

Computational Studies of 1,3-Dipolar [3 + 2]-Cycloaddition Reactions of Fullerene-C₆₀ with Nitrones

Richard Tia*, Jacob Amevor and Evans Adei

Department of Chemistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

Abstract

Solubility of fullerene-C₆₀ improves with functionalization. 1,3-dipolar [3+2]-cycloaddition reactions of fullerene-C₆₀ with substituted nitrones, a versatile method for fullerene functionalization, were investigated at the M06/6-31G*//PM3 level of theory to elucidate the effect of electron-releasing (-CH₃, -CH₂CH₃, -CH₂CH₂CH₃, C₆H₅CH₂) substituents and electron-withdrawing substituents (-F, -Cl, -Br, -NC, and -NO₂) on the energetics of the reaction; the regio- and stereo-selectivity of the mono- and bis-addition of nitrones; and global reactivity descriptors of the molecular systems to rationalize and predict their chemical reactivity and site selectivity. The results show that electron-withdrawing groups on the nitrones increase the activation barrier of the reaction whereas electron-donating groups decrease the activation barriers. However, electron-withdrawing groups on the nitrones result in more stable products compared to the electron-donating groups. It was found that the reactions with electron-donating substituents on the nitrone are normal electron demand reactions, with C₆₀ as the dipolarophile and the substituted nitrones as the dipoles while the reactions with electron-withdrawing substituents on the nitrones are inverse electron demand reactions. The chemical hardness values show greater positive values for adducts with electron-withdrawing substituents on the nitrone and smaller negative values for adducts with electron-donating substituents on the nitrone, confirming the trend that larger activation barriers accompany reactions with electron-withdrawing substituents on the nitrone while electron-donating substituents lower activation barriers. The activation barriers of the second nitrone addition (bisadduct formation) were found to be lower than the barriers for the first nitrone addition (monoadduct formation). Stereo-chemically, *syn*-bisaddition was found to be thermodynamically and kinetically stable favoured over *anti*-bisaddition. Electron donating and electron-withdrawing substituents have a marked effect on the energetics of the reaction.

Keywords: Fullerenes; Functionalization; Cycloaddition; Computational

Introduction

Over the past decades, the field of fullerene chemistry has developed remarkably, driven by the structural novelty and the intriguing properties of fullerenes that offer a wide variety of new possibilities in a diverse range of applications. Since the initial discovery of the fullerene C₆₀ [1] and the development of a method for its preparation [2], fullerene-based complex molecular systems have received great attention [3-5]. Fullerene-C₆₀ has many potential applications such as in synthetic chemistry, artificial photosynthesis, non-linear optics, surface coatings, superconductivity devices, and cosmetics to slow down the aging of the human skin. The high capability of C₆₀ to act as an electron acceptor or even as electron accumulator has led to the synthesis of a large number of compounds in which the fullerene is covalently linked to photoactive groups serving as potential electron donors [6]. The size, hydrophobicity, three-dimensionality and electronic configurations of fullerenes make them an appealing subject in medicinal chemistry. For example, fullerene C₆₀ has interesting photo, electrochemical and physical properties, which can be exploited in various medical fields. Fullerenes are able to fit inside the hydrophobic cavity of HIV-proteases, inhibiting access of substrates to the catalytic site of enzymes [7]. A series of fullerene-C₆₀ derivatives displays a wide range of biological properties, including neuroprotective, enzymatic, antiapoptotic, antibacterial, DNA photocleaving [8], nitric oxide synthase inhibiting, and chemotactic activities. Moreover, C₆₀ is able to efficiently generate cytotoxic singlet oxygen due to a practically unity value of intersystem crossing from the singlet excited state to the first excited triplet state [9]. It can be used as radical scavenger and antioxidant [10]. Water-soluble fullerenes have been investigated as neuroprotective agents, HIV protease inhibitors, MRI contrast agents, etc. [11]. It has been established that C₆₀ can be used as a versatile building block for the construction of globular dendrimers [12]. Furthermore, an antibody

or an antibody fragment can be linked to the fullerene molecule, based on which the C₆₀ can be used as an efficient multiplier in modular drug delivery systems for a photodynamic therapy of tumors [13]. In such systems the antibody linked to the fullerene acts as a selective addressing unit. Special dye molecules which become cytotoxic after illumination with certain wavelength due to singlet oxygen generation which are attached to the C₆₀ directly or via dendritic structure are used as photosensitizers [13,14]. Because fullerene-C₆₀ has a unique spherical geometry, it constitutes a singular scenario in a variety of chemical reactions in which the highly reactive double bonds (30 for the most common C₆₀) partake actively. Even though fullerenes have been among the most studied molecules in science over the last two decades since its preparation in multigram amounts, many important reactions in the arsenal of organic chemistry have not been extensively applied to fullerenes synthetically, despite the unprecedented chemical structures that could be formed.

