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http://www.uom.ac.mu/sites/ccuom/
https://sites.google.com/site/rhymanlydia/

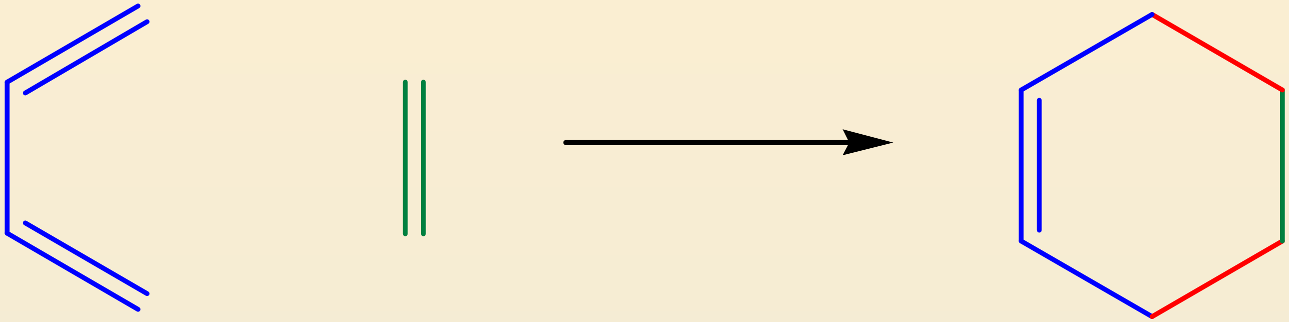
Theoretical Studies
on
Cycloaddition Reactions

L. Rhyman, P. Ramasami,
J. A. Joule and L. R. Domingo

Outline

- Cycloaddition reactions
- Fundamental to applied cycloaddition reactions
- Interplay between experimental and theoretical
- What we have studied?
- What we have been able to achieve?
- Conclusions

Cycloaddition reaction



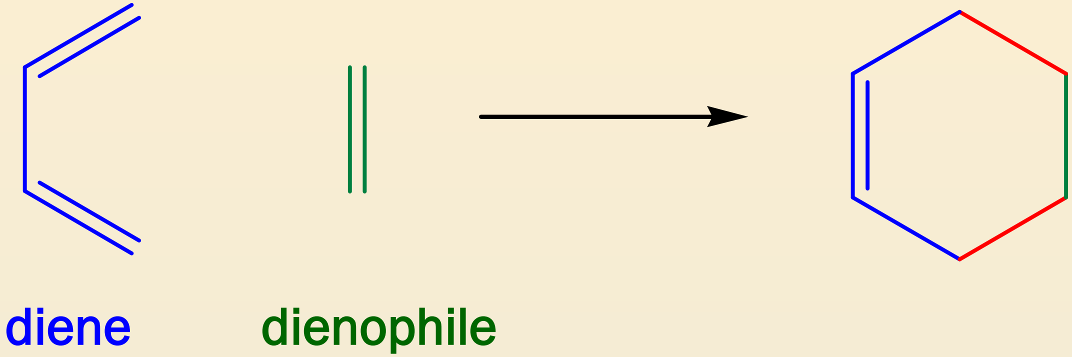
In this type of reaction, two new σ bonds are formed when two π systems interact. It usually leads to the formation of a cyclic compound.

Cycloaddition reaction

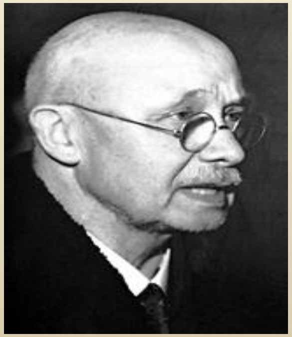
The two most important types of cycloaddition reactions in organic chemistry are:

- Diels-Alder reaction
- 1,3-Dipolar cycloaddition (1,3-DC) reaction

Diels-Alder reaction



The Diels-Alder reaction is the reaction between a diene and a dienophile leading to the formation of a six-membered ring.

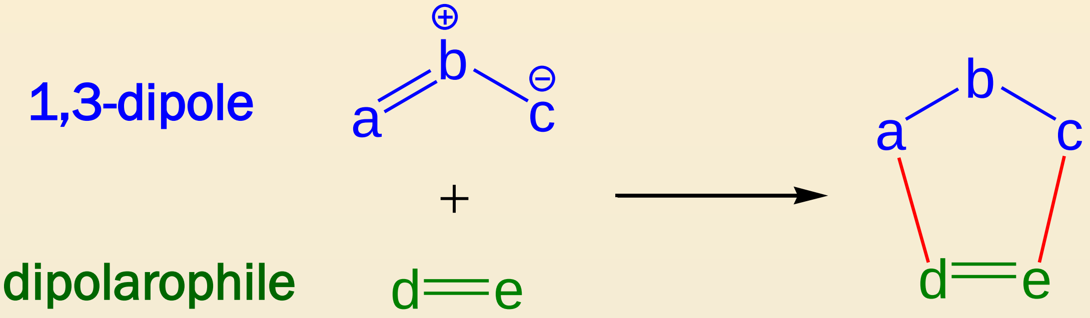


Otto Diels

The Nobel Prize in Chemistry 1950 was awarded jointly to Otto Diels and Kurt Alder "for their discovery and development of the diene synthesis"

http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1950/

1,3-Dipolar cycloaddition reaction



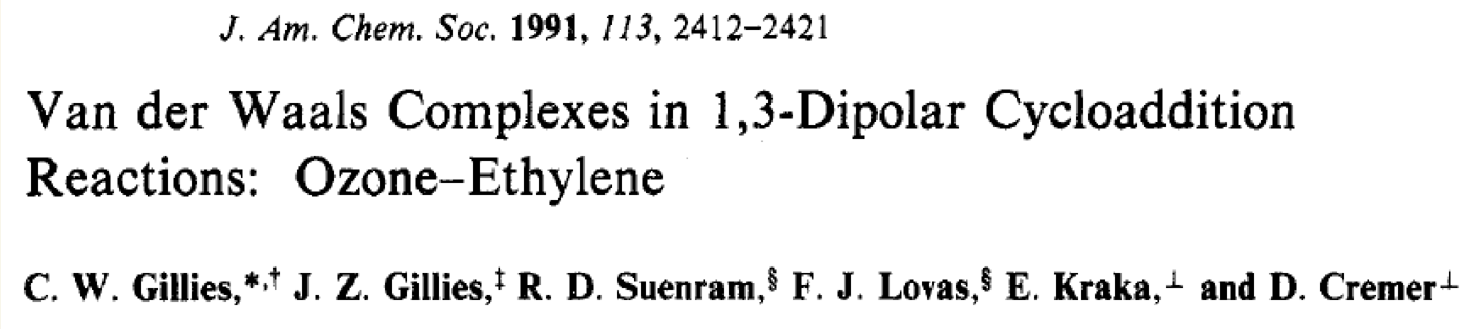
Rolf Huisgen

http://en.wikipedia.org/wiki/Rolf_Huisgen

The 1,3-DC, also known as the Huisgen reaction, is the union of a 1,3-dipole with a dipolarophile to form a five-membered ring. This is reaction is important in the synthesis of heterocyclic compounds.

Fundamental to applied cycloaddition

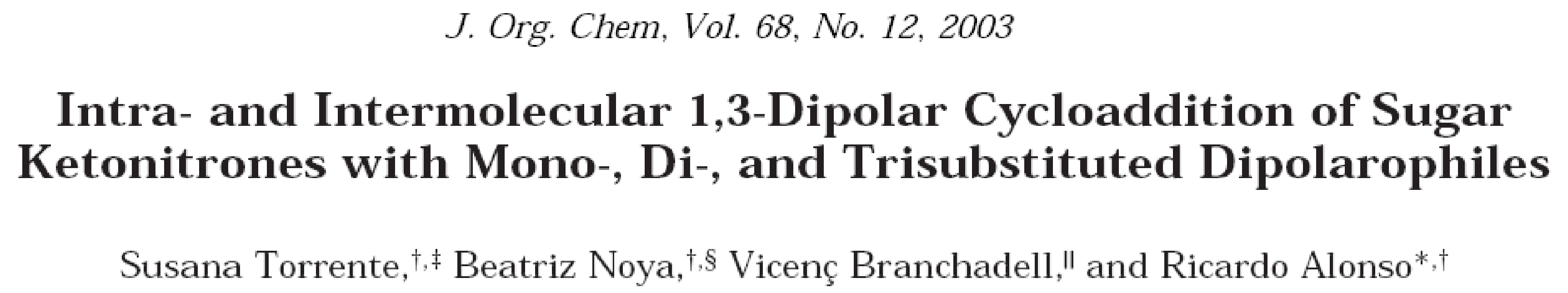
Studies related to cycloaddition reactions have evolved from a fundamental basis to more applied systems.



