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An experimental and quantumchemical study of [2+3] cycloaddition between (Z)-C-(m,m,p-trimethoxyphenyl)-N-(p-methyphenyl)-nitrone and (E)-3,3,3-trichloro-1-nitroprop-1-ene: mechanistic aspects

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Analysis of addent interactions with respect to the theory of electrophilicity and nucleophilicity indexes and kinetic studies shows the polar nature of [2+3] cycloaddition of (Z)-C-(m,m,p-trimethoxyphenyl)-N-(p-methylphenyl)-nitrone to (E)-3,3,3-trichloro-1-nitroprop-1-ene. However, PES exploration results do not confirm any zwitterion on the reaction paths. On the other hand, the nature of the solvent effect and the experimentally determined activation parameter values do not exclude a scenario in which one-step and stepwise processes occur simultaneously.

1. Introduction

Knowledge concerning the [2+3] cycloaddition mechanism has evolved greatly, from views which assumed a one-step mechanism to be the only one possible[1], to modern ones which recognise the possibility of zwitterionic intermediates in the conversion of addents into cycloadducts[2,3]. The two-step zwitterionic mechanism has been shown to be feasible in, for example, the [2+3] cycloaddition of diazo compounds[4], azides[5], nitrile N-oxides[6,7], thiocarbonyl ylides[8-10] and azomethine ylides[11]. However there are no documented experimental support for cases in the literature of a stepwise, zwitterionic mechanism for [2+3] cycloaddition of nitrones. The zwitterionic mechanism is nonetheless very likely to be able to compete effectively with the one-step mechanism when conjugated nitroalkenes are used as the π-deficient components. We previously[12,13] showed using comprehensive kinetic and quantum chemical studies that the cycloaddition of (Z)-C,N-diphenylnitrone (**1a**) to (E)-3,3,3-trichloro-1-nitroprop-1-ene (**2**) occurs through a one-step

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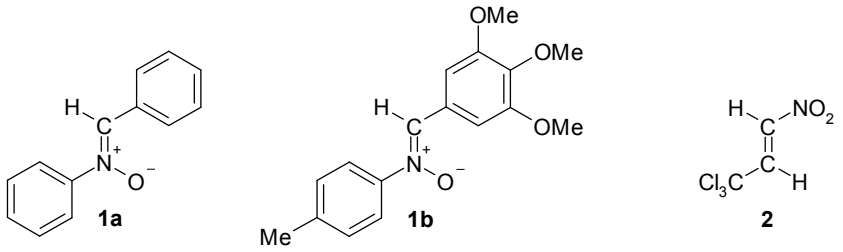
mechanism, though a polar one, through strongly asymmetric transition complexes. It may be assumed that greater asymmetry of these complexes, stimulated by higher electronic density on centres of the nucleophilic component, will be sufficient to force the zwitterionic, stepwise mechanism. For example in the [2+3] cycloaddition of π-deficient cyclic azomethine ylides with disubstituted acetylenes[11], the substitution of one alkyl group in the dipolarophile molecule with a stronger electron donor dimethylamine group leads to the reaction mechanism changing from one-step to stepwise.

Therefore, we decided to perform comprehensive experimental and quantum chemical investigations with (Z)-C-(m,m,p-trimethoxyphenyl)-N-(p-methylphenyl)-nitrone (**1b**) as the 1,3-dipole; due to the presence of a number of electron donor groups, it should be a markedly stronger nucleophile than **1a**.



Scheme 1

In particular, we decided: (i) to analyse the nature of addent interactions with respect to the theory, developed intensively in recent years[14-18], of electrophilicity and nucleophilicity indexes, (ii) identify reaction stereochemistry, (iii) perform kinetic studies (determination of activation parameters and the kinetic solvent effect), and (iv) perform quantumchemical simulations of actual reaction pathways. Such a comprehensive approach should in our opinion give a clear view of the course of the reaction in question and make a large contribution to our knowledge of the mechanistic aspects of nitrone [2+3] cycloaddition.

2. Results and Discussion

2.1. Analysis of nucleophile – electrophile interactions on the basis of reactivity indices theory

The comparison of the electronic chemical potential μ values of the addents shows that charge transfer in the elementary cycloaddition process should occur from nitrone **1b** (μ=-3.33 eV) to nitroalkene **2** (μ=-5.84 eV). Analysis of the global electrophilicity ω of the addents leads to a similar conclusion. In particular, the electrophilicity of nitroalkene **2** turned out to be 3.27 eV; according to Domingo's terminology[16], it should be considered a strong electrophile. However, the electrophilicity of nitrone **1b** is only 1.53 eV. Therefore it will be the nucleophile in the reaction. Its nucleophilicity is given by the N index[19] of 3.99 eV. The electrophilicity difference (Δω) for the reagent pair is more than 1.7 eV. Therefore the reaction is considered strongly polar[18]. The regioselectivity of such reactions may be forecast using local electrophilicity ω_k and nucleophilicity N_k indexes, which were calculated in terms of global reactivity indexes and appropriate Paar functions[18].