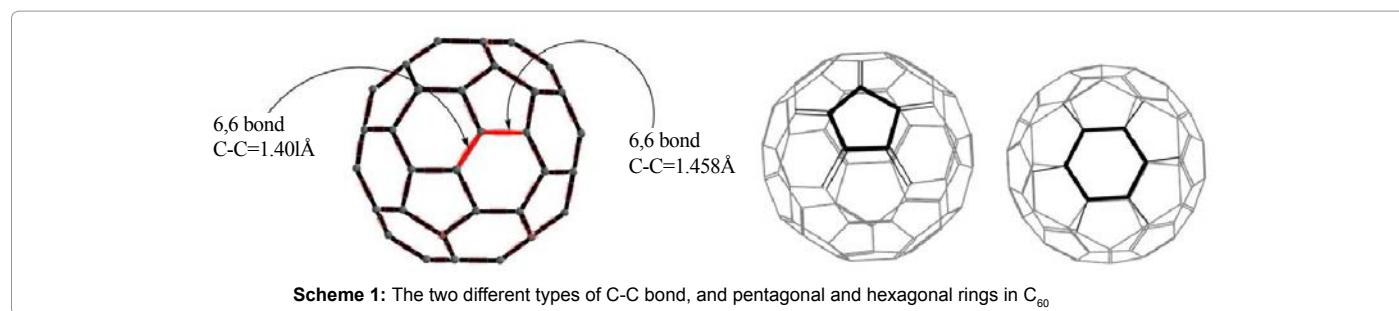
The structure of C₆₀ includes two different types of bonds, those at the junction of two hexagons and those at the junction of a pentagon and a hexagon (Scheme 1). A pentagon in C₆₀ is surrounded by five hexagons thereby forming [5,6] C-C junctions and also [6,6] C-C junctions between the neighbouring hexagons. The mean [5,6] C-C

*Corresponding author: Richard Tia, Department of Chemistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana, Tel: 00233(0) 243574146; E-mail: richtiagh@yahoo.com

Received May 12, 2014; Accepted Sep 12, 2014; Published Sep 18, 2014

Citation: Tia, Amevor, Adei (2014) Computational Studies of 1,3-Dipolar [3 + 2]-Cycloaddition Reactions of Fullerene-C₆₀ with Nitrones. J Theor Comput Sci 1: 138. doi: 10.4172/2376-130X.1000138

Copyright: © 2014 Tia, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



and [6,6] C-C bond distances are 1.458 Å and 1.401 Å respectively [15]. C₆₀ is not a “superarene” or superaromatic as it was previously thought, but rather a weakly conjugated, very strained, and electron-deficient polyene [16,17]. The major drawback of fullerenes is their low solubility in organic solvents, which decreases substantially their processibility and hence their applicability [18]. The solubility of C₆₀ has been studied in a wide variety of solvents [19]. The solvation of C₆₀ requires the disruption of many solvent-solvent interactions, which are not adequately compensated by the interactions between solvent and C₆₀ due to the rigid geometry of the latter and the lack of permanent dipole moment. In fact, C₆₀ is almost completely insoluble in protic or dipolar aprotic solvents like MeOH, MeCN, tetrahydrofuran (THF), and Dimethylsulfoxide (DMSO). It is scarcely soluble in alkanes, with the solubility increasing from pentane to decane. Solubility of fullerene-C₆₀ improves with functionalization. Many reactions have been developed for the functionalization of C₆₀, the main ones being cycloadditions and nucleophilic additions [20]. [3+2] cycloaddition between C₆₀ and an azomethine ylide (the Prato reaction) stand out as the most frequently applied reaction in the preparation of C₆₀ derivatives [21]. The azomethine ylide is generally formed *in situ* from the reaction between an aldehyde or ketone and an amino acid derivative and allows up to five alkyl groups to be introduced to C₆₀ in a one-step reaction. A related reaction that has been frequently used to prepare C₆₀ derivatives is the Bingel reaction [22] in which a halo-ester or ketone is first deprotonated by a base and subsequently added to one of the double bonds in C₆₀, resulting in an anionic intermediate that reacts further into a cyclopropanated C₆₀ derivative. The electron affinity of C₆₀ decreases somewhat upon functionalization as a result of disturbing the conjugated network when converting sp² carbons into sp³, an effect that is more pronounced in higher C₆₀ adducts. Although a large number of fullerene derivatives containing nitrogen and oxygen atoms in the organic addend have been prepared, for example, the C₆₀-based dyads formed with the well-known electron-donating addends [23] fullerene derivatives in which the carbon sphere is directly or otherwise linked to nitrogen and oxygen atoms are among the less studied modified fullerenes and the mechanism of addition is less understood. One of the important goals in physical organic chemistry is to have an appropriate description of the chemical substituents in the reactivity patterns of molecules. Parr et al. [24,25] have proposed the global electrophilicity index, ω of a molecule in terms of its chemical potential and chemical hardness as, $\omega \approx \mu^2/2\eta$ where $\mu \approx -(I + A)/2 = [E(\text{HOMO} + \text{LUMO})/2]$ and $\eta = (I - A)/2 = [E(\text{LUMO}-\text{HOMO})/2]$ are the electronic chemical potential and chemical hardness of the ground state of atoms and molecules respectively, approximated in terms of the vertical ionization potential (I) and electron affinity (A) using Koopmans’ theorem. ω describes the electrophilic power of a ligand and also its propensity to soak up electrons. This index measures the stabilization in energy when the system acquires an additional electronic charge from the environment. By definition, it encompasses