J. Am. Chem. Soc. **1991,** *113,* 2412–2421

Van der Waals Complexes in 1,3-Dipolar Cycloaddition Reactions: Ozone–Ethylene

C. W. Gillies,[*,†] J. Z. Gillies,[‡] R. D. Suenram,[§] F. J. Lovas,[§] E. Kraka,[⊥] and D. Cremer[⊥]



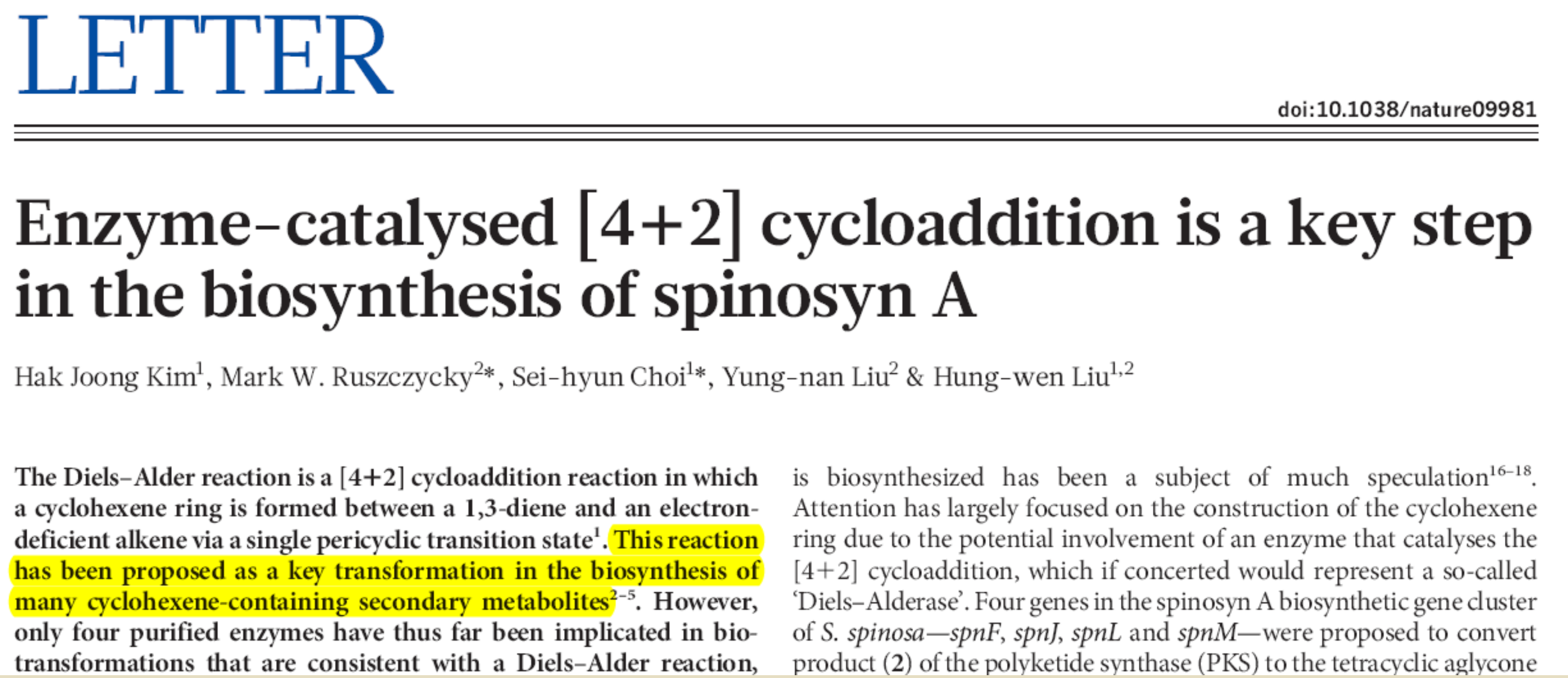
J. Org. Chem., *Vol. 68, No. 12, 2003*

Intra- and Intermolecular 1,3-Dipolar Cycloaddition of Sugar Ketonitrones with Mono-, Di-, and Trisubstituted Dipolarophiles

Susana Torrente,[†,‡] Beatriz Noya,[†,§] Vicenç Branchadell,[∥] and Ricardo Alonso[*,†]

Fundamental to applied cycloaddition

Nature, 473, 2011, 109



LETTER

doi:10.1038/nature09981

Enzyme-catalysed [4+2] cycloaddition is a key step in the biosynthesis of spinosyn A

Hak Joong Kim[1], Mark W. Ruszczycky[2]*, Sei-hyun Choi[1]*, Yung-nan Liu[2] & Hung-wen Liu[1,2]

The Diels–Alder reaction is a [4+2] cycloaddition reaction in which a cyclohexene ring is formed between a 1,3-diene and an electron-deficient alkene via a single pericyclic transition state[1]. This reaction has been proposed as a key transformation in the biosynthesis of many cyclohexene-containing secondary metabolites[2–5]. However, only four purified enzymes have thus far been implicated in biotransformations that are consistent with a Diels–Alder reaction,

is biosynthesized has been a subject of much speculation[16–18]. Attention has largely focused on the construction of the cyclohexene ring due to the potential involvement of an enzyme that catalyses the [4+2] cycloaddition, which if concerted would represent a so-called 'Diels–Alderase'. Four genes in the spinosyn A biosynthetic gene cluster of *S. spinosa*—*spnF*, *spnJ*, *spnL* and *spnM*—were proposed to convert product (**2**) of the polyketide synthase (PKS) to the tetracyclic aglycone

Fundamental to applied cycloaddition

Computational Design of an Enzyme Catalyst for a Stereoselective Bimolecular Diels-Alder Reaction

Justin B. Siegel,[1,2*] Alexandre Zanghellini,[1,2*†] Helena M. Lovick,[3] Gert Kiss,[4] Abigail R. Lambert,[5] Jennifer L. St.Clair,[1] Jasmine L. Gallaher,[1] Donald Hilvert,[6] Michael H. Gelb,[3] Barry L. Stoddard,[5] Kendall N. Houk,[4] Forrest E. Michael,[3] David Baker[1,2,7‡]

The Diels-Alder reaction is a cornerstone in organic synthesis, forming two carbon-carbon bonds and up to four new stereogenic centers in one step. No naturally occurring enzymes
have been showr
computational de
Diels-Alder reacti
confirms that the
binding site subs
for carbon-carbo

Intermolecular
tant in organi
Diels-Alder c
increasing rates a
rally occurring e
(*4*) to catalyze
reaction (*1*, *2*), alt
been generated fi
(*3*, *4*). We have
computational d
novel enzymes (
reactions. Howev
reactions present
both substrates r

dimethylacrylamide (Fig. 1, substrates 1 and 2, respectively) (*8*).

The first step in de novo enzyme design is to decide on a catalytic mechanism and an associated ideal active site. For normal-electron-demand Diels-Alder reactions, frontier molecular orbital theory dictates that the interaction of the highest occupied molecular orbital (HOMO) of the diene with the lowest unoccupied molecular orbital (LUMO) of the dienophile is the dominant interaction in the transition state (*7*). Narrowing the energy gap between the HOMO and LUMO will increase the rate of the Diels-Alder reaction. This can be accomplished by positioning a hydrogen

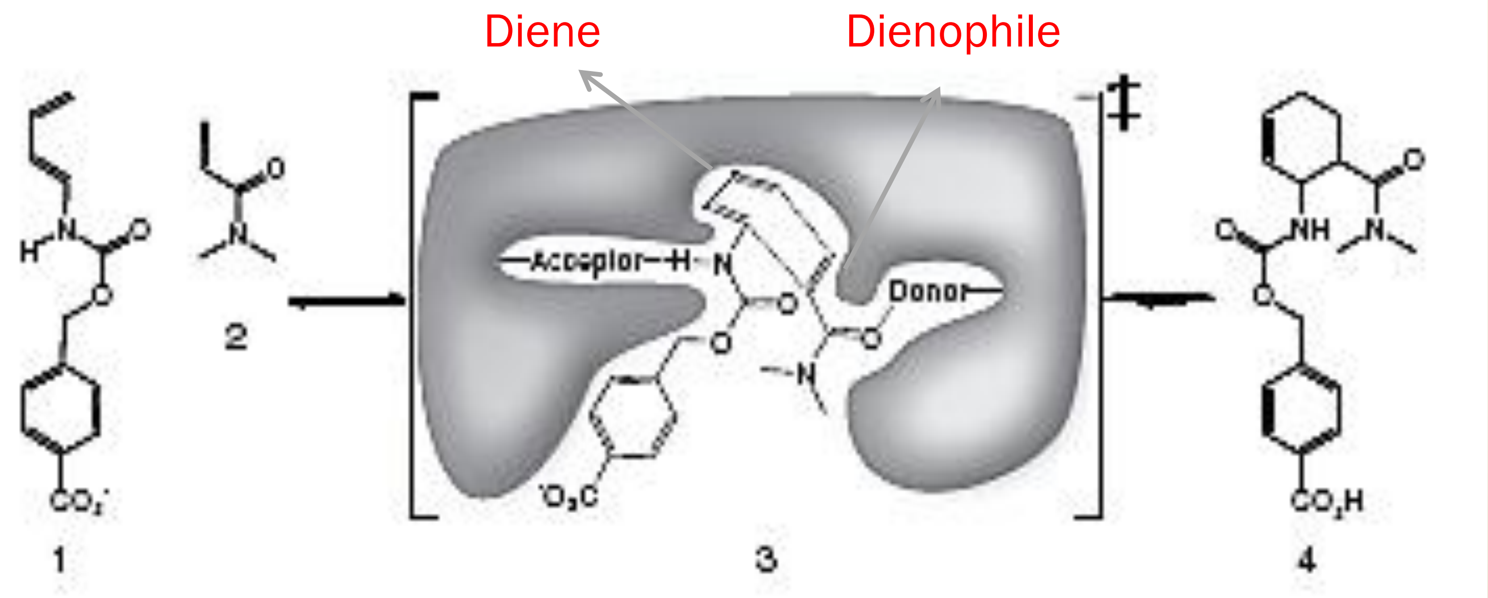


Fig. 1. The Diels-Alder reaction. Diene (1) and dienophile (2) undergo a pericyclic [4 + 2] cycloaddition (3) to form a chiral cyclohexene ring (4). Also shown in (3) is a schematic of the design target active site, with hydrogen bond acceptor and donor groups activating the diene and dienophile and a complementary binding pocket holding the two substrates in an orientation optimal for catalysis.

