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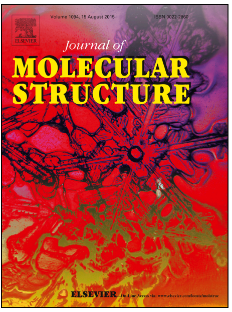

The structural aspects of the transformation of 3-nitroisoxazoline-2-oxide to 1-aza-2,8-dioxabicyclo[3.3.0]octane derivatives: Experimental and MEDT theoretical study

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The structural aspects of the transformation of 3-nitroisoxazoline-2-oxide to 1-aza-2,8-dioxabicyclo[3.3.0]octane derivatives: experimental and MEDT theoretical study

Przemysław Woliński(1), Agnieszka Kącka-Zych*(1), Błażej Dziuk(2),
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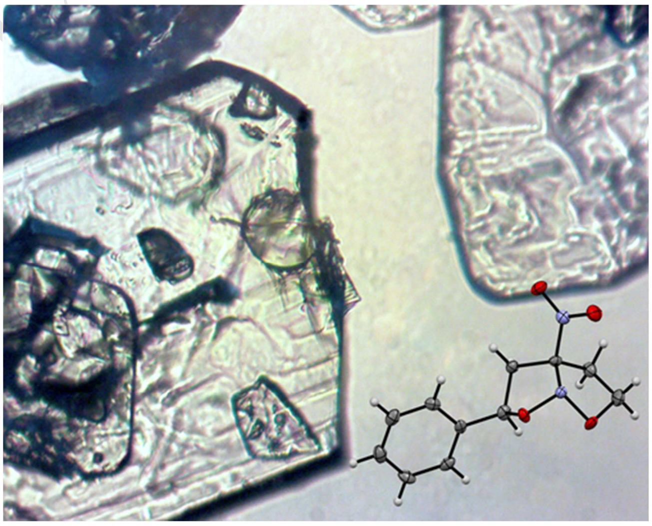
ABSTRACT

Reaction of 3-nitroisoxazoline-2-oxide with monosubstituted ethenes, first time documented fifty years ago, have been reviewed. Structures of phenyl and cyano derivatives of 1-aza-2,8-dioxabicyclo[3.3.0]octane produced in [3+2] cycloaddition (32CA) between styrene and acrylonitrile with 3-nitroisoxazoline-2-oxide were determined through single crystal XRD analysis. The molecular mechanism of the title 32CA has been also analyzed within the Molecular Electron Density Theory (MEDT) based on the M06-2X(PCM)/6-311+G(d,p) calculations.

KEYWORDS: 3-nitroisoxazoline-2-oxide; (3+2) cycloaddition; Molecular Electron Density Theory; Electron Localization Function; XRD analysis

GRAPHICAL ABSTRACT



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1. INTRODUCTION

Nitronates formally are esters of nitronic acids -*aci* form of aliphatic nitro compounds. Thanks to their unique build they possess 1,3-dipolar character allowing them to participate in 32CA. Actually the relatively large library of both acyclic and cyclic nitronates is available. Isoxazoline-2-oxides are example of cyclic nitronates which should be classified as *zw*-type three atom components (TACs) [1] and are useful in synthesis of 1-aza-2,8-dioxabicyclo[3.3.0]octanes through 32CA to substituted ethenes. Particularly, reaction of 3-nitroisoxazoline-2-oxide (**1**) with styrene (**2a**) has been first carried out half century ago [2]. This reaction theoretically leads to four regio- and stereoisomeric 3(4)-exo(endo)-R-5-nitro-1-aza-2,8-dioxabicyclo[3.3.0]octanes (**3a,b** - **6a,b**) (**Figure 1**).

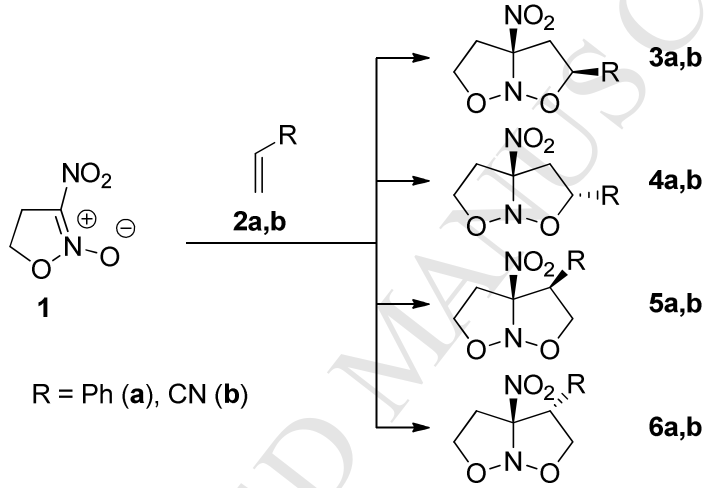


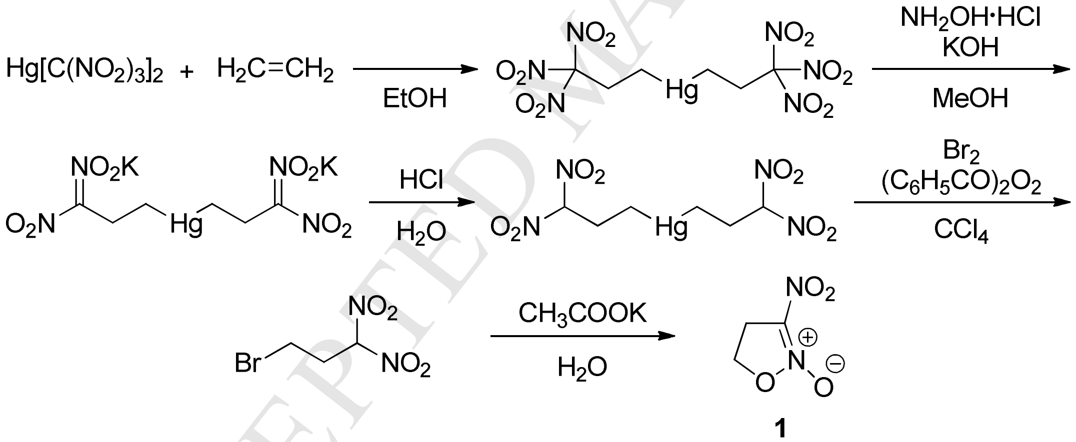
Figure 1. Possible products of 32CA 3-nitroisoxazoline N-oxide with monosubstituted ethenes.

