ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

The study of the chemical behavior of the different nitro alkenes in diene synthesis reactions.

Nadezhda A. Anisimova[1]*, Alena A. Kuzhaeva[2]

[1]Department of Organic Chemistry, Herzen State Pedagogical University of Russia; 191186, Saint-Petersburg, Russian Federation; E-mail: nadia-an@mail.ru
[2]Department of General and Physical Chemistry. National Mineral Resources University; 199106, Saint-Petersburg, Russian Federation; E-mail:kaarlo@mail.ru

ABSTRACT

The deep investigation of the chemical behaviour of β-nitroethenylphosphonates (-carboxylates) and its bromine-containing analogues with 1,3-cyclopentadiene was carried out. The reactivity of these compounds was established. The basic regularities of the interaction between bromine-containing nitroalkenes and cyclopentadiene were revealed. The reaction mechanism of nitroalkenes with cyclopentadiene was studied. A series of the new substituted carbocyclic compounds (norbornenes) with nitro and phosphonate (carboxylate) functional groups were synthesized.

Keywords: chemical, behavior, carboxylate, norbornenes.

**Corresponding author*

INTRODUCTION

The chemistry of conjugated nitroalkenes that are used as a starting materials and building blocks is the fast-growing fundamental research area of organic synthesis [1, 2]. Nitroalkenes with electron-withdrawing substituents in β-position that increase the electrofilicity of double bond are prospective starting materials in the diene synthesis.

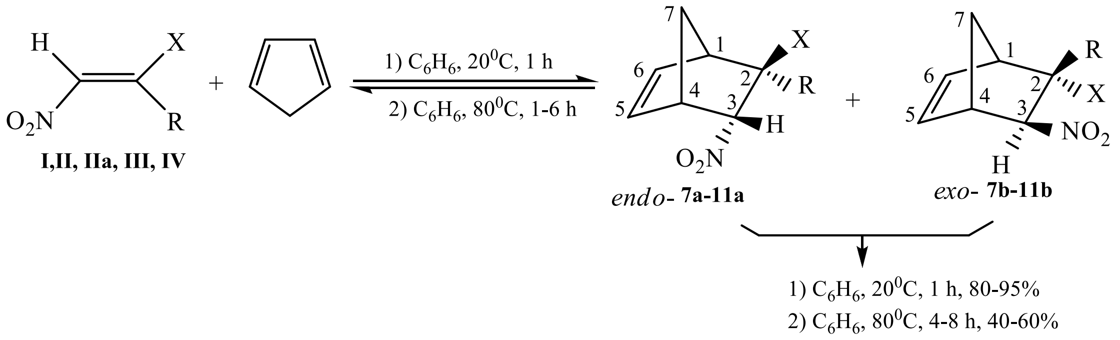
The research objects - β-nitro- and β-halo-β-nitroethenylphosphonates(carboxylates) can be used in synthesis of polyfunctionalized carbo- and heterocyclic compounds with NO_2, $P(O)(OR)_2$, CO_2R moieties which can be easily converted to amino, phosphonic or carboxylic group. Particularly, it is important when regarding the possibility of obtaining the cyclic β-aminophosphonic and β-aminocarboxylic acids [3, 4] as the potential bioactive substances.

The purpose of the research in this field is approved by the great synthetic potential of functionalized nitroalkenes that is particularly important for direct synthesis of substituted carbo- and heterocycles.

DISCUSSION

Due to the fixed s-cis-conformation and optimal bond length between C^1 and C^4 atoms of the diene system the cyclopentadiene is the most reactive in contrast to the non-cyclic dienes.

Actually, the interaction of β-nitroethenylphosphonate **I** and -carboxylate **II** with cyclopentadiene occurred at room temperature and lead to the corresponding *endo*(NO_2)- and *exo*(NO_2)-nitrobicyclo[2.2.1]hepten-2-yl-phosphonates **7a,b** and -carboxylates **8a,b** and **9a,b** [5, 6].



