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Flexible Models of Novichok Agents (A230, A232, A234) for Molecular Dynamics Simulations

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Abstract

Treatment and antidote research for chemical warfare agents (CWAs) is an issue that has concerned the whole western civilization for many years. Specifically, relating to the fourth generation of CWAs, including the Soviet-manufactured Novichok agents, possible deployment has or may be an issue in the near future due to the global terrorism threat. Flexible models for Novichok agents (A230, A232 & A234) have been created for the first time, using a new step-by-step approach, for molecular dynamics simulations. The new models were tested against experiments for available thermodynamic properties. An array of thermodynamic and structural properties is presented but not compared with other simulations and experimental studies due to the lack of them in the literature. Presenting calculated properties for these controlled substances might be vital in the effort for new ways to treat the threat from them.

Keywords: Nerve agents, Novichok, Molecular Dynamics study, Thermodynamic properties, Diffusion Coefficient, Structural Properties

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1. Introduction

The deliberate use of chemical warfare agents (CWAs) to cause harm to life and health of populations as well as to the environment and infrastructure, is among the most dangerous threats in the modern world. The small but non-negligible number of incidents of chemical weapons deliberate use, which have occurred till today increases the global concern about terrorism attack risks with deplorable effects [1-3].

Novichok agents are a class of nerve agents, and they are the novel generation of chemical warfare compounds [4], developed by the Soviet Union during the Cold War. The use of a Novichok agent in Salisbury in March 2018 (Skripal case) is considered the most recent use of CWAs. These series of today nerve agents represents a matter of concern in the field of CWAs.

According to a part of available information for Novichok agents (A230, A232, A234), we can allege that these compounds belong among the most toxic synthetic agents ever [5]. Despite the lack of availability of these compounds for study, a series of studies have been conducted on their physical properties [6-8], toxicity [9] and simulated toxicity in silico [10], degradation conditions, and corresponding pathways[9-10].

Nepovimova and Kuca[11] have reviewed available Eastern and Western data about the A-agents and their precursors NOVICHOKs, including their history, synthesis, physical-chemical properties, pharmacological characteristics and clinical manifestation. Furthermore they conclude that only very little information is available about physical-chemical properties of NOVICHOKs[4,7,12-14].

Bhakhoa et al [15] employed computational methods to study (i) the molecular, spectroscopic, electronic and toxicity properties, (ii) poisoning action and antidotes based on model reactions, and (iii) hydrolysis and thermal degradation of A234 using the chemical structure proposed by Mirzayanov [12]. Some of these parameters were compared with GB, VR and VX. GB is the military acronym for Sarin, a highly toxic nerve agent, with the chemical name isopropyl methylphosphonofluoridate. VX is the military acronym for Ethyl S-2-diisopropylaminoethyl methylphosphonothiolate and R-VX is a modified form of the chemical VX, where the "R" in the name refers to a specific stereoisomer of the molecule.

In another theoretical work Nasim Mirzaei Motlagh et.al[16] investigated the interaction of A234 molecule with the pristine, Si, Ge, Sc doped and aminated C20 fullerene using density functional theory (DFT) Specifically, they applied M062X/6- 311++G(d,p) level of theory which presents the weak interactions well and basis set superposition errors (BSSE) correction were applied for all their calculations.

A controversial issue in the literature is the exact structure of the Novichok agents. The first putative version of the Novichok structures appeared in two 2007 books authored by D. Hank Ellison [8] and Steven Hoenig[7] , respectively, which described the compounds as being based on alkylphosphorofluoridate scaffolds with carbonimidic substituents (Figures 1,2 and 3). The second version of the Novichok structures was reported by Mirzayanov in his book State Secrets: An Insider's Chronicle of the Russian Chemical Weapons Program [12], where the compounds were described as being based on alkylphospho-namido fluoridate and alkylphosphoramidofluoridate scaffolds [6,17]. Novichok agents are classified as a weapon of mass destruction and is banned under the Chemical Weapons Convention. Its use as a chemical weapon has been documented in several conflicts, and its possession, production, and use are strictly regulated by international law.

In the meantime, theoretical and experimental mass spectrometry studies have appeared that ascertain the

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structures proposed by Ellison and Hoenig [10,15,18]. Therefore, this research work is based on the alternative structures proposed by Hoenig and Ellison.

MD simulations are a useful tool that involves using computer algorithms to model the behavior of materials at the molecular level. In MD simulations, the behavior of individual atoms and molecules is modeled using equations of motion, allowing scientists to study the behavior of materials over time. MD simulations have several advantages over experiments. For example, they allow scientists to study materials that are difficult or impossible to study experimentally, such as our agents due to legal restrictions. They also allow scientists to study the behavior of materials over longer timescales and to study the behavior of individual atoms and molecules in detail. In recent years, from the family of nerve agents only sarin and its most common simulants dimethyl methylphosphonate (DMMP) and diisopropylmethylphosphonate (DIMP) has been studied by simulation techniques [19] (MC, MD).