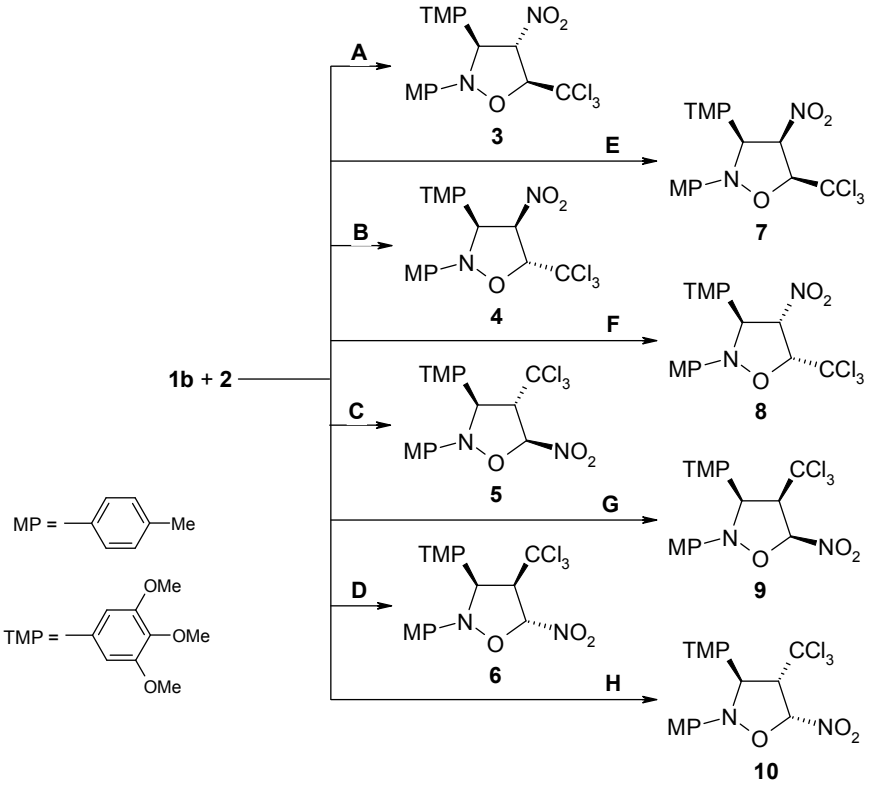
Table 1. Global and local properties for nitrone **1b** and nitroalkene **2**

	Global properties			Local properties			
	μ (eV)	ω (eV)	N (eV)	ω_α (eV)	ω_β (eV)	N_C (eV)	N_O (eV)
1b	-3.33	1.53	3.99			0.23	1.22
2	-5.84	3.27	0.66	0.12	0.75		

As can be seen from Table 1, the β carbon atom of the nitrovinyl moiety is the most strongly electrophilic reaction centre in the nitroalkene (ω_k=0.75 eV). The more strongly nucleophilic centre in the nitrone **1b** molecule is the oxygen atom in the >C=N(O)- moiety (N_k=1.22 eV). If interactions between these centres are taken to determine the reaction course, then the products should be corresponding 4-nitroisoxazolidines.

2.2. Regioselectivity, stereoselecticity and kinetic study

The [2+3] cycloaddition of (Z)-C-(m,m,p-trimethoxyphenyl)-N-(p-methylphenyl)-nitrone **1b** to nitroalkene **2** via a one-step mechanism may theoretically occur on four competing regio- and stereoisomeric pathways (**A-D** – see Scheme 2). When a stepwise mechanism is followed, the number of theoretically possible substrate transformation pathways rises to eight (paths **A-D** and **E-H**). In the first stage we decided to analyse which of them actually occur.