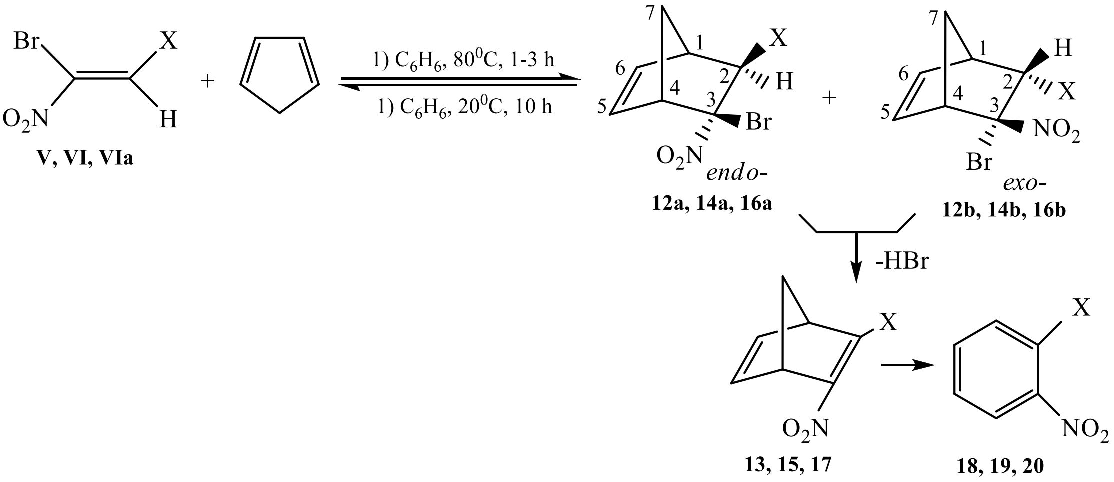
$X=P(O)(OC_2H_4Cl)_2$: R=H(**I, 7a,b**); $X=P(O)(O\text{-}iPr)_2$: R=Me (**III,10a,b**); R=H (**IV, 11a,b**);
$X=CO_2Et$: R=H (**II, 8a,b**); $X=CO_2Me$: R=H (**IIa, 9a,b**);

Scheme 1. Dienophile: endo-, exo-model compounds: vinylphosphonate 1.5:1; ethylacrylate 1:1. Research objects: β-nitroethenylphosphonate 6:1; β-nitroacrylate 5:1.

As it was expected (due to the steric hindrance), nitroalkenes **Ш,IV** with isopropoxyphosphorylic moiety and methyl in α-position (compound III) instead of chloroethoxy- group interacted only under refluxing in benzene (3-6 h) and gave corresponding nitronorbornenes **10a,b**, **11a,b** with lower yields (52 and 34%, correspondingly).

The same effect of the methyl substituent on the decreasing of norbornene yield and endo-selectivity was shown for α-methylacrylate and acrylonitrile in papers [7, 8]. The authors explain it by the steric organization and formation of asymmetric intermediate.

We should note that the presence of nitro group in the molecules of the research objects **V,VI** promotes the endo-selectivity (Scheme 2). The greater effect of nitro group (in contrast to sulfonyl and carboxyl) on the stereoselectivity of Diels-Alder reaction was noted by authors [9, 10].



X=$P(O)(OC_2H_4Cl)_2$: (**V, 12a,b, 13, 18**); X=CO_2Et: (**VI, 14a,b, 15, 19**); X=CO_2Me: (V**Ia, 16a,b, 17, 20**);

Scheme 2. Dienophile: endo-, exo-model compounds: vinylphosphonat 1.5:1; ethylacrylate: 1. Research objects: β-bromo-β-nitroethenyl-phosphonate 9:1; β-bromo-β-nitroacrylate 7:1.

The bromo-containing nitronorbornenes with phosphoric moiety **12a,6** were found to be very stable and didn’t undergo the elimination of hydrobromic acid even when prolonged refluxing (30 h) in the presence of the base (pyridine) was used.

The more violent conditions (C_6H_6, 80ºC, N,N-dimethylaniline, 140 h) just let to establish by the spectral data the formation of unstable intermediate norbornadiene **13** which converts in the reaction to the corresponding nitroarylphosphonate **18**.

The bromo-containing nitronorbornenes with carboxylate residue **14a,b, 16a,b** eliminated HBr even in the absence of the base (C_6H_6, 80ºC, 10 h) and led to nitroarylcarboxylates **19,20** via unstable intermediate norbornadiene **15,17.**

The observed differences in the chemistry of bromonitrocycloalkenylphosphonates and –carboxylaes (as it is noted in literature) are due to the greater tendency of carboxylate moiety to delocalize the negative charge in the forming carbanion in contrast to the phosphonate intermediate.

Also, it is not excluded that the particular impact to the difference in the behavior of phosphonate and carboxylate adducts can be made by the greater proton acceptance ability of the phosphorylic group in contrast to the carboxylic [11].

The aromatization of norbornenes via unstable norbonadiene in the conditions of diene reactions was observed by the other authors [12].

Thus, the studied *β*-nitro- and *β*-bromo- *β*-nitroethenylphosphonates and –carboxylates interacted with the representatives of 1,3-dienes with the formation of diastereomers of functionalized nitrocyclenes (norbornenes) with good yields.

The presence of the nitro group in the molecules of the starting dienophiles caused the higher stereoselectivity. This made it possible to obtain the most stable isomers − the corresponding endo(NO_2)-norbornenes.

