(1E,3E)-1,4-dinitro-1,3-butadiene – synthesis, spectral characteristic and computational study based on MEDT, ADME and PASS simulation

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Keywords: nitrodiene; synthesis; spectral characteristics; DFT reactivity indices; ADME; PASS

Article

(1E,3E)-1,4-dinitro-1,3-butadiene—Synthesis, Spectral Characteristic and Computational Study Based on MEDT, ADME and PASS Simulation

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Abstract: Currently, the chemistry of conjugated nitrodienes is becoming more and more popular. These molecules are successfully applied in cycloaddition to synthesize six-membered rings in Diels-Alder reactions. Nitrodienes can be also applied to obtain bis-compounds in [3+2] cycloaddition. Moreover, the presence of a nitro group in the structure provides a possibility of further modification of the products. The simplest symmetrical representative of conjugated nitrodienes is (1E,3E)-1,4-dinitro-1,3-butadiene. Although the first mentions of the compound date back to the early 1950s, the compound has not yet been examined thoroughly enough. Therefore, in this article a comprehensive study of (1E,3E)-1,4-dinitro-1,3-butadiene has been described. For this purpose, an experimental study including synthesis process as well as spectral characteristic has been conducted. So as to better understand the properties of this compound a computational study of reactivity indices based on MEDT and also assessment of pharmacokinetics and biological activity according to ADME and PASS methodologies have been made. On this basis, some future application trends of (1E,3E)-1,4-dinitro-1,3-butadiene have been proposed.

Keywords: nitrodiene; synthesis; spectral characteristics; DFT reactivity indices; ADME; PASS

1. Introduction

Chemistry of nitro group containing compounds has been of great interest to scientists for many years [1]. These kinds of structures are extremely attractive building blocks in modern organic synthesis. It is due to the presence of a nitro group in the molecule, which creates many possibilities for its transformation. Thanks to this, it is possible to synthesize many nitrogen-containing connections like amines, hydroxylamines, oximes, nitriles, diazocompounds and others as well as to obtain carbonyl compounds [2]. Among all nitro compounds conjugated nitroalkenes (CNAs) deserve a special attention [3,4]. These compounds exhibit various biological activities such as antibacterial [5,6] or antifungal [7]. This makes CNAs often used in many reactions such as *Michael* addition [8,9] as well as cycloaddition (CA) reactions, to synthesize heterocycles, especially for the preparation of five-membered rings [10] like pyrazolines [11,12], isoxazolines [13–16] or pyrrolidine [17,18], and six-membered rings in the Diels-Alder reaction [19–21].

Recently, the chemistry of conjugated nitro dienes (CNDs) has gained greater interest [22,23]. Due to their structure, these compounds offer much more possibilities of transformation compared to CNAs [24].

Undoubtedly, CNDs are primary component in the Diels-Alder ([4+2] cycloaddition, 42CA) reactions [25]. Most often, these compounds play a role of standard diene (**Scheme 1, pathway A**). However, there are known cases of reactions where CNDs are applied in Diels-Alder reaction as dienophiles (**Scheme 1, pathway B**).

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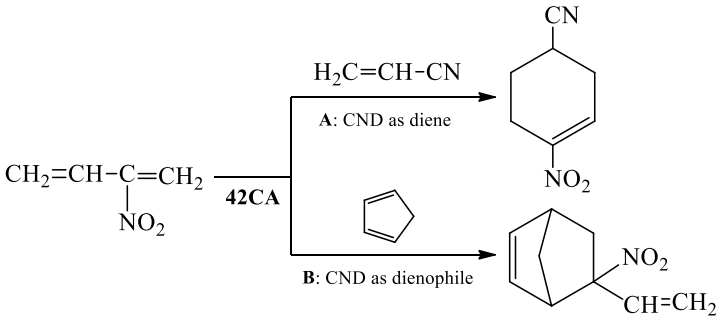
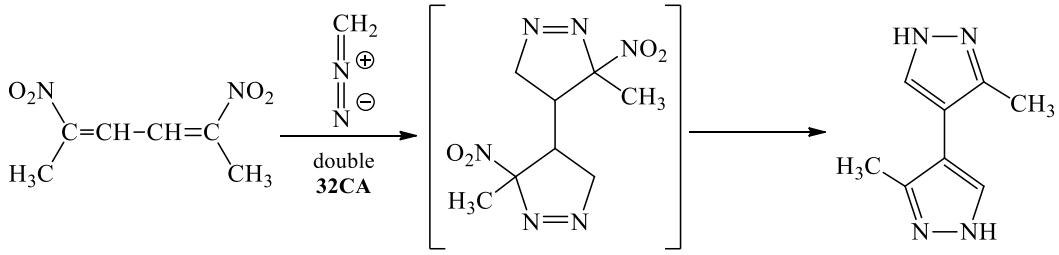


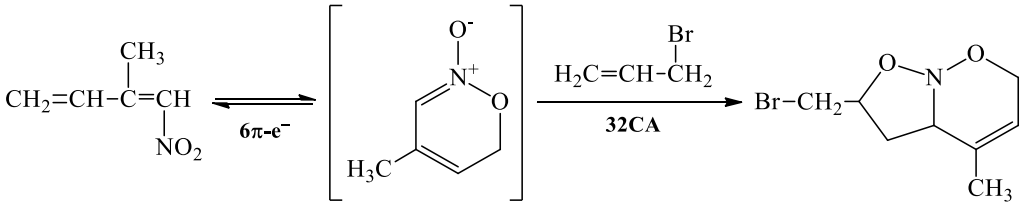
Scheme 1. Application of conjugated nitrodiene (CND) in Diels-Alder reactions in a double role.

What is more, CNDs can be also applied in reactions of [3+2] cycloaddition (32CA) with various three atoms components (TACs) [26]. In a consequence, it is possible to obtain a symmetric biheterocycles (**Scheme 2**) which may successfully use in medicine [27] as well as in optoelectronics [28] and also determine a useful ingredient for dielectric industry [29–31].



Scheme 2. Application of conjugated nitrodiene (CND) in [3+2] cycloaddition reaction to obtain symmetric biheterocyclic system.

Examples of heterocycles obtained via processes of 6π-electrocyclization (6π-e$^-$) of CNDs are also found in the literature [22]. This protocol of ring closure can be useful to synthesize cyclic nitronates, which may react with ethylene systems creating final products (**Scheme 3**) [32].



Scheme 3. Application of conjugated nitrodiene CND 6π-electrocyclization processes to obtain cyclic nitronate.

However, the number of examples of the use of CNDs in CA reactions as well as in 6π-e$^-$ processes is strongly limited. Reactions described in the literature that tackles the application of these compounds in organic synthesis are predominantly limited to nucleophilic additions and substitutions with thiols and amines, and less numerous examples of electrophilic additions of halogens [22–25]. Therefore, the use of CNDs as building blocks to obtain heterocyclic systems is an attractive course of research and determines one of the most promising trend in current organic synthesis.

Despite the fact that the chemistry of CNDs has been known since the middle of the twentieth century, there are still many gaps in the synthesis and spectral characteristics of these compounds [23]. What is more, numerous protocols and reports presented in the scientific literature are incomplete.

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Seeing the wide applicational potential of CNDs in a modern heterocyclic chemistry, we decided to carry out comprehensive study of one compound from this class. (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) was selected as the research object (**Figure 1**). Compound **1** was chosen for several reasons. Firstly, nitrodiene **1** is a representative of the simplest symmetrical CND system. The compound **1** was successfully tested in several reactions, mostly in nucleophilic addition and nucleophilic substitution [23,25]. However, also two examples of application of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) in Diels-Alder reactions are available in the literature [26]. What is more, there are reports that compound **1** is one of the few nitrodienes that has biological properties. In 1970 *Durden et al.* [33] described that (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) can to be active against *Staphylococcus Aureus* and *Aspergillus Niger*. In the same research, the Authors reported that nitrodiene **1** was tested against *Uromyces Phaseoli*. According to in-vivo tests the compound **1** is a promising candidate to be applied in agrochemical industry as a mean prevented the bean rust [33]. In view of the above, systematizing information and filling information gaps regarding the (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) is justified.

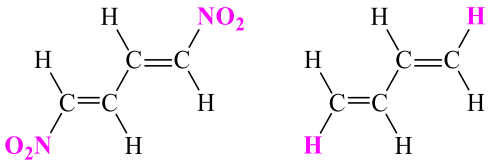

Figure 1. The structures of tested (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) and S-trans-1,3-butadiene (**1'**) as the simplest analogues of nitrodiene **1**.