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‡To whom correspondence should be addressed. E-mail: dabaker@u.washington.edu

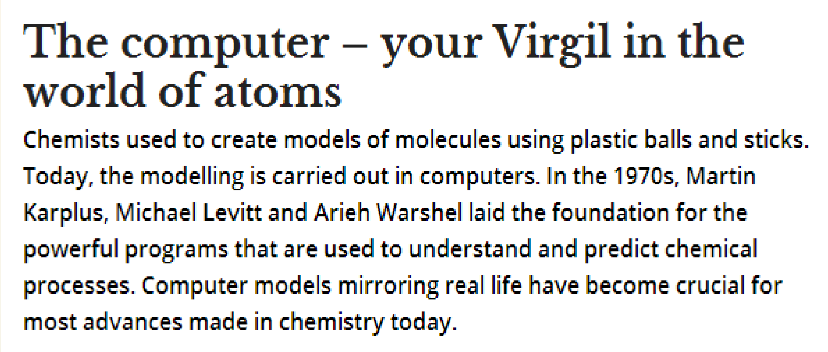
Fundamental to applied cycloaddition

Over the years, the trend has changed. Cycloaddition reactions are being theoretically studied in complex systems as they are effective tools for the synthesis of pharmaceuticals and natural products.

“Today the computer is just as important a tool for chemists as the test tube. Simulations are so realistic that they predict the outcome of traditional experiments.”

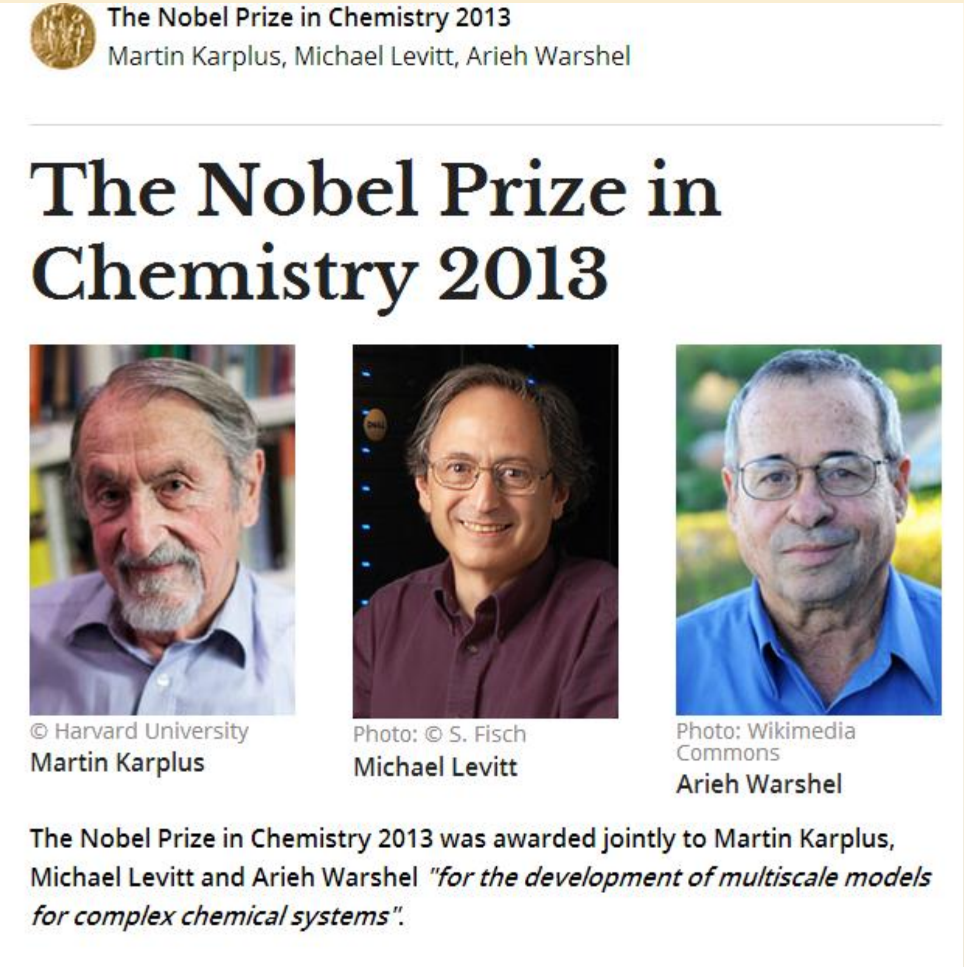
(http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2013/press.html)

Nobel Prize in Chemistry 2013 Awarded to Computational Chemists



The computer – your Virgil in the world of atoms

Chemists used to create models of molecules using plastic balls and sticks. Today, the modelling is carried out in computers. In the 1970s, Martin Karplus, Michael Levitt and Arieh Warshel laid the foundation for the powerful programs that are used to understand and predict chemical processes. Computer models mirroring real life have become crucial for most advances made in chemistry today.



The Nobel Prize in Chemistry 2013
Martin Karplus, Michael Levitt, Arieh Warshel

The Nobel Prize in Chemistry 2013

© Harvard University
Martin Karplus

Photo: © S. Fisch
Michael Levitt

Photo: Wikimedia Commons
Arieh Warshel

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel *"for the development of multiscale models for complex chemical systems"*.

http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2013/

Interplay between experimental and theoretical

- Synthesis of the cycloadducts
- Characterisation by standard methods such as IR, NMR and X-ray
- Based on these parameters, the feasibility of a reaction is predicted

Interplay between experimental and theoretical

Figure 1. Today chemists experiment just as much on their computers as they do in their labs. Theoretical results from computers are confirmed by real experiments that yield new clues to how the world of atoms works. Theory and practice cross-fertilize each other.

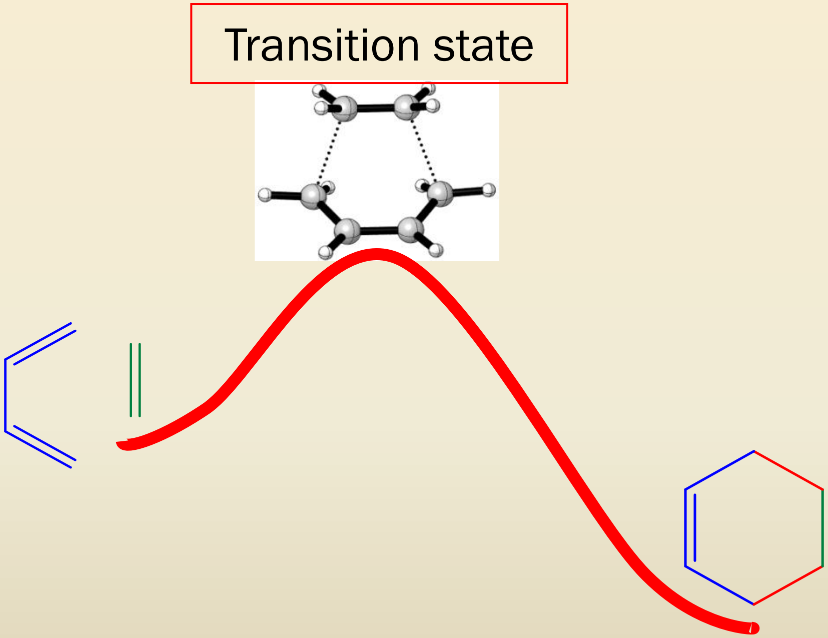
http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2013/popular-chemistryprize2013.pdf