Scheme 2

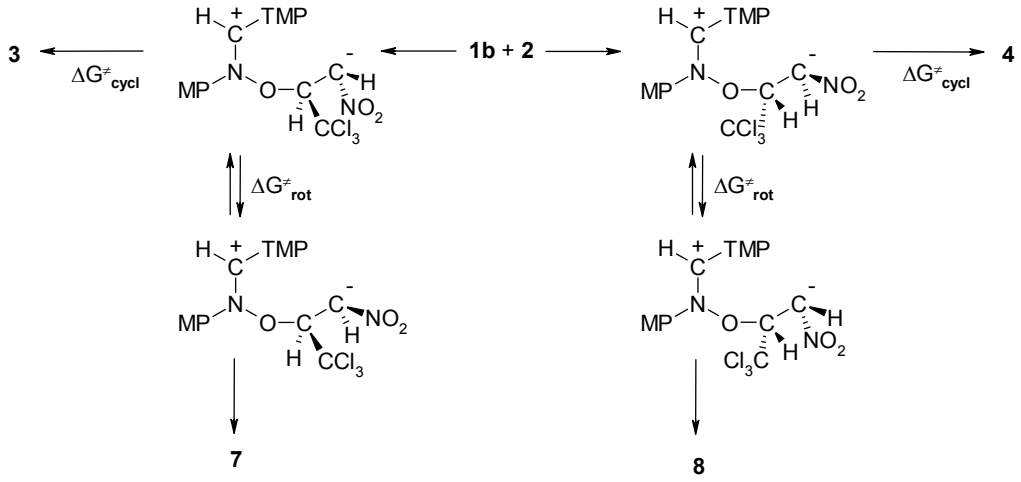
Hence several experiments were conducted with different reaction times, reagent molar ratio, solvent and temperature. The most favourable conditions for the reaction proved to be room temperature, toluene solution and 4-fold molar excess of the nitroalkene. Nitrone conversion in such conditions is completed within 24 hours. HPLC analysis of the post-reaction mass indicated the presence of two products with different retention times (9.2 and 14.0 minutes respectively). The compounds were isolated by semi-preparative HPLC, yielding compounds with sufficient purity to enable a full set of constitutional analyses to be performed.

The molar weights of both products determined by MS spectra were identical, being the sum of the molar weights of the addents. Combined with elementary analysis data, the information gave a gross formula $C_{20}H_{21}N_2O_6Cl_3$ for the isolated compounds. Absorption bands typical of the nitro group and the isoxazolidine ring were identified in the IR spectra. Unfortunately, the isomerism of the compounds cannot be determined using the spectra. This was possible through analysis of fragmentation patterns of the parent ions upon electron impact. It was found, that they are typical for

4-nitroisoxazolidines. In particular, we identified fragmentation ions in the spectra formed due to the cleavage of N2-C3 and C4-C5 bonds in the heterocyclic ring. The m/z values for the ions (239) prove that both isolated compounds are 4-nitroisoxazolidines. Their stereoisomerism was determined by ^{1}HNMR spectra.

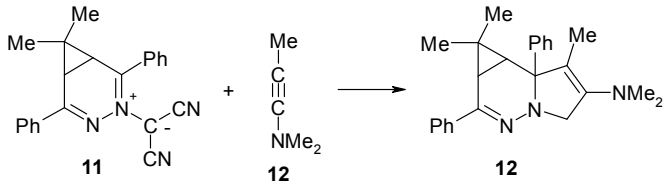
In particular, in the ^{1}HNMR spectrum of the compound with R_T=9.2 min, three signals of protons bound with the heterocyclic ring were identified, along with those from aromatic ring protons and methoxy and methyl groups. The proton H3 signal (a doublet) is in the strongest field (4.82 ppm), while the H4 (5.65 ppm) and H5 (5.69 ppm) signals are in weaker fields. The values of coupling constants $J_{3,4}$ and $J_{4,5}$ prove that the compound has *3,4-cis* and *4,5-trans* configuration. Therefore, the configuration *3,4-cis-4,5-trans*-2-(p-methylphenyl)-3-(m,m,p-trimethoxyphenyl)-4-nitro-5-trichloromethylisoxazolidine (**4**) may be assigned to the R_T=9.0 min compound.

The H4 proton signal (4.98 ppm) is in the strongest field on the spectrum of the R_T=14.0 compound. H3 and H5 proton signals are in a weaker field (5.52 ppm and 5.55 ppm respectively). The values of coupling constants $J_{3,4}$ and $J_{4,5}$ prove that the compound has *3,4-trans* and *4,5-trans* configuration. Therefore the configuration *3,4-trans-4,5-trans*-2-(p-methylphenyl)-3-(m,m,p-trimethoxyphenyl)-4-nitro-5-trichloromethylisoxazolidine (**3**) may be assigned to the R_T=14.0 min compound. Hence, the course of the reaction is consistent with the results of reactivity index analysis. It is determined by the attack of the nucleophilic oxygen atom on the nitroalkene β position. The reaction occurs with retention of the original nitroalkene stereoconfiguration. This, however, does not guarantee a one-step mechanism. A stepwise reaction may occur cis-stereospecifically if the rotation barrier ($\Delta G^{\neq}_{rot}$) within the zwitterionic intermediate (Scheme 3) is higher than the heterocyclic ring closure barrier[2,3]. Therefore, to shed light on the nature of changes which occur during conversion of addents into adducts, we carried out kinetic studies.



