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Some Novichok agents and their interactions with Zn^{+2} ion. A DFT study

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Abstract

The Novichok agents attracted attention, especially in the Soviet Union in order to synthesize very effective warfare chemicals. They belong to the class of organophosphate acetyl cholinesterase inhibitors. In the present study, of those agents A-230, A-232, A-234, A-242 and A-262 have been considered within the restrictions of density functional theory at the level of B3LYP/6-31++G(d,p). Also the Zn^{+2} composites of those agents have been considered. All the structures are electronically stable, thermodynamically exothermic and have favorable Gibbs' free energy of formation values at the standard states. Various quantum chemical properties of them, including UV-VIS spectra, the HOMO and LUMO energies etc., have been obtained and discussed.

1. Introduction

Development of the weapons of mass destruction attracted much attention in the Cold War period. However, information about some of them are still protected under the designation "top secret". NOVICHOK program was developed by the USSR as a reaction to English/American invention of VX agent [1]. Actually, searching for novel more effective substances gradually escalated immediately after the world war-I [2-4]. After 1934, various organophosphorus compounds were synthesized (e.g., tabun, sarin and soman). Tabun, sarin and soman belong to the class of nerve agents that are collectively termed "G-agents" [5-7].

After World War-II, the Soviet and Allied forces developed new chemical warfare agents (CWAs) based on already then present German technologies [8]. After 1949, English and Americans developed VX agents such as (S-{2-[di(propan-2-yl)amino]ethyl}

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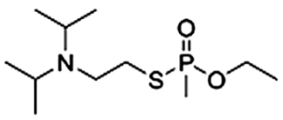
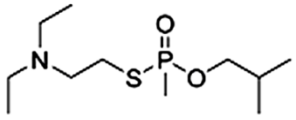
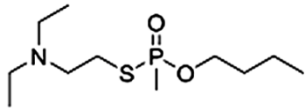
O-ethyl methylphosphonothioate), which had been selected as the most promising substance of the series. During the same period, the Soviet scientists developed independently of the UK and the USA an isomer of VX agent – the so-called Russian VX (VR, RVX, Substance 33, S-[2-(diethylamino)ethyl] O-(2-methylpropyl) methylphosphonothioate), which later became of NOVICHOK agents [9-11]. Another structural analogue of VX known as Chinese VX (CVX, O-butyl S-[2-(diethylamino)ethyl]methylphosphonothioate), was also developed and studied [9]. Note that Novichok agents are believed to be five to eight times more potent than VX, a deadly nerve agent.



VX agent



Russian VX



Chinese VX

In the USSR particular attention was paid to compounds with strong biocidal effect [12]. A-series of compounds were synthesized in the USSR (A-230, A-232 and A-234) [13-18].

Though much of the knowledge about the synthesis and various properties of phosphorylated and/or phosponylated oximes, amidates and related compounds was published in Russian literature in the 1960's and 1970's [13-18], the first exact information on A-agents and NOVICHOKs was posted only after the end of the FOLIANT project (after 1992) from the defectors [19]. The Novichok, or "newcomer" class of nerve agents are lesser characterized, weaponized organophosphate agents [10,11]. A-series nerve agents firstly synthesized in 1970s under the Union of Socialist Soviet Republics (U.S.S.R). In the beginning, A-230 was synthesized by replacing substituting O-isopropyl group of sarin with aceoamydin radical. Later on, Kirpichey et al. synthesized A-232 and A-234 derivatives by introducing methoxy and ethoxy groups in A-230, respectively [10,20].

The use of known Novichok agents in warfare is banned under the Chemical Weapons Convention of 1997. Novichok agents are considered more potent than VX gas and can be applied in unitary and binary forms [10].

As nerve agents, the Novichok agents belong to the class of organophosphate acetyl cholinesterase inhibitors. These chemical compounds irreversibly inhibit the enzyme

acetyl cholinesterase, preventing the normal breakdown of the neurotransmitter acetylcholine [10].

Chemical warfare agents (CWAs) are highly poisonous and their presence may cause diverse effects not only on living organisms but also on environment. Therefore, their detection and removal in a short time span is very important. Chemical warfare agents are highly poisonous and their presence may cause diverse effects not only on living organisms but also on environment. Therefore, their detection and removal in a short time span is very important [20]. Nevertheless, chemical warfare agents have found extensive usage in various industries such as ore refining, metal cleaner, organic synthesis, pharmaceutical, dye and pesticide industries [21,22].

The most widely accepted chemical structures of these A-series agents were reported by the Russian chemist Vil Mirzayanov, who claims participation in the Soviet chemical weapons program named FOLIANT which developed the A-series [19,23]. Some theoretical studies have been done those reported structures [24,25] although still some secrets in their synthesis, analysis and testing remain.

2. Method of Calculation

In the present study, all the initial optimizations of the structures leading to energy minima have been achieved first by using MM2 method which is then followed by semi empirical PM3 self consistent fields molecular orbital method [26-28]. Afterwards, the structure optimizations have been achieved within the framework of Hartree-Fock and finally by using density functional theory (DFT) at the level of B3LYP/6-31++G(d,p) [29,30]. Note that the exchange term of B3LYP consists of hybrid Hartree-Fock and local spin density (LSD) exchange functions with Becke's gradient correlation to LSD exchange [31]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [32] and Lee, Yang, Parr (LYP) correlation correction functional [33]. In the present study, the normal mode analysis for each structure yielded no imaginary frequencies for the $3N–6$ vibrational degrees of freedom, where N is the number of atoms in the system. This search has indicated that the structure of each molecule considered corresponds to at least a local minimum on the potential energy surface. Furthermore, all the bond lengths have been thoroughly searched in order to find out whether any bond cleavage occurred or not during the geometry optimization process. All these computations were performed by using SPARTAN 06 [34].

3. Results and Discussion

The present study deals with some Novichok agents namely, A-230, A-232, A-234, A-242 and A-262. Figure 1 shows the optimized structures and the direction of the dipole moment vectors of the agents considered. The figure also indicates the chirality of the phosphorous atom.

Structures A-230 and A-242 have some resemblance around the phosphorous moiety. The structures A-232 and A-262 possess methoxide groups linked to the phosphorous atom. They all have varying size of the alkyl groups as well.

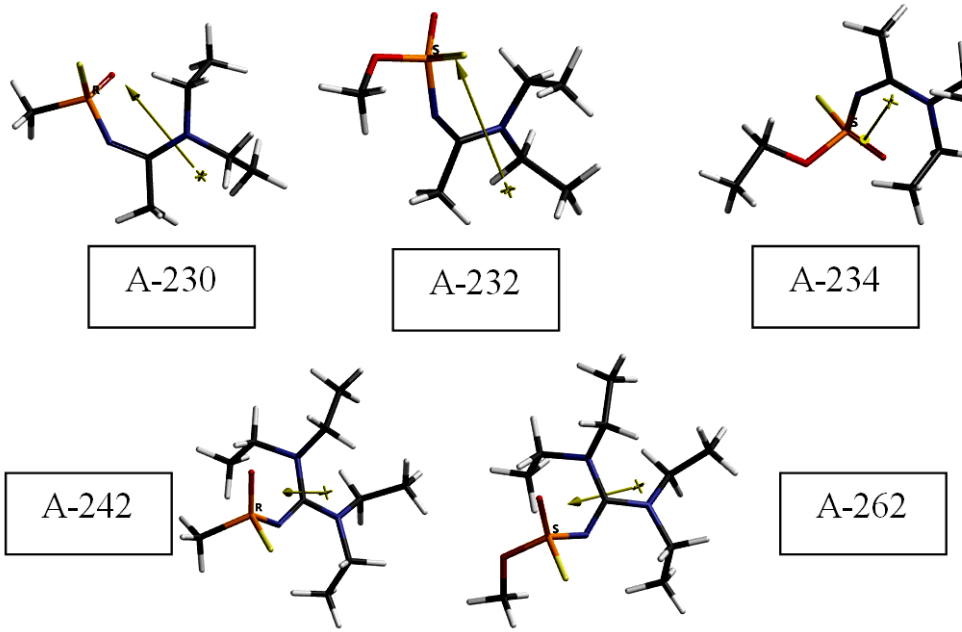


Figure 1. Optimized structures of the Novichok agents considered.

Table 1 shows some of the standard thermo chemical formation data of the Novichok agents considered. The data reveal that the standard heat of formation (H^o) values of all the agents are exothermic and they are favored according to their G^o values.

Table 2 shows some energies of the Novichok agents considered where E, ZPE and E_C stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively. According to the data, they are all electronically stable structures.

Table 1. Some thermo chemical properties of the Novichok agents considered.

Agent	Hº	Sº (J/molº)	Gº
A-230	-2368690.489	458.73	-2368827.26
A-232	-2566192.962	472.74	-2566333.91
A-234	-2669356.134	490.59	-2669502.40
A-242	-2823415.835	533.88	-2823574.99
A-262	-3020922.244	548.10	-3021085.66

Energies in kJ/mol.

T**able 2.** Some energies of the Novichok agents considered.