Interplay between experimental and theoretical

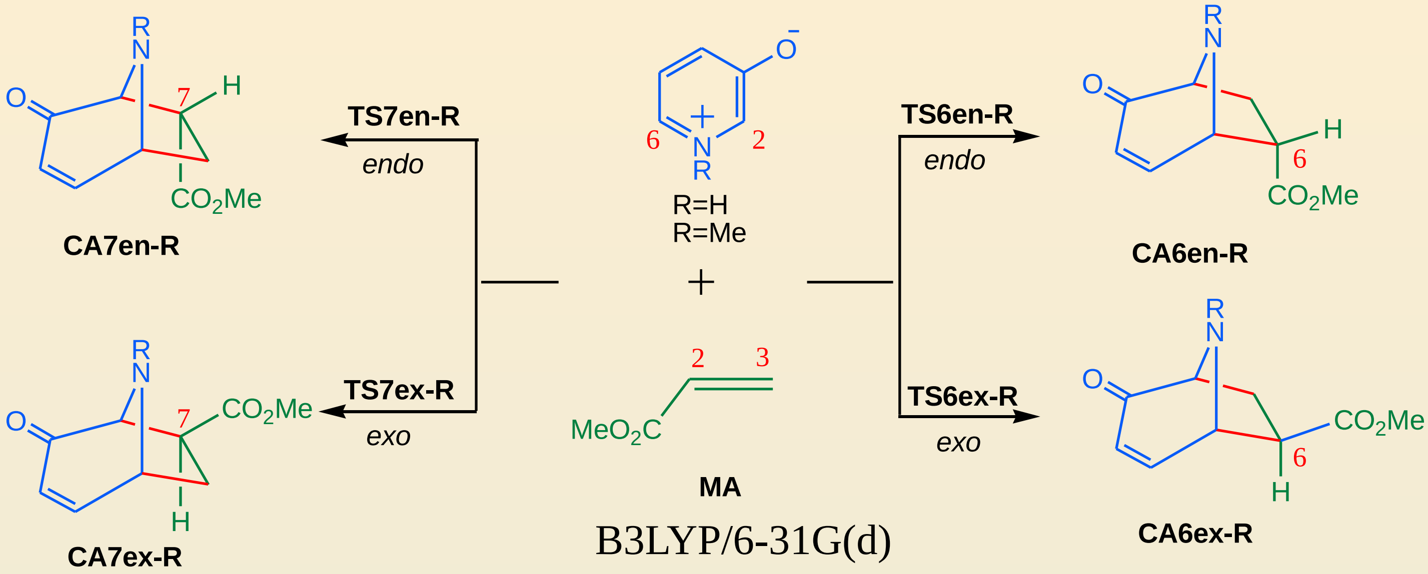
In order to gain a better insight into the mechanism, more details are required.

- Transition states
- Energy of reactants and products; thermodynamic and kinetic parameters
- Types of mechanism; one-step or stepwise

This is where theory plays a vital role.



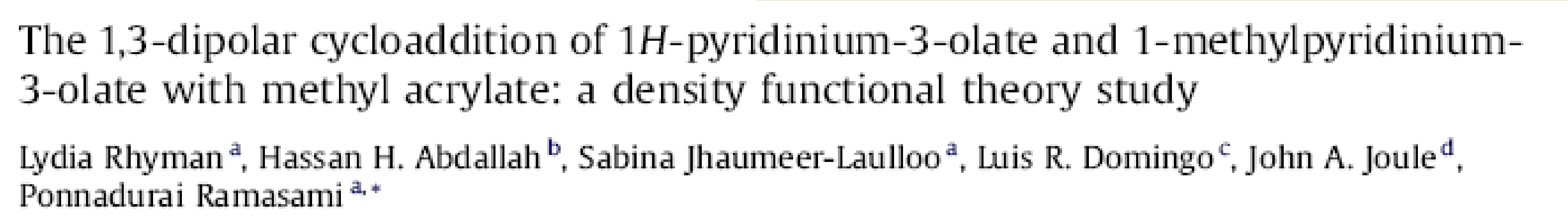
1,3-DC of pyridinium-3-olates with methyl acrylate



B3LYP/6-31G(d)

Our theoretical results indicate that **CA6ex-R** is both kinetically and thermodynamically the most stable and this is in agreement with the experimental findings.

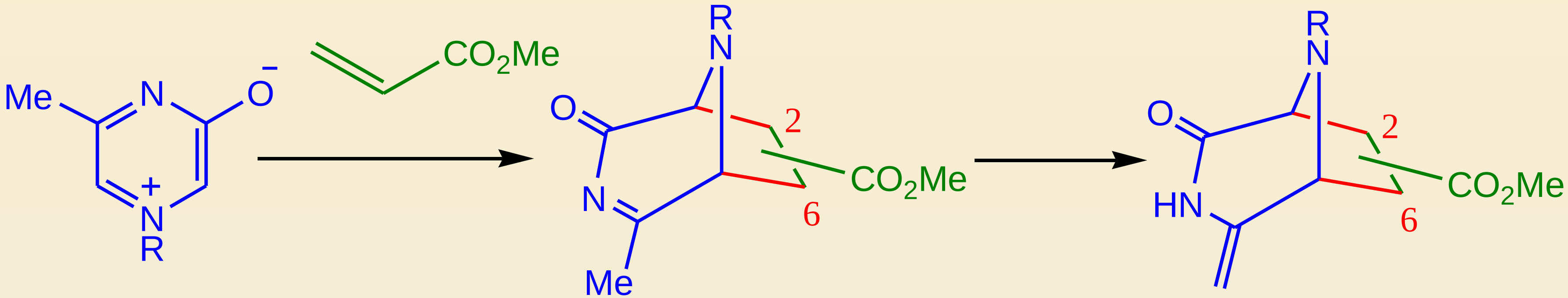
Tetrahedron 66 (2010) 9187-9193



The 1,3-dipolar cycloaddition of 1*H*-pyridinium-3-olate and 1-methylpyridinium-3-olate with methyl acrylate: a density functional theory study

Lydia Rhyman[a], Hassan H. Abdallah[b], Sabina Jhaumeer-Laulloo[a], Luis R. Domingo[c], John A. Joule[d], Ponnadurai Ramasami[a,*]

1,3-DC of pyrazinium-3-olates with methyl acrylate



R = H or Me

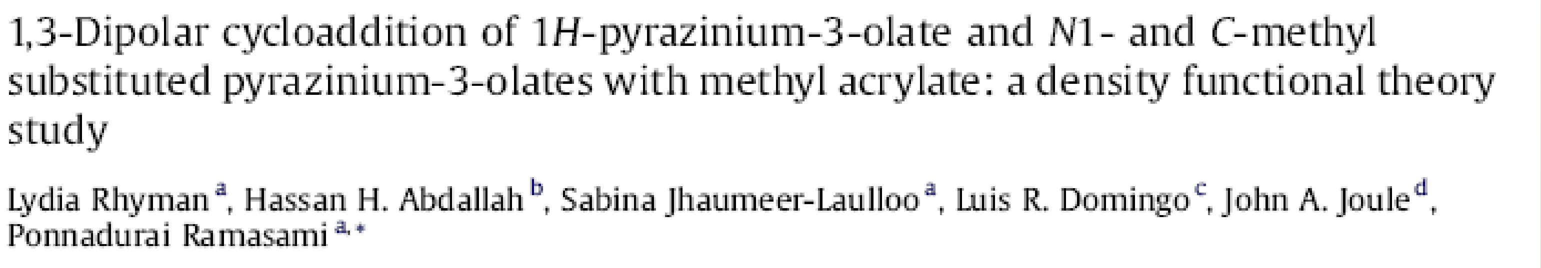
Similarly, the 1,3-DC of pyrazinium-3-olates with methyl acrylate has also been studied theoretically as the resulting cycloadducts are key structural components of biologically active natural products.

1,3-DC of pyrazinium-3-olates with methyl acrylate

It is generally found that the *exo* pathway is preferred and the formation of the 6-esters is dominant over the 7-esters.

On comparing the 1,3-DC of pyridinium-3-olates and pyrazinium-3-olates with methyl acrylate, it is found that lower activation energies and more stable cycloadducts are formed with the inclusion of a second nitrogen in the 1,3-dipole.

Tetrahedron 67 (2011) 8383-8391

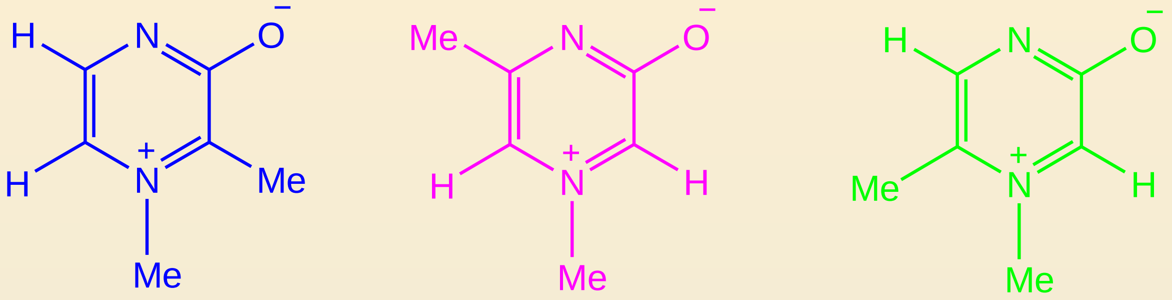


1,3-Dipolar cycloaddition of 1*H*-pyrazinium-3-olate and *N*1- and *C*-methyl substituted pyrazinium-3-olates with methyl acrylate: a density functional theory study

Lydia Rhyman [a], Hassan H. Abdallah [b], Sabina Jhaumeer-Laulloo [a], Luis R. Domingo [c], John A. Joule [d], Ponnadurai Ramasami [a,*]

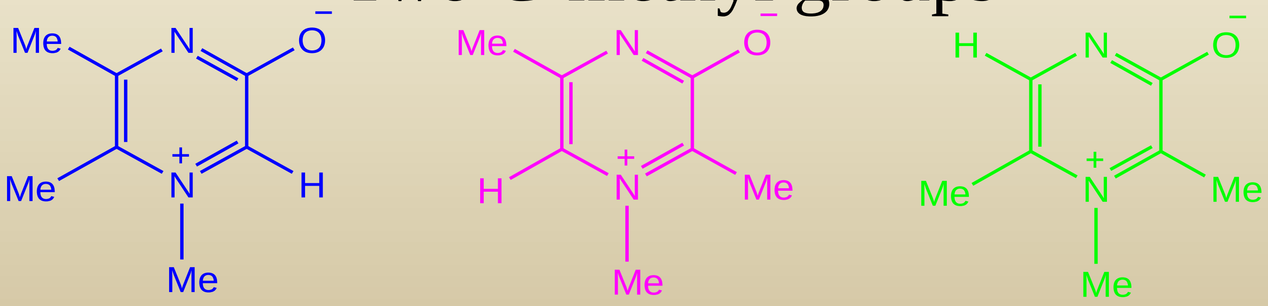
Effect of adding a methyl onto the 1,3-dipole

One C-methyl group



We extended our studies by investigating the effect if adding methyl groups on the pyrazinium-3-olates and compare our results with available experimental data. In general, the 6-exo cycloadduct is predicted to be the major product.