As a result of Diels-Alder reactions of structurally the same pairs of *β*-nitroethenylphosphonates and –carboxylates we found no differences in the reactivity of dienophilic compounds having phosphonate and carboxylate moieties. That is why the additional kinetic studies were conducted.

THE COMPARISON OF THE REACTIVITY OF *β*-NITROETHENYLPHOSPHONATES AND –CARBOXYLATES

In order to compare the reactivity of the structurally similar *β*-nitroethenylphosphonate **I** and –carboxylate **II**, and the corresponding *β*-bromo-*β*-nitroalkanes **V** and **VI** in the Diels-Alder reaction, the cyclopentadiene was used.

According to the approach accepted in the literature (a method of boundary MO) [13] and data of the energy diagram of the reaction of cyclopentadiene (CPD) with the investigated dienophiles (fig. 1, 2, table 1), the interaction of this diene with the model compounds (vinylphosphonate, acrylate) [14], obviously, can be considered as “neutral” type, as the addens have almost symmetrical distribution of the energy levels (ΔE^1~ΔE^2). The interaction of the nitroalkanes **I,II,V,VI** with CPD should be considered as the process with “normal” electronic distribution since the ΔE^1 value significantly exceeds ΔE^2. Hence, the determinative interaction for *β*-nitro- and *β*-bromo-*β*-nitroalkenes **I,II,V,VI** in this reaction is ΔE^1 (HOMO$_{diene}$-LUMO$_{dienophile}$), which can be used for the estimation of the dienophiles reactivity. According to the quatum chemical calculations, the nitroethenylphosphonates can be less active than nitroethenylcarboxylates.

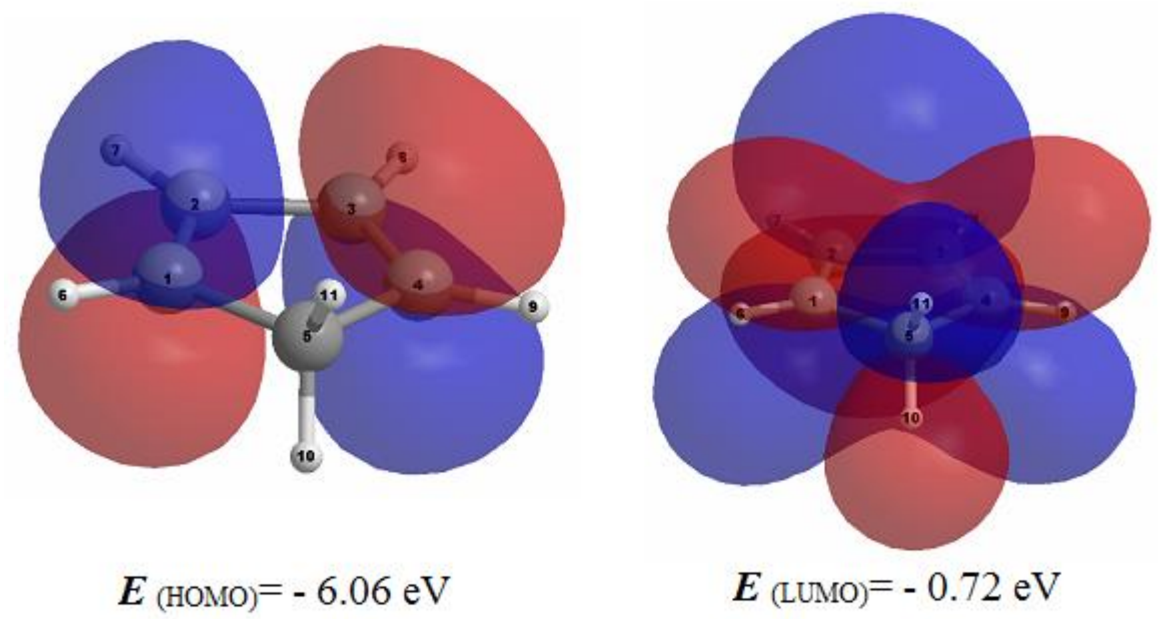


Figure 1: The boundary molecular orbitals of cyclopentadiene, calculated by the quantum chemical method (DFT, B3LYP+G)

Table 1 – The data obtained by the quantum chemical calculations of boundary molecular orbitals of dienophiles I,II,V,VI and the values of the energy of their interactions E^1,E^2 (eV) with cyclopentadiene

	HOMO	LUMO	ΔE^1 LUMO dienophile HOMO diene	ΔE^2 LUMO diene HOMO dienophile
)	- 7.82	- 1.08	4.98	7.10
)	- 7.83	- 1.67	4.39	7.11
	- 8.52	- 3.42	2.64	7.80
I	- 8.5	- 3.70	2.36	7.82
	- 8.00	- 3.29	2.77	7.28