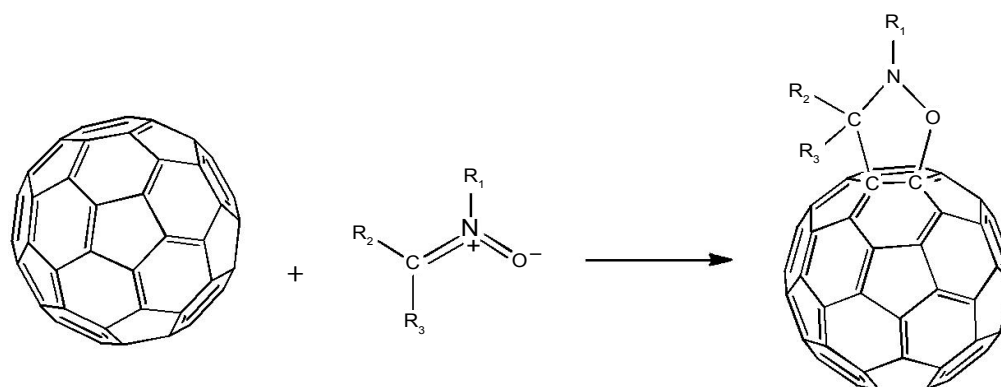
both the ability of an electrophile to acquire additional electronic charge and the resistance of the system to exchange electronic charge with the environment. Global electrophilicity, chemical hardness and chemical potential are very important global reactivity descriptors for studying the chemical reactivity and site selectivity of various molecular systems [26-28]. In view of the above, this work aims at exploring (1) mono- and bis-1,3-dipolar cycloaddition of nitron and its substituted derivatives to fullerene C₆₀ (Scheme 2); (2) the effect of electron-releasing (CH₃, CH₂CH₃, CH₂CH₂CH₃, C₆H₅CH₂) substituents and electron-withdrawing substituents (F, Cl, Br, NC, and NO₂⁻) on the energetics of the reaction; (3) the regio- and stereo-selectivity of the mono- and bis-addition and (4) global reactivity descriptors of the molecular systems to rationalize and predict their chemical reactivity and site selectivity.

Details of Calculation

All calculations were carried out with the Spartan ‘10 V1.1.0 Molecular Modeling program (Wavefunction, 2010) at the MO6/6-31G**/PM3 level of theory. Due to the large size of the systems under study the geometries could not be fully optimized at higher levels of theory [29]. The starting geometries of the molecular systems were constructed using Spartan’s graphical model builder and minimized interactively using the SYBYL force field [30]. Geometry optimizations were carried out without symmetry restrictions. A normal mode analysis was performed to verify the nature of the stationary points. Equilibrium geometries were characterized by the absence of imaginary frequencies. Transition state structures were located by a series of constrained geometry optimizations in which the forming bonds are fixed at various lengths while the remaining internal coordinates were optimized. The approximate stationary points located from such a procedure were then fully optimized using the standard transition state optimization procedure in Spartan. All the critical points were further characterized by analytical computation of vibrational frequencies. The transition state structures were found to have only one negative eigenvalue with the corresponding eigenvector involving the formation of the newly created C–C and C–O bonds. All reported thermodynamic and kinetic parameters of interest include thermal corrections at 298.15 K and 1 atmosphere pressure in the gas phase. Only closed-shell singlet states were considered.