As a part of the research, a comprehensive experimental-computational study was carried out. For this purpose, the (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) was synthesized. During the obtaining process the necessary modifications of synthesis protocol were introduced to increase the efficiency of obtaining nitrodiene **1**. Then, the spectral analyses were performed to confirm the structure of the obtained system. Research of the geometric isomerism aspects was also carried out. In turn, in the computational part, the reactivity of title compound **1** was thoroughly studied. For this purpose, selected aspects of Molecular Electron Density Theory (MEDT) [34] were used. The influence of the presence of the nitro group on the reactivity properties was also examined by comparing nitrodiene **1** with its analogue, the simplest representative of dienes, which is S-trans-1,3-butadiene (**1'**) (**Figure 1**). Finally, in order to address the biological potential of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**), analyses of physicochemical descriptors, pharmacokinetic properties, druglike nature and medicinal chemistry friendliness, based on selected aspects of ADME (Absorption, Distribution, Metabolism, Excretion) and PASS (Prediction of Activity Spectra for Substances) were performed.

2. Results and Discussion

2.1. Synthetic and Computational Aspects of (1E,3E)-1,4-dinitro-1,3-butadiene Preparation

2.1.1. Synthesis Protocol and its Necessary Modification

Generally, in the literature two synthesis methods of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) are available [23,25]. One of them includes an electrochemical process of direct oxidation of the of 1,4-dinitrobut-2-ene (**2**) (**Scheme 4**) by bromine or iodine in the presence of methanolic solution of KOH [35].

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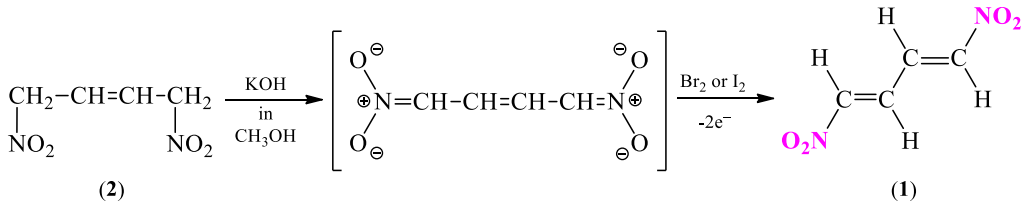
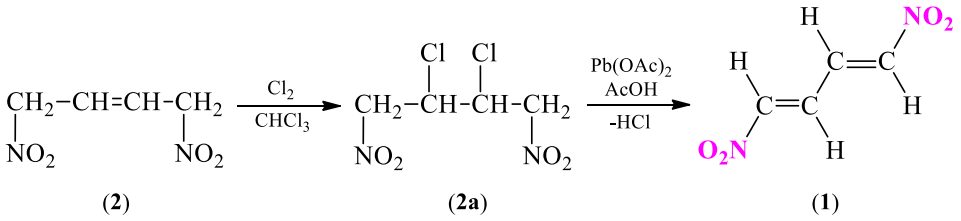


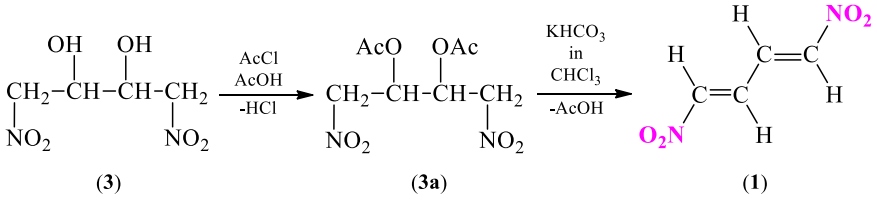
Scheme 4. Synthesis of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) via electrochemical processes.

Definitely, the most popular alternative methods are the thermal eliminations of different fragments like hydrogen halides or acetic acid from 1,4-dinitrobut-2-ene analogues [23,25]. The reaction can be carried out by two different paths. First alternative is started from 1,4-dinitrobut-2-ene (**2**), similarly to previous example (**Scheme 5**). In this case, dinitroalkene **2** is chlorinated with gaseous chlorine, in the presence of iodine to obtain 2,3-dichloro-1,4-dinitrobutane **2a**. In the next stage, the process of dehydrochlorinated of compound **2a** in the presence of lead(II) acetate in glacial acetic acid is carried out [36].



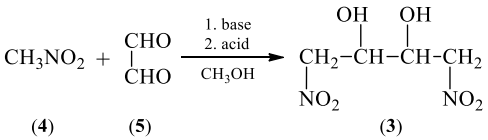
Scheme 5. Synthesis of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) via dehydrochlorination reaction of 2,3-dichloro-1,4-dinitrobutane (**2a**).

Another alternative based on elimination reaction and creation of conjugated system based on 1,4-dinitrobutane-2,3-diol (**3**) (**Scheme 6**). First step includes an acylation process of diol **3** to 2,3-diacetoxy-1,4-dinitrobutane (**3a**). In the next stage, an elimination of two acetic acid molecules from ester **3a** in the presence of potassium bicarbonate in chloroform is carried out [33,37–39].



Scheme 6. Synthesis of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) via dehydro-acetylation reaction of 2,3-diacetoxy-1,4-dinitrobutane (**3a**).

Due to the determined popularity of the last presented method, we decided to check the protocol of synthesis (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) based on **Scheme 6**. In order to obtain the 1,4-dinitrobutane-2,3-diol (**3**) a procedure of condensation reaction between nitromethane (**4**) and glyoxal (**5**) (**Scheme 7**) was applied [33,37–39].



Scheme 7. Synthesis of 1,4-dinitrobutane-2,3-diol (**3**) via condensation reaction between nitromethane (**4**) and glyoxal (**5**).

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In the first stage of the synthesis of nitrodiene **1**, the condensation reaction between nitromethane (**4**) and glyoxal (**5**) (**Scheme 7**) was carried out. In the literature this procedure was described four times [33,37–39]. The differences were in the acidic and basic agents used (**Table 1**). Taking into account both acidic and basic factors as well as the yield, it was decided to synthesize nitrodiol **3** using the modified method presented by *Novikov et al.* [37].The only change that was made was to use glacial acetic acid instead of SO_2 as the acidic agent. Invariably, NaOH was used as the basic agent. It was this stage of synthesis of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) which proved to be the most problematic.

Table 1. Acidic and basic agents together with yields for condensation reaction between nitromethane (**4**) and glyoxal (**5**).

Acidic agent	Basic agent	Yield	Reference
SO_2	NaOH	80.5	*Novikov et al.* [37]
SO_2	NaOH	61.0	*Durden et al.* [33]
SO_2	KOH	36.4	*Carroll* [38]
H_2SO_4 or H_3PO_4 or AcOH or $(COOH)_2$	KOH	24.0	*Plaut* [39]

An aqueous solution of NaOH and glyoxal (**5**) solution were simultaneously added dropwise to an equivolume mixture of nitromethane (**4**) and methanol the temperature was maintained at 0-2 °C. The mixture was maintained at 0 °C for one more hour, acidified with 50.0 % solution of acetic acid in water, until pH of 5 was reached. The organic phase was separated and the organic one was extracted with nitromethane as described by *Novikov et al.* [37].

The solvent from extracts was evaporated, the crystals washed with minimal amount of water, yielding 15.5 %. *Novikov et al.* [37] claim that the process yields 80.5 % of nitrodiol **3** stereoisomers combined. The yield obtained by modification of the procedure was improbable and unsatisfying. Another series of four extractions with nitromethane followed, the evaporation of the extracts from the second round yielded further 16.8 % of compound **3**. The total yield after primal and additional extraction equated to 32.3 % which is still lower than 80.5 % claimed by *Novikov et al.* [37].

Therefore, an attempt to obtain diol **3** by the method described by *Plaut* [39] was undertaken. During the synthesis it was found that the leaving of the reaction mixture unacidified overnight and acidifying it with acetic acid the next day led to unexpected self-heating of the mixture after an hour since addition of the acidic agent. The mixture heated itself to about 40 °C what lead to complete disappearance of diol **3** (as controlled by TLC eluent cyclohexane–ethyl acetate Cy:EtOAc 80:20 *v/v*, developed with iodine).