	-	-	2.51	7.35
I	8.07	3.55		

note: listed are the values for a) vinylphosphonate and b) acrylate

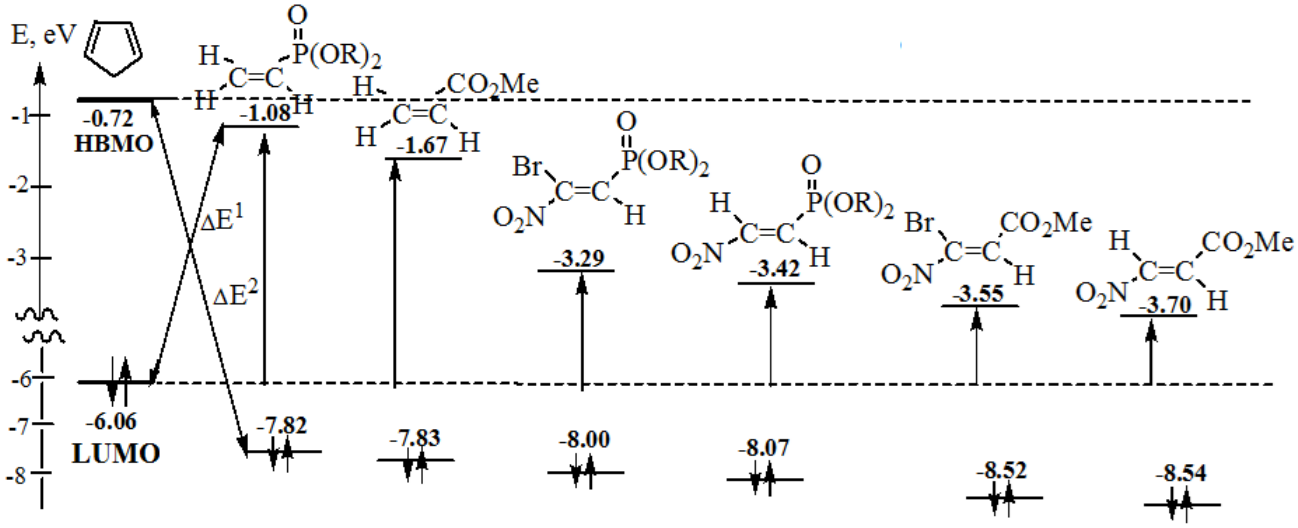


Figure 2: The relative location of the boundary orbitals of CPD and model compounds: vinylphosphonate, acrylate and nitroalkenes I,II,V,VI

To prove the theoretical calculations the estimation of the reactivity of β-nitroethenylphosphonates and –carboxylates was made qualitatively by carrying out the competitive reaction of the mixture of compounds I and II with CPD in the equimolar ratio. The reaction proceeded at room temperature and yielded only substituted norbornenes **7a,b, 8a,b**, which did not undergo the intramolecular transformations in these conditions. The proton signals of the cycle of the forming adducts **7a,b, 8a,b**, and the starting nitroalkenes I, II don't overlap in the NMR ^{1}H spectrum (figure. 3), what made it possible to use this method for monitoring the process. As it was found, the full conversion of the starting materials **I,II** takes 5-10 minutes at 18-20ºC. The products of the reaction are the phosphorylated **7a,b** and carboxylated **8a,b** norbornenes in 45 : 55 ratio, correspondingly.

HOMO

T ativ estimation of the activity of the β-nitroalkenes **I, II**, their bromo-substituted analogues **V,VI**, and model vinylphosphate and acrylate was performed by the kinetic study of these dienophiles in the reaction with CPD using the UV spectroscopy (Figure 4,5).

The values of the reaction speed rate, energy E_a, entalpy $\Delta H^{\#}$ and entropy $\Delta S^{\#}$ of activation are listed in the table 2. The obtained data illustrate the linear relation of the reverse concentration (1/C) with time (τ,s) (figure 4,5), that testifies to the second order of the reaction (n=2). The calculation of the thermodynamic parameters of these reactions showed low entalpy and high negative entropy values what clearly indicates the one-stage (coordinated) mechanism of this reaction. The comparison of the speed rate data of cyclopentadiene interaction with dienophiles **I,II,V,VI** showed that β-nitroalkenes **I** and **II** are more active than their β-bromo derivatives **V** and **VI**.