Tartakovskii et al. [2] investigated title reactions and they isolated the reaction product from the postreaction mixture, but not diagnosed its individuality. Next, they proposed structure based purely on elemental analysis and intuition because of apparatus restrictions. Therefore, the question on the real structure of adduct derived in reaction between 3-nitroisoxazoline-2-oxide (**1**) with monosubstituted, simple ethene derivatives is still actual and require a deeper study. Based on the issues described above, we analyzed in the detail reactions of 3-nitroisoxazoline-2-oxide (**1**) with styrene (**2a**) and acrylonitrile (**2b**) as model ethane derivatives. This is a continuation of our comprehensive, theoretical [3-6] and experimental [5-8] study about regio-, stereochemical aspects and molecular mechanism of 32CA involving nitro substituted components.

2. RESULTS AND DISCUSSION

Synthesis and spectral characteristics

We started our work from synthesis of 1,3-dipolar component of studied reaction. To synthesize 3-nitroisoxazoline-2-oxide (**1**) 1-bromo-3,3-dinitropropane is needed (**Figure 2**). It can be prepared only through use of organomercuric compounds. Apart from their high toxicity, low stability causes the need to perform every step of the synthesis immediately. In the first step a flow of ethene is passed through an ethanolic solution of bis(trinitromethyl)mercury until no more of bis(3,3,3-trinitropropyl)mercury precipitate is formed [9]. Filtered off and dried product is then dissolved in methanol and reacted with hydroxylamine to remove two isolated nitro groups. Precipitated potassium salt of bis(3,3-dinitropropyl)mercury is filtered off, vacuum dried and added to 2N solution of hydrochloric acid [10]. Produced bis(3,3-dinitropropyl)mercury is then brominated with bromine in tetrachloromethane in presence of catalytic amount of benzoyl peroxide. After filtering off precipitated mercuric bromide the 1-bromo-3,3-dinitropropane is then separated from postreaction mixture through vacuum fractional distillation [11]. In the last step the 1-bromo-3,3-dinitropropane is treated with aqueous solution of potassium acetate. In such environment it undergoes intramolecular O-alkylation to form 3-nitroisoxazoline-2-oxide [12].



1

Figure 2. Synthesis of 3-nitroisoxazoline-2-oxide (**1**).

Based on the pure and individual 3-nitroisoxazoline-2-oxide (**1**) we started our tests with choosing of reactions conditions involving ethene derivatives **2a** and **2b**. It was found, that under the convenient conditions, the synthesis proceeds in anhydrous ethanol at room temperature and full conversion of **1** is achieved after 5 to 7 days. Crude products, purified by fractional crystallization from anhydrous ethanol, and its individuality has been confirmed by TLC and HPLC tests. In both cases, single adduct was isolated from the reaction mixture.

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For resolving of the structure of obtained adducts, we performed comprehensive study, started from data of CHN elemental analysis. It was found, that was convergent expected for cycloadducts shown on **Figure 1**.

The IR spectra of the reaction products show the absorption bands, which confirm the presence of nitro group. The NO_2 stretch and bend frequencies are located at 1553 cm^{-1} and 1351 cm^{-1} and 1553, 1354 respectively for **3a** and **3b**. Besides the above-mentioned NO_2 vibrations, there are also the most prominent O-N-O peaks within the isoxazolidinoisoxazolidine ring at 1033 cm^{-1} and CH-stretch in the phenyl ring at 3029 and 2987 cm^{-1} and CH-bent 702 and 763 cm^{-1}. However, there are only very weak band 2245 cm^{-1} confirming the presence of nitrile group of **3b.** From the literature data it is known that this band can be very weak or quite invisible in a situation where the carbon at which the CN group is located is connected to an exocyclic oxygen atom [13]. This may suggest that the nitrile group is located on the C3-position of the heterocyclic system. This implies that the analyzed product could be adduct **3** or **4**. However the IR spectrum does not allow to resolve this problem unambiguously. Therefore, further analysis of the isolated compound was necessary. Further information about the structure of the isolated compounds was obtained from the ^{1}H NMR spectra. In particular, the isoxazolidinoisoxazolidine system in **3a** has two five-membered rings — each with distinctive proton environments and two isolated spin systems ABX (including H4, H4',H3 protons) and ABXY (including H6, H6', H7 and H7').

So, two geminal proton (H4 and H4') signals are in a stronger field (δ = 3.42 – 2.26 ppm), whereas the proton H3 is in a relatively weaker field (δ = 5.39 ppm) due to near present oxygen atom and phenyl ring. Vicynal coupling constant are equal to 10.9 Hz and 5.4 Hz for relation H3–H4 and respectively H3–H4'. This confirms *cis* relative configuration of H3 and H4 protons, and *trans* relations of H3–H4'. Next, two geminal proton H7 and H7' signals are in a stronger field (δ = 4.43 ppm and δ = 4.30 ppm, respectively). The respective values of coupling constants are equal: $J_{H7-H7'}$= 14.5Hz, J_{H6-H7}= 7.3Hz and $J_{H6'-H7}$= 5.4 Hz. On the other hand, the signals of protons H6 and H6' are in weaker field (2.90 and 2.71). The respective value of coupling constants are equal: $J_{H6-H6'}$= 13.3Hz, $J_{H6'-H7}$=5.4 Hz. The multiplets corresponding to the five aryl protons are shifted in the evidently weakest field and appear at δ = 7.47 – 7.34 ppm. In ^{13}C-NMR spectrum, signals of -CH_2- carbon atoms were found at 67.9 (C7), 46.4 (C4), 39.3 (C6) ppm. The position of the signals corresponding to the carbon atom C5 with nitro group is shifted into a regionof much higher frequencies (114.8 ppm). In similar way, the NMR spectrums **3b** can be interpreted. Unfortunately, IR as well as