The condensation of nitromethane (**4**) and glyoxal (**5**) was once again conducted similarly as described by *Novikov et al.* [37] with the substitution of SO_2 to acetic acid until pH reached 5. KOH was also used instead of NaOH, as proposed by *Carroll* and collaborators [38,40]. The time of reaction after the addition of all substrates was also greatly reduced, and the mixture was diluted and acidified right after the substrates were added. This treatment prevented the darkening of the reaction mixture. The acidified mixture was divided, and a few approaches for extraction of 1,4-dinitrobutane-2,3-diol (**3**) were tested.

Next, an effort to find an alternative method of extraction was undertaken. After the acidification of acetic acid until pH 5 the mixture split into two phases, and they were separated. The aqueous phase was extracted with nitromethane, toluene, and diethyl ether separately. The process was monitored by TLC technique (eluent cyclohexane–ethyl acetate Cy:EtOAc 80:20 v/v, developed with iodine). During the research it was found that neither of the tested solvents was appropriate. It was rationalized that due to the glycolic nature of the diol **3** extraction from aqueous phase might be a problematic stage. Therefore, the aqueous phase was evaporated under vacuum at 40 °C. The evaporation yielded a viscous amber-coloured liquid that formed crystals when cooled to -18 °C overnight. A priori, the evaporated mixture could contain diol **3**, potassium acetate, and colored substances. Samples of the dried mixture were washed with various solvents and the solubility of mixture's ingredients was assessed (**Table 2**). Based on information in **Table 2** it can be concluded

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that among all tested solvents the diethyl ether is most suitable because it dissolved the diol, while the coloured fraction as well as potassium acetate were practically insoluble.

Table 2. Results for choice of solvent for extraction of 1,4-dinitrobutane-2,3-diol (**3**) from reaction mixture (✓✓✓-soluble, ✓✓-slightly soluble, ✓-barely soluble, x-insoluble). The solubility of diol **3** was controlled by TLC, the solubility of "coloured substances" was assessed by the colour of the washings (it ranged from brown to pale-yellow), while the solubility of potassium acetate was tested on a pure substance.

Fraction	Solvent					
	DMFA	Nitromethane	Methanol	Acetone	Chloroform	Diethyl Ether
	(ε=37.781)	(ε=36.562)	(ε=32.613)	(ε=20.493)	(ε=4.7113)	(ε=4.240)
1,4-dinitrobutane-2,3-diol (**3**)	✓✓✓	✓✓✓	✓✓✓	✓✓✓	**x**	✓✓
Coloured substances	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓
Potassium acetate	✓✓✓	x	✓✓✓	✓✓✓	**x**	**x**

Based on the conducted research a protocol for extracting diol **3** was proposed and tested. For this purpose, the viscous amber concentrate was mixed with anhydrous sodium sulphate, so that the mixture had a consistency of wet sand. The mixture was covered and set aside for 30 minutes. After that time, the solid was transferred into a Soxhlet extractor and extracted with diethyl ether under an inert gas. After the extraction the extract was cooled, solid that had fallen out was separated and washed sparingly with diethyl ether. The filtrate was evaporated dry on a rotatory evaporator in a bath of 40 °C. The dry crystals were washed with diethyl ether. In total, the isomer mixture of the 1,4-dinitro-2,3-butanediol (**3**) was obtained in the form of white lumpy and needle-like crystals.

Definitely, the hardest challenge for presented experimental part of study was the step of obtaining 1,4-dinitro-2,3-butanediol (**3**). Both of the 2,3-diacetoxy-1,4-dinitrobutane (**3a**) as well as (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) synthesis were carried out based on the procedures described by *Novikov et al.* [37]. The introduced changes in the synthesis protocols are not drastic and were intended only to improve the processes of obtaining ester **3a** and nitrodiene **1**. All modified procedures are collected and presented in section 3.1 *"Materials and Methods"*.

2.1.2. Spectral characteristic

In order to confirm the structure of the obtained compound as well as to supplement the missing in the literature information about (1E,3E)-1,4-dinitro-1,3-butadiene (**1**), the spectral analyses such as UV-Vis, IR, ^{1}H NMR, ^{13}C NMR and 2D ^{1}H-^{13}C HMQC NMR were performed.

In particular, the UV-Vis, showed in **Figure S1**, confirmed [33,40] the presence of only one maximum of absorption in a range of 500-190 nm, which is located at λ = 281 nm (CH_3OH). In turn, in IR spectrum, presented in **Figure S2**, allowed for finding the signals coming from ~C–H fragments, nitro groups as well as fragments characteristic for conjugated alkene connections. signals coming from *trans* alkene fragments also turned out to be Significant for analysis.

The analysis of ^{13}C NMR spectrum, shown in **Figure S4**, indicates that the carbon C1 and C2 atoms, directly connected with nitro groups, are strongly shifted towards the weaker area to δ = 146.60 ppm. In turn, the signal δ = 129.50 ppm can be assigned to the central C2 and C3 carbon atoms. On the other hand, thanks to ^{1}H NMR analysis (Figure **S3** together with 2D ^{1}H-^{13}C HMQC NMR analysis (**Figure S5**), it was possible to assign signals to all hydrogen atoms in the (1E,3E)-1,4-dinitro-1,3-butadiene (**1**).

2.1.3. Understanding the geometric isomerism based on DFT calculation

In 1970 *Durden et al.* [33] reported that the dinitrodiene **1** occurs in (1E,3E) conformation. In order to confirm the presented hypothesis, a comprehensive analysis of dehydro-acetylation reaction of 2,3-diacetoxy-1,4-dinitrobutane (**3a**) to 1,4-dinitro-1,3-butadiene (**1**) (**Scheme 8**) using quantum chemical tools was performed.

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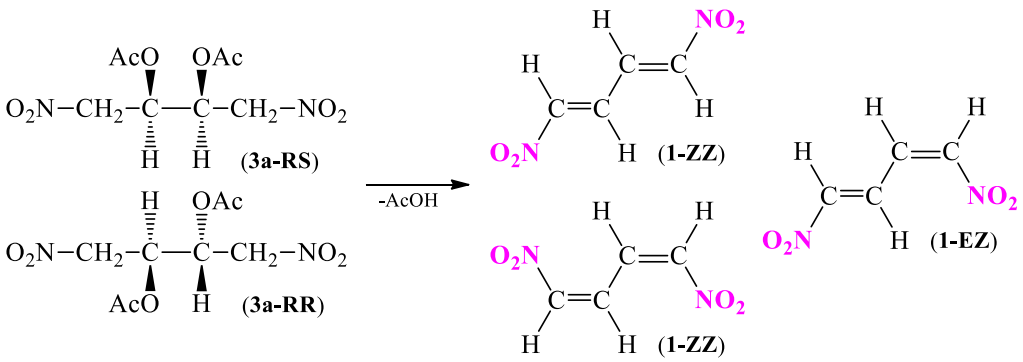

Scheme 8. Possible substrates and products of dehydro-acetylation reaction of 2,3-diacetoxy-1,4-dinitrobutane (**3a**) to 1,4-dinitro-1,3-butadiene (**1**).

For this purpose, the computational calculation using B3LYP/6-31G(d) model in a gas phase was used. Firstly, the optimization process of two forms (RR) and (RS) of 2,3-diacetoxy-1,4-dinitrobutane (**3a**) as well as three forms (EE), (EZ=ZE), (ZZ) of 1,4-dinitro-1,3-butadiene (**1**), and acetic acid molecules was conducted. Then, the thermodynamic properties of all possible combination of decomposition reactions (**Scheme 8**) were calculated (**Table 3**).

Table 3. Thermodynamic parameters of dehydro-acetylation reaction of 2,3-diacetoxy-1,4-dinitrobutane (**3a**) to 1,4-dinitro-1,3-butadiene (**1**), calculated in gas phase according to B3LYP/6-31G(d) (ΔH and ΔG are given in kcal·mol^{-1}, ΔS is given in cal·mol^{-1}·K^{-1}).

Transformation	ΔH	ΔG	ΔS
3a-RR → **1-ZZ** + 2AcOH	**33.64**	**11.98**	72.61
3a-RR → **1-EZ** + 2AcOH	36.09	14.27	73.17
3a-RR → **1-ZZ** + 2AcOH	37.31	15.11	74.45
3a-RS → **1-ZZ** + 2AcOH	**30.31**	**7.65**	75.99
3a-RS → **1-EZ** + 2AcOH	32.76	9.94	76.54
3a-RS → **1-ZZ** + 2AcOH	33.98	10.78	77.83

According to the results presented in **Table 3** it can be observed that regardless of the isomer of 2,3-diacetoxy-1,4-dinitrobutane (**3a**), the more favored product for dehydro-acetylation reaction of ester **3a** from the thermodynamic point of view is (1E,3E)-1,4-dinitro-1,3-butadiene (**1**). The conclusion stands in agreement with observations made by *Durden et al.* [33] and with the results of IR analysis.

