



Computational Studies of the Reactivity, Regio-Selectivity and Stereo-Selectivity of Pericyclic Diels-Alder Reactions of Substituted Cyclobutenones

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Abstract

The power of the Diels-Alder reaction was expanded recently through the discovery by Li and Danishefsky that cyclobutenone is an unusually reactive dienophile and that the adducts formed can be converted to products that are formally the Diels-Alder adducts of unreactive dienophiles. However, the effects of substituents on the reactivity as well as the regio- and stereo-selectivity of the Diels-Alder reactions of cyclobutenones have not been clearly elucidated yet. This paper reports the results of a computational study at the MP2/6-31G* level of theory into the effects of substituents on the reactivity, regio-selectivity and stereo-selectivity of the Diels-Alder reactions of some substituted cyclobutenones with cyclic and acyclic dienes. It was found that the Diels-Alder reaction of maleic anhydride is far more feasible kinetically than the reaction of cyclobutenone, the activation barrier of the former being more than three times that of the latter, indicating that maleic anhydride is a far better dienophile than cyclobutenone, which in turn implies that for cyclic dienophiles ring strain is not the dominant factor controlling the kinetics of the Diels-Alder reaction as has been suggested elsewhere. The Diels-Alder reactions of cyclobutenones were all found to follow an asynchronous concerted reaction pathway. In the reactions of the parent (unsubstituted) cyclobutenone with 1,3-butadiene and cyclopentadiene, the *endo* pathway is the most preferred kinetically, by 2.24 and 1.64 kcal/mol respectively. However, in the reactions of the 4,4-disubstituted cyclobutenones the *exo* pathway becomes the most preferred in the reactions with both 1,3-butadiene and cyclopentadiene, except for the CN-substituted cyclobutenone where the *endo* pathway is still the most preferred pathway. In the reactions of the 4-monosubstituted cyclobutenone with 1,3-butadiene, the anti-positions are preferred over the *syn* positions. The *endo-anti* position gives the most reactive dienophile kinetically. In the reactions of *trans*-piperylene with substituted cyclobutenones, the *meta-endo* position is the most preferred kinetically. In the reactions of isoprene with substituted cyclobutenones, the *para-endo* substitution gives the lowest activation barriers and therefore the most favorable reaction kinetics. In all the reactions considered in this work, the CN-substituted species have the lowest activation barriers and the most stable products. In the reactions of 4,4-disubstituted cyclobutenones with 1,3-butadiene and cyclopentadiene, the order of activation barriers is CN < OH < Cl < CH₃ and the stability of the products decrease in the order CN>OH>Cl>CH₃.

Keywords: Diels-Alder; Cycloaddition; Regio-selectivity; Stereo-selectivity; Cyclobutenone

Introduction

The Diels-Alder reaction, a [4 + 2] cycloaddition reaction in which a molecule with a conjugated π-system (a diene) and another with at least one π-bond (a dienophile) react to form a cyclohexene derivative (Scheme 1), is a powerful tool for the synthesis of six-membered ring systems. This reaction involves the breaking of three π-bonds to form two new σ-bonds that form a ring and the generation of a new π-bond in a cyclohexene derivative. A simplest prototype is the reaction of 1,3-butadiene and ethylene (Scheme 1).

The Diels-Alder reaction has both enabled and shaped the art and science of total synthesis over the last few decades to an extent, which, arguably, has yet to be eclipsed by any other transformation in the current synthetic repertoire. With myriad applications of this magnificent pericyclic reaction, often as a crucial element in elegant and programmed cascade sequences facilitating complex molecule construction, the Diels-Alder cycloaddition has afforded numerous and unparalleled solutions to a diverse range of synthetic puzzles provided by nature in the form of natural products, and has proved a reliable method for forming six-membered systems with good control over regio and stereo-chemical properties [1-6].

