

## FACTORS AFFECTING THE RATES OF DIELS-ALDER REACTION, AND THE CAUSE OF NUCLEOPHILIC-ELECTROPHILIC DUAL BEHAVIOUR OF REACTANTS

ALI F. AL-SHAWABKEH<sup>a\*</sup>, YOUSIF A. SHAHAB<sup>b</sup>,  
WALID Y. AL-KHASHAB<sup>c</sup>

<sup>a</sup>*Department of Applied Sciences, Faculty of Engineering Technology,  
Al-Balqa' Applied University, P.O.Box: 15008 Amman 11134 Jordan*

<sup>b</sup>*Department of Chemistry, College of Science, University of Mosul, Mosul-Iraq*

<sup>c</sup>*Department of Basic Science, College of Agriculture and Forestry,  
University of Mosul, Mosul-Iraq*

Single- and multi - parametric linear regression analysis is applied for the study of the influence of different factors on Diels-Alder reaction. The rate constants of four sets of the reaction are correlated as dependent variable with the frontier orbitals energy levels of reactants, the electron densities of the two pairs of carbons involved in the addition reaction, and the steric energies of the transition states and products as the independent variables. Results of the analysis reveal that all mentioned factors affect the rate of the reaction, but to different extents depending on the electronic and steric nature of the reactants. Furthermore, the rate of the reaction increases with the increase in the difference of electron densities of the two pair of carbons engaged in the addition reaction, the decrease in the ionization potential of the reactant with the higher electron density carbons (donor reactant) the increase in the electron affinity of the reactant with the lower electron density carbons (acceptor reactant).

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### 1. Introduction

The kinetics of several classes of addition reactions leading to the formation of new  $\sigma$ -bonds show a common feature in that the rate constants of the addition of certain reagents can enhance with the increase of both the nucleophilicity and electrophilicity of their reaction partners. These reactions include the Diels-Alder reaction [1], 1,3 dipolar addition [2], and the addition of free radicals to multi- bonds [3,4]. Hence the concepts of “electronic demand” [5], and “inverse electronic demand” [6] were introduced for the Diels-Alder reaction. Similar behaviour was noticed for the activity of dipolarophiles in the 1,3-dipolar cyclo-additions [2].

B. Giese found that certain radicals exhibit nucleophilic as well as electrophilic properties with respect to addition to multiple bonds. He gave the term “amphiphilic” to such radicals [3].

\*Corresponding author: drshawabkeh7@yahoo.com

This “bidirectionality” [7] is not unusual in chemistry. Amphoteric hydroxides behave acidic towards strong bases and basic towards strong acids. The elements in the electrochemical series are oxidative towards those elements situated above them and reductive towards those placed below them. It is the believe of the authors of this paper that the electrophilic-nucleophilic property of molecules participating in electronic donor-acceptor interactions is determined by the levels of electron densities of the molecular sites that are engaged in the interaction. Molecules possessing high electron densities show nucleophilic properties, while those with low electron densities act electrophilic. Molecules with intermediate electron densities are electrophilic to molecules with high electron densities and nucleophilic to molecules with low electron densities. Since the strength of the nucleophilic-electrophilic interaction is determined by the difference in the electron densities between the two interacting sites, irrespective of the sign or the direction of the difference, the dual behaviour mentioned above is obvious. Hence, the difference in the electron densities between the two reactants should, besides other factors, determines their reactivity.

Parabolic curves are obtained from plotting the addition rate constants versus the ionization potentials of the reactants or the electron density of their multiple bonds. However, the U-shaped curves can be distorted and in some cases only half of the U is preserved [8].

R. Sustman and coworkers have successfully applied the MO perturbation theory to the interpretation of the dienophile and dipolarophile activity sequences [9]. According to this theory the reaction of nucleophilic with electrophilic reagent, as is the case in the three classes of reactions discussed here, is controlled by the HOMO-LUMO interaction which depends on frontier orbital energies and electron densities on the carbons participating in the reactions [10]. In addition to the mentioned two factors the steric interaction of substituents in the transition state and product is also expected to influence the rate of the reaction.

In several theoretical [11] and experimental [12-14] contributions, Domingo and co-workers clearly established the effect of the charge on the carbons involved in the addition reaction. The larger the difference in the charge or the electron density between the carbons to be bonded, the faster is the rate of the addition reaction. The importance of this effect can be explained through the stabilization of the transition-state complex, which is formed as a consequence of electron donor-acceptor interaction.