Scheme 3

First, we evaluated the kinetic solvent effect. The total reaction rate constant (k_{total}) in weakly polar toluene (ε=2.3, $E_T(30)$ = 33.9[20,21]) turned out to be more than 14 times higher than in strongly polar nitromethane (ε=38.2, $E_T(30)$ = 46.3[20,21]). By comparison, for the polar but one-step **1a**+**2** [2+3] cycloaddition, the reaction rate constant in toluene is only approx. 1.2 times higher than in nitromethane[13]. However, the rate constant in the two-step cycloaddition between azomethine ylide **11** and dimethylaminopropyne **12**[11] (Scheme 4) changes 69-fold between toluene and acetonitrile (ε=36.6, $E_T(30)$ = 45.6)[20,21]).



Scheme 4

We performed quantitative analysis of the solvent effect by plotting relationships between rate constants in solvents with various polarities, and polarity constants in the medium. This showed the existence of a linear relationship between the rate constant and Dimroth constants, $E_T(30)$:

$$k_{total} = -0.073\ E_T(30) - 0.087 \quad (R = 0.942)$$

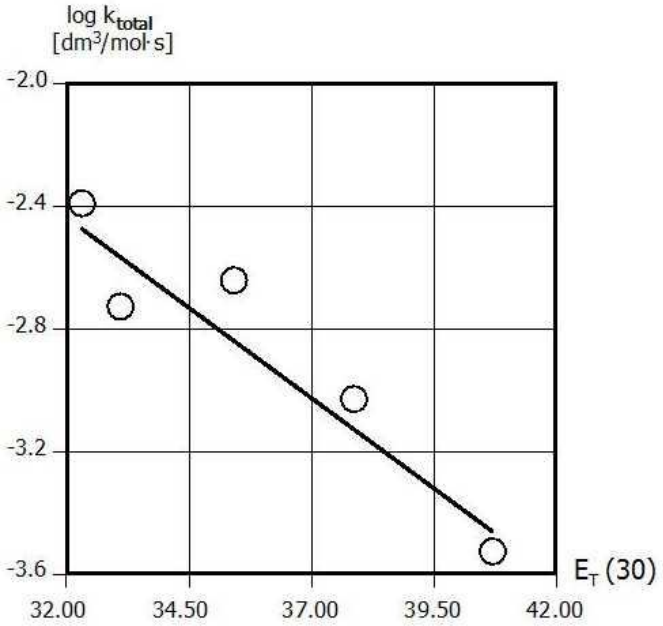


Fig 1. Plot of log k *vs* Dimroth $E_T(30)$ constants for the [2+3] cycloaddition reaction between nitrone **1b** and nitroalkene **2**

The negative sign of the sensitivity coefficient in these relationships confirms that the transition states are more strongly polar than the substrates[21].

Subsequently, on the basis of the rate constants measured at different temperatures, the activation enthalpy ($\Delta H^{\neq}$) and activation entropy ($\Delta S^{\neq}$) were calculated, using Eyring's equation[21]:

$$\log\frac{k}{T} = 10{,}319 + \frac{\Delta S^{\neq}}{4{,}576} - \frac{\Delta H^{\neq}}{4{,}576T}$$

The resulting activation enthalpies for both competing reactions (paths **A** and **B**) are not higher than 15 kcal/mol. This is typical of transition states in which energy changes in the reacting system related to the formation of new σ bonds are balanced by energy changes resulting from breaking of existing bonds[21]. On the other hand, the activation entropies have high negative values, indicating that the transition state is highly ordered[21]. It is noted, however, that the absolute $\Delta S^{\neq}$ values are almost two times smaller than for the [2+3] cycloaddition of nitrone **1a** with nitroalkene **2**, whose one-step nature is not in doubt[13]. To sum up, kinetic studies confirm the highly polar nature of the studied reaction. However some its kinetic characteristics are different than for typical one-step reactions. On the other hand, they do not absolutely prove the existence of zwitterions in the reaction medium. The reaction may be a border case at the interface of areas in which pure one-stage and two-stage

mechanism cases occur. The results of kinetic measurements would then be a compilation of parameters of respective one- and two-stage reaction parameters occurring simultaneously.