Agent	E	ZPE	E_C
A-230	-2369326.09	621.24	-2368704.85
A-232	-2566841.37	634.23	-2566207.14
A-234	-2670080.90	708.83	-2669372.07
A-242	-2824325.05	888.35	-2823436.70
A-262	-3021844.24	901.10	-3020943.14

Energies in kJ/mol.

Table 3 displays some of the calculated properties of the Novichok agents considered. Note that a net dipole moment which is the vector sum of individual bond dipoles are a function of bond charges (charges on the atoms linked by the bond considered) and the bond distance. The order of dipole moments is A-230< A-242< A-262< A-232< A-234. Note that these molecules are different from each other not only by the alkyl groups they possess but also substituents around the phosphorous atom and the imino carbon atom. The dipole moment provides a measure of the extent to which charge distributed in a molecule. The magnitude of the dipole moment also depends on the extent to which charge is separated. All these factors dictate the magnitudes and the direction of the resultant dipole moments.

The polarizability is defined according to a multivariable formula [34] which is the functions of van der Waals volume and hardness, respectively. The later one is dictated by energies of the highest occupied (HOMO) and the lowest unoccupied (LUMO) molecular orbitals [34]. Consequently, the polarizability order becomes A-230< A-232< A-234< A-242< A-262.

On the other hand, as the area, volume and ovality values progressively increase from A-230 to A-262, the PSA values vary subtly as A-230< A-242< A-234< A-232< A-262, because the polar surface area (PSA) is defined as the amount of molecular surface area arising from polar atoms (N,O) together with their attached hydrogen atoms. Thus, the PSA values differ from each other even though the same kind of atoms might be considered due to the fact that they might be influenced by electronic factors differently at different positions.

Table 3. Some properties of the Novichok agents considered.

Agent	Formula	Area (Å²)	Volume (Å³)	PSA (Å²)	Ovality	Dipole moment	Polarizability
A-230	$C_7H_{16}FN_2OP$	229.06	199.18	23.629	1.39	5.32	56.11
A-232	$C_7H_{16}FN_2O_2P$	240.63	207.69	31.352	1.42	7.00	56.79
A-234	$C_8H_{18}FN_2O_2P$	263.57	226.28	30.601	1.47	7.20	58.30
A-242	$C_{10}H_{23}FN_3OP$	306.23	268.57	24.493	1.52	5.63	61.79
A-262	$C_{10}H_{23}FN_3O_2P$	315.97	276.91	33.153	1.54	6.54	62.45

Dipole moments in debye units. Polarizabilities in 10^{-30} m^3 units.

Figure 2 shows the calculated bond lengths of the Novichok agents considered. The data reveal that the respective bond lengths of alkyl backbone do not vary much from one structure to the other. However, the bond lengths incident to the phosphorous atom are not so. It seems bulkiness and conformation of the alkyl groups has some influence on the pharmacophoric moiety.

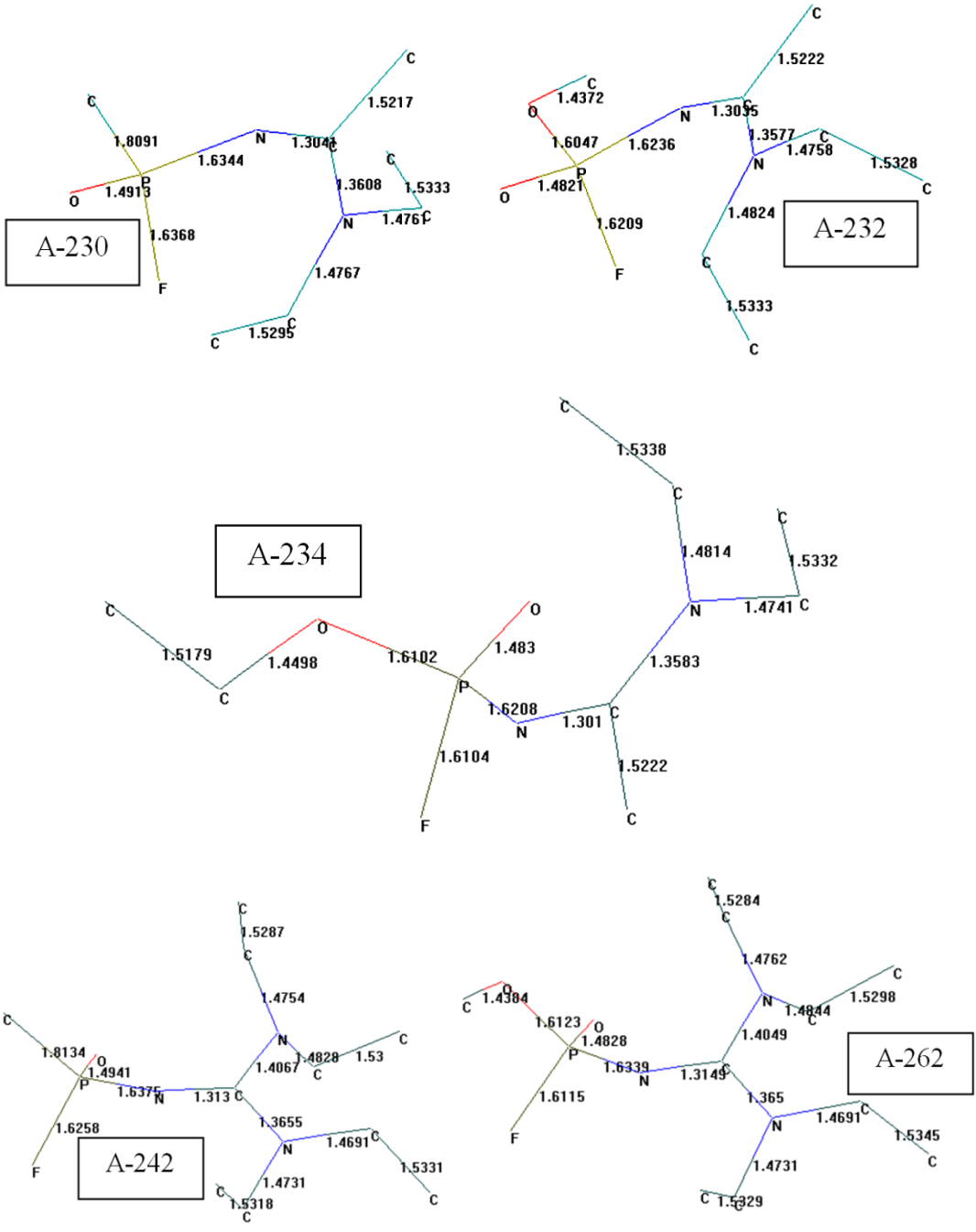
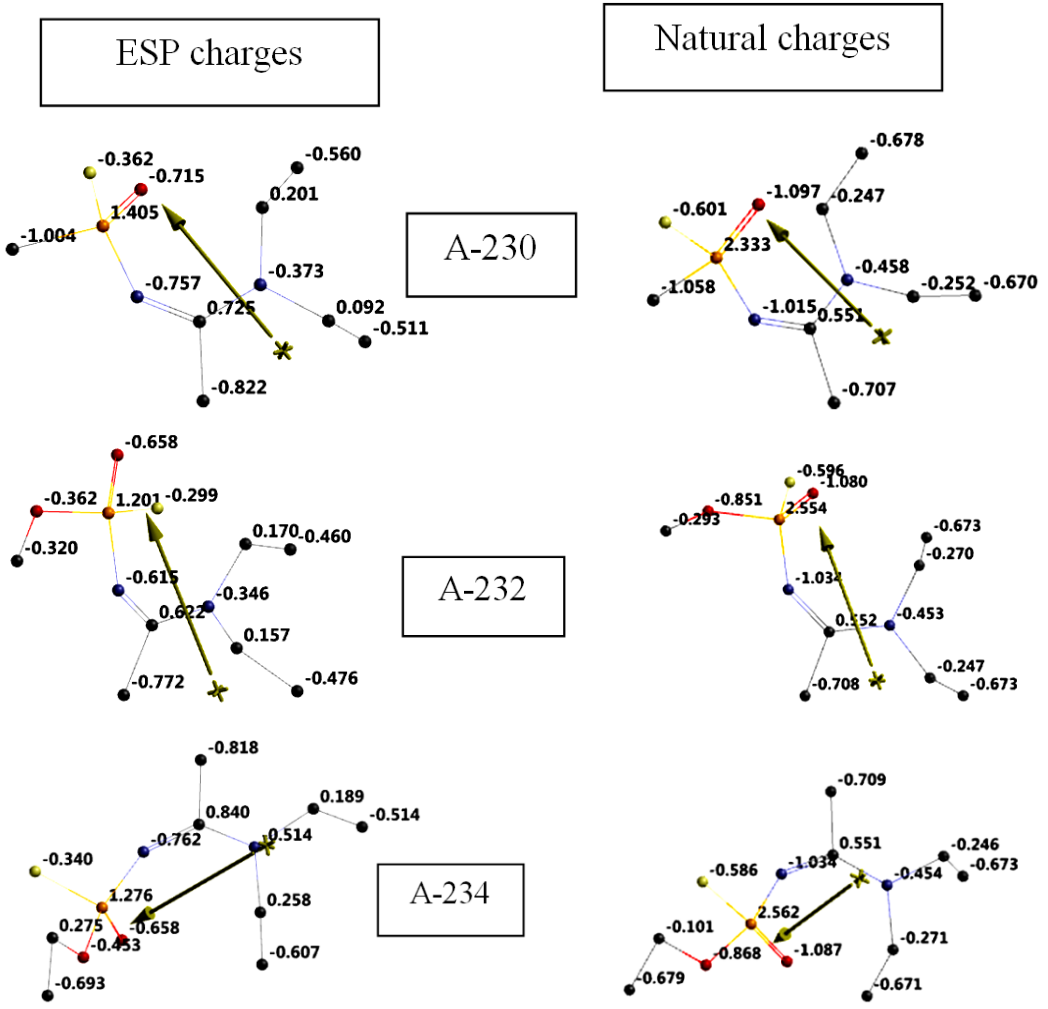


Figure 2. Calculated bond lengths of the Novichok agents considered (hydrogens not shown).