Steric interactions could modify or complicate the FMO interaction effect and the charge effect since it contributes to destabilization of the transition-state complex and the cyclic product.

In the present contribution the three above-mentioned effects, namely FMO effect, charge effect, and steric effect are included in a single model to explain the factors influencing the rate of Diels-Alder reaction. The single- and multi-parametric linear regression analysis is applied for this purpose. The reaction rate is taken as the dependent variable, and the electron density of the carbons involved in the reaction, the frontier orbitals energy levels of reactants, and the steric energy of the transition states and end products as the independent variables. The prime aim of the work is to give a plausible explanation for the nucleophilic-electrophilic dual behaviour of the reactants.

## 2. Results and discussion

The semi-empirical, quantum-mechanical program (MOPAC) was applied to the calculation of the relevant physical properties of the studied reactants. These properties include the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), and the electron density of the  $sp^2$  carbons of reactants. These properties were computed for the most stable conformations as obtained via energy minimization procedure employing AM1 program.

The steric energies for the transition states and products were calculated with the aid of the molecular mechanics program (MM2). A concerted mechanism was assumed for the transition state in which the two pairs of carbons involved in the addition reaction were brought near each

other within a distance of 2.3Å. The regression analysis treatment was performed on the statistical program (SPSS).

### ***Factors affecting the rate of reaction.***

In order to study the effect of substituents on Diels-Alder reaction, it is usual to choose a reaction series in which one of the reagent (Diene or Dienophile) is kept fixed and the other varied. Furthermore, it is important for the kind of investigation presented here to choose the fixed reagent with an electron density either higher or lower than the electron densities of all of its reaction partners. Hence, the following reaction sets were selected.

**Set 1:** the fixed reagent is cyclopentadiene (I) and the reaction partners are: cyanoethene (II), *trans*-1,2-dicyanoethene (III), *cis*-1,2-dicyano-ethene (IV), 1,1-dicyanoethene (V), tricyanoethene (VI), and tetracyano-ethene (VII).

**Set 2:** the fixed reagent is 9,10-dimethyl anthracene (VIII) and the reaction partners are the dienophiles mentioned in set 1.

**Set 3:** the fixed reagent is maleic anhydride (IX) and the reaction partners are: *cis*-2,3-dimethyl butadiene (X), butadiene (XI), 1-methoxybuta-1,3-dien (XII), 2-methylbutadiene (XIII), 2-chlorobutadiene (XIV), *trans*-piperline (XV).

**Set 4:** the fixed reagent is hexachlorocyclopentadiene (XVI) and the reaction partners are: cyclopentadiene (I) cyclopentene (XVII), furan (XVIII), maleic anhydride (IX), norbornene (IXX), styrene (XX), *p*-nitro styrene (XXI), *p*-methoxy styrene (XXII).

Table (1) lists the calculated physical properties of the studied dienes and dienophiles. Table (2) gives relevant data about the studied reactions (rate constants, steric energy of the transition states, steric energy of the products). Table (3) displays the results of the single- and multi- parametric linear regression analysis for the correlation between the rate constants and the factors influencing it.

*Table 1: Some calculated properties of reactants.*

Reactant	HOMO	LUMO	C2	C1
I	-9.07924	0.048155	4.1825	4.1825
II	-10.85761	0.04973	4.1565	4.0994
III	-11.11267	-1.04531	4.0385	4.0384
IV	-11.08237	-0.99469	4.0381	4.0381
V	-11.16711	-0.87834	3.9560	4.1064
VI	-11.33901	-1.81453	3.9875	3.8966
VII	-11.52237	-2.52484	3.8465	3.8465
VIII	-7.89611	-0.4189	4.0464	4.0464
IX	-12.02317	-1.61870	4.1531	4.1531
X	-9.22078	0.66945	4.2164	4.2165
XI	-9.33372	0.44834	4.2086	4.2087
XII	-8.74775	0.49339	4.2264	3.9981
XIII	-9.21280	0.46081	4.2122	4.2118
XIV	-9.49102	0.106250	4.1845	4.2095
XV	-9.03326	0.429003	4.2130	4.151
XVI	-9.60469	-1.41072	4.1313	4.1313
XVII	-9.44015	1.29165	4.1744	4.1744
XVIII	-8.619	0.0920	4.1175	4.2153
IXX	-9.58338	1.028317	4.1742	4.1742
XX	-9.03264	0.05862	4.1249	4.2089
XXI	-9.88098	-1.24393	4.1462	4.1807
XXII	-9.11981	1.19304	4.0176	4.2825

Table2 : Relevant data regarding the studied reactions.