The extensive literature review [6] shows that there are many uncertainties on this issue that still need to be clarified for Novichok agents. An urgent, complete, and undoubtful elucidation of their structures and properties is essential at this moment for a better understanding of the real risks posed by these compounds and for the development of effective protection. However, to the best of our knowledge, there is no force field, and no detailed investigation has been caried out to study at ambient conditions the Novichok agents with molecular dynamic simulation. As a first step toward studying of Novichok agents (A230, A232, A234), we developed three new flexible potential models to identify the thermodynamic and structural properties. Hence, this Molecular Dynamics study of the aforementioned molecules gives a first-time perspective into the behavior and nature of these components in liquid form and ambient conditions, allowing further work to follow on their treatment and specifically antidote research in the unfortunate, though not unlikely, the event of possible contact.

In this study, we describe in detail the parametrization of our new Novichok agents (A230, A232, A234) models, hereafter referred to as CK. Molecular Models were created using a systematic approach, consisting of discrete well-defined steps. The next section gives the computational details of the calculations on isolated A230, A232, A234 and neat A230, A232, A234 liquid. This is followed by a detailed comparison of simulation results with those of available experiments for density. Moreover, we present simulation results for quantities such as enthalpy of vaporization, specific heat at constant pressure, diffusion coefficient, dipole moment, radial distribution functions, thermodynamic quantities and ΔHvaporization for our three systems under study. The final section summarizes these results and describes potential applications of this work. A subsequent publication will describe our results on the effect of temperature at the calculated thermodynamic and structural properties of these agents.

2. Methodology – Simulation Details

As mentioned earlier, Novichok structures proposed by Ellison and Hoenig were employed in the present study. At first all three molecular structures were created in Avogadro software[20]. Universal Force Field (UFF) along with Steepest Descent Algorithm was employed in order to determine most stable molecular geometry in each case. A Unified Atom approach was selected for CH, CH_2 and CH_3 groups in order to facilitate calculations. Derived geometry is presented in Fig. 1,2 and 3 for molecules A230, A232 and A234 respectively.

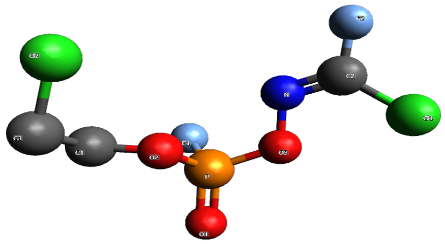


Fig. 1. A230 Structure ([(2-chloroethoxy) fluorohydroxyphosphinyl] oxy) carbonimidic chloride fluoride [7].

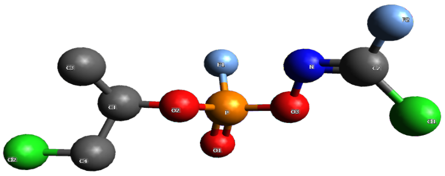


Fig. 2. A232 Structure ([(2-chloro-1-methylethoxy) fluorohydroxyphosphinyl] oxy) carbonimidic chloride fluoride [7]

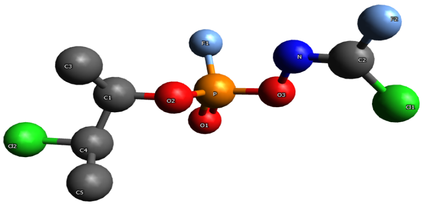


Fig. 3. A234 Structure ([(2-chloro-1-methylpropoxy) fluorohydroxyphosphinyl] oxy) carbonimidic chloride fluoride [7].

Afterwards, extended charge equilibration (eQeq) technique was employed on the rigid body structures to estimate in increased precision the atomic partial charges for each atom/atoms group (molecular sites) [21].

Finally, parameters from already published literature were combined to obtain the full potential model, for a fully flexible structure, using, Lennard-Jones 12-6 potential with long range Ewald corrections, flexible harmonic bond potential, flexible harmonic angle potential and flexible harmonic dihedral potential [19,22]. The aforementioned procedure led to the development of our CK model for Novichok A230, A232 and A234 compounds. Estimated Partial Charges are shown in Tab. 1.