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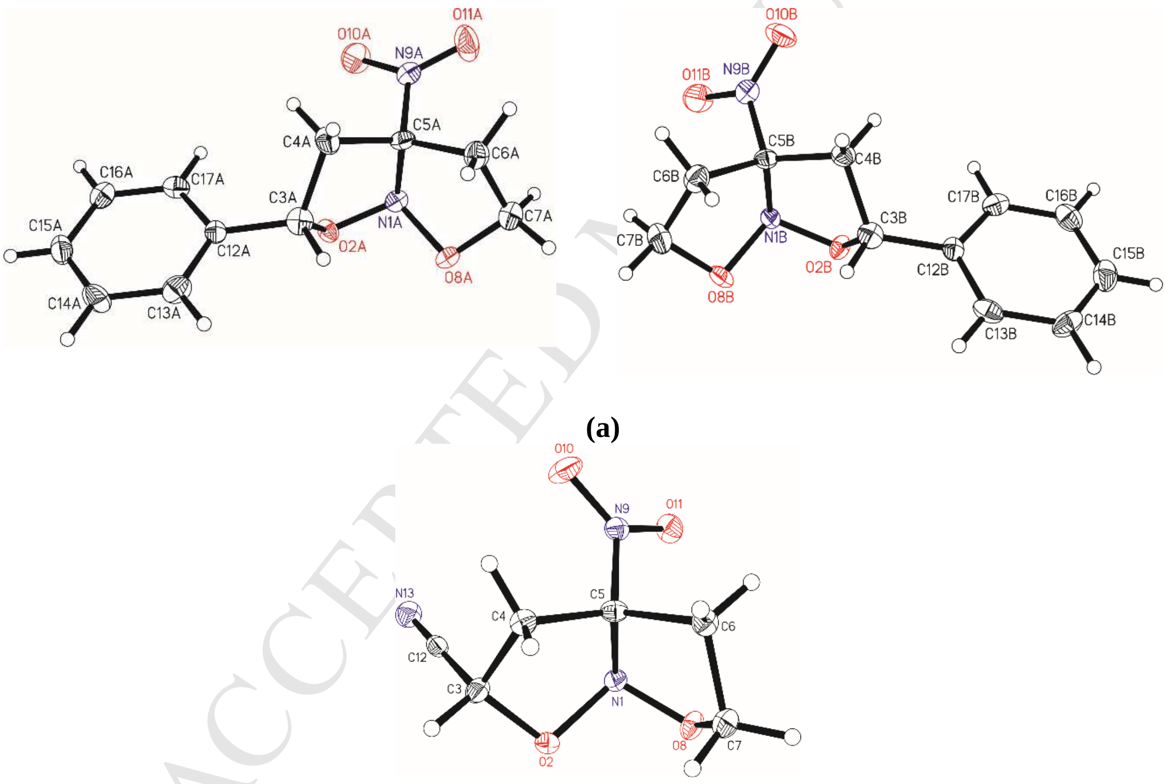
NMR spectrums not provide evidently supports for identification of regio- and stereochemistry of obtained adducts. For this purpose, we applied data obtained using RTG technique.

It was found, that the molecular structures of **3a** and **3b**, with the atomic numbering scheme presented in **Figure 3**, show selected geometric data given in **Table 1**. In the crystal structure of **3a** there are two independent molecules in the asymmetric unit (**Figure 3a**). The N1 atom in the studied compounds lies about 0.6 Å out of the plane defined by the three neighboring atoms (O2, O8 and C5). Additionally, the sum of the valence angles around the N1 atom of 312.6 (1)° and 312.9 (1)° in **3a**, 313.14 (1)° in **3b** demonstrates clear sp^3 hybridization (328° for sp^3 and 360° for sp^2). The other geometric parameters of **3a** and **3b** (**Tables S1** and **S2** in Supplementary information) are normal and compare well with those found in other crystal structures [14-17].



(a)

(b)

Figure 3. The molecular structures of **3a** (a) and **3b** (b) in the asymmetric part of unit cell. Displacement ellipsoids are drawn at the 50% probability level.

Table 1. Selected geometrical parameters (Å, °) in the studied compounds.

Parameters	**3a**		**3b**
	A	**B**	
N1-O8	1.480 (2)	1.479 (2)	1.397 (2)
N1-O2	1.404 (2)	1.411 (2)	1.494 (2)

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O8-C7	1.421 (2)	1.423 (3)	1.458 (2)
O2-C3	1.469 (2)	1.469 (2)	1.420 (2)
N1-C5	1.528 (3)	1.510 (3)	1.518 (2)
O8-N1-C5	102.38 (15)	103.67 (16)	105.86 (13)
O2-N1-C5	105.49 (16)	105.03 (15)	102.97 (13)
O8-N1-O2	104.72 (14)	104.27 (15)	104.31 (12)
C3-O2-N1-O8	81.86 (18)	-85.14 (17)	148.28 (13)
C7-O8-N1-O2	-151.02 (16)	145.91 (16)	-82.74 (15)
N1-O8-C7-C6	49.4 (2)	-45.8 (2)	-41.15 (18)
O8-C7-C6-C5	-37.0 (2)	36.4 (2)	38.32 (17)
C7-C6-C5-C4	128.7 (2)	-131.8 (2)	94.77 (18)
C6-C5-C4-C3	-95.5 (2)	91.0 (2)	-127.71 (16)
C5-C4-C3-O2	-36.7 (2)	39.9 (2)	33.52 (18)
N1-O2-C3-C4	39.9 (2)	-40.7 (2)	-44.92 (17)

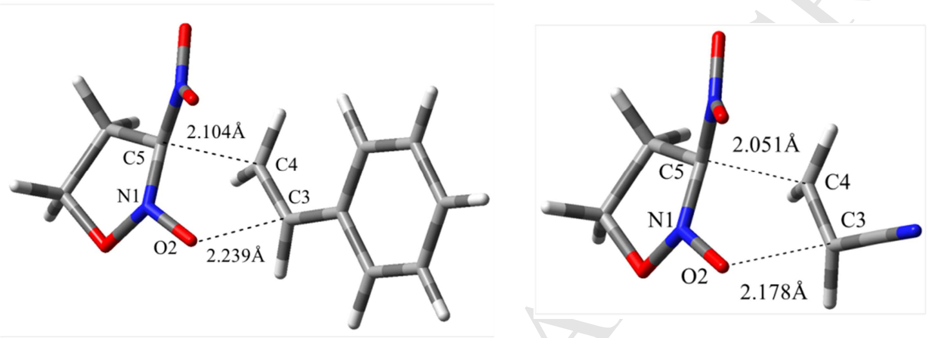
MEDT study of the 32CA 3-nitroisoxazoline-2-oxide (1) with model ethane derivatives (2a,b)

