Cl/Br) and solvent environments (toluene/n-heptane). Conclusively, NMR data showcased the formation of several chlorinated products.



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Protonated Cyclopropane: The Key Intermediate Towards Cationic Cyclopropanation to Form 6,8-Cycloeudesmanes

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Cationic cyclopropanation refers to the loss of a proton from a carbocation leading to the formation of a cyclopropane. While it is considered one of the main pathways in the biosynthesis of cyclopropane-containing metabolites, it is rarely observed in non-enzymatic contexts.

In this work, we have discovered a novel cyclopropanation route through the reaction of cyclodecadienes with halonium sources, resulting in the formation of a product containing a cyclopropane moiety, 6,8-cycloeudesmanes (Figure 1).[1] Density functional theory (DFT) calculations were used to study the mechanism of this transformation, revealing the formation of a key protonated cyclopropane (PCP+) intermediate that can be deprotonated to form a cyclopropane instead of undesired olefin products. Our results revealed that the PCP+ formation needs to occur in a single concerted step to yield the desired cyclopropane product. We reevaluated the mechanism using structurally modified substrates, successfully predicting reactions with enhanced outcomes, and these predictions were experimentally validated.

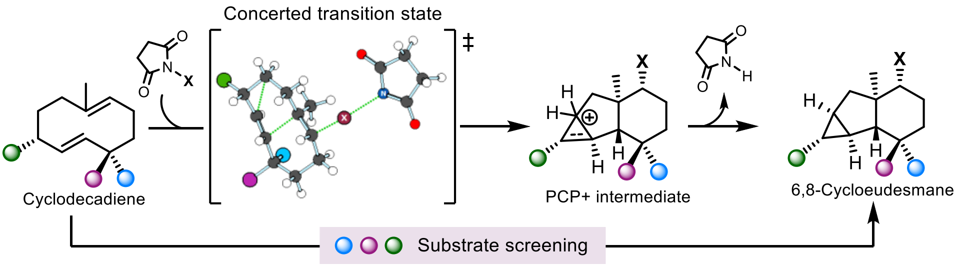

Figure 1. Cationic cyclopropanation with the formation of a protonated cyclopropane intermediate

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A Quinone-Amine Radical-Ion-Pair for Homolytic Bond Activation

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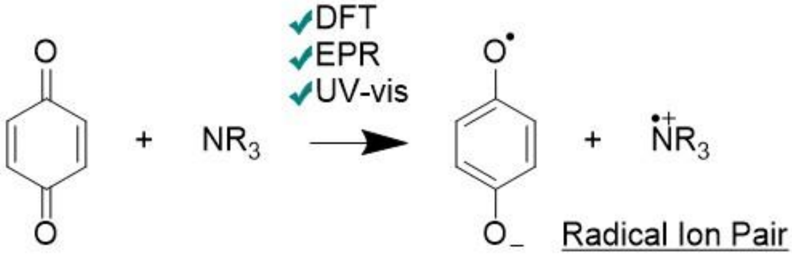
The activation of small molecules is typically performed in an heterolytic fashion. Homolytic splitting, on the other hand, could be advantages for splitting strong covalent bonds. For this, the use of radical ion pairs (RIPs) is of interest as they provide simultaneously two radicals and thus the potential for cooperative reactivity.

The development of novel RIPs has recently been made possible due to the discovery of single electron transfer within Frustrated Lewis Pairs (FLPs).[1] The SET occurs from a Lewis base to a Lewis acid, yielding often a RIP as fleeting intermediate. Recent activities focused on the formation of stable RIPs, e.g. based on quinones as the electron acceptor and amines and phosphines as the electron donor.[2] For all the quinone-based RIPs investigated, the SET is facilitated when the quinone is converted into a stronger acceptor by coordination of a Lewis acid.

To simplify the quinone-based RIPs, we developed a RIP without the need of activating the quinone. Careful design let to a new set of RIPs, which were characterized using multiple methods (UV-vis, EPR, DFT, NMR) and its reactivity explored for homolytic bond activation.



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Revisiting Rotational Isomerism of Organic Compounds

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A firm grasp of the driving forces behind conformational isomerism is crucial for the rational design of molecules with tailor-made properties. With this in mind, we reinvestigate the rotational isomerism around the C–C bond in archetypal organic compounds within the framework of Kohn-Sham molecular orbital (KS-MO) theory. Our bonding analyses reveal that overall rotational energy profiles are *always* set by steric repulsion between occupied–occupied orbitals. However, the conformational preferences can be shifted if one of the two requirements are met: i) if the relative steric repulsion is too weak and thus easily counteracted by subtle attractive interactions (*e.g.*, hyperconjugation[1]; **1** → **2**, Fig. 1); or ii) if stronger intramolecular interactions take place (*e.g.*, hydrogen bonding[2]; **1**→ **3**, Fig. 1). Our analyses lead to a novel, fundamentally revisited picture of the physical mechanisms behind well-known conformational effects in organic chemistry.

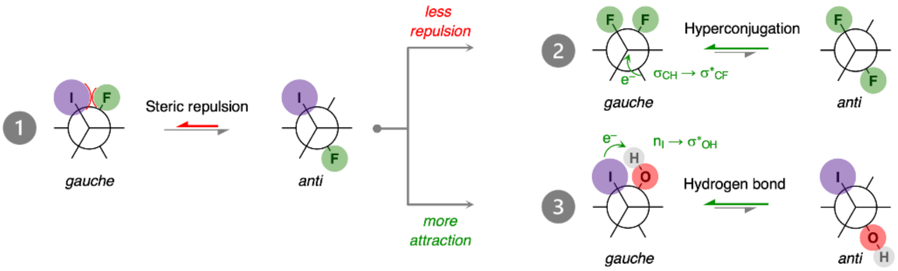

Figure 1. Conformational preferences of 1,2-disubstituted ethanes.