Table 2. Results of kinetic measurements for the [2+3] cycloaddition reaction between nitrone **1b** and nitroalkene **2**

Experiment	1	2	3	4	5	6	7
Initial nitrone concentration (mol/dm^3)	0.0069	0.0069	0.0069	0.0069	0.0079	0.0079	0.0079
Initial alkene concentration (mol/dm^3)	0.0813	0.0814	0.0812	0.0812	0.0933	0.0931	0.0934
Solvent	CCl_4	Toluene	Toluene	Toluene	Chloro-benzene	MEK	Nitrometane
E_T (30) (kcal/mol)	32.5	33.9	33.9	33.9	37.5	41.3	46.3
Temperature (^{o}C)	25	15	25	35	25	25	25
$k_{total} \cdot 10^4$ (dm^3/mol·s)	40.38	7.17	16.71	35.30	21.95	9.14	2.86
R	0.998	0.997	0.997	0.999	0.999	0.998	0.998
Ψ	0.071	0.083	0.087	0.054	0.0314	0.063	0.072
SD	0.04	0.04	0.03	0.05	0.02	0.03	0.02

Table 3. Isomer ratios and rate constants for reaction **1b**+**2**→**3** (path **A**) and **1b**+**2**→**4** (path **B**).

Temperature (^{o}C)	$k_{total} \cdot 10^4$ (dm^3/mol·s)	Isomer ratio γ [**3**]/[**4**]	$k_A \cdot 10^4$ (dm^3/mol·s)	$k_B \cdot 10^4$ (dm^3/mol·s)
15	7.17	0.091	0.59	6.58
25	16.71	0.089	1.37	15.34
35	35.30	0.107	3.41	31.89

Table 4. Eyring paramaters for reaction **1b**+**2**→**3** (path **A**) and **1b**+**2**→**4** (path **B**)

Path	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (cal/mol K)
A	14.7	-26.6
B	13.3	-26.7

2.3. Quantumchemical exploration of reaction paths

In addition to the experimental data, we performed simulations of actual reaction pathways. We hoped that this approach would provide supportive information about the nature of critical structures in the studied reaction. The quantum chemical simulations were carried out using the B3LYP/6-31G(d) theoretical level[22]. The same approach was recently used for the analysis of [2+3] cycloaddition pathways of diarylnitrones with several dipolarophiles[23-26].

Table 5. Selected molecular properties of critical structures and Eyring parameters of [2+3] cycloaddition reaction between nitrone **1b** and nitroalkene **2** according to B3LYP/6-31G(d) (PCM) calculations (toluene, 298K)

Path	Struc-ture	C3-C4		C5-O1		Δl	μ_D	t **)	ΔH	ΔS
		r (Å)	l *)	r (Å)	l *)		(D)	(e)	(kcal/mol)	(cal/molK)
A	**TS**	2.383	0.479	1.824	0.730	0.25	4.42	0.23	13.8	-47.3
	3	1.567		1.437			1.14		-13.2	-49.9
	LM	3.806		5.171			3.92		-1.7	-36.5
B	**TS**	2.514	0.400	1.691	0.819	0.42	6.97	0.27	15.9	-49.4
	4	1.572		1.432			2.62		-10.0	-49.2

*) $l_{X-Y} = 1 - \frac{r^{TS}_{X-Y} - r^{P}_{X-Y}}{r^{P}_{X-Y}}$

where r^{TS}_{X-Y} is the distance between the reaction centers X and Y at the transition structure and r^{P}_{X-Y} is the same distance at the corresponding product (see[24]).

**) Charge transfer (t)[27] was calculated according to the formula $t=-\Sigma q_A$; where q_A is the net charge and the sum is taken over all the atoms of dipolarophile.