Analysis of the stationary points involved in the 32CA 3-nitroisoxazoline-2-oxide (**1**) with model ethane derivatives (**2a,b**) in ethanol indicates that this reaction takes place via a one-step mechanism. These reactions begins with the formation of the molecular complex MC (**MC-1** and **MC-2**). Formation of these complexes are endergonic for reaction with styrene (**2a**) and acrylonitrile (**2b**) by 6.1 kcal/mol (**MC-1**) and 6.5 kcal/mol (**MC-2**), respectively. Further conversion of the reactions lead to the transition state structures (**TS-1** and **TS-2**, **Figure 4**). As the data of M06-2X(PCM)/6-311+G(d,p) calculations show, this change demands a Gibbs free energy of 26.7 kcal/mol for reaction with participation of **2a** and 27.5 kcal/mol for reaction with **2b**. Afterwards, the TSs are converted to products **3a** and **3b** (**Table 2**).

Table 2. Thermodynamic parameters for the 32CA 3-nitroisoxazoline-2-oxide (**1**) with model ethane derivatives (**2a,b**) in ethanol (T=298 K; ΔH, ΔG in kcal·mol^{-1}, ΔS in cal·mol^{-1}·K^{-1}).

Functional	**Transition**	**ΔH**	**ΔG**	**ΔS**
B3LYP-D3	**1+2a→MC-1**	-6.7	3.6	-34.5
	1+2a→TS-1	11.6	25.6	-47.0
	1+2a→3a	-23.5	-10.2	-44.3
	1+2b→MC-2	-2.1	6.3	-28.1
	1+2b→TS-2	14.4	27.7	-44.6
	1+2b→3b	-16.2	-2.5	-46.0
M06-2X	**1+2a→MC-1**	-4.9	6.1	-37.0

	1+2a→TS-1	12.0	26.7	-49.3
	1+2a→3a	-37.3	-22.3	-50.4
	1+2b→MC-2	-2.9	6.5	-31.4
	1+2b→TS-2	14.0	27.5	-45.3
	1+2b→3b	-29.8	-15.5	-48.0
M11	**1+2a→MC-1**	-8.5	2.0	-42.9
	1+2a→TS-1	12.5	25.3	-42.9
	1+2a→3a	-35.3	-21.8	-45.2
	1+2b→MC-2	-3.1	6.4	-31.6
	1+2b→TS-2	14.2	27.3	-43.8
	1+2b→3b	-28.3	-14.1	-47.6



TS-1 **TS-2**

Figure 4. M06-2X(PCM)/6-311+G(d,p) Geometry of transition states (**TS-1** and **TS-2**) of the 32CA 3-nitroisoxazoline-2-oxide (**1**) with model ethane derivatives (**2a,b**).

It should also be mentioned that DFT study using different B3LYP and M11 functionals with 6-311+G(d,p), 6-31G(d) and 6-31++G(d) basic sets gives a similar representation of these reactions. In the case of calculations based on M11(PCM)/6-311+G(d,p) theory levels, we observed a decrease in the Gibbs free energy and B3LYP(PCM)/6-311+G(d,p) calculations for reactions with **2a** suggests a decrease the Gibbs free energy (**Table 2**). The thermodynamic parameters for the 32CA 3-nitroisoxazoline-2-oxide (**1**) with model ethane derivatives (**2a,b**) for B3LYP, M06-2X and M11 functionals with 6-311+G(d,p), 6-31G(d) and 6-31++G(d) basic sets are given in **Tables S3** and **S4** of the Supplementary Materials.

Recently, Domingo proposed new reactivity theory – MEDT [1]. This theory, in which stablishes that changes in electron–density, and not molecular orbital interactions, are responsible for reactivity in organic chemistry, uses quantum chemical tools such as the conceptual Density Functional Theory (DFT) reactivity indicator. Within MEDT, quantum chemical tools based on the analysis of the electron density, such as the Electron Localization

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Function (ELF) [18], Bonding Evolution Theory (BET) [19] and Catastrophe Theory (CT) [20-22] are used to study the molecular electron-density along the reaction path, in order to study organic reaction. CT in combination with ELF gradient field constitutes a way to rationalize the reorganization of electron pairing and a powerful tool for the unambiguous determination of the molecular mechanisms of a given chemical reaction [20].

This theory is the basic tool for explaining the molecular mechanism of many types of reactions [23-27]. To present changes in the course of the reactions of 3-nitroisoxazoline-2-oxide (**1**) with styrene (**2a**) and acrylonitrile (**2b**), a MEDT study were carried out.

In order to characterize the molecular mechanism of the reaction of 3-nitroisoxazoline-2-oxide (**1**) with styrene (**2a**), a BET study along the reaction was carried out. The complete BET study is provided in the Supplementary Materials (**Table S5**). The sequential bonding changes received from the MEDT analysis of the reaction of 3-nitroisoxazoline-2-oxide (**1**) with styrene (**2a**) is shown in **Table 3**. From the BET analysis of this reaction some appealing conclusions can be drawn: (i) molecular mechanism of the reaction of the 3-nitroisoxazoline-2-oxide (**1**) to styrene (**2a**) can be topologically characterized by eight different phases, which have been grouped into three different A-C Groups (**Table 3, Figure 5**); (ii) Group A, containing Phases I-IV, in which the C3-C4 double bond breaks and we are also noticed disappearance of pseudoradical center of V'(C5) and formation a new pseudoradical center near the atom N1 – V(N1); (iii) Group B, containing Phases V and VI, in which we observed the formation of pseudoradical center V(C4) which is next converted into the new bond between atoms C4 and C5. At the beginning of the only phase of Group B, the **TS-1** is found; (iv) The last Group C, containing Phases VII and VIII, in which the bond O2-C3 is formed. (v) It is worth nothing that the formation of bond between atoms C4 and C5 takes place homolitically, while the O2-C3 bond is formed heterolytically.

Table 3. Sequential bonding changes along the reaction of the 3-nitroisoxazoline-2-oxide (**1**) with styrene (**2a**), showing the equivalence between the topological characterization of the different phases and the chemical processes occurring along them. Distances are given in angstroms, Å, GEDT values in average number of electrons, [e] and relative energies are given in kcal·mol^{-1}.