Reaction	Steric energy of Transition state kcal/mole	Steric energy of endo products kcal/mole	K rate const*
I-II	0.78163	1.134414	0.00001
I-III	0.895602	1.305381	0.00081
I-IV	0.966682	1.428113	0.0009
I-V	0.96599	1.600957	0.455
I-VI	1.228973	2.052282	4.8
I-VII	1.677002	2.949685	43.0
VIII-II	0.217168	0.599228	0.0001
VIII-III	0.3666	0.819561	0.000139
VIII-IV	0.428208	0.959670	0.000131
VIII-V	0.382758	1.096419	0.127
VIII-VI	0.67754	1.619413	5.9
VIII-VII	1.20705	2.59580	13
IX-X	2.529647	1.175324	0.000336
IX-XI	2.221906	1.106439	0.000068
IX-XII	1.784075	1.402146	0.000841
IX-XIII	1.480294	1.089006	0.000145
IX-XIV	1.530975	1.147792	0.000007
IX-V	1.578602	1.160806	0.000227
XVI-XVII	2.368294	2.890826	0.000590
XVI-XVIII	0.941031	2.89472	0.105800
XVI-XIV	3.049260	5.643799	0.000720
XVI-XX	1.64538	2.599651	0.007930
XVI-XXI	0.628733	2.727090	0.005380
XVI-XXII	2.531928	2.968658	0.003330
XVI-I	2.275991	2.854419	0.152000
XVI-XI	5.04229	3.763709	0.002900

\*= Lit.mol<sup>-1</sup>.sec<sup>-1</sup>, taken from references 5,6,7,8

Table 3: Result of single-and multi-parametric linear regression analysis for Set 1 – 4.

Factor	R <sup>2</sup>	a	R <sup>2</sup>	a	R <sup>2</sup>	a	R <sup>2</sup>	a
Steric transition	0.522729	-570	0.6561	-79	0.005476	-5.32E-6	0.0090	-1.25E-3
Steric of product	0.795664	-2320	0.783225	-643	0.887364	-2.420E-6	0.04796	-1.13E-2
HOMO	0.540225	-5648.8	0.540225	-1170.486	0.831744	1.07E-3	0.0645	1.263E-2
LUMO	0.544644	-1473.5	0.544644	-446.189	0.206116	7.42E-3	0.0084	4.280E-3
ED	0.561001	-12770.3	0.561001	-3862	0.0961	3.493E-3	0.0265	0.137
Steric transition	0.908209	-473.394	0.829921	-15428.359	0.784996	-1.07E-5	0.030276	-1.84E-4
ED		-10788.3		-7631.486		+3.2E-3		0.169
Steric transition	0.863041	-461.190	0.917764	-25170	0.937024	-2.41E-5	0.064516	-9.866E-6
HOMO		-4614.574		-19531.883		1.174E-3		1.264E-2
Steric transition	0.942841	-376.627	0.842724	-28947.529	0.893	-3.138E-3	0.3398	-2.28E-2
Steric of product		-1279.882		-7532.872		-2.43E-6		-8.49E-2
ED		-3778.8		-574.506		1.043E-3		0.862

In linear regression analysis the correlation coefficient ( $R^2$ ), and the regression coefficients ( $a_1, a_2, \dots$  etc.) are very important for the evaluation of the regression analysis results. A multiparametric linear equation may be written in the form:

$$y = a_0 + a_1x_1 + a_2x_2 + \dots + a_nx_n$$

$y$ - stands for the dependent variable (the rate constant in our case),  $a_0$  is a scaling constant that depends on the reference state,  $x_1, x_2, \dots$  etc are the independent variables (the relevant physical properties of reactants in our case),  $a_1, a_2, \dots$  etc. are the regression coefficients that have the significance of statistical weighting factors and they describe the susceptibility of the dependent variable  $y$  to the associated independent variable  $x$ . The quality of the linear correlation is given in terms of the correlation coefficient ( $R^2$ ) which ranges between zero to one. Good correlations should possess values larger than 0.9. Even larger values than 0.9 are necessary if the aim of the application of the analysis is for prediction purposes. Smaller values than 0.9 can be helpful for the interpretation of experimental results or theoretical calculations.