2.2. Study of electron density distribution, bioactivity and pharmacokinetics indices based on MEDT, ADME and PASS

The computational study has been conducted for (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) and its simpler analogue S-trans-1,3-butadiene (**1′**) to show changes in the structure of the molecule introduced by the presence of the nitro group. The obtained results have been divided into four parts. Firstly, a topological analysis of Electron Localization Function (ELF) together with Natural Population Analysis (NPA), and Molecular Electrostatic Potential (MEP) for molecules **1** and **1′** at the ground states (GS) has been done in order to characterize their electronic structures. Secondly, an analysis of reactivity indices based on Conceptual Density Functional Theory (CDFT) for compounds **1** and **1′** at the ground state has been carried out. In the next part, the Non-Covalent Interactions (NCI) analysis is performed in order to obtain a deeper insight of the structure of molecules **1** and **1′**. Finally, the comprehensive evaluation of the chemical structure of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) has been studied to determine the likeness of nitrodiene **1** activity as pharmaceutics. To assess the potential biological activity an in-silico protocol of Absorption, Distribution, Metabolism, Excretion

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(ADME) has been used. In order to better research the biological significance of nitrodiene **1** a simple protocol of Prediction of Activity Spectra for Substances (PASS) was carried out.

2.2.1. Analysis of the Electronic Structure of the Molecules 1 and 1′ based on ELF, NPA and MEP

The ELF is a technique which allows prediction of the likelihood of finding an electron in the neighborhood space of a reference electron located at a given point and with the same spin. The technique is based on electron density distribution in molecules and allows both to characterize the electronic structure of compounds, and to predict their reactivity in chemical processes [41]. The ELF attractor positions of the core and valence basins together with ELF localization domains for (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) and S-trans-1,3-butadiene (**1′**) are shown in **Figure 2**, while the most relevant valence basin populations are given in **Table 4**.

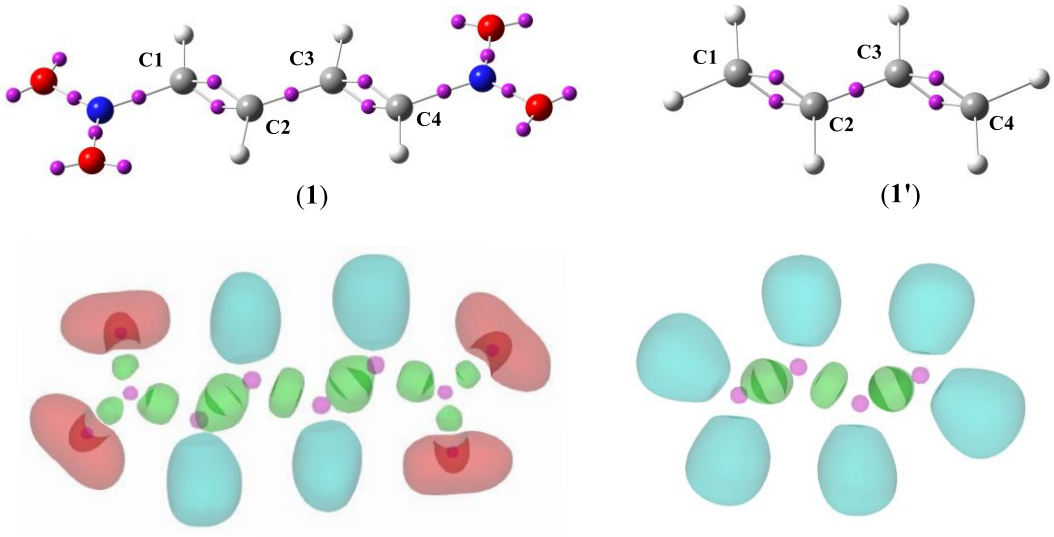

Figure 2. B3LYP/6-31G(d) ELF attractor positions of the core and valence basins for (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) and S-trans-1,3-butadiene (**1′**) together with ELF localization domains of represented at an isosurface value of ELF = 0.75. For ELF localization domains, protonated basins are shown in blue, monosynaptic basins in red, disynaptic basins in green, and core basins in magenta. In the first row the ELF attractors are shown as pink spheres.

The ELF topology of S-trans-1,3-butadiene (**1′**) presents two pairs of disynaptic basins V(C1,C2) and V′(C1,C2) (**Figure 2**), integrating a total electron population of 3.44 e (**Table 4**) as well as V(C3,C4) and V′(C3,C4) (**Figure 2**), integrating the same value of total electron population of 3.44 e (**Table 4**). The presence of these pairs is associated with somewhat depopulated C1-C2 and C3-C4 double bonds. In turn, the presence of disynaptic basin V(C2,C3) (**Figure 2**), integrating a population of 2.30 e (**Table 4**), is associated with C2-C3 single bond.

Table 4. B3LYP/6-31G(d) the most significant ELF valence basin populations N giving in average number of electrons [e].

	1	**1′**
ELF basins	**N [e]**	**N [e]**
V(C1,C2)	1.73	1.72
V′(C1,C2)	1.73	1.72
V(C2,C3)	2.23	2.20
V(C1,C2)	1.73	1.72
V′(C1,C2)	1.73	1.72

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In turn, the ELF topology for (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) is practically identical. when compared with the S-trans-1,3-butadiene (**1'**), the total electron population associate with the presents of two double bonds C1-C2 as well as C3-C4 is slightly higher and the total electron population associate with the presents of single bond C2-C3 is slightly smaller (**Table 4**). Therefore, the introduction of two nitro groups located symmetrically to the structure does not affect the electron localization. Based on ELF analysis the proposed Lewis-like structures together with the natural atomic charges for compounds **1** and **1'** are given in **Figure 3**.

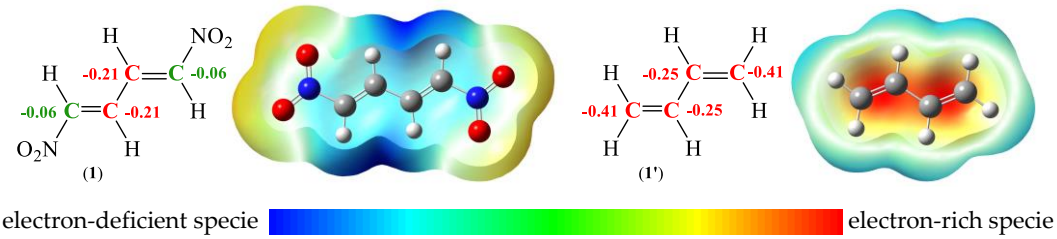

Figure 3. B3LYP/6-31G(d) proposed ELF-based Lewis-like structures with the natural atomic charges for (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) and S-trans-1,3-butadiene (**1'**) together with the molecular electrostatic potential maps. Negative charges are coloured in red, while negligible charges are coloured in green. Natural atomic charges are given in average number of electrons [e].

Charge distributions for molecules **1** and **1'** were examined through the NPA [42,43]. The analysis indicates a similar negative distribution located at the central carbon atoms C2 and C3 which form a single bond. For S-trans-1,3-butadiene (**1'**) both natural atomic charges are -0.25 e (**Figure 3**). In a case of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) for analogous carbon atoms C2 and C3, a slight decrease of electron-rich specie to -0.21 e is noticeable (**Figure 3**). A different situation is observed in the case of terminal carbon atoms. Both carbon atoms C1 and C4 in diene **1'** are represented by highly electronegative region, -0.41 e (**Figure 3**). On the other hand, the introduced nitro groups at nitrodiene **1** strongly interact with C1 and C4 carbon atoms. As a result, these centres are depleted of electrons to a value practically typical of neutral regions, -0.06 e (**Figure 3**). The presented results correlate well with MEP [44]. The analysis of a surface localized a high negative electrostatic potential around all carbon atoms in diene **1'** (in red) and poorly electropositive region within the vicinity of the hydrogen atoms (in green-blue). In turn, the positive electrostatic potential is both found around the carbon atoms (in light-blue) in nitrodiene 1 as well as stronger electropositive region within the vicinity of the hydrogen (**Figure 3**).