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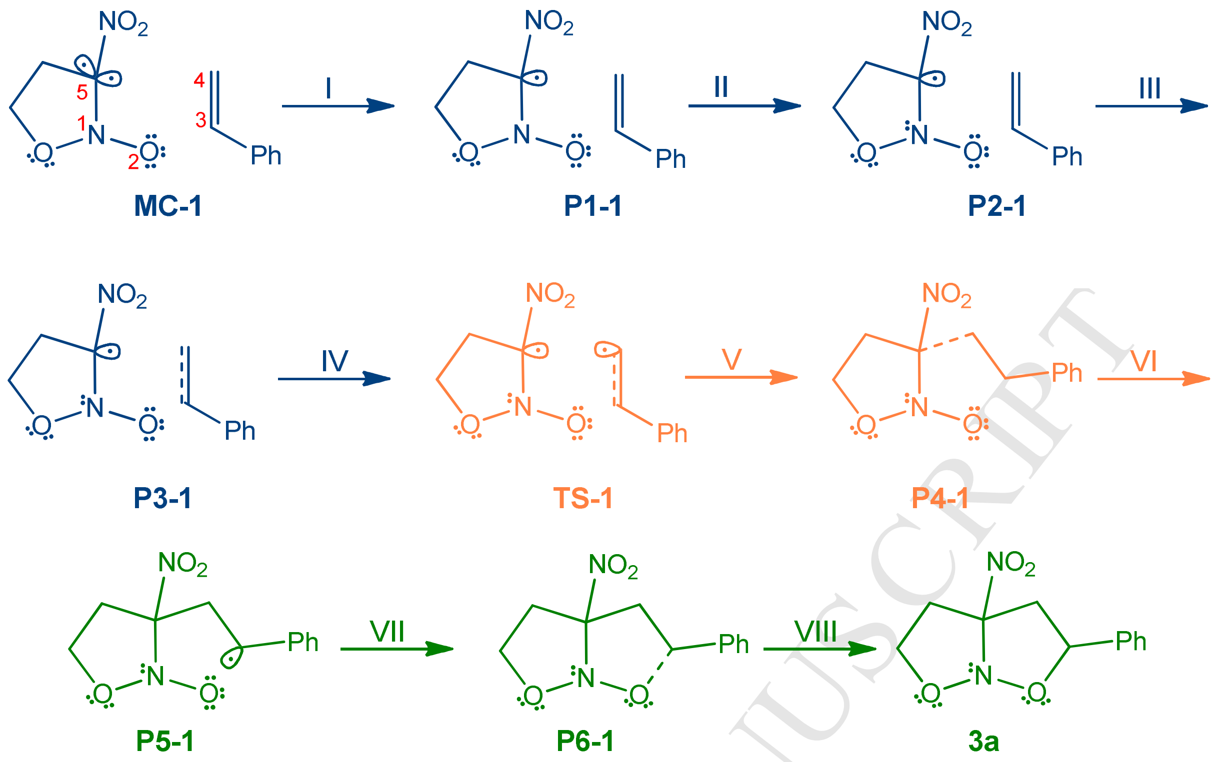

Group	Phases	d_1(O2-C3) d_2(C4-C5)	GEDT	ΔE	Topological characterization	Chemical process
A	*I-IV*	$6.47 \geq d_1 > 4.38$ $6.51 \geq d_2 > 3.94$	0.07	11.1	Disappearance of the V'(C3,C4) disynaptic basin and V'(C5) monosynaptic basin and formation of V(N1) monosynaptic basin	Rupture of the C3-C4 double bond
B	*V-VI*	$4.38 \geq d_1 > 3.90$ $3.94 \geq d_2 > 3.16$	0.03	2.1	Formation of the V(C4,C5) disynaptic basin and V(C4) monosynaptic basin and disappearance of V(C5) monosynaptic basin	Formation of the C4-C5 bond
C	*VII-VIII*	$3.90 \geq d_1 > 2.72$ $3.16 \geq d_2 > 2.88$	0.02	-22.9	Formation of V(C3) monosynaptic basin and V(O2,C3) disynaptic basin	Formation of the O2-C3 bond

In the case of reaction of the 3-nitroisoxazoline-2-oxide (**1**) with acrylonitrile (**2b**), according to the BET analysis, we can distinguish nine topological changes along the reaction path (**Table 4**, **Figure 5**). The complete BET study is provided in the Supplementary Materials (**Table S6**). From this analysis, some appealing conclusion can be obtained: (i) the reaction of the 3-nitroisoxazoline-2-oxide (**1**) with acrylonitrile (**2b**) can be characterized by nine different phases which, in turn can be reorganized in three Groups A-C associated to significant chemical changes (**Table 4, Figure 5**); (ii) in Group A, which containing Phases I-IV, we observed the rupture of the double bond between atoms C3 and C4; (iii) in the next Group B, which containing Phases V and VI, we observed the formation of C4-C5 bond.