Results and Discussion

Fullerene-C₆₀, a polyolefin reacts with a typical 1,3-dipole such as nitrones to yield fullerenoisoxazolines and substituted derivatives. As established by Kavitha and Venuvanalignam (2005) in a theoretical study at the B3LYP/6-31G (d,p)//AM1 level, dipolar cycloaddition to fullerene - C₆₀ can occur at the 6,6 and 6,5 C-C junctions and can form both open and closed adducts, namely closed 6-6, open 6-6, closed 6-5 and open 6-5 adducts but among these, the closed 6-6 is the most favoured. Preliminary calculations in this work to ascertain this



Scheme 2: 1,3-Dipolar [3 + 2]-Cycloaddition Reaction Of Fullerene-C₆₀ with Nitrones

assertion has shown that the closed 6-6 is the most preferred. Therefore, all the calculations reported herein are restricted to closed-shell singlet states at the 6,6 C-C bonds [31].

Substituent effects on the energetics of the reaction

The two types of substituents used are the electron-donating (nucleophilic) and electron-withdrawing (electrophilic) substituents. These substituents are characterized by the presence or absence of electron density in their molecular orbitals. The presence of the electron-donating (ED) and electron-withdrawing (EW) groups defines the direction of flow of electrons between any two or more reacting systems. In the course of a chemical interaction, EW substituents and ED substituents on either the dipole or the dipolarophile affects the transfer of electrons from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) of the reacting species according to frontier molecular orbital (FMO) approximation. The possible substituent positions on the nitron considered in this work are shown below as R₁, R₂ and R₃. R₁ is on the nitrogen whereas R₂ and R₃ are both on the carbon atom. The reactions involving the various permutations of substituents R₁, R₂, and R₃ are indicated by serial numbers (SN) as given in (Tables 1 and 2).

The effect of electron-donating groups on the energetics

The electron-donating groups considered in this work are H, methyl (CH₃), ethyl (CH₃CH₂), propyl (CH₃CH₂CH₂), pentyl (CH₃CH₂CH₂CH₂CH₂), benzyl (C₆H₅CH₂), and 1-naphthyl (C₁₀H₇) groups. In each reaction, different combination of R₁, R₂ and R₃ are considered. The most feasible [3+2] concerted addition pathway (lowest activation energy) was observed for SN 8 in which R₁ is a propyl group and the other substituents are H atoms, with activation energy of 19.5 kcal/mol. This reaction has an enthalpy of formation of -34.2 kcal/mol. The C-C and C-O forming bonds of the transition state of this reaction are 2.10 Å and 2.10 Å compared to 1.53 Å and 1.41 Å respectively in the product. The reaction with the highest activation barrier (37.4 kcal/mol) has a naphthyl group on R₁ and benzyl groups on R₂ and R₃. The heat of formation of this reaction is -8.9 kcal/mol. The results (Table 1) show that generally, for electron-donating groups increasing the size of the substituent increases the activation energy and decreases the enthalpy of formation, probably due to steric effects.

Effect of electron-withdrawing substituents on energetics

Electron-withdrawing (EW) substituents F, Br, Cl, NC-, and NO₂-

were placed one after the other at the R₂ position of the nitron while keeping CH₃ on the R₁ and R₃ positions. The results (Table 2) show that the EW substituents increase the activation barriers for the formation of the products significantly as compared to their ED counterparts for both the concerted (R₂=Cl, O₂N) and stepwise (R₂=F, Br, NC) pathways. In the stepwise reactions, the activation barriers for the first step are significantly higher than for the second step. The exothermicity of the reactions involving the EW substituents was observed to increase steadily as compared to ED substituents. Analyses of all the stepwise pathways in both cases involving ED substituents and EW substituents show that addition through C-O bond formation first followed by the C-C bond formation is more kinetically favourable than the reverse. Energetics for EW substituents is listed in the (Table 2).

Substituent effect on chemical hardness, chemical potential and global electrophilicity

Table 3 shows the various HOMO-LUMO energy gaps for the adducts

SN	R ₁	R ₂	R ₃	ER (kcal/mol)	E _a (kcal/mol)
1	H	H	H	-33.1	22.2
2	Methyl	H	H	-33.1	20.3
3	Methyl	Methyl	H	-27.8	21.2
4	Methyl	Methyl	Methyl	-37.3	25.8
5	Ethyl	H	H	-30.9	20.1
6	Ethyl	CH ₃	H	-26.7	21.3
7	Ethyl	CH ₃	CH ₃	-37.9	26.7
8	Propyl	H	H	-34.2	19.5
9	Propyl	CH ₃	H	-27.4	9.5 ^a , 48.4 ^c
10	Propyl	CH ₃	CH ₃	-32.4	15.8 ^b , 29.7 ^c
11	Propyl	Ethyl	H	-22.8	16.4 ^b , 3.6 ^c
12	Ethyl	Ethyl	Ethyl	-33.6	27.0
13	Pentyl	Pentyl	Pentyl	-23.7	26.7
14	Benzyl	H	H	-36.4	19.8
15	Benzyl	Methyl	Methyl	-26.4	26.6
16	Benzyl	Benzyl	Methyl	-14.4	-
17	Benzyl	Benzyl	Benzyl	-9.4	35.4
18	Naphthyl	Benzyl	Benzyl	-8.9	37.4
19	Naphthyl	Naphthyl	Benzyl	-10.3	37.2
20	Naphthyl	Naphthyl	Naphthyl	-9.4	37.0