2.2.2. Analysis of the CDFT Reactivity Indices for the compounds 1 and 1'

The CDFT is a very important tool in understanding the reactivity of molecules in polar processes. The theory is to connect well established chemical concepts, like ionization potential I, electron affinity A, electronic chemical potential μ, Milliken electronegativity X, chemical hardness η and chemical softness S with electronic structure of a molecule. Based on those, the indication of global electronic properties of substrates, such as global electrophilicity ω, and global nucleophilicity N for molecules, can be established. As an effect, it is possible to assign addends either the role of electrophile or nucleophile in studied reactions [45–47]. Furthermore, with application of either Parr functions, not only global, but also local electronic properties of a molecule can be estimated, thus allowing to predict reactivity of molecules in the studied reactions, based only on substrate structures [48,49]. The global reactivity indices for (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) and S-trans-1,3-butadiene (**1'**) are given in **Table 5**, while the local electronic properties are shown in **Figure 4**.

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Table 5. B3LYP/6-31G(d) HOMO and LUMO energy as well as the global reactivity indices giving in electronvolts [eV].

[eV]	1	1′
HOMO energy	-8.31	-6.23
LUMO energy	-3.91	-0.61
Energy gap, ΔE	4.40	5.62
Ionization potential, I	8.31	6.23
Electron affinity, A	3.91	0.61
Electronic chemical potential, μ	-6.11	-3.42
Milliken electronegativity, X	-4.40	-5.62
Chemical hardness, η	4.40	5.62
Chemical softness, S	0.23	0.18
Global electrophilicity, ω	4.24	1.04
Global nucleophilicity, N	0.81	2.89

The calculated HOMO energy [45] of S-trans-1,3-butadiene (**1′**) is -6.23 eV and the calculated LUMO energy [45] for diene **1′** is 0.61 eV (**Table 5**). In turn, the presence in the structure two strongly electron withdrawing nitro groups to molecule in (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) causes a reduction of both HOMO energy, to -8.31 eV, and LUMO energy, to 3.91 eV (**Table 5**). Consequently, the HOMO-LUMO energy gap shrinks. For diene **1**' it equates to 5.62 eV and for nitrodiene **1** it is 4.40 eV (**Table 5**). It means that the (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) is a less stable compound compared to S-trans-1,3-butadiene (**1′**).

The calculated global electrophilicity [50] ω index of S-trans-1,3-butadiene (**1′**) is 1.04 eV and the calculated global nucleophilicity [51] N index for this diene **1′** is 2.89 eV (**Table 5**). These values give the conclusion that diene **1′** can be classified as moderate electrophile as well as moderate nucleophile in polar reactions, within the electrophilicity and nucleophilicity scale [45]. In turn, the introduction of two strongly electron withdrawing nitro groups to the molecule, in (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) completely changes the preference of reactivity indices. In particular, the calculated global electrophilicity [50] ω index is significantly increased to 4.24 eV and also the calculated global nucleophilicity [51] N index is significantly reduced to 0.81 eV (**Table 5**). These values give the conclusion that nitrodiene **1** can be classified as super strong electrophile and marginal nucleophile in a polar reaction, within the electrophilicity and nucleophilicity scale [45]. The presented information is an important conclusion, as in the reactions, including the participation of non-symmetric reagents, the regioselectivity can be defined through interaction between the most electrophilic centre of the electrophile and the most nucleophilic centre of the nucleophile [48]. To characterise the most nucleophilic and the most electrophilic centres for (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) and S-trans-1,3-butadiene (**1′**) the electrophilic P_k^+ and nucleophilic P_k^- Parr functions together with local electrophilicity ω_k and local nucleophilicity N_k of diene **1′** and nitrodiene **1** were analysed (**Figure 4**) [49].

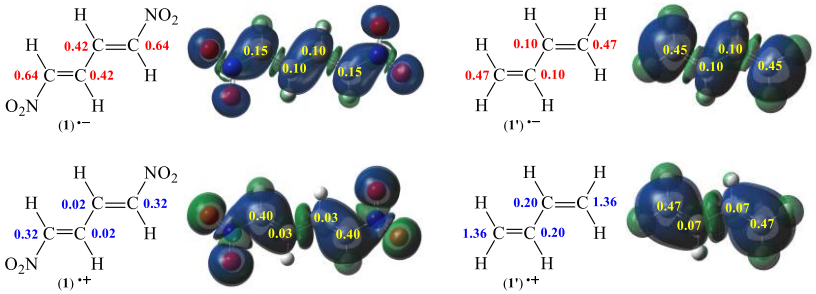

Figure 4. B3LYP/6-31G(d) local electronic properties of diene **1′** and nitrodiene **1** presented as three-dimensional representations (3D) of Mulliken atomic spin densities for radical anions **1**$^{\bullet-}$ and **1′**$^{\bullet-}$ and

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also radical cations **1**$^{\cdot+}$ and **1′**$^{\cdot+}$ together with the electrophilic P_k^+ and the nucleophilic P_k^- Parr functions values (given in yellow) as well as the indexes of the local electrophilicity ω_k of **1**$^{\cdot-}$ and **1′**$^{\cdot-}$ (given in red, in eV) and the local nucleophilicity N_k of **1**$^{\cdot+}$ and **1′**$^{\cdot+}$ (given in blue, in eV).

Analysis of the electrophilic P_k^+ Parr function [49] of S-trans-1,3-butadiene (**1′**) indicates that the terminal carbon atoms are the most electrophilic centres of this species, both presenting the value $P_C^+ = 0.45$. At these atoms, the value of the local electrophilicity ω_k index is $\omega_C = 0.47$ eV (**Figure 4**). In turn, electrophilic P_k^+ Parr functions for the centric atoms of diene **1′** are visibly reduced to $P_C^+ = 0.10$ ($\omega_C = 0.10$ eV) (**Figure 4**). Analysis of the electrophilic P_k^+ Parr function of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) show a similar tendency. In particular, the most electrophilic centres in this molecule **1** are situated on the terminal carbon atoms, presenting the value $P_C^+ = 0.15$. At these atoms, the value of the local electrophilicity ω_k index is $\omega_C = 0.64$ eV (**Figure 4**). In turn, the values of electrophilic P_k^+ Parr function for the centric atoms of nitrodiene **1** are slightly reduced to $P_C^- = 0.10$ ($\omega_C = 0.42$ eV) (**Figure 4**). Based on presented analysis it can be concluded that the direct neighbourhood of strongly electron withdrawing nitro groups causes a significant reduction of local electrophilic properties in dinitrodiene **1** when compared to diene **1′**.

On the other hand, analysis of the nucleophilic P_k^- Parr functions [49] of S-trans-1,3-butadiene (**1′**) indicates that the terminal carbon atoms are also the most nucleophilic centres of this species, presenting the values $P_C^- = 0.47$. At these atoms, the values of the local nucleophilicity N_k index is $N_C = 1.36$ eV (**Figure 4**). In turn, values of nucleophilic P_k^- Parr functions for the centric atoms of diene **1′** are extremely reduced to $P_C^- = 0.07$ ($N_C = 0.20$ eV) (**Figure 4**). The differences between nucleophilic properties for nonsymetric atoms in molecule **1′** are a slightly greater than for electrophilic properties. Another situation is observed in a case of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**). Analysis of the nucleophilic P_k^- Parr function of nitrodiene **1** show that the most nucleophilic centres in molecule **1** are also situated on the terminal carbon atoms, presenting the value $P_C^- = 0.40$. At these atoms, the values of the local nucleophilicity N_k index is $N_C = 0.32$ eV (**Figure 4**). In turn, values of nucleophilic P_k^- Parr function for the centric atoms of nitrodiene **1** are reduced practically to zero, $P_C^- = 0.03$ ($N_C = 0.02$ eV) (**Figure 4**). Based on presented analysis it can be concluded that the direct neighbourhood of strongly electron withdrawing nitro group does not cause a significant reduction of local nucleophilic properties of nitrodiene **1** in comparison to diene **1′**.

2.2.3. Analysis of the Non-covalent Interaction of the Molecules 1 and 1′ based on NCI

The NCI is a very useful and popular method for revealing regions and types of weak interactions in chemical systems. The analysis is related with the electron density (ϱ) and the reduced density gradient (s). Due to the size of molecules, the most common approach is assigning of van der Waals interactions (vdW), steric effects (SEs), and hydrogen bonds (HBs) based on pairwise distances between atoms according to their vdW radii. In an effect, the direct representation and characterization of non-covalent interactions in three-dimensional space is possible. Therefore, NCI is an useful tool in understanding many chemical, biological, and technological problems [52,53]. The non-covalent interaction scatter diagram together with the reduced density gradient (RDG) analysis for diene **1′** and nitrodiene **1** are presented in **Figure 5**. A negative sign, indicates attractive forces connected with hydrogen and halogen bonding, is marked in blue colour; van der Waals forces are coloured in green, whereas red fragment, to the right from zero, expresses the repulsive forces, which mostly occur in steric interactions as well as in presence of rings.