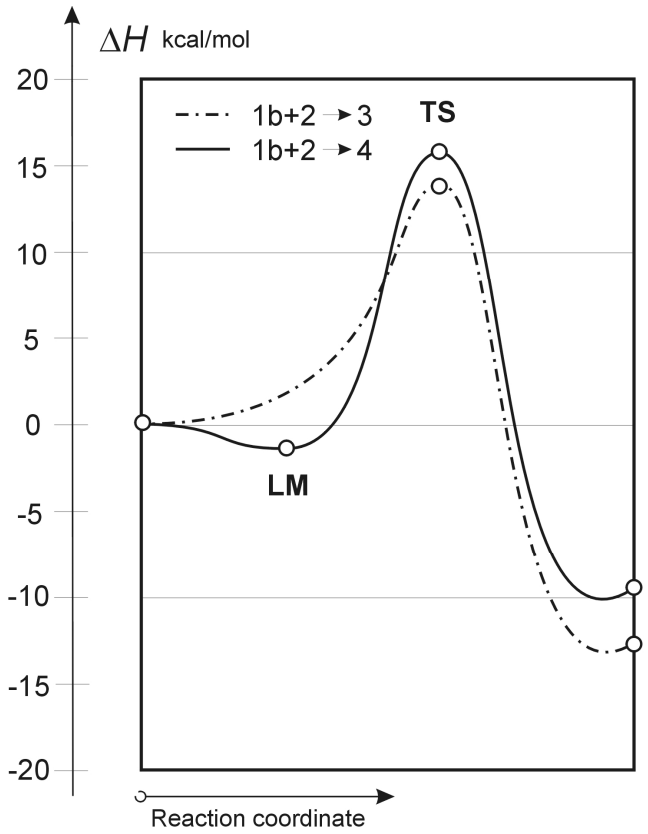


Fig. 2. Enthalpy profiles for [2+3] cycloaddition reaction between nitrone **1b** and nitroalkene **2** according to B3LYP/6-31G(d) (PCM) calculations (toluene, 298K)

The profiles of reaction pathways **A** and **B** in toluene were found to differ. In particular, three critical points corresponding to individual substrates (**1b+2**), the transition complex ($\mathbf{TS_A}$) and the cycloadduct **3** were located in the **1b**+**2**→**3** reaction profile. In the **1b**+**2**→**4** reaction profile, four critical points corresponding to individual substrates (**1b+2**), the pre-reaction complex[28] ($\mathbf{LM_B}$), the transition complex ($\mathbf{TS_B}$) and the cycloadduct **4** were located. Therefore, B3LYP/6-31g(d) calculations suggest that a one-step mechanism is favoured for the **1b**+**2**→**3** and **1b**+**2**→**4** reactions. This is confirmed by the analysis of transition complex characteristics.

Both transition complexes are polar, as is shown by the dipole moment values (μ_D>4.4D; t=0.23÷0.27). These can be considered as zwitterionic structures. Two new σ bonds form within them. Their degree of advancement, however, is significantly different. In particular, the C5-O1 bond forms more rapidly (l=0.730 for $\mathbf{TS_A}$ and l=0.819 for $\mathbf{TS_B}$). The C3-C4 bond is much less advanced (l=0.479 for $\mathbf{TS_A}$ and l=0.400 for $\mathbf{TS_B}$). The Δl asymmetry index for the complexes is 0.23 for $\mathbf{TS_A}$ and as high as 0.42 for $\mathbf{TS_B}$. This asymmetry, however, is insufficient to stimulate a stepwise mechanism. This is confirmed by IRC calculations. The hill drop movement from the transition states leads to addents and appropriate cycloadducts.