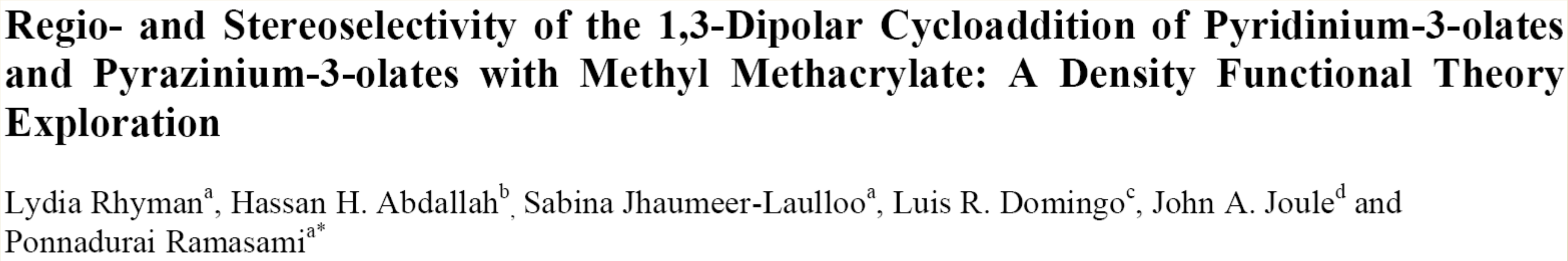
Two C-methyl groups



Effect of adding methyl on the dipolarophile

The thermodynamic and kinetic preferences for the reactions of the pyridinium-3-olates and pyrazinium-3-olates with methyl methacrylate decrease in the order **6**-*exo* > **7**-*exo* > **6**-*endo* > **7**-*endo*.

Curr. Org. Chem. 16 (2012) 1711-1722



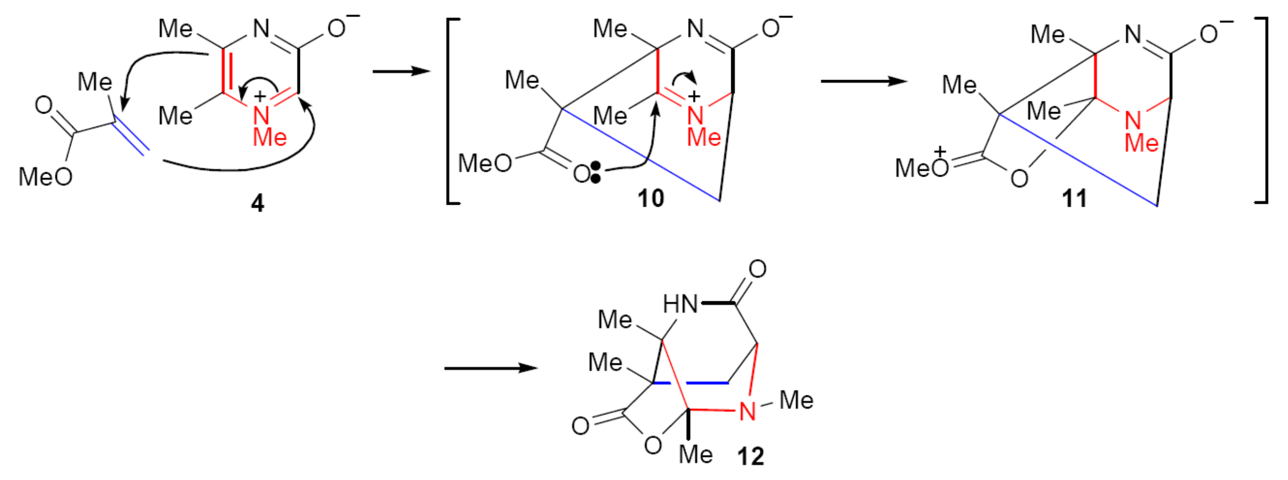
Regio- and Stereoselectivity of the 1,3-Dipolar Cycloaddition of Pyridinium-3-olates and Pyrazinium-3-olates with Methyl Methacrylate: A Density Functional Theory Exploration

Lydia Rhyman[a], Hassan H. Abdallah[b], Sabina Jhaumeer-Laulloo[a], Luis R. Domingo[c], John A. Joule[d] and Ponnadurai Ramasami[a*]

Effect of adding methyl on the dipolarophile

When methyl methacrylate was added to a hindered pyrazinium-3-olate, a different mechanism was proposed to explain the formation of an unexpected product. The proposed mechanism is showed in the scheme below.

Experimental observation



1,3-Dipolar Cycloaddition versus Diels-Alder

1,3-Dipolar cycloaddition reaction *versus* Diels-Alder

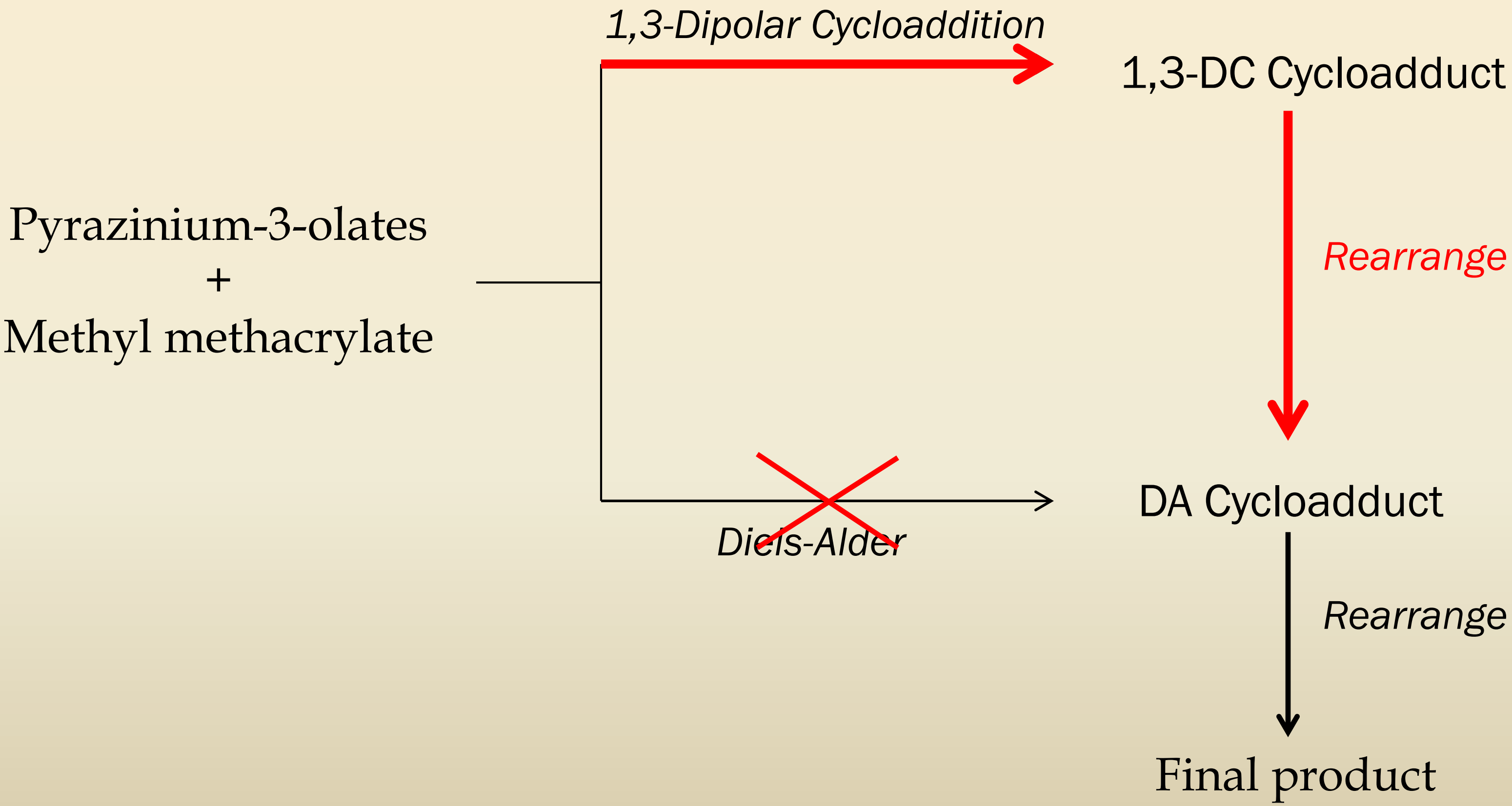
- This called into question all the 1,3-DC of the pyrazinium-3-olates which were previously investigated.