Figure 3 displays the electrostatic potential (ESP) and the natural charges of the species considered. It is to be noted that the ESP charges are obtained by the program based on a numerical method that generates charges that reproduce the electrostatic potential field from the entire wavefunction [34]. Namely, atomic charges chosen to best match the electrostatic potential at points surrounding a molecule, subject to overall charge balance [35].

Figure 4 stands for the electrostatic potential maps of the agents considered. It is noteworthy that an electrostatic potential map is a graph that shows the value of electrostatic potential on an electron density isosurface.



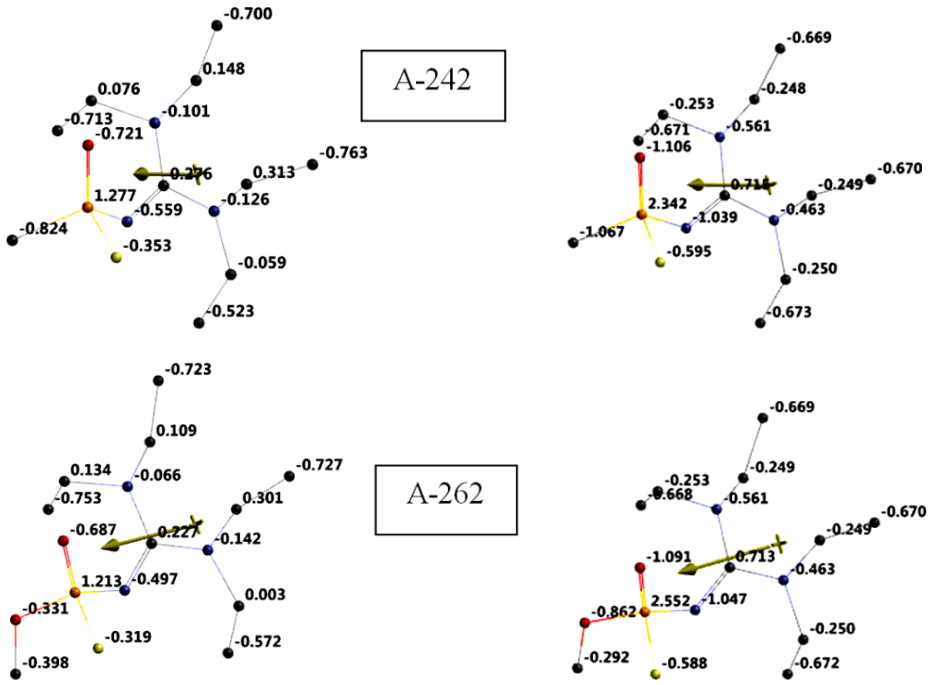


Figure 3. ESP and natural charges on the atoms of the Novichok agents considered (Hydrogens not shown).

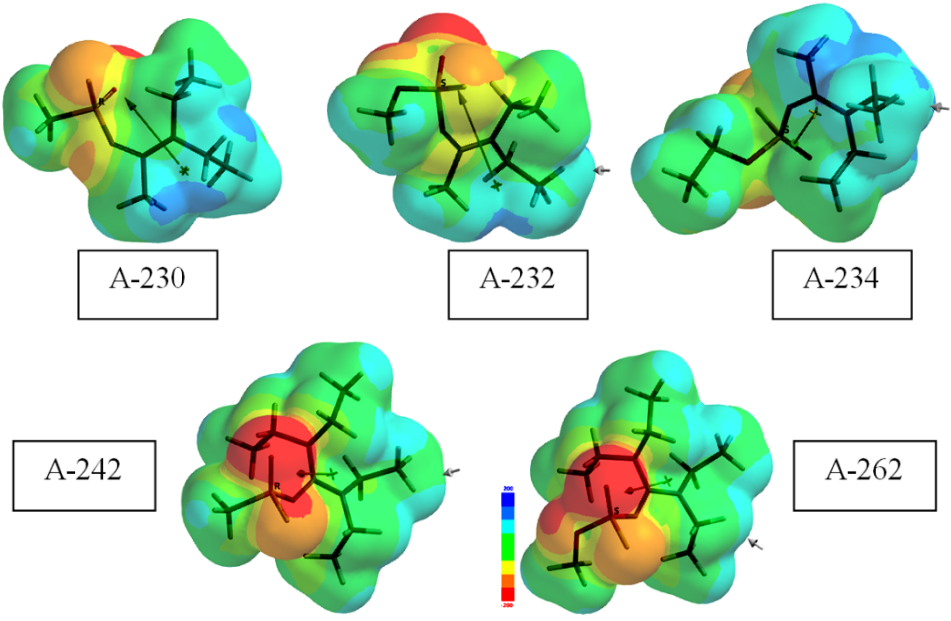


Figure 4. ESP maps of the Novichok agents considered.

Figure 5 shows the local ionization potential maps of the molecules considered where conventionally red/reddish regions (if any exists) on the density surface indicate areas from which electron removal is relatively easy, meaning that they are subject to electrophilic attack. Note that a local ionization potential map is a graph of the value of the local ionization potential on an isodensity surface corresponding to a van der Waals surface.

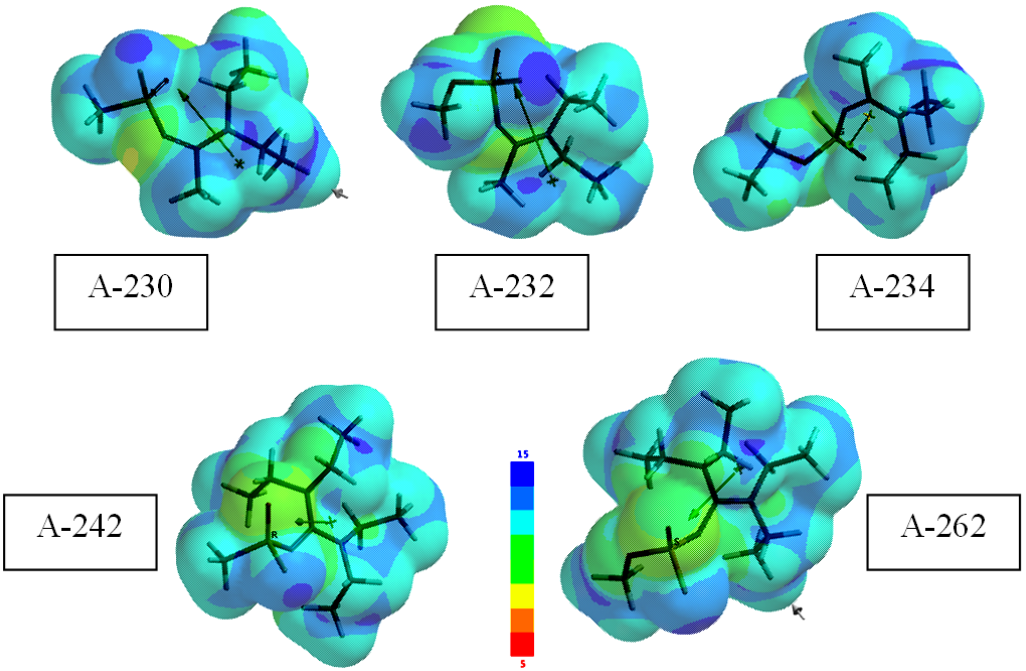


Figure 5. Local ionization potential maps of the Novichok agents considered.

Figure 6 shows the LUMO maps of the species considered. Note that a LUMO map displays the absolute value of the LUMO on the electron density surface. It indicates the most likely regions for the electrons to be added and would be expected to correlate with the likelihood of nucleophilic attack. The blue color (if any exists) stands for the maximum value of the LUMO and the red colored region, associates with the minimum value.