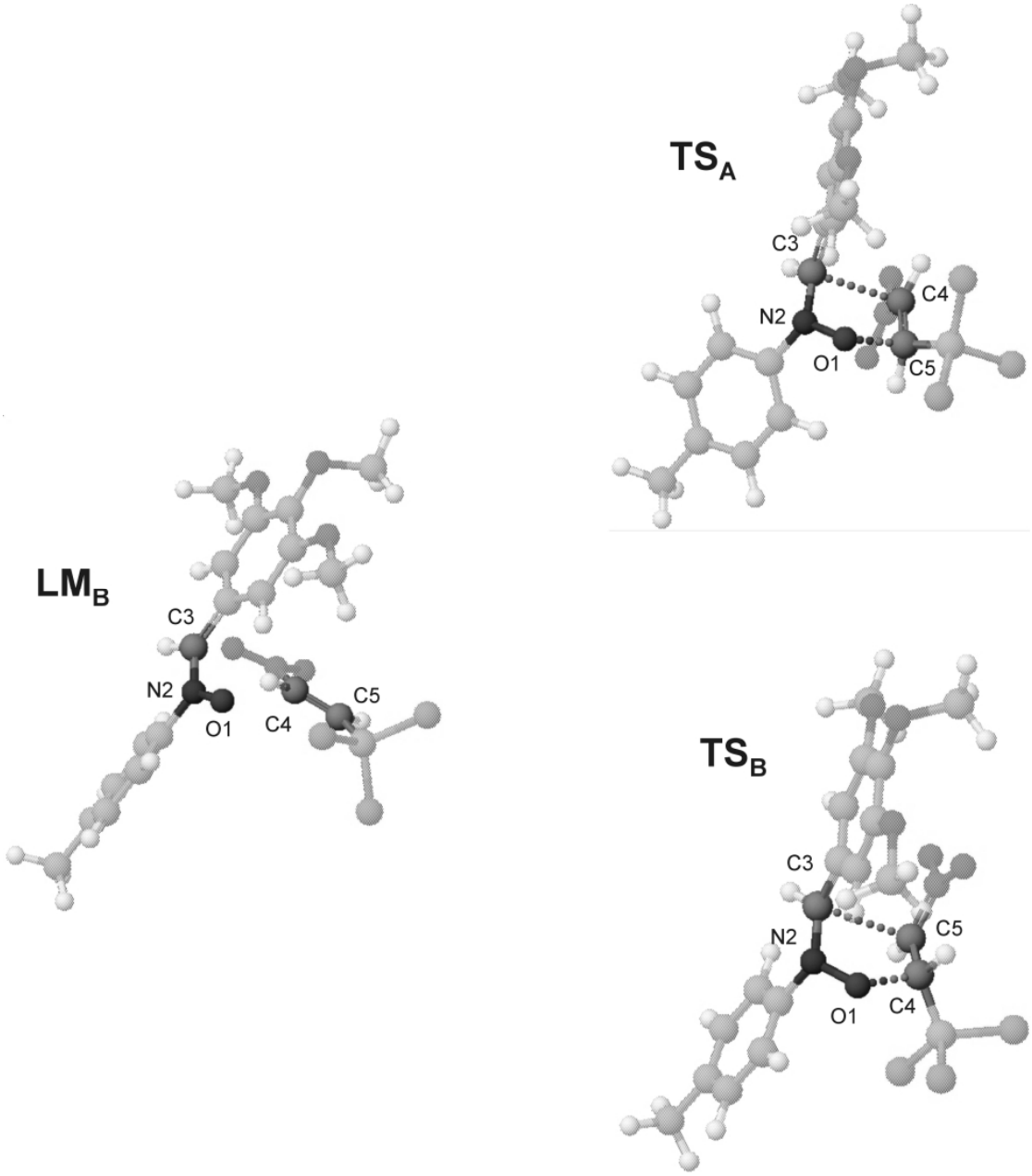


Fig 3. Views of critical structures of [2+3] cycloaddition reaction between nitrone **1b** and nitroalkene **2** according to B3LYP/6-31G(d) (PCM) calculations (toluene, 298K)

3. Conclusions

Both the analysis of the nature of addent interactions with respect to the theory of electrophilicity and nucleophilicity indexes, and the kinetic studies, indicate the polar nature of the [2+3] cycloaddition of (Z)-C-(m,m,p-trimethoxyphenyl)-N-(p-methylphenyl)-nitrone to (E)-3,3,3-trichloro-1-nitroprop-1-ene. Its course is determined by the attack of the nucleophilic oxygen atom of the CNO moiety on the β position of the nitrovinyl moiety of the dipolarophile. However, the kinetic studies and PES investigation results do not confirm any zwitterion in the reaction environment. On the other hand, the nature of the solvent effect and the experimentally determined activation parameter values do not exclude a scenario in which one-step and stepwise processes occur simultaneously.

Acknowledgements

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4. Experimental

4.1. Instruments

Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer PE-2400 CHN apparatus. Mass spectra (EI, 70eV) were obtained using a Hewlett-Packards 5989B spectrometer. IR spectra were recorded on a Bio-Rad spectrophotometer. ^{1}H-NMR spectra were taken on a Bruker (500 MHz) spectrometer, using TMS as an internal standard, and $CDCl_3$ as a solvent. Liquid chromatography (HPLC) was done using a Knauer apparatus equipped with a UV-VIS detector. For monitoring of the reaction progress, LiChrospher 100-10-RP column (4x240 mm) and 55 % THF as the eluent at flow rate 1 ml/min were used. The separation of the post-reaction mixtures was performed on the same Knauer apparatus, using a semipreparative column (LiChrospher 100-10-RP, 16x240 mm) and 50 % THF as the eluent at flow rate 10 ml/min.

4.2. Materials

(Z)-C-(m,m,p-trimethoxyphenyl)-N-(p-methylphenyl)-nitrone was prepared by condensation of p-methylphenylhydroxylamine with m,m,p-trimethoxybenzaldehyde in ethanol[29]. (E)-3,3,3-trichloro-1-nitroprop-1-ene was prepared in Schmidt-Rutz reaction starting from 3,3,3-trichloro-1-nitropropan-2-ol [30,31]. Their purity was confirmed by HPLC analyses. Pure grade (POCh, Merck) tetrachloromethane, toluene, methylethylketone, chlorobenzene and nitromethane were used as solvents. Before usage they were carefully purified according to standard procedures. Their purity was confirmed by GC analyses.