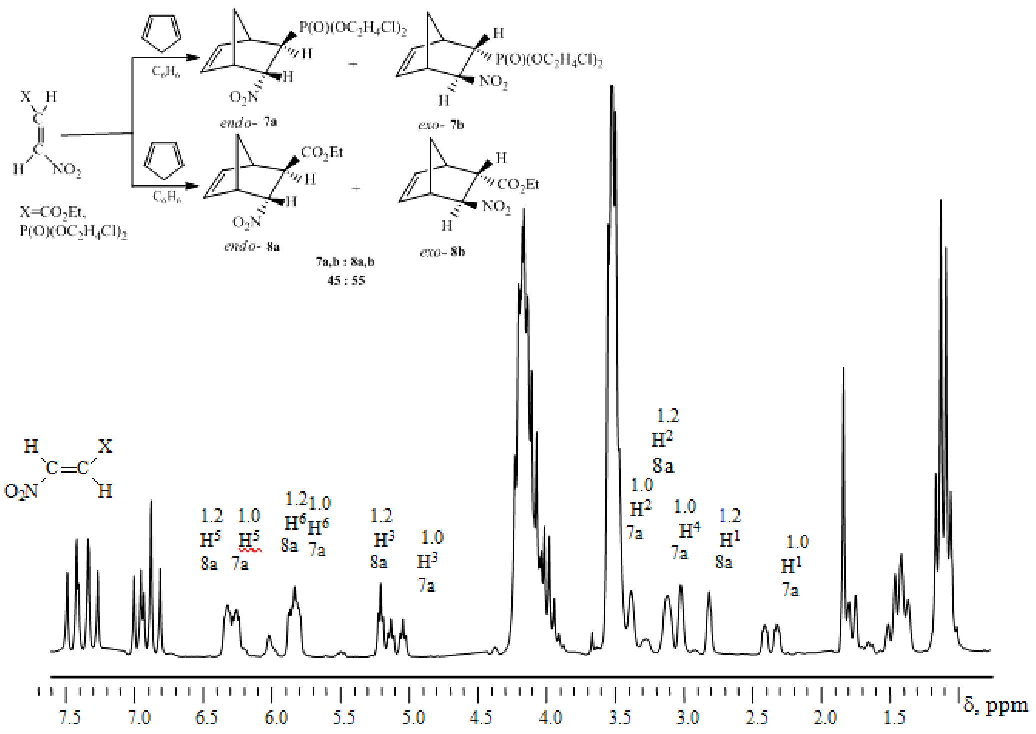


Figure 3: The NMR 1H spectrum of the products mixture formed in the competetive reaction of cyclopentadiene with β-nitroethenylphosphonate I and β-nitroacrylate II

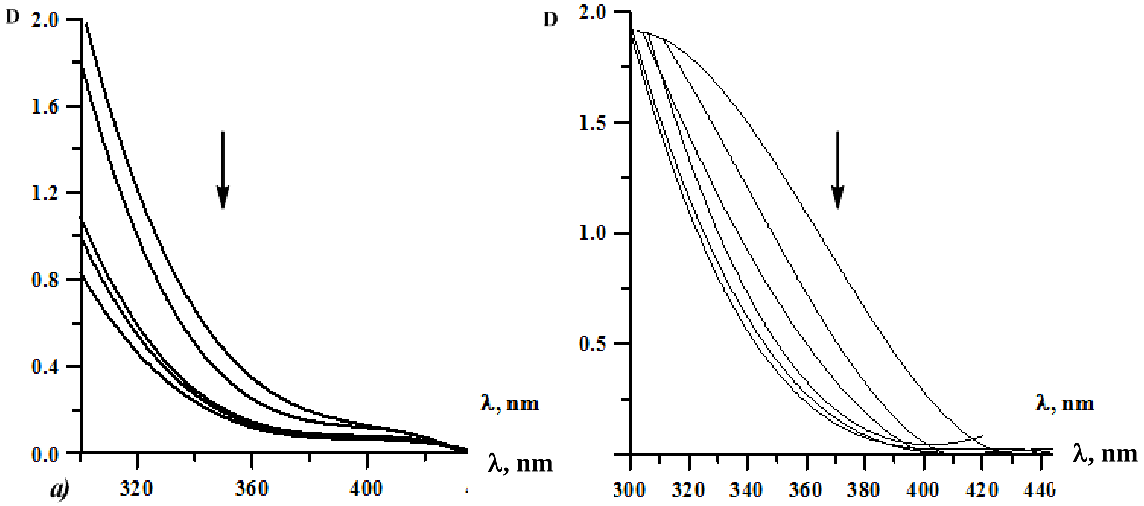


Figure 4: The qualitative changes of the absorbtion band in the UV sp in the reaction of cyclopentadiene with a) 2-nitroethenylphosphonates I, b) 3 rylate II.

The analysis of the speed rate values of the reactions of cyclopentadiene and the structurally similar pairs of vinylphosphonate and acrylate ($2.14\cdot10^{-2}$ and $2.86\cdot10^{-2}$, at 50ºC correspondingly), β-nitroethenylphosphonate **I** and -carboxylate **II** ($2.87\cdot10^{-2}$ and $5.05\cdot10^{-2}$, at 16ºC) showed the similar reactivity of the acrylate derivatives and ethenylphosphonates, with predomination of the first.