Table 1. Partial Charges for atoms/sites of A230/A232/A234 molecules (all charges are in elementary charge units, ie $1.6022*10^{-19}C$)

	Partial Charges		
	A230	**A232**	**A234**
P	0.554	0.564	0.553
F1	-0.368	-0.352	-0.377
O=	-0.131	-0.123	-0.158
O2	-0.161	-0.176	-0.213
C1	0.241	0.118	0.196
O3	-0.097	-0.097	-0.111
N	-0.061	-0.060	-0.071
C=	0.526	0.527	0.518
F2	-0.370	-0.366	-0.388
Cl1	-0.194	-0.184	-0.222

CH2	0.227	0.181	0.177
Cl2	-0.164	-0.174	-0.248
CH3		0.142	0.177
CH3 (2)			0.164

Since CK model is to our knowledge the first flexible model of the Novichock agents (A230, A232, A234). Data from several sources were incorporated into the model.

Lennard – Jones 12-6 parameters refer to the well-known Eq. (1) [23]

$$E = 4\epsilon[(\frac{\sigma}{r})^{12} - (\frac{\sigma}{r})^{6}]r < r_c \tag{1}$$

Bond potential parameters were set according to harmonic bond potential as shown in Eq. (2) [23]

$$E = K(r - r_0)^2 \tag{2}$$

Where r_0 denotes equilibrium distance calculated from most stable rigid-body geometry and constant K incorporates ½ factor.

Angle potential parameters were adjusted to fit the harmonic angle potential of Eq. (3) [23]:

$$E = K(\theta - \theta_0)^2 \tag{3}$$

θ_0 is the equilibrium angle calculated from most stable rigid body geometry and constant K incorporates as well as the ½ factor.

Dihedral angle parameters were fitted to the harmonic dihedral potential of Eq. (4) [23]:

$$E = K[1 + d\cos(n\phi)] \tag{4}$$

Where K is an energy factor and d equals 1 and n equals 3.

The final set of Lennard-Jones, bond, angle and dihedral parameters is given in Tab. 2, 3, 4 and 5 respectively.

Table 2. Pair Interaction Parameters (LENNARD-JONES 12-6)

	A230		**A232**		**A234**	
	ε(kcal/mol)	**σ(Angstrom)**	**ε(kcal/mol)**	**σ(Angstrom)**	**ε(kcal/mol)**	**σ(Angstrom)**
P-P	0.200	3.74	0.200	3.74	0.200	3.74
F1-F1	0.053	2.95	0.053	2.95	0.053	2.95
O= - O=	0.109	3.05	0.109	3.05	0.109	3.05
O2-O2	0.109	2.80	0.109	2.80	0.109	2.80
C1-C1	0.115	3.905	0.080	3.85	0.080	3.85
O3-O3	0.109	2.80	0.109	2.80	0.109	2.80
N-N	0.159	3.28	0.159	3.28	0.159	3.28
C= - C=	0.115	3.80	0.115	3.80	0.115	3.80
F2-F2	0.053	2.95	0.053	2.95	0.053	2.95
Cl1-Cl1	0.266	3.47	0.266	3.47	0.266	3.47
CH2(230-232) - CH(234)	0.118	3.91	0.118	3.91	0.080	3.85
CH3(232-234)			0.160	3.91	0.160	3.91
Cl2	0.266	3.47	0.266	3.47	0.266	3.47
Cl2-CH-CH3 (234)					0.145	3.96

Table 3. Bond Interaction Parameters (Harmonic Potential)

	A230		**A232**		**A234**	
Bond	**K (kcal/(mol*Å^2)**	**Length (Å))**	**K (kcal/(mol*Å^2)**	**Length (Å)**	**K (kcal/(mol*Å^2)**	**Length (Å)**
P-F1	461	1.569	461	1.569	461	1.569
P=O	525	1.499	525	1.498	525	1.498
P-O2	230	1.613	230	1.615	230	1.615
O2-C1	386	1.417	386	1.427	386	1.428
P-O3	230	1.625	230	1.624	230	1.624
O3-N	320	1.416	310	1.414	320	1.414
N-C=	483	1.294	483	1.295	483	1.295
=C-F2	420	1.339	420	1.339	420	1.339
=C2-Cl1	300	1.710	300	1.711	300	1.711
C1-CH2 (230-232) C1-CH(234)	260	1.521	260	1.531	260	1.543
CH2-Cl2 (230-232) CH-Cl2 (234)	245	1.784	245	1.778	245	1.791
C1-CH3			260	1.523	260	1.526
CH-CH3 (234)					260	1.526

Table 4. Angle Interaction Parameters (Harmonic Potential)