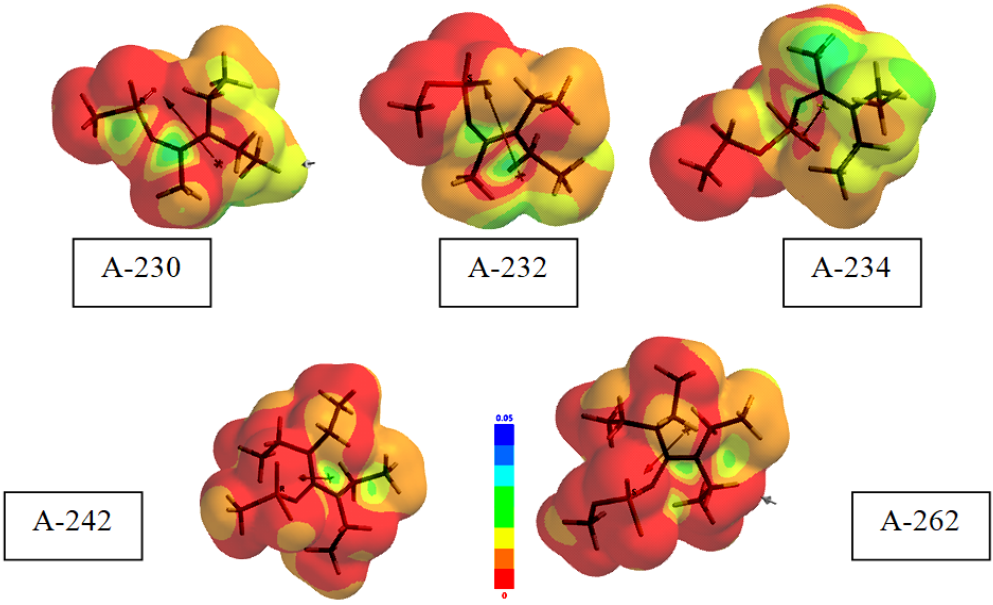


Figure 6. LUMO maps of the Novichok agents considered.

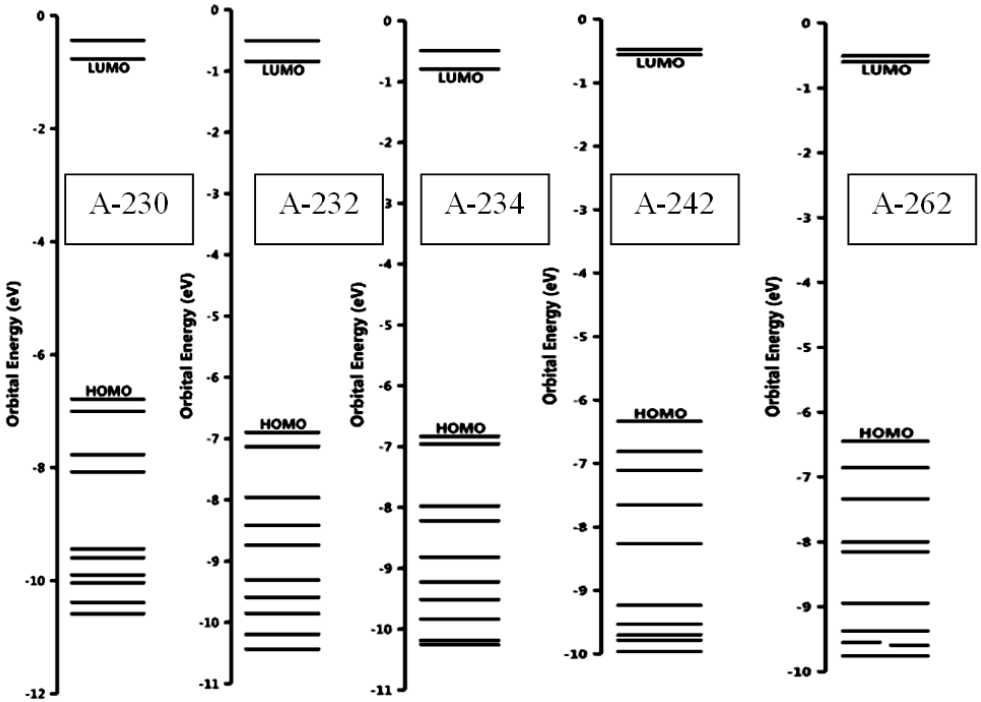


Figure 7. Some of the molecular orbital energy levels of the Novichok agents considered.

Figure 7 displays some of the molecular orbital energy levels of the Novichok agents considered. Note that distribution of the inner lying orbital energies is related to the thermal stability. The HOMO, LUMO energies and the interfrontier molecular orbital energy gap values, Δε, ($\Delta\varepsilon=\varepsilon_{LUMO}-\varepsilon_{HOMO}$) of the agents considered are shown in Table 4.

The HOMO and LUMO energies follow the same algebriacal order that is A-232< A-234< A-230< A-262< A-242. Various bonding and nonbonding interactions prevalent in the structures dictate the orders obtained. The order of Δε values is A-242< A-262< A-230< A-234< A-232.

Table 4. The HOMO and LUMO energies the Novichok agents considered.

	Novichok agents				
	A-230	A-232	A-234	A-242	A-262
LUMO	-74.11	-81.56	-76.71	-53.62	-57.25
HOMO	-654.95	-665.68	-659.17	-611.11	-621.52
Δε	580.84	584.12	582.46	557.49	564.27

Energies in kJ/mol.

The chemical function descriptors (CFD) of Novichok agents considered are shown in Figure 8, where HBA stands for hydrogen bond acceptor. Note that CFDs are attributes given to a molecule in order to characterize or anticipate its chemical behavior.

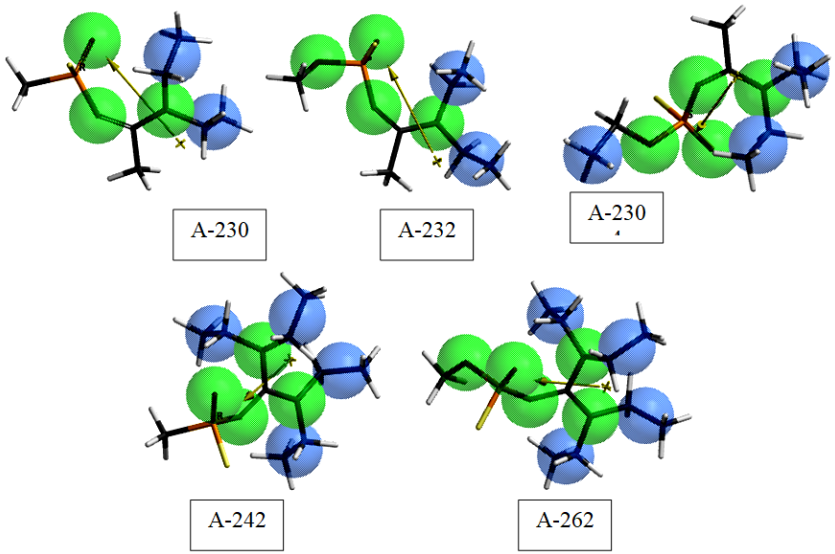
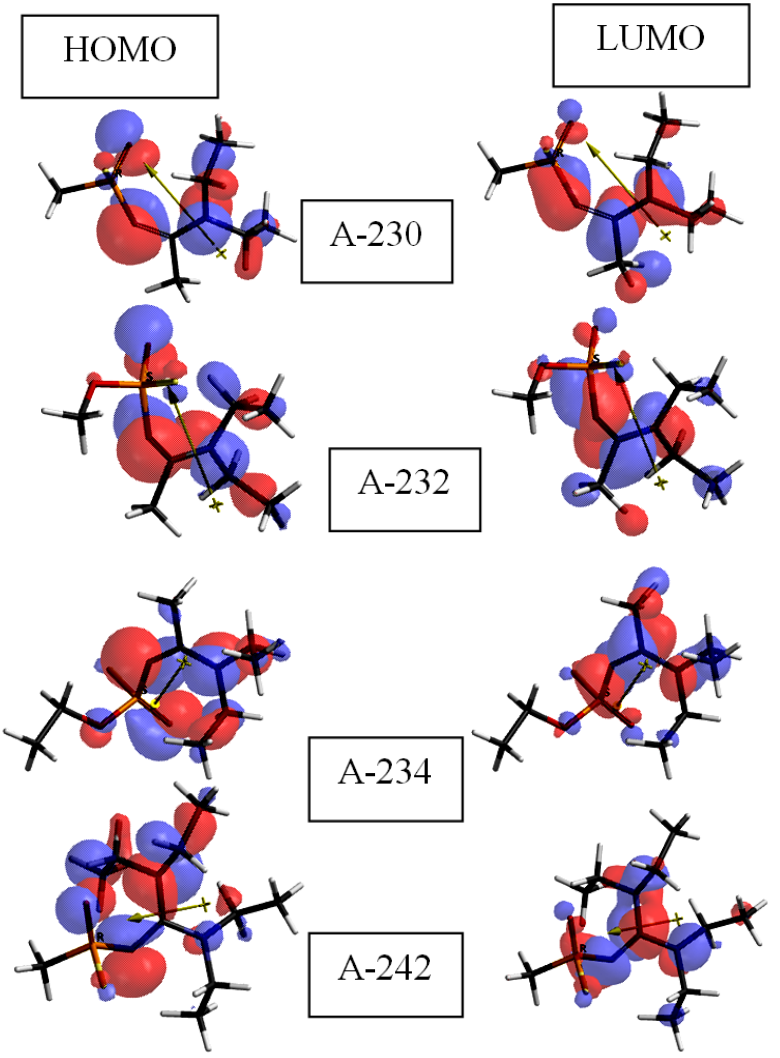


Figure 8. The CFD patterns of the Novichok agents considered. (Green: HBA, Bluish: Hydrophobe).