Table 1: Reaction Energies (E_r) and Activation Barriers (E_a) of the cycloaddition reactions with the various electron-donating substituents on the nitrones^a Reactions 9, 10, and 11 are stepwise reactions while the rest are concerted ^bBarriers of first step in a stepwise mechanism. ^cBarrier of second step in a stepwise reaction. All energies are calculated relative to the separated reactants (fullerene+nitron).

SN	R ₂	R ₁	R ₃	E _a			E _R
21	-F	-CH ₃	-CH ₃	48.7	-166.3	0.1	-214.4
22	-Br	-CH ₃	-CH ₃	55.8	-160.9	2.1	-216.2
23	-NC-	-CH ₃	-CH ₃	48.0	-167.0	2.8	-214.7
24	-Cl	-CH ₃	-CH ₃	56.5	-		-213.1
25	-NO ₂ -	-CH ₃	-CH ₃	50.7	-		-216.2

Table 2: Energetics of the cycloaddition reactions involving electron withdrawing groups^b E_a: activation barrier of first step; : reaction energy of intermediate; : activation energy of second step; E_R: reaction energy. All energies are calculated relative to the separated reactants (fullerene+nitrone).

SN	E(HOMO-LUMO) /eV					
	NED	IED	μ (eV)	η (eV)	ω (eV)	DM (debye)
1	6.9	9.9	-6.3	-3.5	-5.8	1.9
2	6.7	9.9	-6.3	-3.4	-5.8	2.7
3	8.9	9.8	-7.4	-4.5	-6.1	2.8
4	6.1	9.8	-5.9	-3.1	-5.8	3.1
5	6.7	9.9	-6.2	-3.3	-5.8	2.7
6	6.3	9.9	-6.1	-3.2	-5.8	2.8
7	6.1	9.8	-5.9	-3.0	-5.8	3.1
8	6.7	9.9	-6.2	-3.3	-5.8	2.7
9	6.3	9.9	-6.6	-3.2	-5.8	3.0
10	6.1	9.9	-5.9	-3.0	-5.8	3.1
11	6.4	9.9	-6.1	-3.2	-5.8	2.9
12	6.2	9.9	-6.0	-3.1	-5.8	3.3
13	6.1	9.9	-6.0	-3.1	-5.8	2.5
14	6.6	8.8	-6.2	-3.3	-5.8	2.2
15	6.1	9.0	-5.9	-3.0	-5.8	2.6
16	6.2	9.1	-6.0	-3.1	-5.8	2.6
17	6.3	9.0	-6.1	-3.2	-5.8	2.5
18	6.3	8.5	-6.0	-3.1	-5.8	2.8
19	6.0	8.5	-6.0	-3.0	-5.8	2.7
20	5.8	8.5	-5.8	-2.9	-5.8	2.6

^aNED: Normal Electron Demand, IED: Inverse Electron Demand, μ: Chemical Potential, η: Chemical Hardness, ω: Global Electrophilicity Index, DM: Dipole Moment.

Table 3: HOMO-LUMO energy gap and global and local properties of the adducts with ED substituents^c

with ED substituents and other global and local properties such as global electrophilicity index (ω). From the calculated energy gaps it is observed that the reactions with electron-donating substituents on the nitrene are normal electron demand (NED) reactions. Considering the two reactants, C₆₀ and substituted nitrones, calculations are done with regards to both as dipole and dipolarophile and vice versa. It is thence deduced from these calculations that C₆₀ is the dipolarophile and the substituted nitrene is the dipole since NED values are smaller than inverse electron demand (IED) values. This means that electron density is drawn from the nitrene to the C₆₀ moiety when the substituents involved are electron-rich. Conversely an inverse electron demand (IED) is observed for reactions with EW substituents ie. F, Br, Cl, NC-, and NO₂- at the R₂ position on the nitrene. Table 4 lists the properties of adducts with EW substituents in comparison with the properties of ED substituents. In the case of adducts with EW substituents, there is an electron transfer from the HOMO of the dipolarophile (C₆₀) to the LUMO of the dipole (nitrene). This order best explains the fact that EW substituent pulls electron density to itself in the course of a chemical reaction. The order of decreasing global electrophilicity is: Cl>Br>F>NC->NO₂->>>methyl>ethyl>propyl>benzyl. Calculated parameters show that higher electrophilicity is most experienced with EW substituents since their global electrophilicity indices are far

