PREDICTION OF DIENE-DIENOPHILE REACTIVITY IN CYCLOADDITIONS AND PROBING THE NATURE OF SHORT C-C BONDS: A COMPUTATIONAL APPROACH

A Synopsis of thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

To

OSMANIA UNIVERSITY

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October 2008
Synopsis

The thesis entitled “Prediction of Diene-Dienophile Reactivity in Cycloadditions and Probing the Nature of Short C-C Bonds: A Computational Approach” is divided into seven chapters.

Chapter 1: Introduction

Computational methods have become increasingly popular practical tools for chemists to predict a reaction’s outcome and the physical properties of the chemical systems. The development of *ab initio* and density functional theory based methods and their effective implementation in software packages has made a great impact on virtually all branches of chemistry, physics as well as in biology. Organic chemistry is perhaps one of the areas where the contribution from computations and their impact on experimental chemistry is outstanding. With the advent of a range of computational tools and software packages, and effective implementation of various theoretical methodologies, now computational chemistry has become an extremely important area of research in chemistry, and particularly in delineating organic chemical structures and mechanisms. Besides structural determinations, these methods have proved to be better in explaining the reaction barriers and electronic characteristics of the transition structures, especially in the case of pericyclic reactions, energies of the molecular systems, spectroscopic properties, etc.

Pericyclic reactions were defined by R. B. Woodward and R. Hofmann as ‘reactions in which all the first-order changes in bonding relationships occur in a concert or closed curve’. This definition arose from the systematic study of the conservation of orbital symmetry in a series of reactions: electrocyclic reactions, cycloaddition reactions, sigmatropic shifts, cheletropic reactions and group transfer and elimination reactions.
The first insight of the pericyclic reactions was provided by Woodward and Hofmann in their monograph ‘The Conservation of Orbital Symmetry’. The basic idea is that the reactions occur readily ie thermally allowed, when there is congruence between the orbital symmetry characteristics of the reactants and products, while they occur with difficulty, ie thermally forbidden, when there is no congruence. In other words orbital symmetry is maintained in concerted reactions. This has been proved by Pearson by means of perturbation theory.

Another important contribution was made by Fukui with his frontier orbital theory. According to this theory reactions should take place in the direction of maximum overlap of the HOMO and LUMO of the reacting molecules. The most important interaction involves the HOMO and LUMO with the smaller energy gap, while the maximum overlap is obtained by bonding the termini with larger coefficients. This has been very much successful in predicting the regioselectivity of the reactions. The regioselectivity can also be explained by DFT based descriptors such as Fukui function indices, softness, electrophilicity indices, triplet spin densities etc.

Atoms in Molecules (AIM) and energy decomposition analysis (EDA) are proved to be reliable methods to understand the concepts of bonding. With the AIM approach, one can determine if there is or not a bond involved in a system by using criteria based on the electron density, which is a scalar field obtained by several quantum chemistry methods or by experimental techniques. EDA involves the electron-electron attractive and repulsive interactions.

**Chapter 2: Methodology**

Chapter 2 deals with the various computational methodologies such as Hartree-Fock (HF), coupled cluster(CC) method, Møller-Plesset perturbation(MP) theory, density functional theory (DFT) and semiempirical methods that are employed in the thesis. This is
followed by a discussion on the appropriateness of the adopted methodologies on each of the problems tackled in the thesis. After dealing with the theoretical basis for the quantitative methodologies employed in the thesis, we turned to the qualitative models. Most of these models are derived from the quantum chemical principles and they include frontier molecular orbital theory, density functional theory descriptors such as chemical hardness, Fukui function indices, electrophilicity index, softness, electrochemical potential, Koopmans’ theorem, Hammond’s postulate, Valence Bond Configuration Mixing, etc. These qualitative models are used to rationalize the computed structural, stability and reactivity trends.