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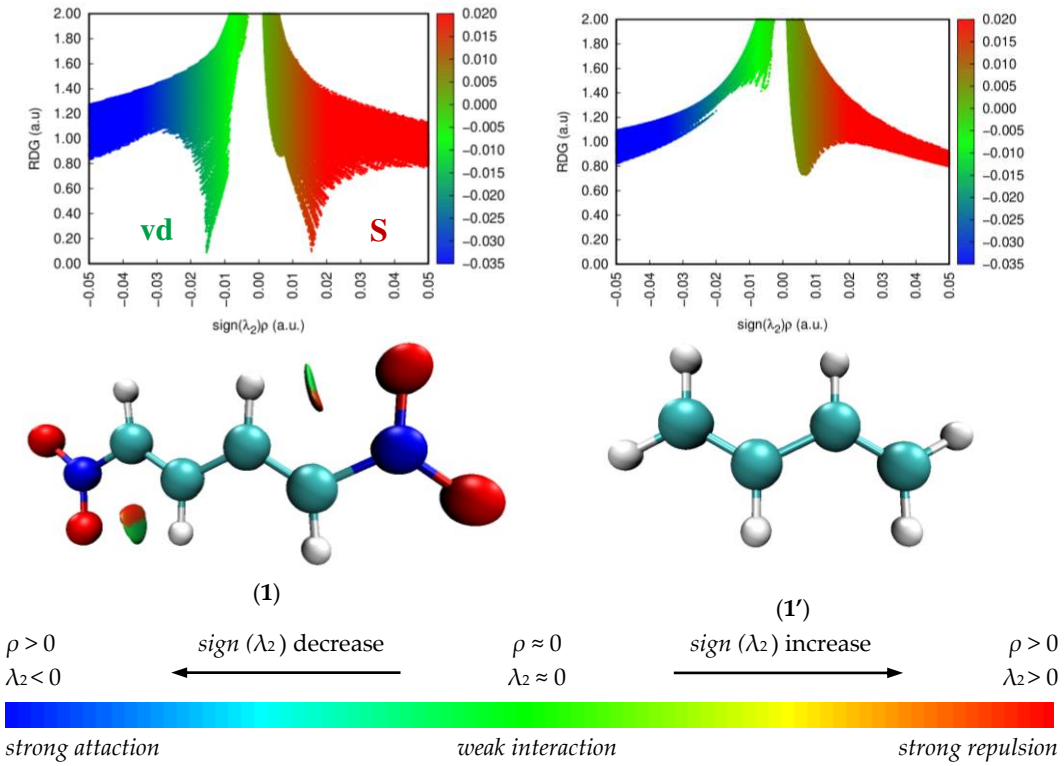

Figure 5. B3LYP/6-31G(d) non-covalent interaction scatter diagram together with the reduced density gradient (RDG) analysis for diene **1′** and nitrodiene **1**.The strong attractive interactions like H-bond or halogen-bond are colored in blue, the van der Waals interactions are colored in green while the repulsive or steric interactions are colored in red.

The NCI analysis of S-trans-1,3-butadiene (**1′**) indicates that molecule **1′** does not have any characteristic non-covalent interactions (**Figure 5**). A completely different situation occurs in the case of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**). The NCI analysis shows that the introduction of two strongly electron withdrawing nitro groups significantly effects intramolecular interactions inside the molecule **1**. Particularly in the area between nitrogen atom, the terminal carbon atom and the centric carbon atom (O_2**N**−**C**H=**C**H− fragment) an intramolecular interaction, located symmetrically on both sides, is observed. The occurrence of these interactions is related to two types of non-covalent effects. The first of them is due to steric interactions (part of red colour, sign (λ_2)ρ between -0.02 and -0.01 a.u.) (**Figure 5**). The second component relates to van der Waals interactions (part of green colour, sign (λ_2)ρ between 0.02 and 0.01 a.u.). It can be identified with the interaction of the oxygen atom of the nitro group and the hydrogen atom in the diene part (**Figure 5**).

2.2.4. Analysis of Drug-Likeness and ADME Studies of the Molecule 1

ADME studies are critical in modern drug discovery [54]. The process of predicting a good drug by analysing its pharmacokinetic properties in the laboratory is expensive, and labour intensive. So, to accelerate the research and more rationally dispense the financing ADME parameters can be inspected using *in silico* tools. The undoubted advantage of the ADME approach is the fact that the analysis is based on structure of compound, including the atoms presence in the molecule and their connections. Therefore, ADME is one of the simplest and most useful methodology for the initial examination of drug-likeness [55,56]. Within the ADME approach for (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) some physicochemical properties like lipophilicity, water solubility, pharmacokinetics and also medicinal chemistry assessments were performed by online server SwissADME [54] and summarized in **Table 6**.

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Table 6. Drug-likeness parameters for (1E,3E)-1,4-dinitro-1,3-butadiene (**1**).

Physicochemical Properties					
Formula	$C_4H_4N_2O_4$				
Molecular weight MW	144.09 g/mol				
#heavy atoms	10				
#aromatic heavy atoms	0				
#rotatable bonds	3				
#H-bond acceptors	4				
#H-bond donors	0				
Molar refractivity MR	36.6				
Topological polar surface area TPSA	91.64 Å^2				
Lipophilicity Log $P_{o/w}$					
iLOGP	**XLOGP**	**WLOGP**	**MLOGP**	**SILICOS-IT**	**Consensus**
-1.9	0.81	1.61	-0.78	-2.34	-0.52
Water Solubility Log S					
Log S (ESOL)	**Solubility**	**Class**	**Log S (Ali)**	**Solubility**	**Class**
-1.05	1.300 mg/ml	very soluble	-2.32	0.696 mg/ml	soluble
Pharmacokinetics					
CYP1A2 INH	**CYP2C19 INH**	**CYP2C9 INH**	**CYP2D6 INH**	**CYP3A4 INH**	**Skin permeation**
No	No	No	No	No	-6.60 cm/s
Medicinal Chemistry Friendliness					
PAINS		**Brenk**		**Synthetic accessibility**	
0 alert		2 alerts		29.5%	

According to the obtained parameters the assessment using models developed by *Lipinski et al.* [57], *Ghose et al.* [58], *Veber et al.* [59], *Egan et al.* [60] and *Muegge et al.* [61] was performed, to evaluate the drug-likeness. The main features and conditions of these rules and filters are collected in **Table 7**.

Table 7. Main features of the five druglikeness rules evaluated throughout this work.

Lipinski et al. [57] (Pfizer)	*Ghose et al.* [58] (Amgen)	*Veber et al.* [59] (GSK)	*Egan et al.* [60] (Pharmacia)	*Muegge et al.* [61] (Bayer)
MW ≤ 500 Da MLOGP ≤ 4.15 #H-bond donors ≤ 5 #H-bond acceptors ≤ 10	160 Da ≤ MW ≤ 480 Da -0.4 ≤ WLOGP ≤ 5.6 40 ≤ MR ≤ 130 20 ≤ #atoms ≤ 70	#rotatable bonds ≤ 10 TPSA ≤ 140 Å^2	WLOGP ≤ 5.88 TPSA ≤ 131.6 Å^2	200 Da ≤ MW ≤ 600 Da -0.4 ≤ XLOGP ≤ 5.6 TPSA ≤ 150 Å^2 #rings ≤ 7 #carbons > 4 #heteroatoms > 1 #rotatable bonds ≤ 15 #H-bond donors ≤ 5 #H-bond acceptors ≤ 10

Based on physicochemical descriptors, predicted ADME parameters shown in **Table 6,** and the main features of the five druglikeness rules shown in **Table 7** it can be concluded that (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) is a good drug candidate according to the filters by *Lipinski et al.* [57], *Veber et al.* [59], and *Egan et al.* [60]. The compound **1** has appropriate: molecular weight, number of rotatable bonds, H-bond donor – acceptor ratio, and satisfactory value of topological polar surface area (TPSA), which is commonly used parameter for the optimization of a drug's ability to permeate cells [62]. What is more, dinitrodiene **1** has excellent lipophilicity properties.