greater than those for the ED substituents. It is also noteworthy that as the chain of the ED substituents increases, its electrophilic character decreases accordingly. The chemical hardness values (Table 4) show greater positive values for adducts with EW substituents and smaller negative values for adducts with ED substituent. This implies that as the system evolves toward a state of greater hardness, its stability increases. The adduct with the greatest chemical hardness will be the most stable hence least reactive. This conforms perfectly with the activation energies obtained from calculation for both EW and ED systems. Larger activation barriers accompanied EW substituents whereas ED substituents lower the activation barrier.

Geometrical parameters of transition states and mechanistic pathways

An analyses of the geometries of the transition states associated with these 1,3-dipolar cycloadditions for the various substituents show that most of the concerted reactions follow a synchronous pathway as shown in (Table 5).

Further addition of nitrene to monoadduct (bis-addition)

The addition of nitrene to the cis-1 position of the monoadduct of C₆₀ has two possibilities depending on the orientation of the incoming nitrene. It can be oriented *syn* or *anti* to the first nitrene on the buckyball. It is observed that both the *syn* and *anti*-additions follow stepwise mechanistic pathways. The *syn*-addition pathway was found to be kinetically and thermodynamically favoured over the *anti*-addition pathway. For the *syn*-pathway, the activation barrier for the first step is 8.3 kcal/mol and that for the second step is 4.2 kcal/mol. The enthalpy of formation of the *syn*-product is found to be -29.7 kcal/mol as compared to -14.9 kcal/mol for the *anti*-product which has an activation barrier of 24.2 kcal/mol for the first step and 15.6 kcal/mol for the second step (Figure 1). C-O bond formation in the first steps of both additions is observed to be favoured over the C-C bond formation. The kinetics reveal that formation of the C-O bonds in the first step is about 13.0 kcal/mol favored over the formation of C-C bonds so in both the mono and bis-additions, the C-O is formed in the first step [32].

Conclusions

The following deductions were made from the results obtained from this work:

1. Electron-withdrawing groups on the nitrones increase the activation

Substituent	E(LUMO-HOMO)	μ (eV)	η (eV)	ω (eV)		
		/eV				
(R2)						
		NED	IED			
EW						
-F		15.1	1.9	-8.5	1.0	35.0
-Br		13.1	2.0	-8.5	1.0	35.8
-NC-		13.8	1.9	-8.5	0.9	34.7
-Cl		12.6	2.1	-8.4	1.0	37.0
-NO ₂		14.1	1.8	-8.5	0.9	33.8
ED						
Methyl		6.1	9.8	-5.9	-3.1	-5.8
Ethyl		6.1	9.9	-5.9	-3.0	-5.8
Propyl		6.1	9.9	-5.9	-3.0	-5.8
Benzyl		6.0	9.0	-5.9	-3.0	-5.8

NED: Normal Electron Demand, IED: Inverse Electron Demand, μ: Chemical Potential, η: Chemical Hardness, ω: Global Electrophilicity Index

Table 4: Comparison of HOMO-LUMO energy gap and global and local properties of the adducts with electron-withdrawing (EW) and electron-donating (ED) substituents

SN	Product bond length/Å		TS bond length/Å		i-freq./cm ⁻¹
	C-C	C-O	C-C	C-O	
1	1.54	1.42	2.074	2.07	600
2	1.53	1.41	2.074	2.07	603
3	1.55	1.41	2.103	2.10	492
4	1.57	1.41	2.113	2.11	506
5	1.53	1.41	2.103	2.10	524
6	1.55	1.41	2.103	2.10	490
7	1.57	1.41	2.103	2.10	514
8	1.53	1.41	2.103	2.10	526
12	1.55	1.42	2.103	2.10	496
13	1.58	1.42	2.158	2.16	393
14	1.53	1.41	2.113	2.11	486
15	1.57	1.41	2.113	2.11	488
17	1.60	1.42	2.112	2.11	452
18	1.59	1.42	2.113	2.11	442
19	1.59	1.42	2.113	2.11	443
20	1.59	1.42	2.113	2.11	441

TS: Transition State, i-freq: Imaginary Frequency

Table 5: Optimized C-C and C-O bond lengths of the transition states and products involved in the various reactions.