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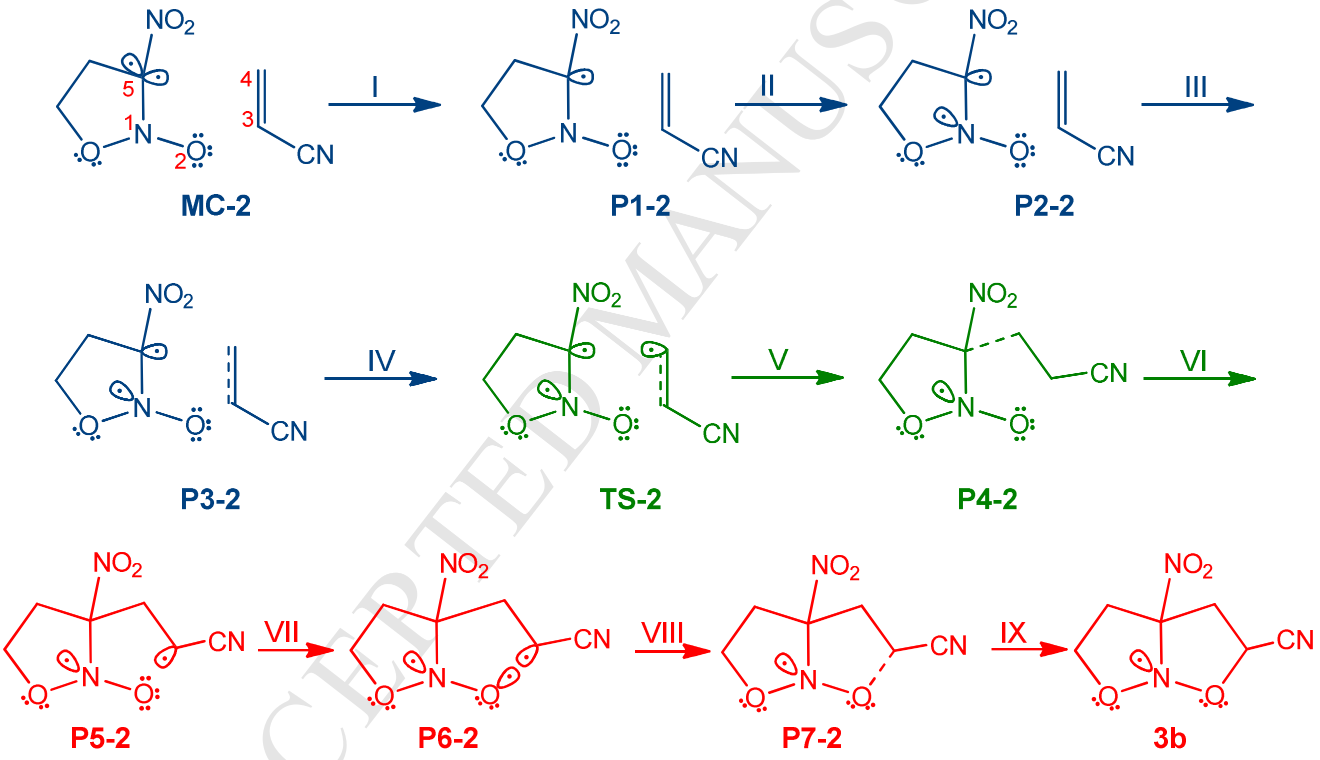
Formation of this bond takes place at C4-C5 lengths of 3.74 Å. At the beginning of this Group, we observed the presence of **TS-2** of this reaction; (iv) Group C containing Phases VII-IX. This group is associated with the formation of O2-C3 bond. This O2-C3 bond, in the case of reaction of the 3-nitroisoxazoline-2-oxide (**1**) with acrylonitrile (**2b**), take place homolitically.

Table 4. Sequential bonding changes along the reaction of the 3-nitroisoxazoline-2-oxide (**1**) with acrylonitrile (**2b**), showing the equivalence between the topological characterization of the different phases and the chemical processes occurring along them. Distances are given in angstroms, Å, GEDT values in average number of electrons, [e] and relative energies are given in kcal·mol^{-1}.



Group	Phases	d_1(O2-C3) d_2(C4-C5)	GEDT	ΔE	Topological characterization	Chemical process
A	*I-IV*	$6.04 \geq d_1 > 4.31$ $6.44 \geq d_2 > 3.80$	0.10	12.2	Disappearance of the V'(C3,C4) disynaptic basin and V'(C5) monosynaptic basin and formation of V(N1) monosynaptic basin	Rupture of the C3-C4 double bond
B	*V-VI*	$4.31 \geq d_1 > 3.98$ $3.80 \geq d_2 > 3.28$	0.09	9.8	Formation of the V(C4,C5) disynaptic basin and V(C4) monosynaptic basin and disappearance of V(C5) monosynaptic basin	Formation of the C4-C5 bond

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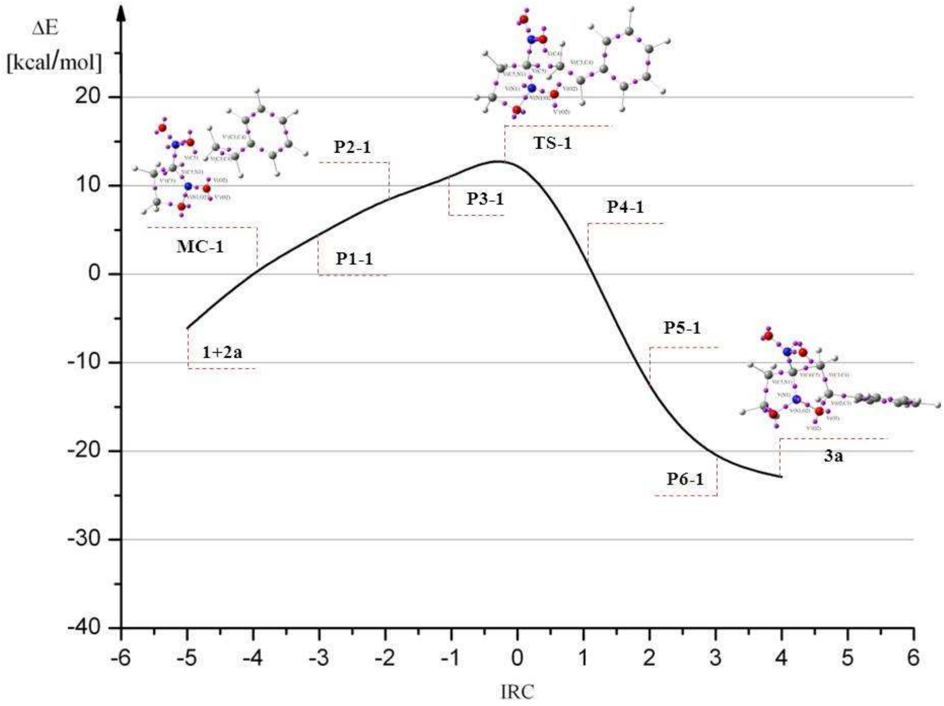
C	*VII-IX*	$3.98 \geq d_1 > 2.70$ $3.28 \geq d_2 > 2.88$	0.02	-15.6	Formation of V(C3) and V’’(O2) monosynaptic basins and V(O2,C3) disynaptic basin	Formation of the O2-C3 bond