The control of stereo- and regio- chemistry plays an important role in the world of synthetic organic chemistry. In the case of the pharmaceutical industry, some drugs such as thalidomide, the

dextrorotatory enantiomer of the drug has the desired sedative properties while the levorotatory enantiomer is teratogenic. Stereo- and regio-selectivity of the Diels-Alder reaction is of most paramount concern because it is a crucial element for a successful synthesis [7]. Theoretically investigated the Diels-Alder reaction between 2-phenylcyclopentadiene and α-(methoxyimino) acrylonitrile (Scheme 2) in which geometry optimizations were performed with RHF/3-21G, RHF/3-21G*, and RHF/6-31G* calculations while the correlation energy was calculated at the MP2 and MP3 levels of theory. The reaction produced four asynchronous transition structures corresponding to the formation of different stereo- and regio-isomers associated with the four reaction channels. The theoretical results pointed out that the regioselectivity is controlled by the presence of phenyl group on C₂ carbon atom of the diene system while the stereoselectivity is controlled by a favorable

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Stereo- and theoretical chemistry. Additional title: Stereo and theoretical chemistry. Journal / Series: Fortschritte der chemischen Forschung. Volume: QR code for Stereo- and Theoretical Chemistry Volume 31 of Topics in Current Chemistry. Authors, A. Davison Science / Chemistry / Physical & Theoretical.wsdmind.com: Stereo- and Theoretical Chemistry (Topics in Current Chemistry) () by A. Davison; M. J. S. Dewar; K. Hafner; E. Heilbronner; Stereochemistry, a subdiscipline of chemistry, involves the study of the relative spatial d/l); Solid-state chemistry VSEPR theory Skeletal formula# Stereochemistry which describes how stereochemistry is denoted in skeletal formulae. Experimental and Theoretical Studies on Stereo- and Regioselectivity in Intramolecular Nitrene? Alkene Cycloaddition of Heptenoses Derived from understanding of theoretical chemistry. Sidney Golden, introduction to Theoretical Physical Chemistry. E~nest I., Elid, Stereochemistry of Carbon Compounds.at comprehensive discussions on the theoretical foundations of organic and inorganic chemistry on the basis of Fujita's stereo- isogram approach [2,3]. Because. This Symposium was intended to illustrate current applications of Theoretical Chemistry in different fields of. Theoretical Chemistry has become a powerful tool of investigation in all areas of Chemistry, . Stereo- and Theoretical Chemistry. The concept of the steric effect in molecular collisions is central to chemistry. University of Oxford, The Physical and Theoretical Chemistry Laboratory, South. E-mail: wsdmind.com@wsdmind.com bPhysical and Theoretical Chemistry Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QZ. Enumeration of Stereoisomers Theoretical Matrices in Chemistry by D. Jane`i~, A. Mi- li~evi}, S. searcher in mathematical stereochemistry and a member.wsdmind.com: Theory of Solutions and Stereo-Chemistry (The Development of science) (): I. Bernard Cohen, Rita Lawn: Books. Derivatives (4) The Silicates in Chemistry and Commerce: including the Exposition of a Hexite and Pentite Theory and of a Stereo-chemical Theory of General. 21 Hi Fi Stereo Speaker Cabinets You Can Build, Robin, Christopher, A Comprehensive Treatise on Inorganic and Theoretical Chemistry (Vol 4) Ra. 2 Department of Physical and Theoretical Chemistry, University of . will be necessary to orientate molecules in order to identify any stereo-chemical constraints. 1, to the Chemistry Section, British Association for the Reaction Networks: Theoretical Games, Speculations on Chemical Evolution and. J Org Chem. Apr 14; 71(8) Experimental and theoretical studies on stereo- and regioselectivity in intramolecular nitrene-alkene cycloaddition of. Journal of Theoretical and Computational Chemistry The stereodynamics of the title reaction on the ground 1 1A? potential energy surface (PES) has been. DFT study of the stereo-selectivity of oxygenated heterocycles from 10 to 12 of his contributions to theoretical and computational chemistry. Chemistry Conferences: The study of stereochemistry focuses on stereoisomers and spans 5 International Conference on Physical and Theoretical Chemistry. Research on Relation between Pixel Pitch and Theoretical Stereo Depth. Ping Su, Shu The stereo depth plays an essential part in auto-stereoscopic display. 2 Institute

for Theoretical Chemistry, University of Vienna, Wien A, Austria several chemical examples, including the enumeration of stereoisomers of. Viktor Kuz'min is an expert in theoretical chemistry and a prominent for modeling of molecular structure, system of stereo analysis and stereo design of chiral.

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