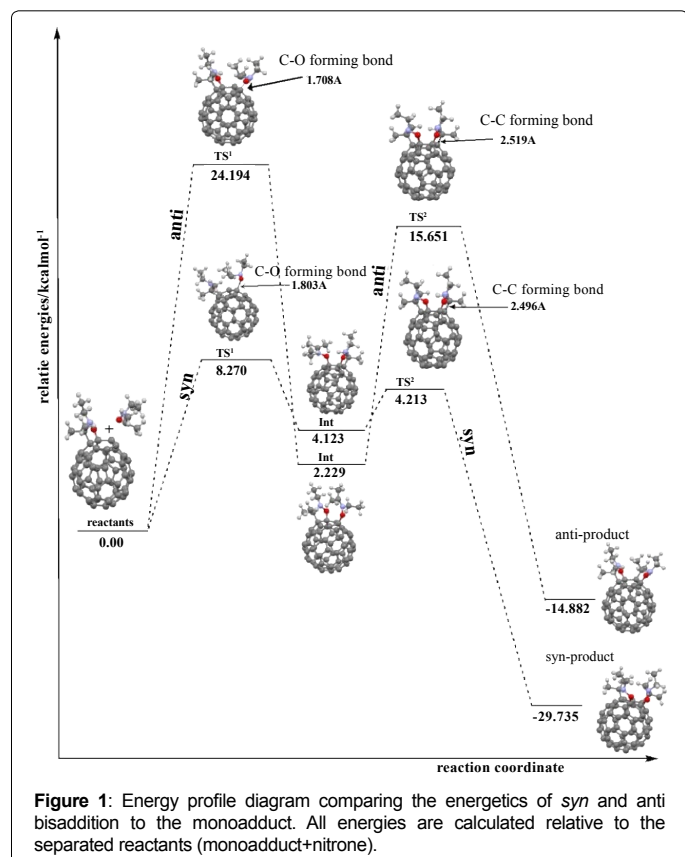


Figure 1: Energy profile diagram comparing the energetics of *syn* and *anti* bisaddition to the monoadduct. All energies are calculated relative to the separated reactants (monoadduct+nitrone).

barrier of the reaction whereas electron-donating groups decrease the activation barriers.

2. However, electron-withdrawing groups on the nitrones result in more stable products compared to the electron-donating groups.
3. The chemical hardness values show greater positive values for adducts with electron-withdrawing substituents on the nitrone

and smaller negative values for adducts with electron-donating substituents on the nitrone, confirming the trend that larger activation barriers accompany reactions with electron-withdrawing substituents on the nitrone while electron-donating substituents lower activation barriers.

4. Generally, the activation barriers of the second nitrone addition (bisadduct formation) were found to be less than barriers for the first nitrone addition (monoadduct formation).
5. Stereo-chemically, *syn*-bisaddition was found to be thermodynamically and kinetically stable favoured over *anti*-bisaddition.
6. The C-O bond formation is favored kinetically over the C-C bond at the saddle point in both the concerted and stepwise mechanistic pathways for all the reactions considered.