Chapter 3: Bottlenecks in the Prediction of Regioselectivity of \([4+2]\) Cycloaddition Reactions: An Assessment of Reactivity Descriptors

Regioselectivity has been one of the most important aspects to keep in mind and understanding the factors controlling regioselectivity helps a great deal in synthetic strategies. A quick perusal of the combined experimental and computational studies reveal that prediction of regioselectivity in cycloaddition reactions is still a challenging task and no reliable criterion exists which explains all the expected observations involving regioselectivity. The present chapter deals with the regioselectivity of 128 distinct reaction channels of Diels–Alder reactions by taking all possible combinations from a series of dienes \((1N-a, 1N-b, 2N, 1P-a, 1P-b, 2P, 1O, 1S)\) and dienophiles \((NE, PE, OE, SE, AE, OHE, MeE, CNE)\) as in Scheme 1. B3LYP/6-31G(d) calculations were performed on all the reactants, transition states and products. The predictive ability of the values to gauge the regioselectivity of the putative \([4+2]\) cycloaddition reactions is analyzed. No correlation is obtained between the reaction energies and activation energies. The extent of asynchronicity is measured based on the bond order analysis and all the reactions are found to be asynchronous. DFT-based descriptors such as local softness \((s_k^+\) and \(s_k^-\)), Fukui function
indices ($f_k^+$ and $f_k^-$), global electrophilicity index ($\omega$) and local electrophilicity index ($\omega_k$) were found to be better than the conventional FMO predictions. These results are compared with that of the activation energies to measure performance of the DFT based descriptors. The success rate of regioselectivity prediction is found to be much higher with any of the DFT-based descriptors, which could explain the regioselectivity in about 38-43 cases, compared to conventional FMO-based descriptors, which predict the regioselectivity only in 29 out of 64 cases.

\begin{align*}
\text{Scheme 1}\end{align*}

**Chapter 4: Hetero Diels-Alder Reactions: A Testing Ground for the Predictive Performance of Qualitative and Quantitative Methods**

When more than one possible coupling route is available, the mechanism of transition state formation differs for different orientations of coupling, thereby preferring one over the other. The major task to be solved in such cases is regioselectivity, stereoselectivity and exo-endo selectivity of the products. Testing the reliability of any quantitative or qualitative approach requires the application of these methods on a large number of compounds. The purpose of the current study is to perform an exhaustive and systematic computational study on a large number of hetero Diels-Alder reactions. A total of 64 reactions which essentially lead to 247 distinct reactions channels by taking all possible combinations from a series of dienes ($\text{1, 1N-a, 1N-b, 2N, 1P-a, 1P-b, 2P, 1O, 1S}$) and dienophiles ($\text{E, NE, PE, OE, SE, AE, OHE, MeE, CNE}$) are considered. B3LYP/6-31G(d), HF/6-31G(d), CCSD(T)/6-
31G(d) and MP2/6-31g(d) calculations are performed in order to look at the method dependency on the activation energies and the exothermicities of the series of reactions under study. Concerted and stepwise reactions for a set of reactions are evaluated which suggest that such reactions proceed through asynchronous and concerted mechanism. Singlet-triplet energy gaps are computed to understand the stability of the products. All the reactions studied are asynchronous with the asynchronicity ranging from 0.01 to 1.18 Å.

In general head-to-head arrangement is observed to be less asynchronous compared to head-to-tail arrangement in case of dienophiles NE, PE, OE, SE. However in the case of dienophiles AE, OHE, MeE, CNE head-to-head arrangement is observed to be more asynchronous. syn isomer is found to be more asynchronous than the anti isomer which can be attributed to lone pair-lone pair and lone pair-bond pair interactions. However for the TSs where acroleine is the dienophile favorable secondary orbital interactions operate to
facilitate the regioselectivity. To estimate how the activation energies can be predicted using simple measure, correlations are drawn with the singlet-triplet energy gaps of the dienes and the dienophiles, reaction energies and $\text{HOMO}_{\text{diene}}-\text{LUMO}_{\text{dienophile}}$ and $\text{LUMO}_{\text{diene}}-\text{HOMO}_{\text{dienophile}}$. The regioselectivity for the present set of compounds is explained based on the Fukui function indices and triplet spin densities.

**Chapter 5: Competitive Diels-Alder Reactions: Cyclopentadiene and Phospholes with Butadiene.**

Cycloaddition reactions of phospholes have been employed to access novel polycyclic organophosphorus compounds. Many of the phosphorus-containing cycloadducts have promising applications in the fields of homogeneous catalysis and molecular materials. The present chapter deals with the diene-dienophile competing Diels-Alder reaction pathways of cyclopentadiene, 1H-, 2H- and 3H-phospholes with butadiene (Scheme 3). The results are explored at B3LYP level using 6-31G(d) and 6-31+G(d,p) basis sets, and at CCSD(T)/6-31G(d)//B3LYP/6-31G(d) level. Activation barriers show that cyclopentadiene acts as a diene rather than a dienophile. Pathways 1 and 2 (A and B) corresponding to butadiene as diene and dienophile respectively are predicted to be highly competitive in the case of 1H-phospholes.