- We questioned whether the reaction may proceed either via a 1,3-DC or via a Diels-Alder reaction.

- This was a challenging problem which we had to solve theoretically.

1,3-Dipolar cycloaddition reaction *versus* Diels-Alder

The results of our theoretical studies are illustrated below.



Pyrazinium-3-olates
+
Methyl methacrylate

1,3-Dipolar Cycloaddition

1,3-DC Cycloadduct

Rearrange

Diels-Alder

DA Cycloadduct

Rearrange

Final product

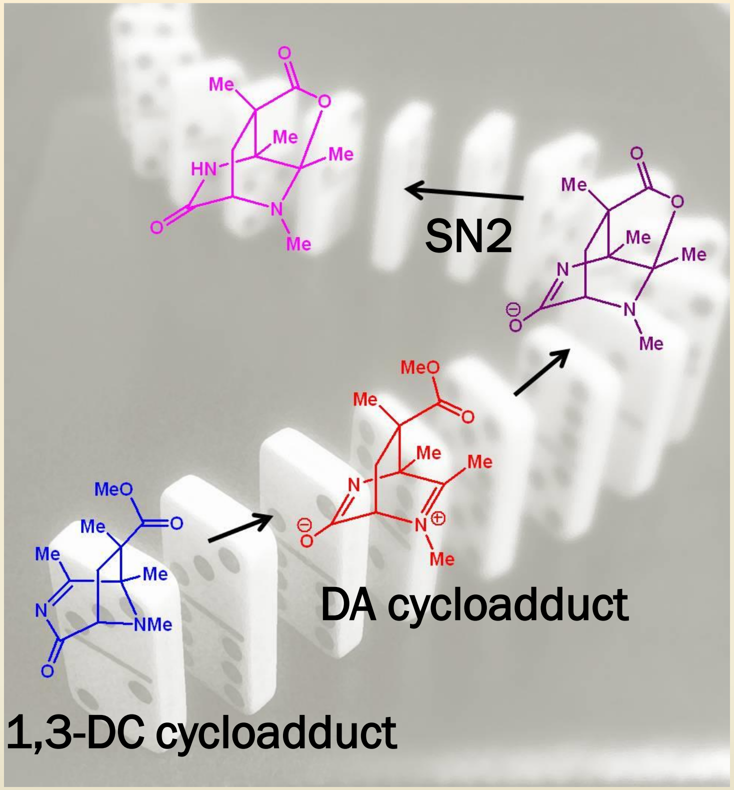
Domino process

Formation of the final product is a domino process involving three consecutive steps:

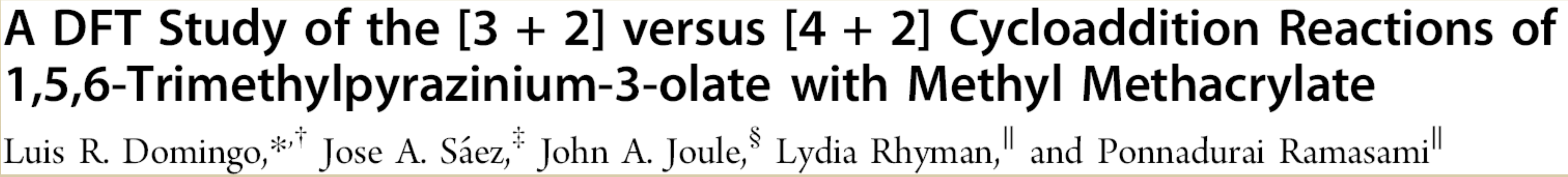
1.1,3-DC

2.Skeletal rearrangement of the 1,3-DC cycloadduct to the Diels-Alder [4 + 2] cycloadduct

3.S_N2 reaction



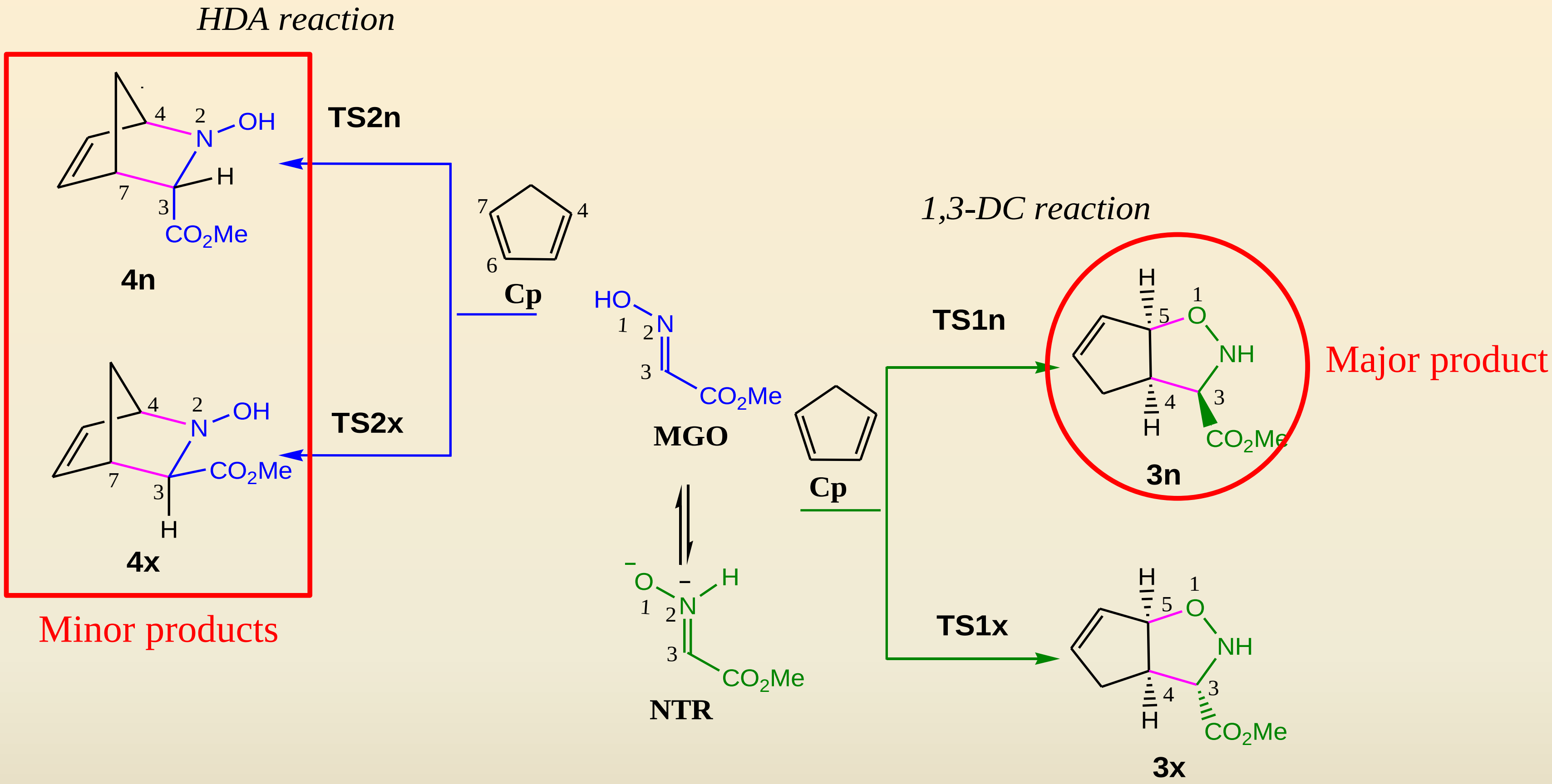
J. Org. Chem. 78 (2013) 1621-1629



A DFT Study of the [3 + 2] versus [4 + 2] Cycloaddition Reactions of 1,5,6-Trimethylpyrazinium-3-olate with Methyl Methacrylate

Luis R. Domingo,*,† Jose A. Sáez,‡ John A. Joule,§ Lydia Rhyman,‖ and Ponnadurai Ramasami‖