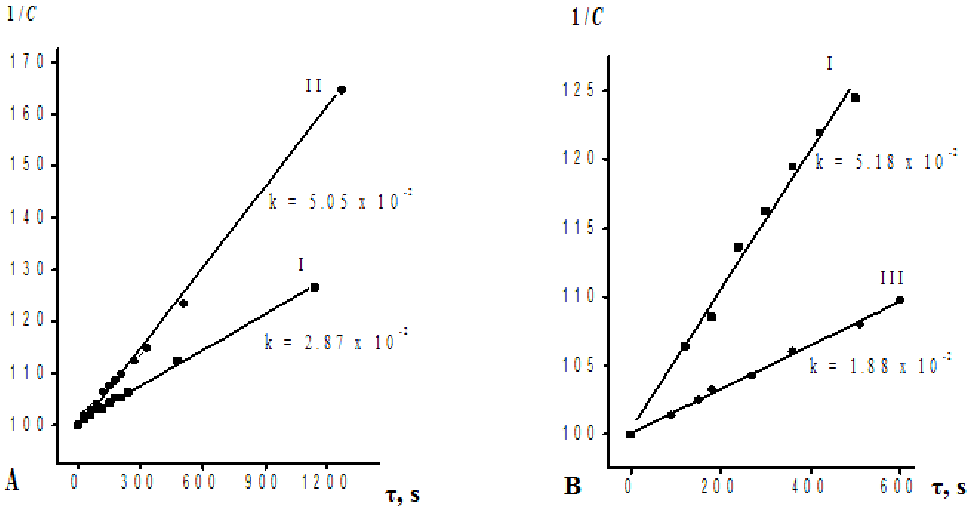


Figure 5. The graph of the linear relation of the reverse concentration (1/C) with time (τ,s) of the cyclopentadiene reaction: A) at 16 C with nitroacrylate II and nitroethenylphosphonate I, B) at 28 C with b-nitro- I and *β*-bromo-*β*-nitroethenylphosphonates V.

The values of the rate constants of the reactions of cyclopentadiene and dienophiles **I,II,V,VI** (table 2) as a whole correlates with the values of ΔE^1 of the interaction of HOMO$_{diene}$-LUMO$_{dienophile}$, obtained by the quantum chemical calculations of boundary molecular orbitals (figure 2), what is in agreement with the orbita; control of these reactions

Table 2 – The activation parameters and the values of the rate constants of the reaction of dienophiles I,II,V,VI with cyclopentadiene

№ dienophiles	Rate constants, L mole^{-1} s^{-1}				E$_a$, kJ mol^{-1}	ΔH$^{\#}$ kJ mol^{-1}	ΔS$^{\#}$ J mol^{-1} K^{-1}
	+16ºC	+18ºC	+26ºC	+28ºC			
Nitroalkenes							
I	2.87·10^{-2}	3.81·10^{-2}	4.39·10^{-2}	5.18·10^{-2}	30	27	-180
II	5.05·10^{-2}	5.17·10^{-2}	6.10·10^{-2}	6.50·10^{-2}	16	14	-222
β-Bromo-*β*-nitroalkenes							
	+18ºC	+20ºC	+28ºC	+30ºC			
V	7.85·10^{-2}	1.24·10^{-2}	1.88·10^{-2}	1.92·10^{-2}	50	48	-120
VI	3.25·10^{-2}	3.81·10^{-2}	3.99·10^{-2}	4.36·10^{-2}	17	14	-244

On the base of the literature and personal experimental data of the diene condensation with the model vinilphosphonate, acrylate and the research objects **I,II,V,VI** we can conclude that the latter exhibits enough high activity and can be used as the dienophiles in the classical diene synthesis [15,16].

The structures of the obtained norbornene series were established by the IR, NMR ^{1}H and ^{31}P spectroscopy and by the comparison of the obtained data with the data for structurally similar compounds described in literature [17, 18]. The X-ray diffraction study performed for the one of the synthesized norbornenes confirmed the assigned structure and the spatial orientation of molecules [5].

THE STRUCTURE OF THE SYNTHESIZED (NITRO)NORBORNENES

The structure of the synthesized (nitro)norbornenes **7a,b-12a,b, 14a,b, 16a,b** was established by the NMR ^{1}H (^{31}P) spectroscopy and the X-ray diffraction study. The doubling of the signals of the cycle protons and the protons of functional groups [P(O) (OR)$_2$, CO$_2$R] in the NMR ^{1}H (^{31}P) spectra indicates that these substances exist as the endo- and exo- diastereoisomers. The configuration was established on the base of the spectral data analysis (figure 8). When assigning the signals to the *endo*-(NO$_2$) or *exo*-(NO$_2$) form, the chemical shift values of the nitromethene protons attached to C3 atom were used as a test signals as it is described in literature [19] for the structurally similar compounds.