However, according to more demanding filters such as *Ghose et al.* [58] and *Muegge et al.* [61] the (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) has low potential as a drug candidate. Both of filters are define

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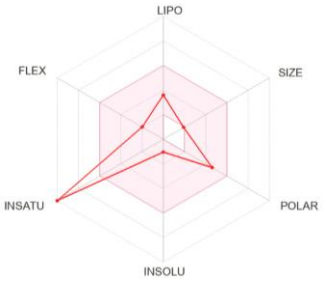
a minimum molecular weight. The nitrodiene **1** does not meet their criteria due to too low weight and molar refractivity [63]. Nitrodiene **1** has only 14 atoms in total, only 4 of which are carbon atoms.

The analysis of another drug-likeness parameters (**Table 6**), not included in the tested filters, shows that (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) not only has good lipophilic properties but also is water-soluble. These physicochemical properties are crucial to drugs' uptake and their further metabolism [64,65]. What is more, nitrodiene **1** not is Pan-Assay Interference Compounds (PAINS) but due to its structure causes two alerts, namely nitro group and absence of organic ring. The (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) is also not a good option as a drug candidate based on pharmacokinetic aspects. In particular, nitrodiene **1** is not an inhibitor candidate in the case of all studied isoforms CYP.

Finally, the Bioavailability Radar which allows us to assess the similarity of the drug-likeness of a nitrodiene **1** is presented in **Figure 6**. Based on analysis it can be concluded that the main problem presented in Bioavailability Radar is totall insaturation in the molecule of nitrodiene **1**. It is caused by the sp^2 hybrydization of all the carbon atoms. It should be underlined that the optimal ratio of carbon atoms in the sp^3 hybridization to all carbon atoms lays in the range of 0.25 – 1 [55,56].



LIPO (lipophilicity)	-0.7 < XLOGP < 5.0
SIZE	150 Da < MW < 500 Da
POLAR (polarity)	20 Å^2 < TPSA < 130 Å^2
INSOLU (insolubility)	-6 < Log S (ESOL) < 0
INSATU (insaturation)	0.25 < fraction C sp^3 < 1
FLEX (flexibility)	0 < #rotatable bonds < 9

Figure 6. The Bioavailability Radar of the drug-likeness for (1E,3E)-1,4-dinitro-1,3-butadiene (**1**). On the pink area represents the optimal range for each property like lipophilicity, size, polarity, insolubility, insaturation and flexibility.

2.2.5. Assessment of Antimicrobial Activities based on PASS for the Molecule 1

At the end, the antimicrobial activity of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) was predicted applying PASS which is component of Way2Drug portal [66]. The PASS is a simple and very useful tool that calculates the potential biological activity of a molecule and allows to preliminary assess molecule's drug-likeness, possible mechanisms of its action, pharmacological effects, toxicity, adverse effects, and other parameters. The assessment is made based on structural formula. The results of PASS analysis are expressed as probabilities to be active (Pa) or inactive (Pi). The values of Pa and Pi are in a range from 0.000 to 1.000, where the value of 0.000 means complete lack of probability, while a value of 1.000 means certainty. The compound can be assigned as probably active when Pa > Pi. The obtained data is useful to decide (I) if the synthesis and characterization of new compounds is justified prior to preparing them; and (II) if the screened compounds are good candidates for further biological research [67]. In order to evaluate primary biological properties of nitrodiene **1** the assessment of antimicrobial activities was performed by online server PASS [66] and summarized in **Table 8**.

Table 8. Prediction of the main antimicrobial activity of the (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) using PASS. The results are expressed as probability to be active (Pa) or inactive (Pi).

Antimicrobial activity	Pa	Pi
Antiviral (Picornavirus)	0,581	0,024
Antifungal	0,416	0,047
Antibacterial	0,396	0,031
Antiparasitic	0,274	0,065

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According to the PASS analysis, presented in **Table 8**, (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) has a very low antimicrobial activity. All Pa parameters against microorganisms, namely antiviral, antifungal, antibacterial as well as antiparasitic are lower than 0.6. So as to deem a compound potentially active the Pa parameter should be higher than 0.7 [68]. However, nitrodiene **1** shows partial biological activity. For example, compound **1** can be tested in a role of an inhibitor against enzyme of *Saccharopepsin* (Pa = 0.912), *Acrocylindropepsin* (Pa = 0.912), *Polyporopepsin* (Pa = 0.864) or applied in pancreatic disorders treatment (Pa = 0.826) as well as many others. The full information about biological activity and potential application direction of nitrodiene **1** (Pa > 0.7) is collected in **Table S3** in Supplementary Materials. It should be underlined that in all cases Pa > Pi. Therefore, the mentioned activities are possible.

3. Materials and Methods

3.1. Materials

Commercially available (Sigma–Aldrich, Szelągowska 30, 61-626 Poznań, Poland) reagents and solvents were used. All solvents were tested with high pressure liquid chromatography before use.

3.2. General Procedure for 1,4-dinitro-2,3-butanediol (3) Isomers Synthesis

In a flask 35 cm^3 of nitromethane (**4**) and 35 cm^3 of methanol were added and stirred. Then, everything was cooled to temperature 0 °C. To the cold mixture in an alternating way, drop by drop, 5.8 cm^3 of glyoxal (**5**) as well as a solution of 6.4 g KOH in 6.0 cm^3 distilled water was added, all time maintaining the temperature below 5 °C. Immediately after the glyoxal and KOH solution, to the flask 25 cm^3 of distilled water was added, the mixture was neutralized by 12.0 cm^3 of glacial acetic acid, to pH = 5. At the end, the mixture was delivered to the ambient temperature.

After the reaction, the post-reaction mixture was concentrated by vacuum evaporator. The obtained concentrate in the form of thick syrup, slowly darkening at the room temperature. When the concentrate must be stored it should be stored frozen at around -18°C. Anhydrous Na_2SO_4 (5.0 g of Na_2SO_4 for 1.0 g of concentrate) was mixed with the concentrate and left under cover for 30 minutes so as the inorganic salt could absorb the residual water. The final mixture should have the consistency of slightly damp sand.

Extract the solid with diethyl ether in a Soxhlet extractor, under an inert gas, for around 90 minutes. After extraction, the solvent was cooled. If solid have precipitated from the diethyl ether, it should be separated by filtering and washing with a small amount of diethyl ether, the filtrate should be evaporated dry in rotatory evaporator, and obtained solids washed sparingly with diethyl ether. If not, the extract should be evaporated in a vacuum evaporator, and the solids washed sparingly with diethyl ether. In total, 4.0 g (44.5 %) of the mixed isomers of the 1,4-dinitro-2,3-butanediol (**3**) was obtained in the form of white lumpy and needle-like crystals. The melting points of the products are respectively 87.5–88.0 °C and 92.5–93.0 °C.

3.3. General Procedure for 2,3-diacetoxy-1,4-dinitrobutane (3a) Isomers Synthesis

In a flask a 7.7 g of isomers mixture of 1,4-dinitro-2,3-butanediol (**3**), 19.3 cm^3 of acetyl chloride and 95 cm^3 of glacial acetic acid were added and stirred. Then, all was heated under reflux until the end of release of hydrogen chloride gas. This moment was monitored through clouding of a drop of 3.0 % solution of $AgNO_3$ under the influence of HCl fumes. Next, the heating was stopped, and mixture was delivered to ambient temperature. After cooling, the mixture was added to 400 g of finely crushed ice. When the ice completely melted, the obtained solid was ground under the liquid, then the mixture was filtered and the solid washed sparingly with water. The wet ester was dried in a desiccator over phosphorus pentoxide under vacuum until the powder was completely dry (when tested with cobalt chloride test strip). In total, 9.2 g (81.0 %) of the isomers mixture of the 2,3-diacetoxy-1,4-dinitrobutane (**3a**) was obtained in the form of a white dust. According to the melting point measurement the product was a mixture of two fractions. The melting points of those are respectively 71.0–73.0 °C and 75.0–77.0 °C (after recrystallization from ethanol).

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3.4. General Procedure for (1E,3E)-1,4-dinitro-1,3-butadiene (1) Synthesis

In a 500 cm^3 flask, equipped with a magnetic stirrer, a reflux condenser, and a heating mantle 8.19 g of a mixture of 2,3-diacetoxy-1,4-dinitrobutane (**3a**) isomers, 0.3 g of $KHCO_3$ and 230 cm^3 of chloroform were added. The reagents were heated together under reflux for 4 hours. After that, the post-reaction mixture was cooled and filtered under vacuum. The obtained sediment was washed with chloroform. Then, the filtrate was evaporated on a vacuum evaporator to obtain about 4.0 g of slightly moist, yellow crystals, smelling strongly of vinegar. The crystals should be washed with a small amount of distilled water to remove the rest of acetic acid. Immediately after rinsing, the crystals must be dried in a desiccator over phosphorus oxide, under vacuum and without access to light. In total, 3.0 g (65.0 %) of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) was obtained in the form of yellow crystals with the scent of freshly cut cedar wood.