Figure 9 displays the HOMO and LUMO patterns of the Novichok agents considered. As seen in the figure the alkyl or alkoxy groups linked to the phosphorous atom either do not contribute the HOMO and LUMO at all or the contribution is very little.

Figure 10 displays some representative calculated UV-VIS spectra (TDDFT) of the Novichok agents of interest. All the spectrums reside in the ultraviolet region of the spectrum. Since the agents considered do not have any extended conjugation, their spectra are confined to UV-region only.



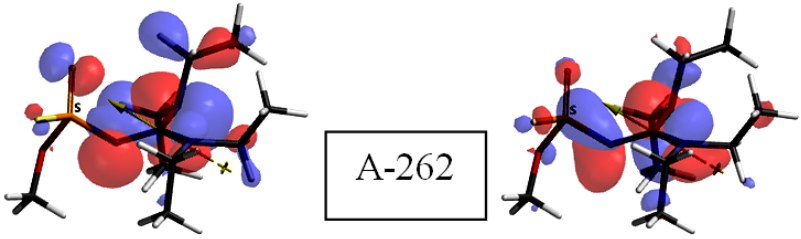


Figure 9. The HOMO and LUMO patterns of the Novichok agents considered.

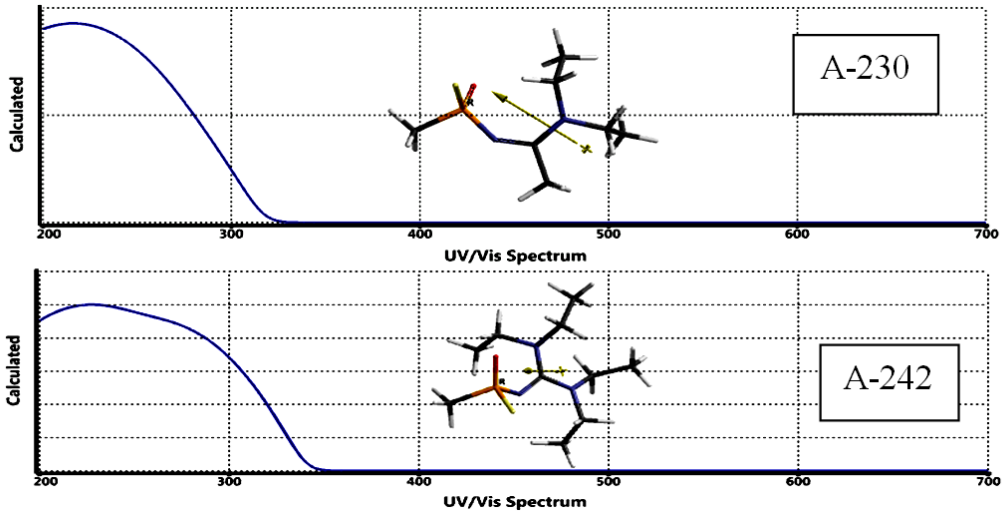


Figure 10. Two representative calculated UV-VIS spectra of the Novichok agents considered.

Interaction with Zn^{+2}

Zinc atom has the electronic configuration of [Ar] $3d^{10}4s^2$ in the ground state [36]. Zinc is a nutritionally essential mineral needed for catalytic, structural, and regulatory functions in the body and involved in cell growth and division, immune function, enzyme reactions, DNA synthesis, and protein production. The zinc cation occurs in many enzyme systems in various living organisms [37,38] but there are various agents which bind the zinc cation in metabolism [39].

Figure 11 shows the optimized structures and the direction of their dipole moment vectors of Zn^{+2} composites of the Novichok agents considered. As seen in the figure phosphonate group and the substituents orient themselves around the cation to minimize the energy. Consequently, the dipole moment in each case points to a different direction.

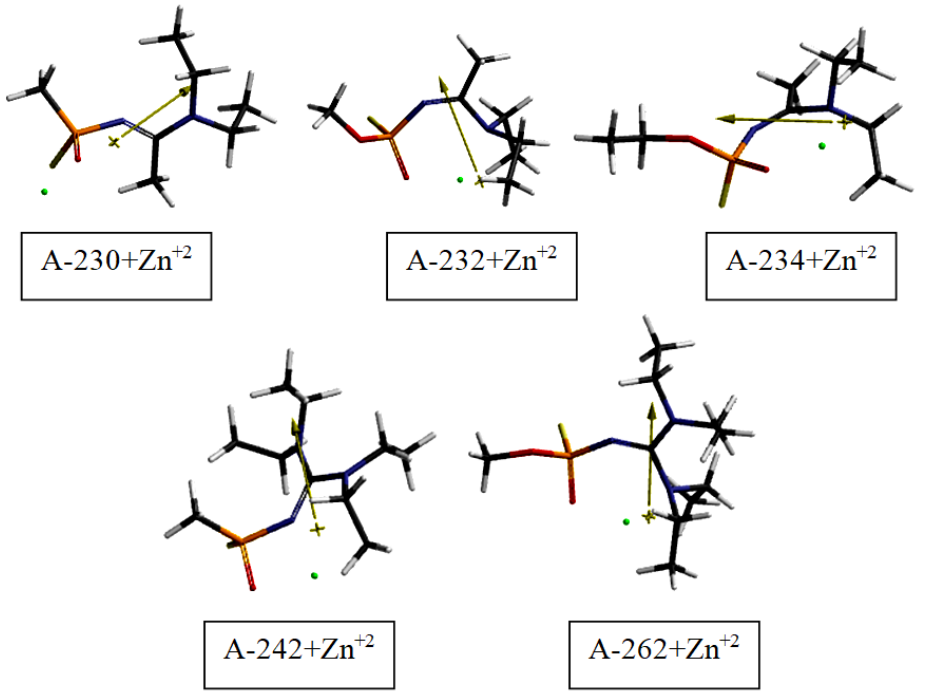


Figure 11. Optimized structures of Zn^{+2} composites of the Novichok agents considered.

Table 5 shows some properties of composites of the Novichok agents considered. As seen in the table, all the properties, except the dipole moments and the PSA values progressively increase as the sizes increase. The dipole moments fluctuate because the dipole moment is the vector sum of individual bond dipoles which are a function of bond charges and bond lengths in between them.

Table 5. Some properties of composites of the Novichok agents considered.

Composite	Dipole	Area (Å²)	Volume (Å³)	PSA (Å²)	Ovality	Polarizability
A-230+Zn^{+2}	22.72	247.35	206.39	20.925	1.46	57.84
A-232+Zn^{+2}	3.47	252.00	214.68	29.602	1.45	57.65
A-234+Zn^{+2}	6.11	273.01	233.36	29.335	1.49	59.20
A-242+Zn^{+2}	9.77	305.25	273.45	20.813	1.50	62.74
A-262+Zn^{+2}	7.87	320.73	282.82	28.986	1.54	63.35

Dipole moments in Debye units.

The polar surface area (PSA) is the amount of molecular surface area arising from polar atoms (N,O) together with their attached hydrogen atoms. They might be influenced by electronic factors differently at different positions. Hence, the PSA values differ from each other even for the same kind of atoms considered.

Table 6 shows some thermo chemical properties of composites of the Novichok agents considered. The data reveal that the standard heat of formation (H^o) values of all the composite agents are exothermic and they are favored according to their G^o values.

Table 6. Some thermo chemical properties of composites of the Novichok agents considered.

Composite	H^o	S^o (J/mol^o)	G^o
A-230+Zn^{+2}	-7038127.593	491.91	-7038274.255
A-232+Zn^{+2}	-7235730.648	499.41	-7235879.541
A-234+Zn^{+2}	-7338912.747	514.97	-7339066.288
A-242+Zn^{+2}	-7493014.221	551.97	-7493178.789
A-262+Zn^{+2}	-7690560.563	570.01	-7690730.488

Energies in kJ/mol.

Table 7 shows some energies of the composites of Novichok agents considered. According to the data, they are all electronically stable structures.

Table 7. Some energies of composites of the Novichok agents considered.

Composite	E	ZPE	E_C
A-230+Zn^{+2}	-7038724.22	621.91	-7038102.31
A-232+Zn^{+2}	-7236336.51	631.41	-7235705.10
A-234+Zn^{+2}	-7339594.81	706.01	-7338888.80
A-242+Zn^{+2}	-7493889.00	894.78	-7492994.22
A-262+Zn^{+2}	-7691445.97	904.74	-7690541.23

Energies in kJ/mol.