Competitive hetero-DA and 1,3-DCs



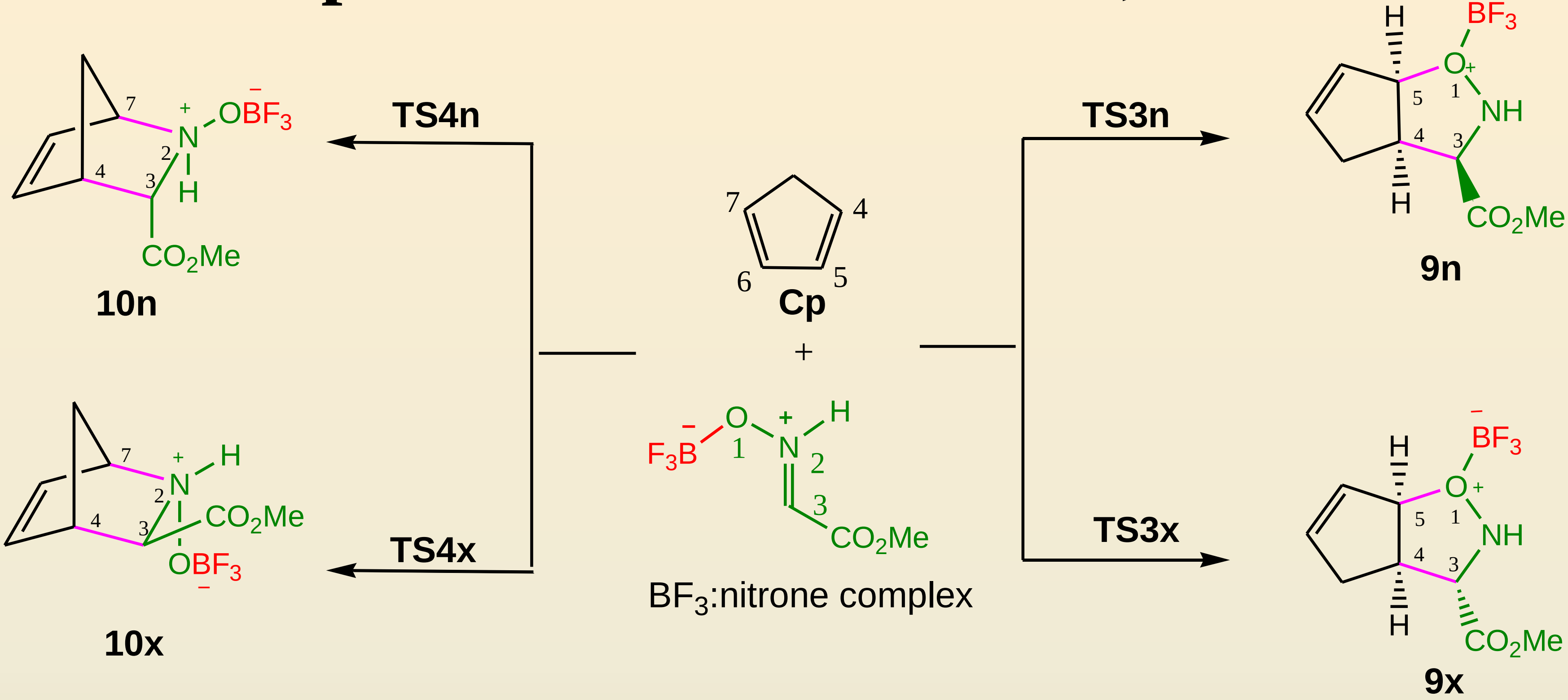
It is well-known that when cyclopentadiene (Cp) reacts with an oxime, a Diels-Alder reaction occurs, the C=N of the oxime being the dienophile.

Competitive hetero-DA and 1,3-DCs

However, when Cp reacts with the oxime of methyl glyoxylate (MGO), an unexpected product was observed as major product.

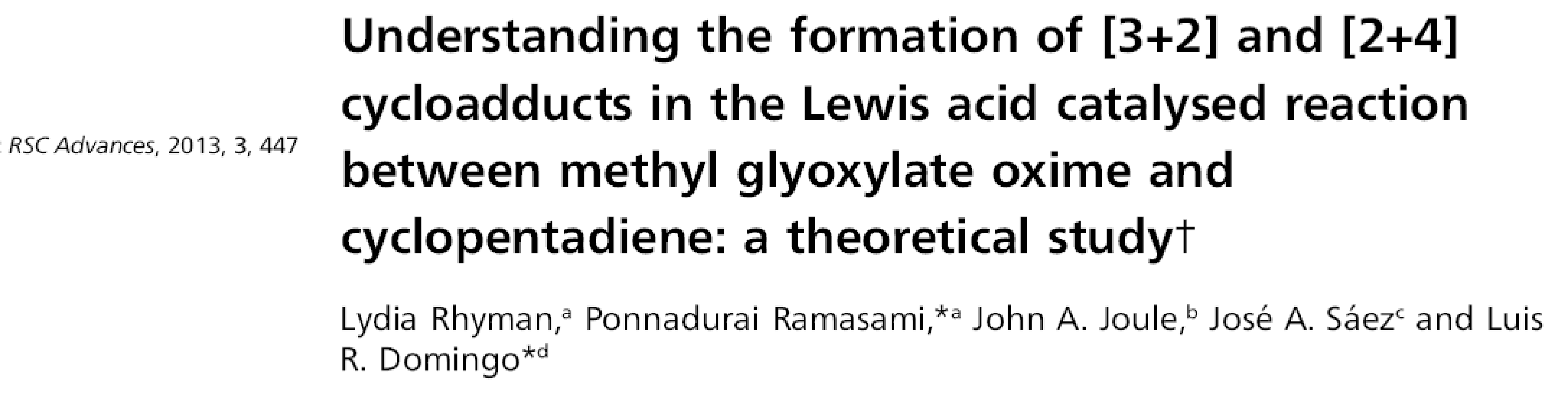
In order to rationalise the formation of these products, we carried out a theoretical study where we reported that the formation of the major product occurs via a 1,3-DC of one double bond of Cp with the nitrone tautomer of the oxime.

Competitive hetero-DA and 1,3-DCs



We have also considered the effect of adding a Lewis-acid catalyst. We found that the catalyst converts the nitrone into a more reactive species and therefore favours the formation of the 1,3-DC cycloadducts over the Diels-Alder cycloadducts.

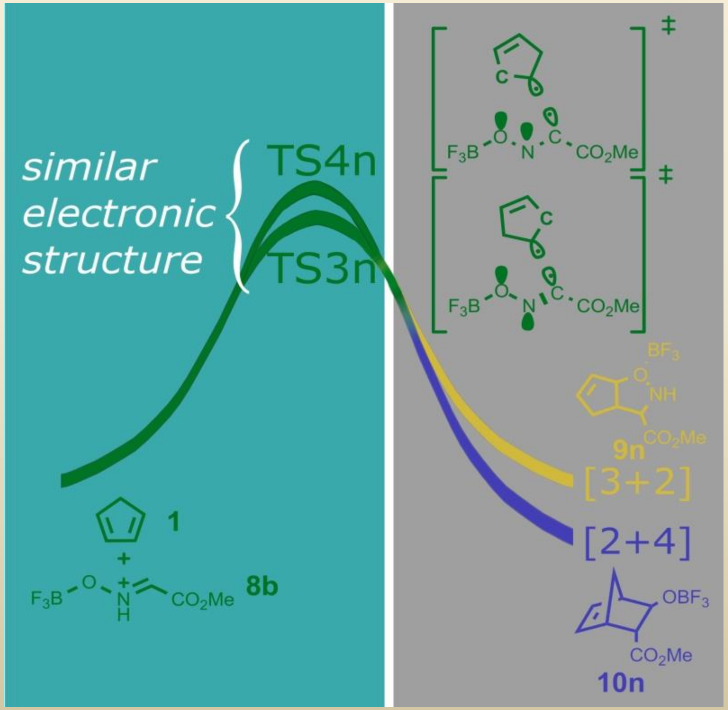
Competitive hetero-DA and 1,3-DCs



RSC Advances, 2013, 3, 447

Understanding the formation of [3+2] and [2+4] cycloadducts in the Lewis acid catalysed reaction between methyl glyoxylate oxime and cyclopentadiene: a theoretical study†

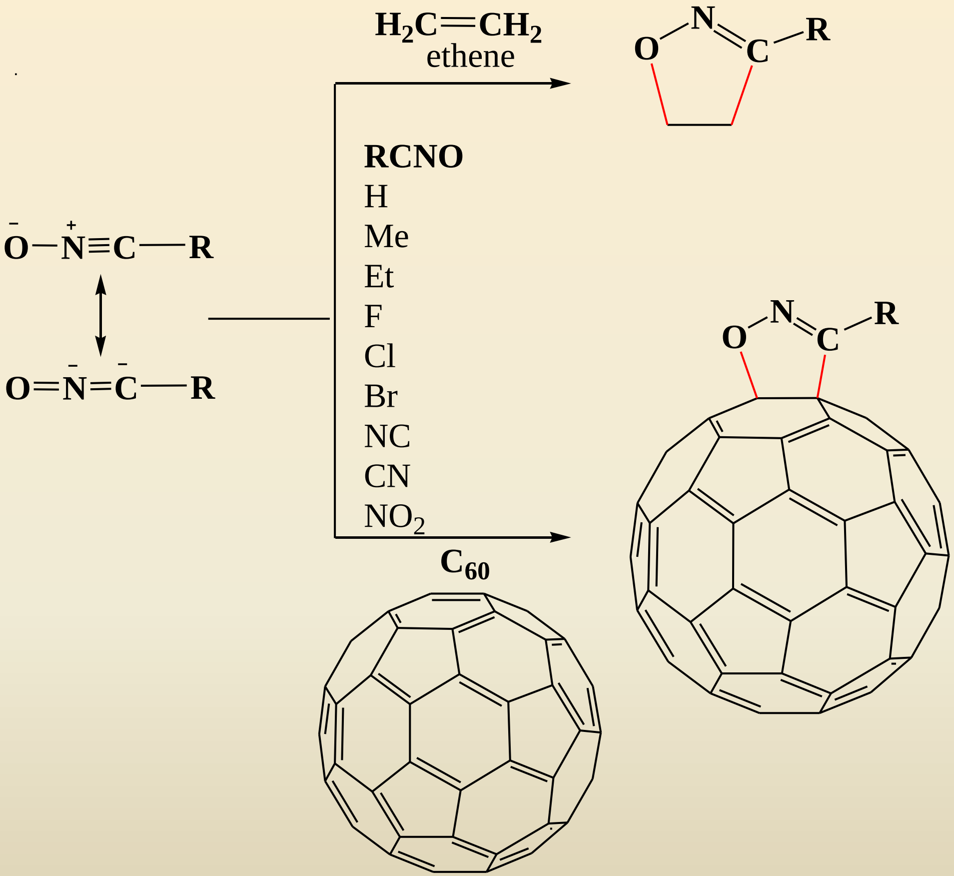
Lydia Rhyman,[a] Ponnadurai Ramasami,*[a] John A. Joule,[b] José A. Sáez[c] and Luis R. Domingo*[d]