Synthesis of 2,3-diaryl-4-nitro-5-trichloromethylisoxazolidines

A mixture of a suitable nitroalkene (0.02mol) and nitrone (0.005mol) in 10cm^3 of dry toluene was stirred at room temperature for 24h. The solvent was evaporated *in vacuo* to dryness and the semiliquid residue was separated by semipreparative HPLC. Evaporation of the eluent from the obtained fractions gave the diarylnitroisoxazolidines **3** and **4**.

3,4-trans-4,5-trans-2-(p-methylphenyl)-3-(m,m,p-trimethoxyphenyl)-4-nitro-5-trichloromethylisoxazolidine (3)

Oil. R_T (55 % THF, min.): 14.0. IR (cm^{-1}): 1563, 1352 (NO_2); 1185, 924 (isoxazolidine ring). ^{1}H NMR, δ (ppm): 2.30 (3 H, s), 3.85 (9 H, s), 4.98 (1 H, dd, J = 1.44 Hz, J = 5.60 Hz), 5.52 (1 H, d, J = 1.44 Hz), 5.55 (1 H, d, J = 5.60 Hz), 6.69 (2 H, s), 7.07 (4 H, m). MS (m/z): 490 (100 %), 323 (40 %), 301 (5 %), 285 (92 %), 239 (8 %), 121 (6 %), 105 (15 %), 91 (29 %). Elemental analysis: calc. for $C_{20}H_{21}N_2O_6Cl_3$: 48.5 % C, 4.30 % H, 5.70 % N; found: 47.51 % C, 4.46 % H, 5.49 % N.

3,4-cis-4,5-trans-2-(p-methylphenyl)-3-(m,m,p-trimethoxyphenyl)-4-nitro-5-trichloromethylisoxazolidine (4)

Colorless crystals; mp = 121-122 ºC (ethanol). R_T (55 % THF, min.): 9.2. IR (cm^{-1}): 1565, 1349 (NO_2); 1186, 920 (isoxazolidine ring). ^{1}H NMR, δ (ppm): 2.29 (3 H, s), 3.84 (9 H, s), 4.82 (1 H, d, J = 7.28 Hz), 5.65 (1 H, dd, J = 7.28 Hz, 4.64 Hz), 5.69 (1 H, d, J = 4.64 Hz), 6.62 (2 H, s), 7.11 (4 H,

m). MS (m/z): 490 (100 %), 323 (72 %), 301 (7 %), 285 (29 %), 239 (7 %), 121 (4 %), 105 (15 %), 91 (28 %). Elemental analysis: calc. for $C_{20}H_{21}N_2O_6Cl_3$: 48.5 % C, 4.30 % H, 5.70 % N; found: 47.72 % C, 4.40 % H, 5.55 % N.

4.3. Kinetic procedure

The kinetic experiments were carried out in a glass reactor up to 80% conversion of nitrone, using a 12 molar excess of nitroalkene. The pseudo-first order rate constans were followed by measuring the area of HPLC peak at the wavelength characteristic of the K-band of nitrone (λ_{max}=331nm). Durring the runs, 0.2 ml samples were taken periodically from the reaction mixture with the pipette, quenched with the cold THF and diluted to 10 ml in volumetric flask. The solution was immediately analyzed by HPLC. It was found that for the band, the Bouger-Beer plot was linear within the concentration range studied. The second-order rate constants k_{total}, were obtained according to the typical method[21]. The k_{total} and γ values were then applied in calculation of the rate constants k_A and k_B according to formulas:

$$k_A=\gamma\, k_{total}/(\gamma+1) \qquad k_B= k_{total}/(\gamma+1)$$

The results are presented in Table 2

4.4. Quantumchemical calculations

The quantum-chemical calculations were performed on a SGI-2800 computer in the Cracov Computing Center "CYFRONET". Hybrid B3LYP functional and 6-31G(d) basis set included within GAUSSIAN 2003 software were applied[22]. For structure optimization of the reactants and the reaction products the *Berny* algorithm was applied. Global and local reactivity indexes (electronic chemical potential μ, electrophilicity power ω, nucleophilicity N, local electrophilicity ω_k, local nuclephilicity N_k) were calculated according to expressions recommended by *Parr*[32] and *Domingo*[16]. First-order saddle points were localized using the QST2 procedure. The transition states were verified by diagonalization of the Hessian matrix and by analysis of the internal reaction coordinates (IRC). For the simulation of the solvent effect, the polarisable continuum model (PCM)[33] was applied. Calculations of critical structures were performed for the temperature T=298K and pressure p=1atm. The results of calculations are collected in Table 5.

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