Figure 12 displays the calculated bond lengths of composites of the Novichok agents of the present interest. As compared to the data presented in Figures 2 and 12, the

influence of the cation on the bond lengths of the composites is obvious. Even among the composites themselves, the P-F, P-N and P-O bond lengths are highly different. One of the reasons, is some electron population transfer occurs in each case from the organic part

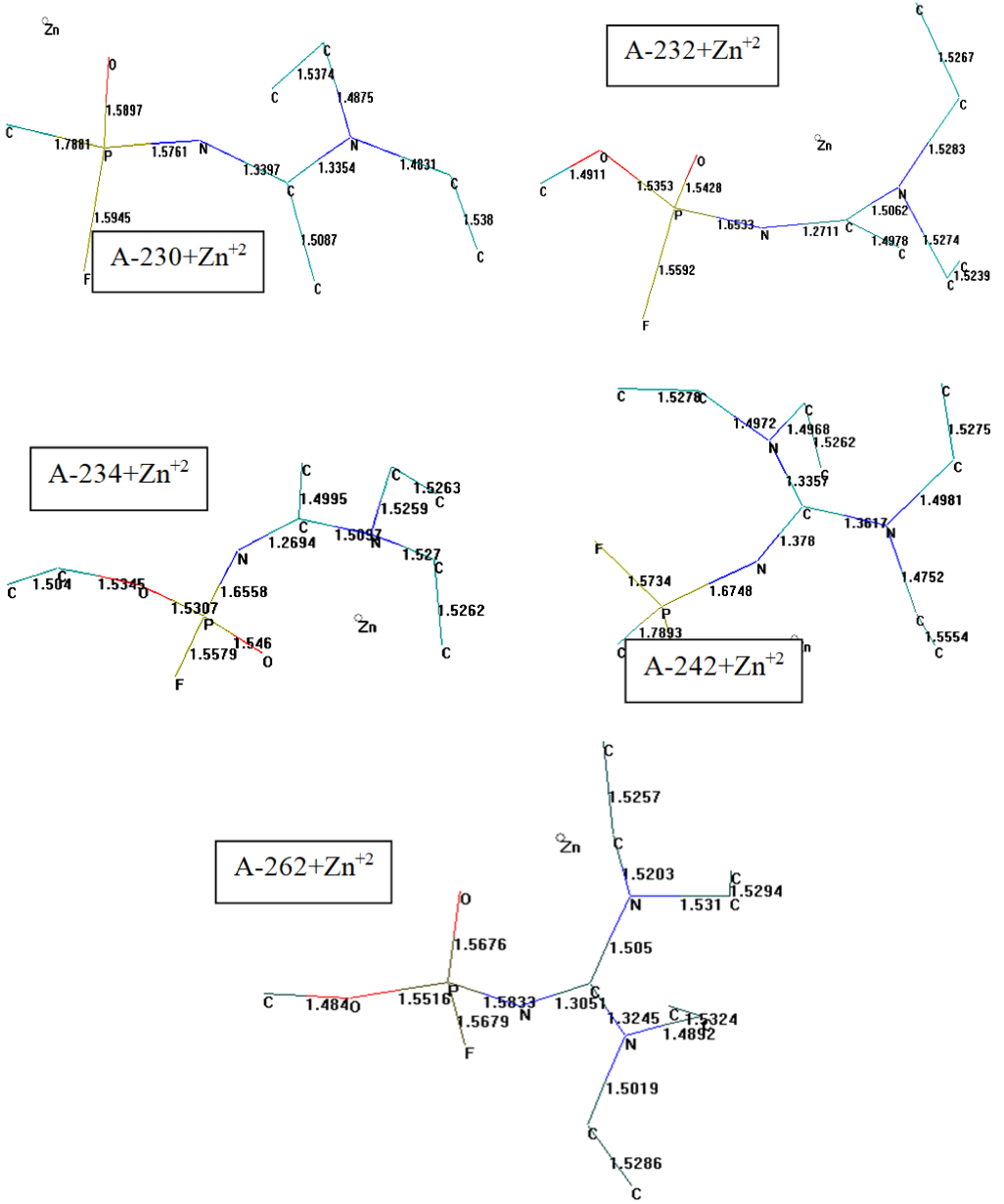


Figure 12. Calculated bond lengths of composites of the Novichok agents considered (hydrogens not shown).

of the composite to the zinc cation. As seen in Figure 13, the cation in each case possesses a partial charge less than the initial formal charge of it. The charge order of the cation is A-232+Zn^{+2}> A-234+Zn^{+2}> A-242+Zn^{+2}> A-262+Zn^{+2}> A-230+Zn^{+2}. The transfer of electron population should require some degree of overlap of certain orbitals which depends on the electronic surrounding hence the structural environment.

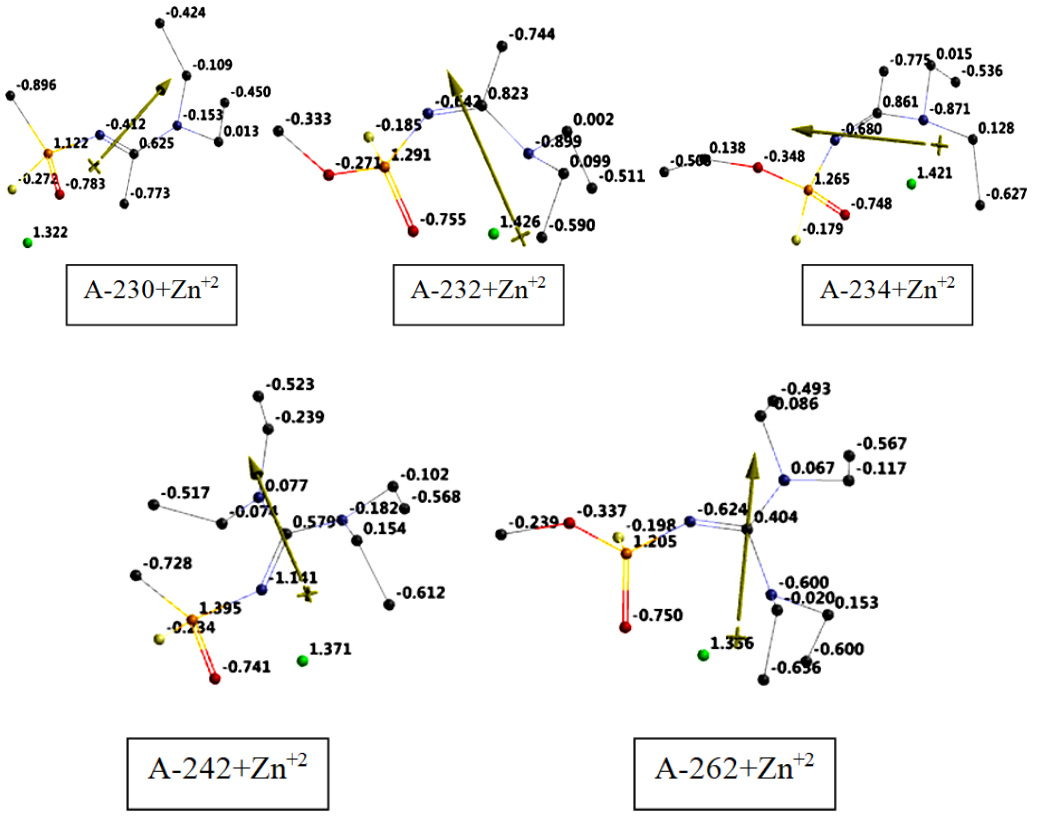


Figure 13. ESP charges on the atoms of Zn^{+2} composites of the Novichok agents considered (Hydrogens not shown).

Figure 14 displays the LUMO maps of Zn^{+2} composites of the Novichok agents considered. Note that in a LUMO map the blue color stands for the maximum value of the LUMO and the red colored region, associates with the minimum value. The blue colored regions indicate the most likely regions for the electrons to be added and would be expected to correlate with the likelihood of nucleophilic attack.

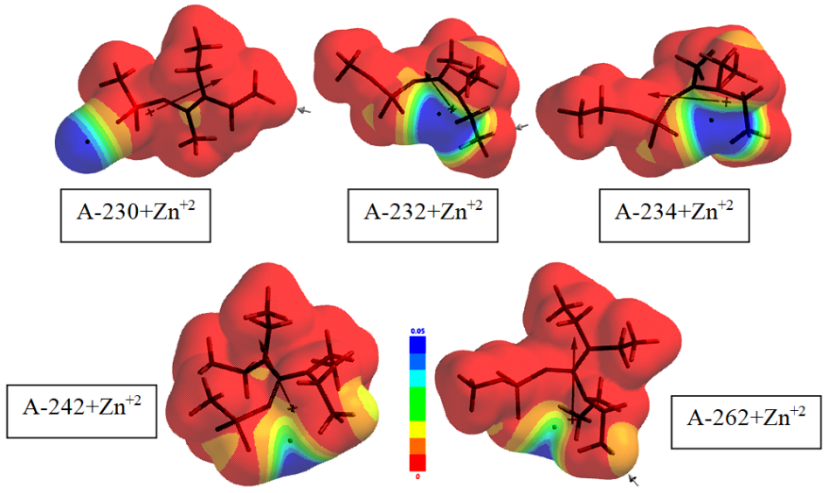


Figure 14. The LUMO maps of Zn^{+2} composites of the Novichok agents considered.