Table (3) reveals that a single parameter gives unsatisfactory correlation coefficients and the coefficients improve when two parameters are considered, and they improve further when three parameters are applied in the correlation. This means that three factors influence the Diels-Alder reaction, namely, the electron density of the carbons taking part in the addition reaction, the frontier orbital energy levels of the reactants, and, the steric energy of the transition state and the end product. It is clearly seen from the sign and magnitude of the regression coefficient ( $a$ ) that the various factors contribute to different extents to the rate constants of the four sets.

In sets 1 and 2 the carbons engaged in the addition reaction, and which belong to the fixed reaction reagents, possess higher electron densities than the corresponding carbons of their reaction partners. The negative sign of the regression coefficients which are associated with the HOMO and LUMO energy levels of reactants, and the electron density of the carbons to be bonded indicates that the rate constant of the reaction enhances with increased electron affinity (low LUMO values) and decreased electron density of the reactants inferring a direction of charge delocalization from the fixed reagent to the new  $\sigma$ -bonds.

The electron densities of the carbons participating in the reaction and which belong to the fixed reactant in series 3 and 4 are lower than the electron densities of the corresponding carbons of their reaction partners. The positive sign of the regression coefficients of the HOMO and electron density factors suggests that the rate constant of the reaction improves with low ionization potentials of the reactants and higher electron densities of involved carbons suggesting that the direction of electronic charge delocalization is from the reactants towards the bonds to be formed.

These results are best explained assuming the following reaction mechanism:

1. A cyclic transition-state complex is formed via electron donor-acceptor interaction between the two pairs carbons involved in the addition reaction. The stability of the complex is supposed to increase with the increase in the difference in charge of the interacting two carbons.

2. The direction of charge delocalization during the formation of the new  $\sigma$ -bonds is from the carbons of higher electron densities (donor reactant) towards the carbons of lower electron densities (acceptor reactant). Therefore, the rate of delocalization, and thus the rate of the reaction, increase with the donor reactant and the decrease in the LUMO energy level (increased electron affinity) of the acceptor reactant. This means that the rate of the reaction increases with the narrowing of the HOMO-LUMO energy gap between the reactants, which are the central concept of the Frontier Molecular Orbital Theory (FMO) [19].

### ***The Cause of Nucleophilic-Electrophilic Dual Behaviour.***

To explain the cause of the nucleophilic-electrophilic behaviour of reactants in the Diels-Alder reaction it is convenient to construct a vertical series of reactants based on their electron densities with the one of highest electron density at the top. Any reactant within this series behaves electrophilic towards reactants lying above it and nucleophilic towards reactants situated

below it. This view provides in the same time a theoretical explanation for the concepts of “electronic demand” and “inverse electronic demand” in the Diels-Alder reaction.

### *Cause of distortion of the U-shaped curves*

The position of the fixed reactant in the electronic density series proposed above gives the reason for the distortion of the U-shaped curves resulting from plotting the rate constants versus the electron densities of the multiple bonds of reactants. When the fixed reactant lies in the middle of the series an undistorted U-shaped curve results, while the curve is biased towards one of the halves if the fixed reactant moves upwards or downwards in the series. Only one half of the curve is preserved if the fixed reactant lies at the ends of the two extremes of the series.

## **Conclusions**

The rates of addition of a set of dienophiles to a certain diene and vice versa is mainly influenced by the difference in the electron densities of the two pairs of carbons involved in the addition reaction, and not by the sign or direction of the difference. This explains the reason behind the nucleophilic-electrophilic dual behaviour of certain reagents. The frontier energy levels of reactants and the steric energies of the transition states and products also contribute to the rate of the reaction. The rate of the reaction improves with increased electron density and decreased ionization potential of the electron-donor reactant, and with decreased electron density and increased electron affinity of the acceptor. This leads to the conclusion that the direction of the initial charge delocalization from the vanishing double bonds to the new  $\sigma$ -bonds is from the reactant of higher electron density towards the new bonds. The rate of initial charge delocalization besides the stability of the transition-state cyclic complex, which are both affected by the difference in the electron densities of the interacting carbons, and the FMO energy levels, are evidently the decisive factors in the determination of the rate of Diels-Alder reaction.

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