References

1. Kroto HW, Heath JR, O'Brien SC, Curl RF, Smalley RE, et al. (1985) C₆₀: Buckminsterfullerene. Nature 318: 162-163.
2. Krätschmer W, Lamb LD, Fostiropoulos K, Huffman DRS (1990) C₆₀: a new form of carbon. Nature 347: 354-358.
3. Imahori H, Mori Y, Matano Y (2003) Nanostructured artificial photosynthesis. J. Photochem. Photobiol C 4: 51-83.
4. Osuna S, Morera J, Cases M, Morokuma K, Solà M (2009) Diels-Alder reaction between cyclopentadiene and C₆₀: an analysis of the performance of the ONIOM method for the study of chemical reactivity in fullerenes and nanotubes. J Phys Chem A 113: 9721-9726.
5. Gao XF, Cui CX, Liu YJ (2012) Trapping intermediates and comparing relative reactivities: a DFT M06-2X study on Diels-Alder cycloadditions of butadiene to C₆₀ and C₇₀. J Phy Org Chem 25: 850-855.
6. Liddell PA, Kodis G, Andréasson J, de la Garza L, Bandyopadhyay S (2004) Photonic switching of photoinduced electron transfer in a dihydroporphyrin-fullerene molecular triad. J Am Chem Soc 126: 4803-4811.
7. Bakry R, Vallant RM, Najam-ul-Haq M, Rainer M, Szabo Z, et al. (2007) Medicinal applications of fullerenes. Int J Nanomedicine 2: 639-649.
8. Yamakoshi YN, Yagami T, Sueyoshi S, Miyata N (1996) Acridine Adduct of [60] Fullerene with Enhanced DNA-Cleaving Activity. J Org Chem 61: 7236-7237.
9. Krusic PJ, Wasserman E, Keizer PN, Morton JR, Preston KF (1991) Radical reactions of C₆₀. Science 254: 1183-1185.
10. Gharbi N, Pressac M, Hadchouel M, Szwarc H, Wilson SR, et al. (2005) [60] fullerene is a powerful antioxidant in vivo with no acute or subacute toxicity. Nano Lett 5: 2578-2585.
11. Tokuyama H, Nakamura M, Nakamura E (1993) [1 + 2] and [3 + 2] cycloaddition reactions of vinylcarbenes with C₆₀. Tetrahedron Lett 34: 7429-7432.
12. Xavier C, Elke D, Andreas H, Soom P, Luis E, et al. (1999) Globular dendrimers involving a C₆₀ Core and a tetraphenylporphyrine function. Chem Eur J 5: 2362-2373.
13. Röder B (2000) Photodynamic therapy in Encyclopedia Analytical Chemistry. Edited by R. A. Meyers. John Wiley and Sons Ltd: Chichester 302-320.
14. Yamakoshi Y, Umezawa N, Ryu A, Arakane K, Miyata N, et al. (2003) Active oxygen species generated from photoexcited fullerene (C₆₀) as potential medicines: O₂^{-•} versus 1O₂. J Am Chem Soc 125: 12803-12809.
15. Taylor R, Watson D (1993) the chemistry of fullerenes. Nature 363: 685-693
16. Ohno M, Kojima S, Shirakawa Y, Eguchi S (1995) Hetero-Diels-Alder reaction of fullerene: Synthesis of thiochroman-fused C₆₀ with O-thioquinone methide and oxidation to its S-oxides. Tetrahedron Lett 36: 6899-6902.
17. Wang X-B, Ding C-F, Wang L-S (1999) High resolution photoelectron spectroscopy of C₆₀^{-•}. J Chem Phys 110: 8217-8220.
18. Diederich F (1997) Covalent fullerene chemistry. Pure Appl Chem 69: 395-400.
19. Korobov MV, Allan L (2000) in: Fullerenes: Chemistry, Physics, and Technology, Edited by Kadish, K.M.; Ruoff, R.S. Wiley Interscience New York 53.

20. Prato M (1997) [60] Fullerene chemistry for materials science applications. *J Mater Chem* 7: 1097-1109.
21. Prato M, Maggini M (1998) Fulleropyrrolidines: A Family of Full-Fledged Fullerene Derivatives. *Acc Chem Res* 31: 519-526.
22. Bingel C (1993) Cyclopropanierung von Fullerenen. *Chemische Berichte* 126: 1957-1959
23. Martín N (2006) New challenges in fullerene chemistry. *Chem Commun (Camb)* : 2093-2104.
24. Parr RG, Szentpaly LV, Liu S (1999) Electrophilicity index. *J Am Chem Soc* 121: 1922-1924.
25. Chattaraj PK, Sarkar U, Roy DR (2006) Electrophilicity index. *Chem Rev* 106: 2065-2091.
26. Elango M, Parthasarathi R, Karthik G, Narayanan A, Sabeelullah MD, et al. (2005) Relationship between Electrophilicity index, Hammett constant and nucleus-independent chemical shift. *J Chem Sci* 117: 61-65.
27. Meneses L, Fuetelba P, Contreras R (2005) Relationship between the electrophilicity of substituting agents and substrate selectivity in Friedel-Crafts reactions. *Tetrahedron* 61: 831-836.
28. Castillo R, Andres J (2011) A DFT Study of the Reactivity Indexes of Ionic [4 + 2+] Diels-Alder Cycloaddition to Nitrilium and Immonium Ions. *Letters in Organic Chemistry* 8: 104-107.
29. Spartan (2014) Wavefunction Inc.
30. Cases M, Duran M, Mestres J, Martín N, Solà M (2001) Mechanism of the addition reaction of alkyl azides to [60]fullerene and the subsequent N2 extrusion to form monoimino-[60]fullerenes. *J Org Chem* 66: 433-442.
31. Clark M, Cramer RD, Opdenbosch NV (1989) Validation of the general purpose tripos 5.2 force field. *J Comput Chem* 10: 982-1012.
32. Kavitha K, Venuvanalingam P (2005) Open versus closed 1,3-dipolar additions of C₆₀: a theoretical investigation on their mechanism and regioselectivity. *J Org Chem* 70: 5426-5435.