Figure 15 displays some of the molecular orbital energy levels of Zn^{+2} composites of the Novichok agents considered.

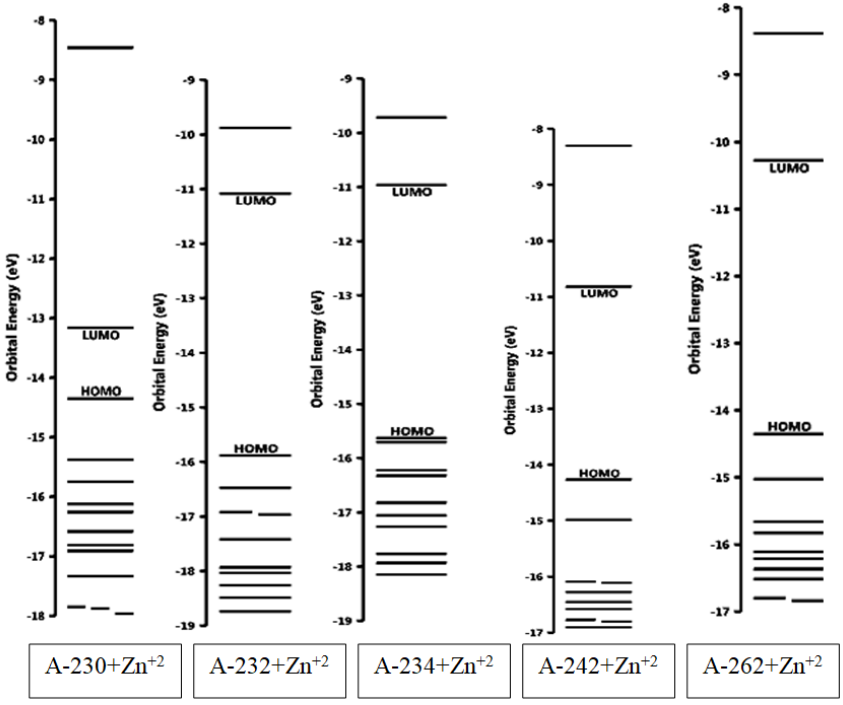


Figure 15. Some of the molecular orbital energy levels of Zn^{+2} composites of the Novichok agents considered.

Table 8 shows the HOMO, LUMO energies and Δε values of the composites of the Novichok agents considered.

Table 8. The HOMO and LUMO energies of the composites of the Novichok agents considered.

	Composites of the Novichok agents considered.				
	A-230+Zn^{+2}	A-232+Zn^{+2}	A-234+Zn^{+2}	A-242+Zn^{+2}	A-262+Zn^{+2}
LUMO	-1269.81	-1069.42	-1057.55	-1043.95	-991.20
HOMO	-1384.57	-1531.96	-1507.71	-1376.40	-1384.76
Δε	114.76	462.54	450.16	332.45	393.56

Energies in kJ/mol.

The HOMO energy orders (algebraic) is A-232+Zn^{+2}< A-234+Zn^{+2}< A-262+Zn^{+2}< A-242+Zn^{+2} whereas the LUMO energies follow the order of A-230+Zn^{+2}< A-232+Zn^{+2}< A-234+Zn^{+2}< A-242+Zn^{+2}< A-262+Zn^{+2}. The HOMO energies with the exception of A-262+Zn^{+2} composite increases with the sizes of the molecules. On the other hand, the LUMO energy order goes parallel to the sizes of the composite molecules. These molecules are actually differ from each other by the number of alkyl groups contained. Note that alkyl groups are inductively electron donors and their presence additively should increase the HOMO and LUMO energies at unequal extents [40,41]. On the other hand, the cation should have some perturbative effect on the molecular orbitals as well as on their energies, by lowering the energy levels. The overall effect dictates the orders of the HOMO and LUMO energy levels. Consequently, the order of inter frontier molecular orbital energy (Δε) levels becomes; A-230+Zn^{+2}< A-242+Zn^{+2}< A-262+Zn^{+2}< A-234+Zn^{+2}< A-232+Zn^{+2}.

Figure 16 shows the HOMO and LUMO patterns of the composite Novichok agents considered. As seen in the figure, with exception of A-234+Zn^{+2} case, the alkyl or alkoxy groups on the phosphonate moiety do not contribute to the HOMO. They do not contribute at all or very little to the LUMO. The same conclusion can be drawn for contribution of the rest of the alkyl groups as well.

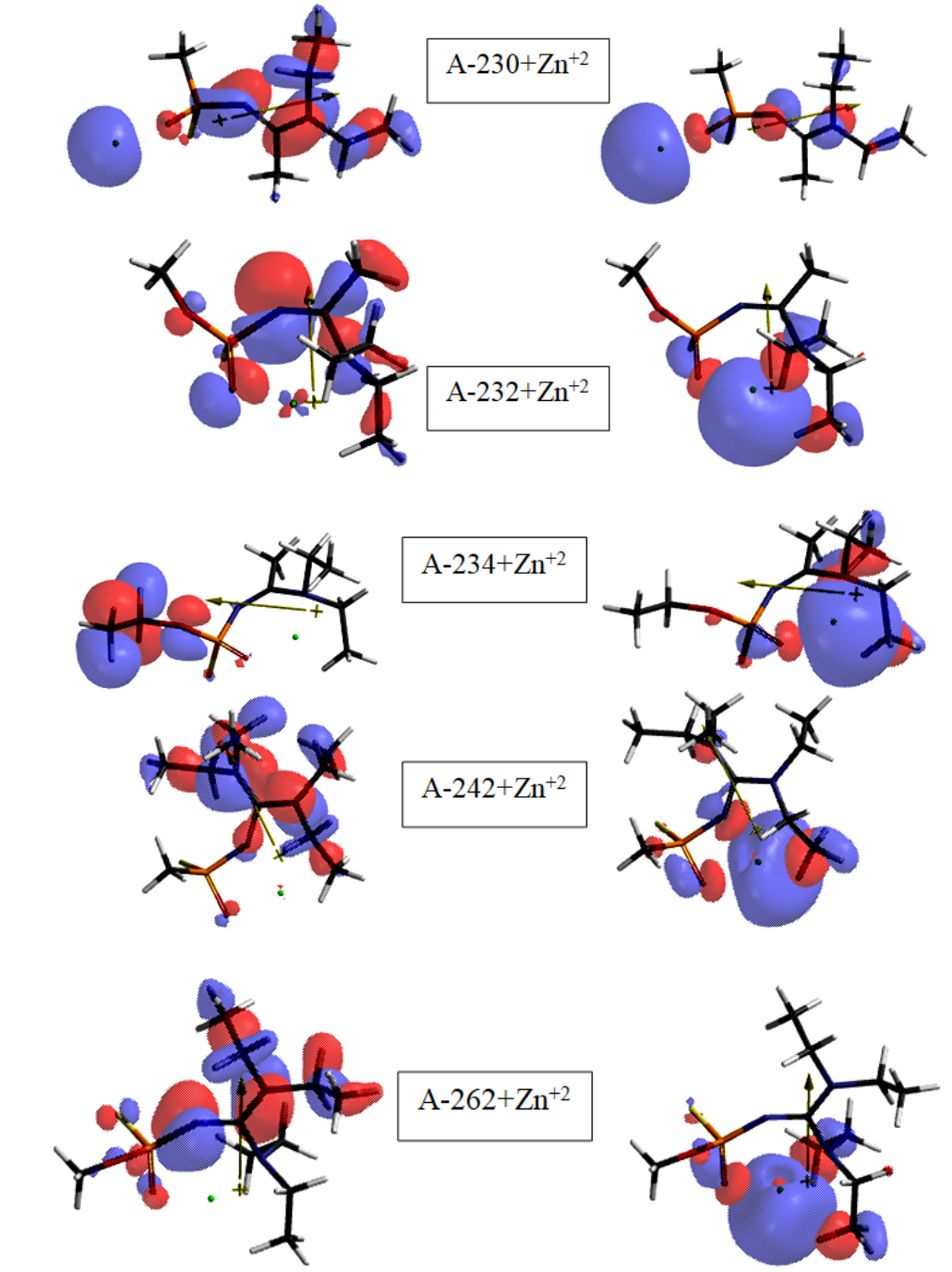


Figure 16. The HOMO and LUMO patterns of the composite Novichok agents considered.

Figure 17 displays the CFD patterns of the composite Novichok agents considered. Comparing with Figure 8 (includes the parent agents), one observes that presence of Zn^{+2} causes to change the CFD patterns in the composites. For instance, nitrogen atom bound to phosphorous changes its character from HBA to HBA, +ionizable forms in the corresponding composite.