(1E,3E)-1,4-dinitro-1,3-butadiene (**1**): m.p. 146.5 °C; UV-Vis (CH_3OH): λ_{max} [nm] 281; FT-IR (ATR): υ [cm^{-1}] 3106 and 3059 (~C–H stretch, alkene, medium), 1749 (stretch, *trans* alkene, weak); 1606 (>C=C< stretch, conjugated alkene, medium), 1502 (~N–O stretch, asymmetrical, nitro group, strong), 1342 (~N–O stretch, symmetrical, nitro group, strong), 985 (>C=C< bend, *trans* alkene, strong); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 7.63 (d, 1H, C**H**–NO_2, J = 9.6 Hz), 7.63 (dd, 1H, =C**H**–, J_1 = 3.2 Hz, J_1 = 9.6 Hz), 7.48 (dd, 1H, =C**H**–, J_1 = 3.2 Hz, J_1 = 9.7 Hz), 7.47 (d, 1H, =C**H**–NO_2, J = 9.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm] 146.60 (C1 and C4); 129.50 (C2 and C3).

3.5. Analytical Techniques

For reaction progress testing, thin layer chromatography (TLC) was performed using an aluminum plates with silica (unmodified layers) as the standard procedure in a case of nitrogen-contaning organic compounds [69–71]. In the role of eluent cyclohexane–ethyl acetate Cy:EtOAc (80:20 *v*/*v*) was applied. The plates were developed by iodine treatment. Melting points were determined with the Boetius PHMK 05 apparatus and were not corrected. FT-IR spectra were derived from the FTS Nicolet IS 10 spectrophotometer with Attenuated Total Reflectance (ATR).^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Bruker AVANCE NMR spectrometer. All spectra were obtained in $CDCl_3$ (visible at 7.27 ppm for ^{1}H NMR and at 77.00 ppm for ^{13}C NMR) solution and the chemical shifts (δ) are expressed in ppm, while the J-couplings (J) are giving in Hz. TMS was used as an internal standard. UV-Vis spectra were determined in methanolic solution for the 190–500 nm range through usage of spectrometer UV-5100 Biosens. The maximum of absorption was detected below 1 AU of absorbance and adheres to Beer-Lambert Law.

3.6. Computational Details

All computations were performed using the Gaussian 16 package [72] in the Ares computer cluster of the CYFRONET regional computer centre in Cracow. DFT calculations were performed using the functional B3LYP [73] together with 6-31G(d) basis set [74]. This computational level is widely used in optimization and evaluation of processes employing nitroalkenes [75–77]. Calculations of all critical structures were performed at temperature T = 298 K and pressure *p* = 1 atm in a gas phase. All localized stationary points were characterized using vibrational analysis. It was found that starting molecules as well as products had positive Hessian matrices.

The electronic structures of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) and S-*trans*-1,3-butadiene (**1'**) were characterized by the Electron Localization Function (ELF) [41], the Natural Population Analysis (NPA) [42,43], the Molecular Electrostatic Potential (MEP) [44] and Non-Covalent Interactions (NCI) [52,53]. Global electronic properties of reactants were performed according to Domingo's recommendations [45–47]. Electrophilic Parr functions P_k^+ and nucleophilic Parr functions P_k^- were obtained from the Atomic Spin Density (ASD) of the reagents' radical ions [48,49]. The physicochemical properties were evaluated by online server SwissADME [54]. In order to assess a Drug-Likeness, models based on rules of *Lipinski et al.* [57], *Ghose et al.* [58], *Veber et al.* [59], *Egan et al.* [60] and *Muegge et al.* [61] were applied. In turn, the analysis of prediction of activity spectra for substances were prepared by online server PASS [66].

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The NPA, the ELF as well as the NCI studies were performed with TopMod [78] and Multiwfn [79] software. For visualization of the molecular geometries of all structures, and 3D representations of the radical anions and the radical cations GaussView software [80] was used. In turn, the ELF localization domains were represented by using the Paraview software [81,82] at an isovalue of 0.75 a.u. Calculations of NCI analysis were performed by using VMD [83] software and visualized as an isosurface by value of 0.5.

4. Conclusions and Future Perspective

In this research a comprehensive study on the synthesis and spectral characteristics of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) was presented. Additionally, a computational analysis of electronic chemical parameters based on MEDT has been made. At the end, the forecasting study of biological properties of nitrodiene **1** using ADME and PASS simulation was performed.

Among the available alternatives for synthesis of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**), a three-step method from nitromethane (**4**) and glyoxal (**5**) was selected in the presented study. Modifications of synthesis protocol were carried out in order to increase efficiency of obtaining the final nitrodiene **1,** and overall process safety. In particular, the modification of extraction method for the synthesis of 1,4-dinitrobutane-2,3-diol (**3**), led to greater yields of extracted product to ca. 40 % as compared to 17 % when the extraction protocol proposed by *Novikov et al.* [37] was applied. Furthermore, the new method uses less expensive diethyl ether instead of nitromethane. What is worth noting, the nitromethane is classified in the category 2B as possibly carcinogenic to humans by the International Agency for Research on Cancer [84], whereas diethyl ether , among other volatile anaesthetics, is classified in category 3, which means not classifiable as to its carcinogenicity to humans [85]. According to NIOSH the permissible exposure limits for diethyl ether and nitromethane are respectively: 400 ppm and 100 ppm [86]. Thus the diethyl ether can be treated as a more favoured solvent compared to nitromethane.

The structure of obtained (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) has been verified based on measured melting point and data available in the literature [33,36,37,40]. In order to further confirm the structure of the nitrodiene **1** as well as to supplement the information missing in the literature, spectral analyses such as UV-Vis, IR, ^{1}H NMR, ^{13}C NMR and 2D ^{1}H-^{13}C HMQC NMR were performed.

A comprehensive MEDT analysis of (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) in comparison to S-trans-1,3-butadiene (**1'**) shows that the introduction of two nitro groups into the molecule causes changes in the electron density and its distribution parameters, but not to all studied aspects. The ELF analysis showed practically identical distribution of electron population for molecules **1** and **1'**, but the presence of nitro groups had a significant effect on charge distribution. In particular, the NPA and MEP analyses indicate drastic increase of natural atomic charges on terminal carbon atoms. Based on the analysis of CDFT it can be concluded that nitrodiene **1** will play a role of a super strong electrophile and marginal nucleophile in polar reactions. The most electrophilic and nucleophilic centre for nitrodiene **1** will be located on the terminal carbon atoms in direct neighbourhood of the nitro groups. Finally, the NCI analysis presented that in the space between nitrogen atom, the terminal carbon atom and the centric carbon atom (O_2N−CH=CH− fragment) an intramolecular interaction, related to two types of non-covalent effects is observed. Its first component is a steric interaction while the second component is connected with van der Waals interactions between the oxygen atom of the nitro group and the hydrogen atom in the diene part.

Based on physicochemical descriptors as well as predicted ADME and PASS parameters it can be concluded that (1E,3E)-1,4-dinitro-1,3-butadiene (1) as system can possess potential biological activity but compound **1** is not a good candidate on a drug. In particular, nitrodiene **1** has too few atoms in its structure, therefore, nitrodiene **1** also has insufficient molecular weight. After all, according to the PASS analysis the (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) can be active, among others, as an inhibitor of *Saccharopepsin*, *Acrocylindropepsin*, and *Polyporopepsin* as well as a treatment for pancreatic disorders.

Presented computational study shows that the future perspective for (1E,3E)-1,4-dinitro-1,3-butadiene (**1**) is application of this compound as a building block in synthesis of carbo- and

heterocyclic systems. For this purpose, the protocol of cycloaddition is one of the most significant reactions. Thanks to the protocol it is possible to obtain mostly five and six-membered ring. Future directions for compounds thus obtained might be determined through conversion of the nitro group to other functional groups to obtain complex cyclic systems the desired structure and properties as well as 6π-electrocyclization reaction to create bigger polycyclic systems.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Experimental details: pp. S2–S4, Computational data: pp. S5, Comprehensive PASS details: pp. S6–S7.

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