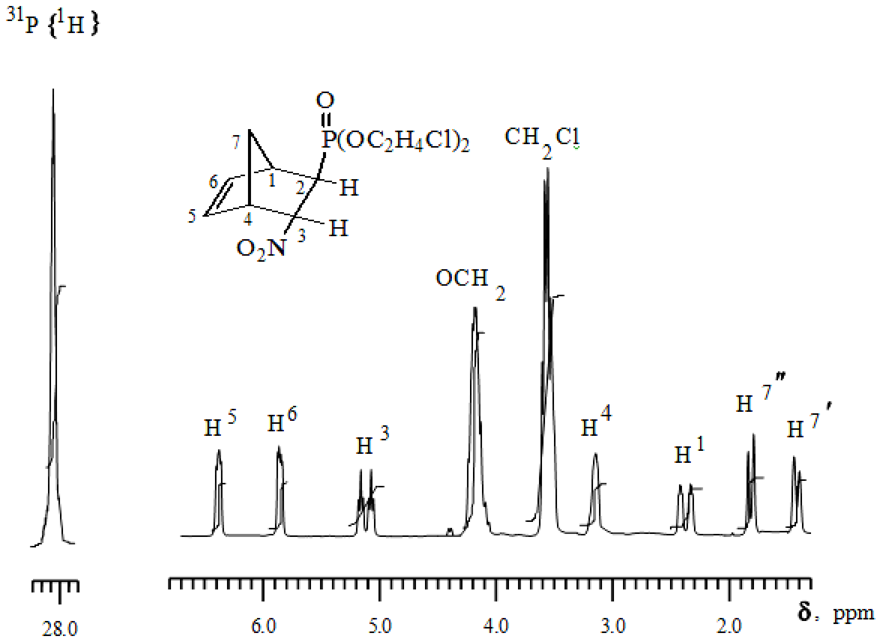


Figure 6: The NMR ^{31}P and 1H spectra of *endo*-bis(2-chloroethyl)-3-nitrobicyclo*[2.2.1]*-5-hepten-2-yl-phosphonate 7a *in CDCl$_3$.*

The exact structure of phosphorilated nitronorbornenes was established by the X-ray diffraction study of the compound 12a. The NMR ^{1}H, ^{31}P spectra and the spatial configuration of the molecule 12a is shown in a figure 9. The bicyclic part has the usual for norbornene fragments geometry – the five-membered cycles has the "envelope" confofmation and the six-membered – "bath" conformation. The bulk bis(chloroethoxy)phosphorylic substituent at C2 and the bromine atom at C3 have equatorial and the nitro group at C3 – axial positions.

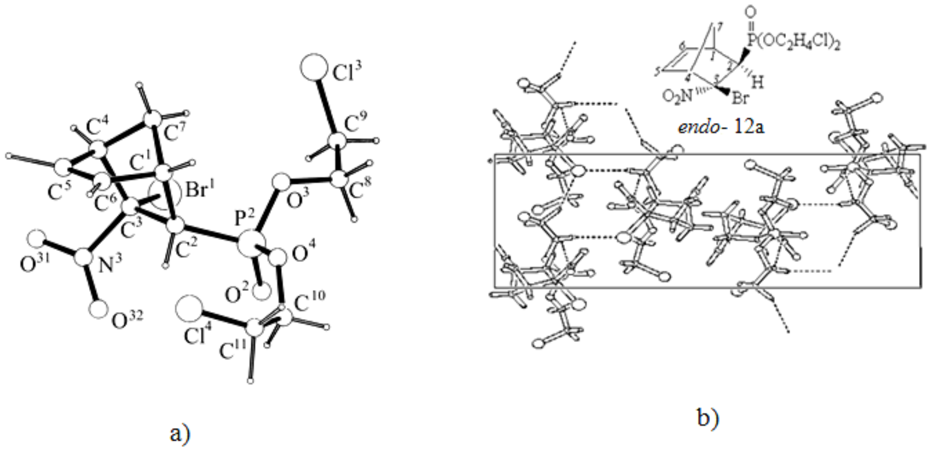


Figure 7: The structure of *endo*-bis(2-chloroethyl)-3-bromo-3-nitrobicyclo[2.2.1]-5-hepten-2-yl-phosphonate molecule 12a.

CONCLUSION

The comparison of the reactivity of the vinylphosphonates esters and acrylate, nitro- and gem-bromonitroethenylphosphonates(carboxylates) showed their similar activity. By the example of the interaction of nitro- and gem-bromonitroethenylphosphonates(carboxylates) with cyclopentadiene, the coordinated one-stage mechanism with "normal" electron distribution. A new series of functionalized nitronorbornenes was obtained.