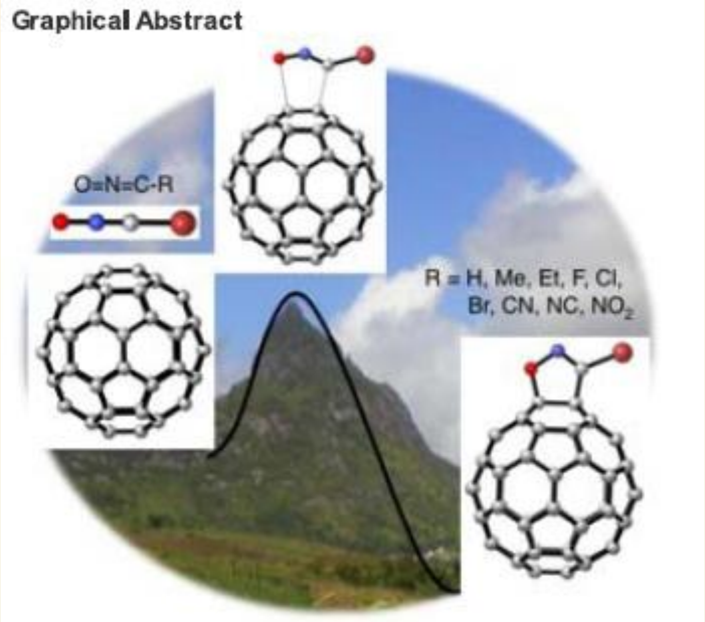
1,3-DCs of C_{60} with substituted nitrile oxides

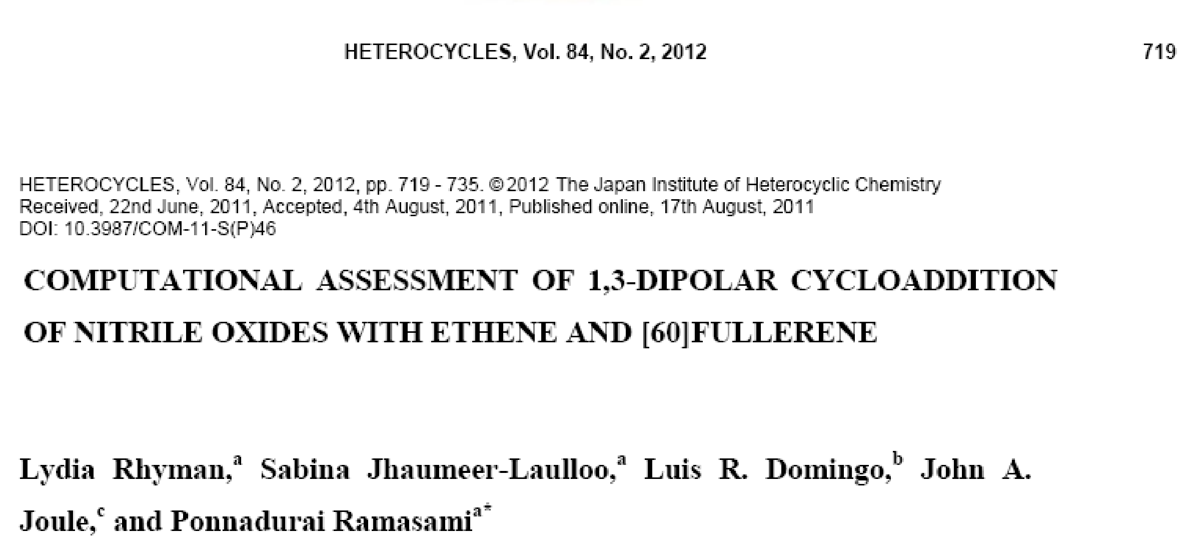
The 1,3-DCs of ethene and C_{60} with substituted nitrile oxides have been studied theoretically at the B3LYP/6-31G(d) level of theory.

An atypical behaviour was observed with FCNO as it has some pseudodiradical character.



1,3-DCs of C_{60} with substituted nitrile oxides




HETEROCYCLES, Vol. 84, No. 2, 2012 719

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Received, 22nd June, 2011, Accepted, 4th August, 2011, Published online, 17th August, 2011
DOI: 10.3987/COM-11-S(P)46

COMPUTATIONAL ASSESSMENT OF 1,3-DIPOLAR CYCLOADDITION OF NITRILE OXIDES WITH ETHENE AND [60]FULLERENE

Lydia Rhyman,[a] Sabina Jhaumeer-Laulloo,[a] Luis R. Domingo,[b] John A. Joule,[c] and Ponnadurai Ramasami[a*]

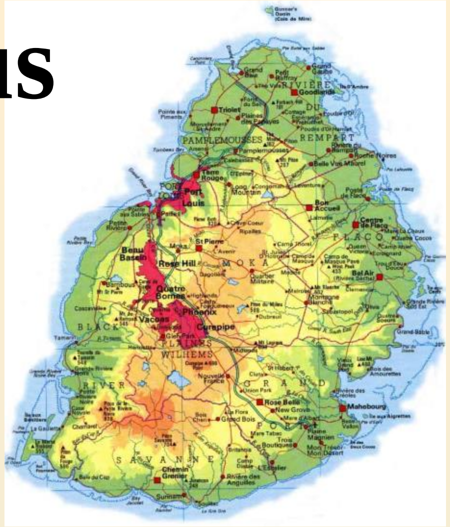
Overall conclusions

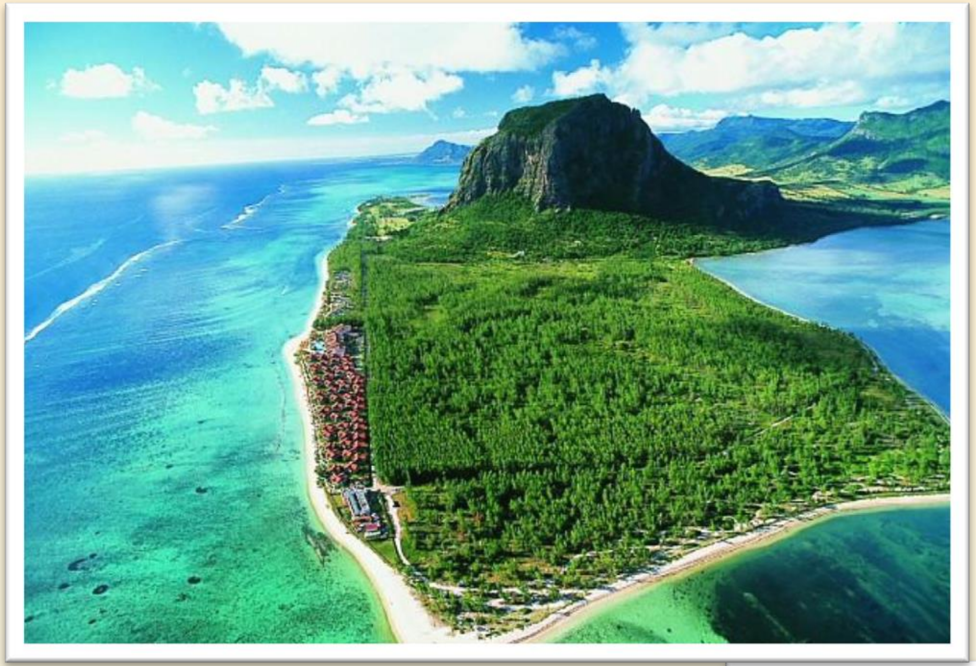
- The theoretical results are in good accord with available experimental findings
- Provide incentive to study cycloaddition reactions which are chemically untried
- Theoretical results are important for experimentalists
- Still more parameters need to be investigated such as rate of reactions and percentage yield

Acknowledgements

- Organising Committee of the 17th ECSOC
- Collaborators: Prof Ponnadurai Ramasami, Prof John A Joule, Prof Luis R Domingo, Dr Hassan H Abdallah
- Facilities from Gridchem
- University of Mauritius
- Tertiary Education Commission of Mauritius

A glimpse of Mauritius





Forthcoming conferences

8th Workshop on Computational Chemistry and Its Applications (10-12 June 2014)

International Conference on Pure and Applied Chemistry, ICPAC-2014 (23-27 June 2014)

Virtual Conference on Computational Chemistry, VCCC-2014 (1-31 August 2014)

Thank you