In case of 2H- and 3H-phospholes the reactions require lower activation energy when the conversion of weak C=P to C-P occurs. Secondary orbital interactions and preferable bispericyclic nature of transition states are responsible for the stability of *endo* transition state. Some of the transition states are bispericyclic and most of them are highly asynchronous. The high stability of the products resulting via path 1 can be attributed to the less strain in the bicyclo[4.3.0]nonadiene skeleton compared to the norbornene derivatives obtained from path 2. Activation and reaction energy values for these Diels-Alder reaction
pathways are compared with the values reported for the [4+2] cyclodimerizations of each of the reactants to examine the likelihood of cyclodimerizations along these pathways.

Scheme 3

Various Diels-Alder methodologies have been implemented for a long time for synthesizing natural products and also in pharmaceutical chemistry. One among these methodologies involves the use of alkenyl-substituted heteroaromatic systems. The present chapter is aimed to computationally explore the regio and stereo chemical preference of vinyl cyclopentadiene (1 and 2) and vinyl heterocyclic (1-N, 1-O, 1-S, 2-N, 2-O and 2-S) systems as dienes with maleic anhydride as dienophile. Stepwise and concerted pathways of pristine model systems 1 and 2 as dienes with ethylene as dienophile have been systematically explored and they are found to proceed through asynchronous and concerted pathway. The activation barriers and exothermicities of 1, 1-N, 1-O, 1-S, 2, 2-N, 2-O and 2-S with maleic anhydride are evaluated. 3-vinyl systems are found to be more reactive compared to 2-vinyl systems. The regio- and stereo-selectivity preferences are evaluated based on activation energies, reaction energies, DFT based descriptors and Atoms in Molecules (AIM) analysis. Extra-annular cycloadducts are more feasible compared to the intra-annular cycloadducts. The formation of endo adduct is found to be more facile compared to exo adduct which may be traced to the favorable secondary orbital interactions. Computational results thus obtained are compared with earlier experimental observations that are available.
Scheme 4

Chapter 7: Further Shortening of the C-C Single Bond in Substituted Tetrahedranyl Tetrahedrane Systems

Bond lengths and bond strengths are fundamental parameters in chemistry. It is generally assumed that bond lengths and bond strengths which are given by the bond dissociation energy (BDE) are inversely related to each other. However such a correlation is not always given and there are many cases known where a longer bond may be stronger than a shorter bond between the same atoms. The present chapter explores the electronic fine tuning of the exocyclic C-C single bond length in tetrahedranyl tetrahedrane (THTH)
as a function of various substituents. The factors which determine the bond lengths and bond strengths are examined by energy decomposition analysis (EDA) and Atoms in Molecules (AIM) analysis. The very short exocyclic C-C single bond in \textbf{THTH-X} where X=H can be further shortened when X is a halogen atom. The calculations predict that the C-C bond will become shorter by \(~0.012 \ \text{Å}\) when X = F, Cl, Br compared to the silyl substituted compound \textbf{THTH-SiH}_3. The EDA results reveal that the equilibrium bond length of the exocyclic C-C single bond is determined by the interplay of attractive forces (electrostatic bonding and orbital interactions) and repulsive forces (Pauli repulsion) where it is the latter which prevents shorter bonds. Although the hyperconjugation in THTH-X is slightly stronger than in substituted ethanes X\_3C-CX\_3 the main reason for the very short exoskeletal C-C single bond in the former compound is the very high \%s character of the bonding orbital at carbon. AIM analysis has been done on the systems to look at the molecular structures and the electronic charge densities of the eclipsed and staggered conformers which helped in the clear demarcation of the two conformers.

\begin{center}
\textbf{Scheme 5}
\end{center}

\begin{center}
\text{Eclipsed} \hspace{1cm} \text{Staggered}
\end{center}

\begin{center}
X= H, CH\_3, OH, OCH\_3, NH\_2, SiH\_3, F, Cl, Br, CN
\end{center}