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Kinetic and mechanistic insights into SPOCQ click chemistry

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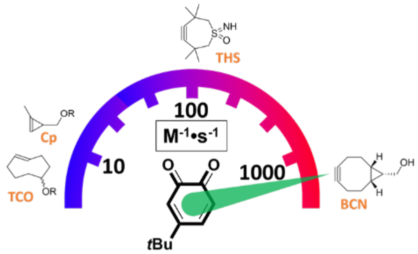

The strain-promoted oxidation-controlled ortho-quinone (SPOCQ) cycloaddition is an oxidation-inducible [4+2] cycloaddition of a 1,2-quinone with a strained cyclic alkyne or alkene that follows an inverse electron-demand Diels-Alder mechanism[1,2]. Due to its high rates and efficiency, SPOCQ chemistry has been successfully employed for the chemical modification of surfaces and for the preparation of bioconjugates such as antibody-drug conjugates[2]. In comparison to the widely applied strain-promoted azide–alkyne cycloaddition (SPAAC), SPOCQ benefits from reaction rates that are orders of magnitude higher. In our research, the experimental determination of second-order rate constants and of the thermodynamic activation parameters of the reactions of o-quinones with strained alkynes/alkenes were established[3]. This provides quantitative insight in the dominant forces driving the conversion, which surprisingly contradict earlier deduced explanations for why the rates are so high in these click reactions.

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Description of the substituent effect in polyenes, polyynes and acenes

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Our recent research focused on a detailed analysis of the substituent effect (SE) in disubstituted polyenes, polyynes and acenes (spacers) with n = 1 – 5 and 10 repeatable units (Figure 1, *left*).[1] In order to quantitatively describe the SE, homodesmotic reactions and the cSAR (*charge of the substituent active region*) parameter were used. Study also included analyses of geometry and electron delocalization with a recent EDDB (*electron density of delocalized bonds*) method. The obtained results allowed to evaluate how the SE weakens with n (Figure 1, *left*), depending on the Y group and the spacer type. The weakening is best approximated by exponential functions and differs for Y = NO_2 and O^-.

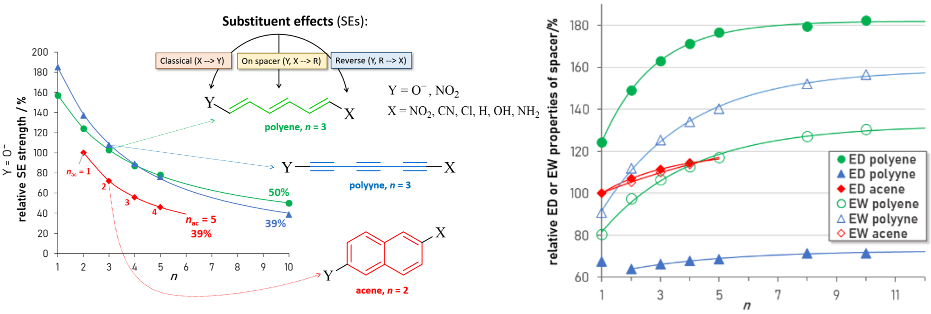

Figure 1. (*left*) Studied systems and aspects of the SEs; SE strength in % relative to the *p*-benzene derivatives as a function of spacer length, n.[1] (*right*) Electron-donating (ED) and withdrawing (EW) properties of spacers in % relative to benzene, as a function of n.[2]

For the first time, we also show how electron-donating and withdrawing properties of spacers change with n (Figure 1, *right*), and visualize the changes in electron delocalization within spacers and substituents using the EDDB method. The latter provides great insight into the nature of SEs and the interaction between substituents and spacers.

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Surprising insights into electronic effects on rearrangement reactions

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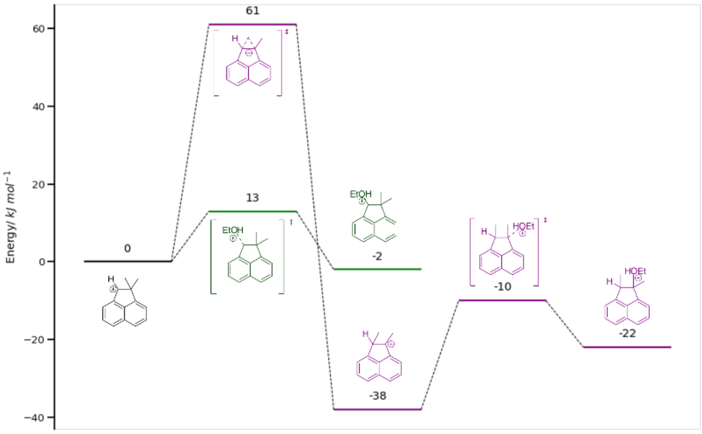
Migration processes, such as 1,2-methyl shifts, represent an interesting class of reactions both for preparative chemistry and understanding solvent effects. However, kinetic studies of these process have been limited and generally the processes have been performed under harsh conditions (in SO_2ClF at -78° C with addition of SbF_5).[1] We have studied the effects of changing the electronic nature of the substrate on 1,2-methyl shifts by considering the acenaphthene series **1**. These were chosen as separately[2] as it had been shown that there was no rearrangement in the parent case (**1a** R, R' = H). A systematic study using DFT methods in conjunction with implicit solvent models was used to evaluate under which conditions 1,2-methyl shifts might be observed.

From these results, it is possible to propose reaction conditions and modifications to the base acenaphthene that will facilitate the rearrangement reaction, making it preferential in comparison to the corresponding reaction with the nucleophile.



R = H, Me, Ph, Cl, Br, NO_2

R' = H, Me, Ph, Cl, Br, NO_2

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