REFERENCES

[1] Ono N. The Nitro Group in organic synthesis. Organic Nitro Chem. Ser., VCH, New York, 2001.

[2] Perekalin VV, Lipina ES, Berestovitskaya VM, Efremov DA. Nitroalkenes. Conjugated nitrocompounds. J. Wiley and Sons, London, 1994.

[3] Anisimova NA, Kuzhaeva AA, Berkova GA, Berestovitskaya VM. Synthesis β-aminophosphonic acids of cyclohexane, norbornane, bicyclooctane. *Russian Journal of General Chemistry*, 2006; 76(12), 2026-2031.

[4] Kuzhaeva AA, Anisimova NA, Ivanov II. Synthesis of β-amino acids by nitrocycloalkenylcarboxylates. *Book of abstracts of the Russian Congress on Catalysis "RusCatalysis-2011", Moscow*, 2011; 2: 347.

[5] Berestovitskaya VM, Anisimova NA, Litvinov IA, Kuzhaeva AA, Berkova GA, Gubaidullin AT, Deiko LI. Phosphorylated nitronorbornens: Synthesis and Structure. *Russian Journal of General Chemistry*, 2004; 74(4): 574-580.

[6] Anisimova NA, Berestovitskaya VM. Functionalized nitroalkenes in reactions of diene synthesis and 1,3-dipolar cycloaddition. Asterion, Saint-Petersburg, 2008.

[7] Kobuke Y, Fueno T, Furukawa J. Interestingly, methacrolein was shown to produce exo Diels-Alder products when reacting with cyclopentadiene. *Journal of American Chemistry Society*. 1970; 92(22), 6548-6553.

[8] Konovalov AI, Kamasheva GI. The symmetry of the transition state in the diene synthesis reaction of cyclopentadiene with dienophiles acrylic, methacrylic and trans-crotonic series. *Russian Journal of Organic Chemistry*. 1973; 9(10), 2048-2055.

[9] Wade PA, Murray JK, Shoh-Patel JS, Carrall PJ. *Tetrahedron Letters*. 2002; 43: 2585-2588.

[10] Michael J, Blom N, Glintenkamp L-A. Nitrobicyclo 2.2.1. heptanes. Neighbouring-group participation by nitro groups during the reaction of endo-nitrobicyclo[2.2.1] heptenes with electrophiles. *Journal of Chemistry. Society*. 1991; 8: 1855-1862.

[11] Timofeeva TN, Jonas BI, Petrov AA. The study of organic phosphorus compounds by NMR spectroscopy. *Russian Journal of General Chemistry*. 1969; 39(2), 354-359.

[12] Seyferth D, Paetsch J. Tetramethyl Acetylenediphoshonate and dimethyl chloroacetylenephosphonate and their reactions with cyclopenthadiene, 1,3-cycloheadiene and *Diazomethane. Journal of Organic Chemistry*. 1969; 34(5), 1483-1485.

[13] Konovalov AI. The reactivity of the addends in diene synthesis reaction. *Russian Chemical Reviews*. 1983; 11: 1852-1878.

[14] Anisimova NA, Berkova GA, Berestvitskaya VM. Bis (2-chloroethyl) etenylphosphonate in the Diels-Alder reaction. *Russian Journal of Organic Chemistry*. 2007; 77(5): 774-776.

[15] Berestovitskaya VM, Anisimova NA, Kuzhaeva AA, Berkova GA, Deiko LI. Synthesis of nitroalkenylphosphonates by the Diels-Alder reaction. *Book of abstract of the International Conference "The development and practical application of alicyclic compounds", Samara*, 2004, pp. 33-34.

[16] Berestovitskaya VM, Deiko LI, Anisimova NA. β-Nitroethenylphosphonates are perspective syntons for versatile functionalized organophosphorus compounds. *Book of abstract of XIV international conference on chemistry of phosphorus compounds, Kazan*, 2005, p. 4.

[17] Ono N, Kamimura A, Kaji A. Regioselective preparation of cyclohexadienes or aromatic nitro compounds by Diels-Alder reactions of β-sulfonylnitroolefins or β-sulfinylnitroethylene. *Journal of Organic Chemistry*. 1988; 53(2): 251-258.

[18] Ono N, Miyake H, Kamimura A, Kaji A. Regioselective Diels-Alder reactions. The nitro group as a regiochemical control element. *Journal of Chemistry Society*. 1987; 9: 1929-1935.

[19] Barltrop BJ, Nicholson JS. Synthesis in the Morphine series. Substituted hexahydrodiphenyls and related topics. *Journal of Chemistry Society*. 1951; 2524-2529.