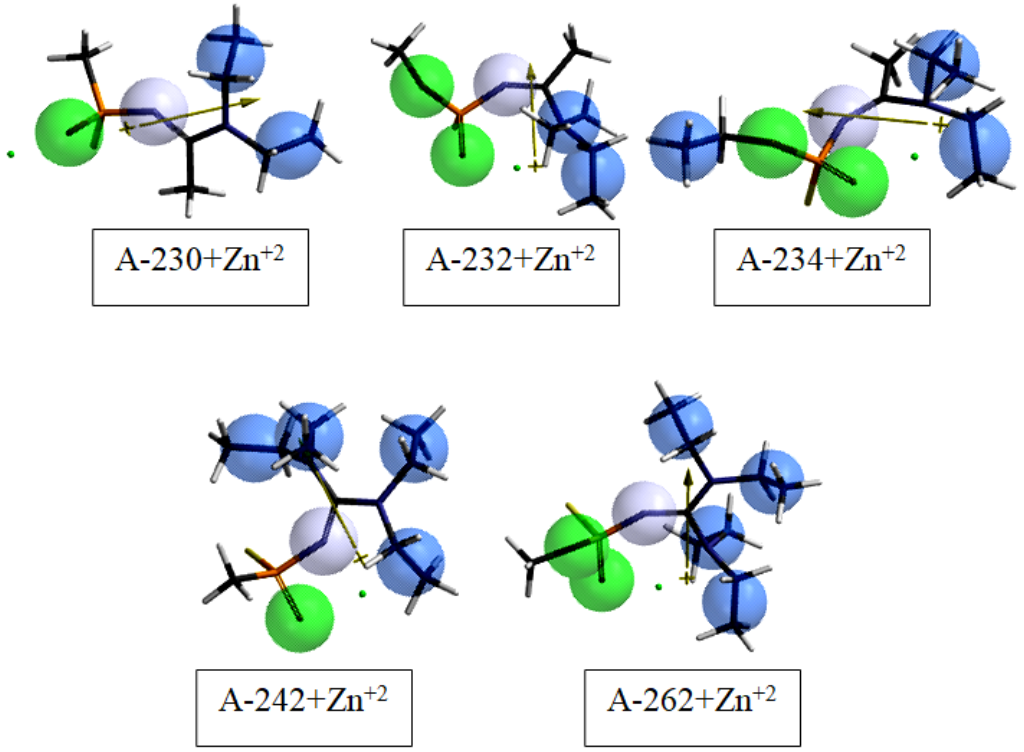
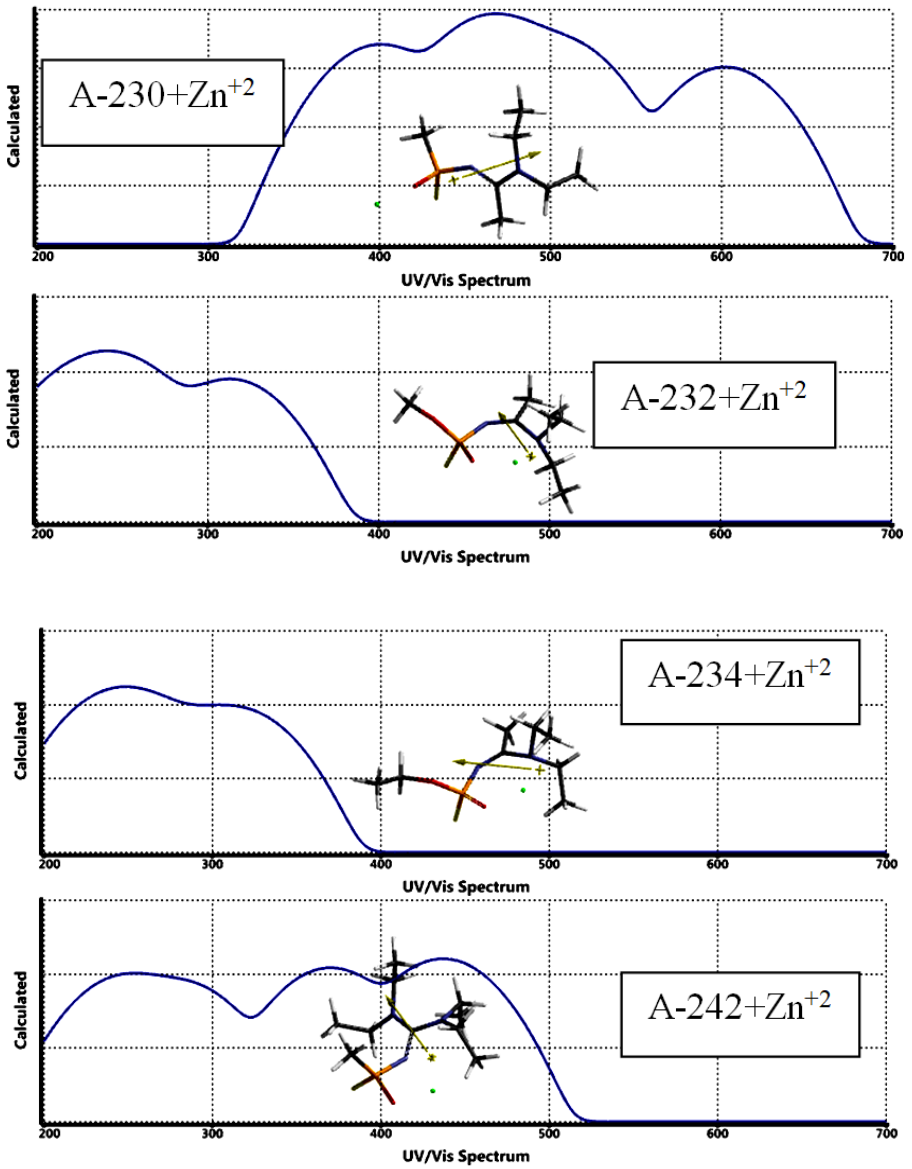


Figure 17. The CFD patterns of the composite Novichok agents considered. (Green: HBA, Purplish: HBA, +ionizable, Blue: Hydrophobe).

Figure 18 displays the TDDFT UV-VIS spectra of the composite Novichok agents considered. As seen in the figure, with the exceptions of A-230+Zn^{+2} and A-242+Zn^{+2} composites, the spectra are mostly confined to ultraviolet region whereas the exceptional ones lie mostly (A-230+Zn^{+2}) and partly (A-242+Zn^{+2}) in the visible part. Note that A-230+Zn^{+2} and A-242+Zn^{+2} cases possess the two succeccesively the smallest interfrontier molecular orbital energy gaps ($\Delta\varepsilon$) values. Hence, a bathochromic effect is expected for their spectrums as expected by calculations. On the other hand, A-232+Zn^{+2} and A-234+Zn^{+2} possess the largest two $\Delta\varepsilon$ values, thus their spectrums lie in the UV region.

Table 9 shows the interaction energies between the zinc cation and the Novichok agents, based on the corrected total electronic energies (see Tables 2 and 7) of the species considered. Table reveals that as the size increases, the interaction becomes more pronounced. Since the interaction with the cation occurs nearby the phosphonate moiety, steric effects around the hetero atoms might be influential. Note that in each case the dipole moment vector points to the phosphonate moiety (see Figure 1).



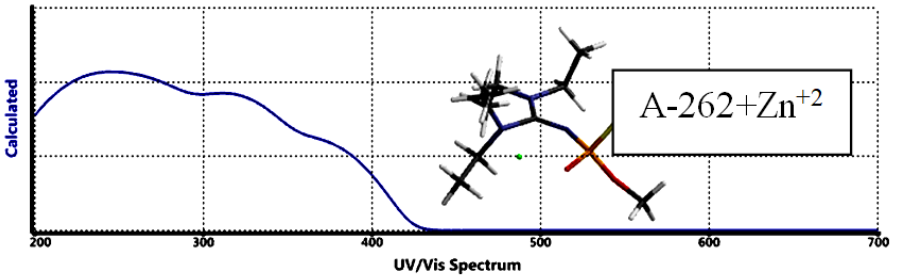


Figure 18. The calculated UV-VIS spectra of the composite Novichok agents considered.

Table 9. Relative interaction energies of the considered Novichok agents with the Zn^{+2} ion.

A-230	A-232	A-234	A-242	A-262
0	-100.50	-119.27	-160.06	-200.63

Energies in kJ/mol.

4. Conclusion

In the present computational study, within the restrictions of DFT study at the level of B3LYP/6-31++G(d,p), five A-series Novichok agents and their Zn^{+2} composites have been considered. Zinc is one of the most crucial cation in metabolism. These mysterious warfare agents still possess some secrets in their synthesis, analysis and testing. The present results indicate that in the vacuum conditions, all the structures (the agents and their composites) are characterized with exothermic heat of formation and favorable Gibbs free energy of formation values and they are electronically stable. This study aimed to get better understanding of their physicochemical properties at the molecular level and provide information for distinction of them.

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