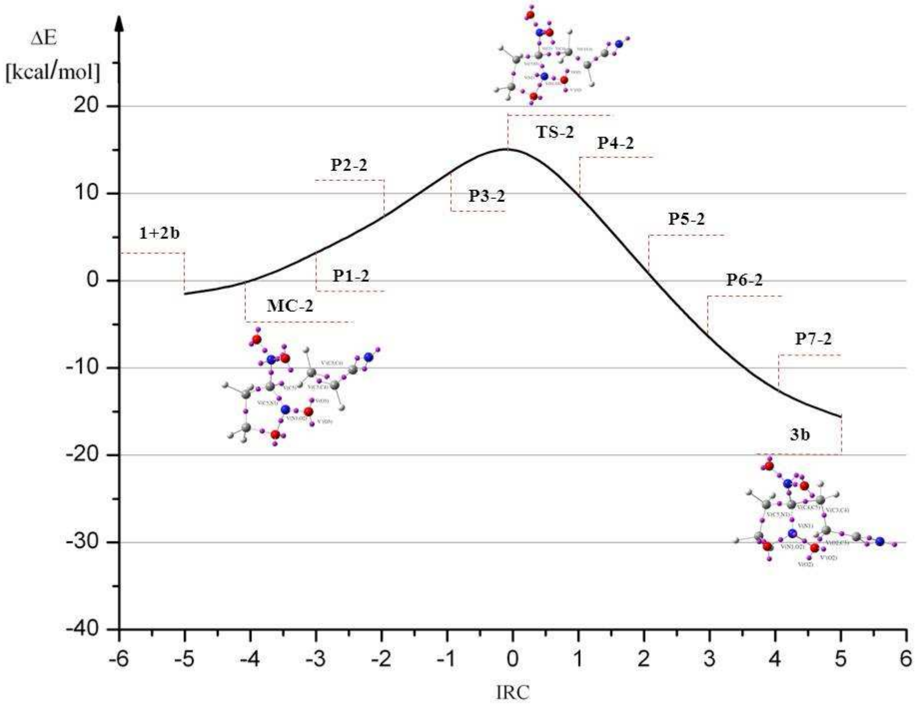


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Figure 5. M06-2X(PCM)/6-31G(d) IRC profile including the ELF attractor positions for the most relevant points of the reaction of the 3-nitroisoxazoline-2-oxide (**1**) with styrene (**2a**) (top) and acrylonitrile (**2b**) (bottom).

3. EXPERIMENTAL

General

Materials used in our work were purchased from Sigma-Aldrich, POCh, and Chempure and were used as received except for styrene and acrylonitrile which were distilled prior use. Reactions advancement were monitored using Fluka's silicagel (60F254) on Al foil TLC plates with benzene and THF (8:2 v/v) as elution solution. We also used Knauer HPLC with LiChrospher RP-18 250 x 4 mm column with precolumn from the same manufacturer. HPLC eluent was acetonitrile and water (60:40 v/v). Melting points were measured using Boetius PH MK-05 apparatus and are uncorrected. Elemental analysis was performed with Perkin Elmer PE 2400 analyzer. Infrared spectra were recorded on Thermo Fisher Scientific Nicolet iS 10 FT-IR using KBr pellets. ^{1}H NMR spectra were measured on Bruker AMX500 spectrometer using TMS as internal standard.

X-ray crystallography

The single crystals of the compounds **3a** and **3b** were mounted on a CCD Xcalibur diffractometer (graphite monochromatic, Mo$K\alpha$ radiation, λ= 0.71073 Å) at 100.0(1) K. The reciprocal space was explored by ω scans with detector positions at 60 mm distance from the crystal. The diffraction data processing of studied compounds (Lorentz and polarization corrections were applied) was performed using the CrysAlis CCD [28]. Both crystal structures were solved by direct methods using SHELXS14program [29,30]. All non-hydrogen atoms were located from difference Fourier synthesis and refined by least squares method in the full-matrix anisotropic approximation using SHELXL14 software [29,30]. In both structures the H atoms were located from difference Fourier synthesis and were refined using a riding model. The structure drawings were prepared using SHELXTL program [29,30]. The crystallographic data for the studied compounds and details of X-ray experiment are collected in the **Table 5**. Crystallographic data for the both structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC: 1898859 for **3a** and 1898860 for **3b**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic

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Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 144 1223 336 033; email:deposit@ccdc.cam.ac.uk.

Table 5. The crystal data, experimental details and refinement parameters for **3a** and **3b**.

Crystal data		
	3a	**3b**
Chemical formula	$C_{11}H_{12}N_2O_4$	$C_6H_7N_3O_4$
M_r	236.23	185.15
Crystal system, space group	Triclinic, *P*-1	Monoclinic, $P2_1/c$
a, *b*, *c* (Å)	8.0478 (3), 11.3416 (4), 13.0227 (6)	6.1090 (3), 11.7490 (5), 10.8456 (5)
α, β, γ (°)	68.287 (4), 82.932 (3), 79.360 (3)	90, 105.082 (5), 90
V (Å^3)	1083.37 (8)	751.63 (6)
μ (mm^{-1})	0.11	0.14
Crystal size (mm)	0.15 × 0.10 × 0.05	0.20 × 0.15 × 0.10
Data collection		
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	7431, 4172, 2254	4950, 1479, 1107
R_{int}	0.045	0.040
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.617	0.616
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.049, 0.082, 0.86	0.043, 0.085, 1.04
No. of reflections	4172	1479
No. of parameters	307	118
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.23 -0.24	0.24 -0.21

Synthesis of 3-nitroisoxazoline-2-oxide (1)

To a beaker containing solution of 4.7 g potassium acetate in 50 mL of distilled water, 10.2 g (0.048 mol) of 1,1-dinitro-3-bromopropane was added during 5 hours of stirring. The reaction mixture was left to the next day. Precipitated crystals were filtered off, washed with distilled water, dried, and crystallized twice from ethanol. Synthesized 3-nitroisoxazoline-2-oxide weighted 5.2 g, which corresponds to 82% yield.

Physical data for **1**: m.p. 96.1 °C (96.5°C [12]), found: 27.35% C, 2.87% H, 20.93% N, calc. for $C_3H_4N_2O_4$ 27.28% C, 3.05% H, 21.21% N; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (t, $2H_5$),

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3.82 (t, $2H_4$); ^{13}C NMR (125 MHz, $CDCl_3$) 126 (C3), 64 (C5), 28 (C4); IR spectrum (KBr) (ν, cm^{-1}) 1619 (C=N), 1500, 1296 (NO_2).

32CA of 3-nitroisoxazoline-2-oxide (1) with styrene (2a)

In a Erlenmeyer flask 0.66 g (0.005 mol) of **1** and 2.60 g (0.025 mol) of **2a** in 10 mL of anhydrous ethanol was combined. The reaction mixture was stirred in dark to full conversion of **1** (monitored with HPLC and TLC) for 7 days. The unreacted alkene and solvent was removed on rotary evaporator. The crude product was refined with fractional crystallization from anhydrous ethanol to give 3-exo-phenyl-5-nitro-1-aza-2,8-dioxabicyclo[3.3.0]octane pure enough for XRD analysis. Yield of the main product was 1.02 g which corresponds to 86% of theoretical yield.

Physical data for **3a**: m.p. 81-83 °C, found: 55.90% C, 4.98% H, 11.75% N, calc. for $C_{11}H_{12}N_2O_4$ 55.93% C, 5.12% H, 11.86% N, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.34 (m, 5HPh), 5.69 (dd, *J* = 10.9, 5.4 Hz, 1H3), 4.43 (dd, *J* = 14.5, 7.3 Hz, 1H7), 4.30 (m,1H7), 3.42 – 3.26 (m, 2H4), 2.90 (dd, *J* = 13.3, 5.4 Hz, 1H6), 2.71 (m, 1H6); ^{13}C NMR (125 MHz, $CDCl_3$) 114.8 (C5), 85.4 (C3), 67.9 (C7), 46.4 (C4), 39.3 (C6); IR spectrum (KBr) (ν, cm^{-1}) 702, 763, 2987, 3029 (Ph),1553, 1351 ($-NO_2$), 1033 (O-N-O).

32CA of 3-nitroisoxazoline-2-oxide (1) with acrylonitrile (2b)

In a Erlenmeyer flask 0.66 g (0.005 mol) of **1** and 1.33 g (0.025 mol) of **2b** in 10 mL of anhydrous ethanol was combined. The reaction mixture was stirred in dark to full conversion of **1** (monitored with HPLC and TLC) for 5 days. The unreacted alkene and solvent was removed on rotary evaporator. The crude product was purified with fractional crystallization from anhydrous ethanol to give 3-exo-cyano-5-nitro-1-aza-2,8-dioxabicyclo[3.3.0]octane pure enough for XRD analysis. Yield of the main product was 1.02 g which corresponds to 86% of theoretical yield.

Physical data for **3b**: m.p. 98-100 °C, found: 38.97% C, 3.62% H, 22.52% N, calc. for $C_6H_7N_3O_4$ 38.92% C, 3.81% H, 22.70% N; ^{1}H NMR (500 MHz, acetone) δ 5.65 (dd, *J* = 8.4, 3.4 Hz, 1H3), 4.76 – 4.48 (m, 2H7), 3.79 (ddd, *J* = 14.8, 3.4, 0.8 Hz, 1H4), 3.48 (dd, *J* = 14.8, 8.4 Hz, 1H4), 3.31 (m, 1H6), 2.90 (ddd, *J* = 13.5, 6.3, 2.9 Hz, 1H6); ^{13}C NMR (125 MHz, $CDCl_3$) 116.8 (CN), 114.7 (C5), 72.4 (C3), 64.9 (C7), 41.7 (C4), 38.0 (C6); IR spectrum (KBr) (ν, cm^{-1}) 2245 (-CN),1553, 1354 ($-NO_2$), 1001 (O-N-O).

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DFT calculations

Calculations were performed using the Prometheus computer cluster in the CYFRONET regional computer centre in Cracow. All calculations were carried out with the GAUSSIAN 16 package [31]. DFT calculations were performed using the B3LYP-D3 [32-35], M06-2X [36] and M11 [37] functional together with the 6-311+G(d,p), 6-31G(d) and 6-311+G(d) basis sets. The stationary points were characterized by frequency calculations in order to verify the number of imaginary frequencies (zero for local minima and one for TSs). The IRC [38] paths, computed using the second order González-Schlegel integration method [39,40], were traced in order to obtain the energy profiles connecting TS to the two associated minima of the proposed mechanism. Solvent effect of ethanol in the optimizations were taken into account using the polarizable continuum model (PCM) as developed by Tomasi's group [41-43] in the framework of the self-consistent reaction field (SCRF) [44,45]. Values of free energies in all calculations were calculated with the standard statistical thermodynamics at 25ºC and 1 atm [34].

Charge global electron density transfer (GEDT) [46] was calculated according to the formula:

$$\mathrm{GEDT}=-\Sigma q_A$$

where q_A is the net charge and the sum is taken over all the atoms of the substructure.

The topological analyses of the Electron Localization Function (ELF) were performed with the TopMod [47] program using the corresponding M06-2X(PCM)/6-311+G(d,p) monodeterminantal wavefuctions. ELF calculations were computed over a grid spacing of 0.1 a.u. for each structure and ELF localization domains were obtained for an ELF value of 0.75. For the Bonding Evolution Theory (BET) [19] studies, the corresponding reaction paths were followed by performing the topological analysis of the ELF for at least 195 nuclear configurations along the IRC paths.

4. CONCLUSIONS

The structural aspects of the 1-aza-2,8-dioxabicyclo[3.3.0]octane derivatives synthesis on the basis of the 3-nitroisoxazoline-2-oxide has been examined using experimental and computational techniques. The constitution of isolated products has been confirmed without any doubts using spectral methods and single crystal XRD analysis. The molecular mechanism of the 32CA reactions leading to 1-aza-2,8-dioxabicyclo[3.3.0]octane derivatives has been studied within the MEDT using DFT method at the M06-2X(PCM)/6-311+G(d,p) calculations. These reactions take place through a one-step mechanism. The reaction of the 3-nitroisoxazoline-2-oxide (**1**) with styrene (**2a**), according to the BET analysis, can be characterized by eight different phases, while in the reaction of the 3-nitroisoxazoline-2-oxide (**1**) with acrylonitrile (**2b**) we can distinguish nine different phases. Worth noting is the fact that the bond between atoms C4 and C5, in the case of reaction **1**+**2a**, is formed homolitically, while the bond O2-C3 take place heterolytically. In the case of reaction **1**+**2b**, both C4-C5 and O2-C3 bonds are formed homolitically.

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