	A230		**A232**		**A234**	
Angle	**K (kcal/mol*deg^2)**	**θ (degrees)**	**K (kcal/mol*deg^2)**	**θ (degrees)**	**K (kcal/mol*deg^2)**	**θ (degrees)**
F1-P=O	45	111.7	45	111.9	45	111.9
F1-P-O2	45	104.3	45	104.0	45	104.0
F1-P-O3	45	104.7	45	105.0	45	105.0
O=P-O2	100	114.5	100	114.3	100	114.4
O=P-O3	100	116.3	100	115.9	100	115.9
O2-P-O3	45	104.2	45	104.5	45	104.5
P-O2-C1	100	116.6	100	116.8	100	117.0
O2-C1-CH2 (230-232) O2-C1-CH (234)	50	110.0	50	108.9	50	109.7
P-O3-N	100	114.7	100	115.6	100	115.6
O3-N=C2	70	112.2	70	111.9	70	111.9

N=C-F2	50	117.2	50	117.4	50	117.7
N=C-Cl1	50	125.1	50	125.1	50	125.1
F2-C-Cl1	50	117.7	50	117.7	50	117.7
C1-CH2-Cl2 (230-232) C1-CH-Cl2(234)	50	111.1	50	112.3	50	110.9
O2-C1-CH3			50	106.8	50	106.7
CH3-C1-CH2 (232) CH3-C1-CH (234)			40	112.8	40	114.6
C1-CH-CH3 (234)					50	114.0
Cl2-CH-CH3 (234)					50	109.3

Table 5. Dihedral Angle Interaction Parameters (Harmonic Potential) Edihedral=K[1+cos(3φ)]

	A230	**A232**	**A234**
Dihedral	**K (kcal/mol)**	**K (kcal/mol)**	**K (kcal/mol)**
F1-P-O=-C1	0.50	0.50	0.50
O=-P-O2-C1	0.61	0.61	0.61
O3-P-O2-C1	0.08	0.08	0.08
P-O2-C1-CH2 (230-232) P-O2-C1-CH (234)	0.50	0.50	0.50
F1-P-O3-N	0.50	0.50	0.50
O=-P-O3-N	0.50	0.50	0.50
O2-P-O3-N	0.50	0.50	0.50
P-O3-N=C	0.50	0.50	0.50
O3-N=C-F2	0.50	0.50	0.50
O3-N=C-Cl1	0.50	0.50	0.50
O2-C1-CH2-Cl2 (230-232) O1-C1-CH-Cl2 (234)	0.50	0.50	0.50
P-O2-C1-CH3 (232-234)		0.50	0.50
CH3-C1-CH2-Cl2(232) CH3-C1-CH-CL2(234)		0.50	0.50
O2-C1-CH-CH3 (234)			0.50
CH3-C1-CH-CH3 (234)			0.50

Simulations were performed using LAMMPS software package [24]. In order to obtain dipole moment data for an isolated molecule without periodic boundary conditions and Uvap (Internal Energy without any intermolecular interactions), simulations with timestep of 0.5fs and duration of 500ns were performed in NVE statistical ensemble, following 0.25ns of equilibration.

For the bulk calculations 500 molecule systems were simulated for each of the three under research molecules using timestep of 1fs and duration of 1ns for the production runs. Cut-off radious was set to 14Å. Nose-Hoover Thermostat and Barostats were used in all cases. Specifically, three sets of thermodynamic data were obtained, to clarify molecular model was performing as expected.

Fistly a 1ns NPT simulation (0.25ns equilibration in NVT and 0.05ns equilibration in NPT afterwards before production runs) to verify experimental density was reproduced in a statistically accepted margin.

Afterwards two simulations were performed in NVE ensemble for 1ns, one with 0.25ns equilibration in NVT and one with 0.5ns Equilibration in NVT.

Simulations in NVT were performed only for clarification of the model-software combination performance, to ensure that thermodynamic quantities were comparison in all three cases, since this is a totally new molecular model and needed thorough testing. Two sets of equilibration time in NVT were selected also to achieve better understanding of model performance under different time/statistical ensembles in equilibration and production run respectively. NVE initial conditions were selected from NVT/NPT equilibration configurations. All results are presented in the following section.

3. Results – Discussion

3.1 Thermodynamic Results

Bulk thermodynamic results are depicted in Tab. 6. All energies are measured in kcal/mol, temperature is measured in K.

Table 6. Thermodynamic Results from production runs (all energy units kcal/mol)

	NPT			**NVE**	**0.25ns equilibration**		**NVE**	**0.5ns equilibration**	
Energy (kcal/mol)	A230	A232	A234	A230	A232	A234	A230	A232	A234
Sim. Temperature	298.00	298.00	298.00	302.00	301.09	305.00	297.15	298.75	295.61
Pot. Energy U	-52.06	-63.02	-64.62	-51.97	-62.30	-62.95	-52.15	-62.41	-63.48
Tot. Energy K+U	-41.40	-51.48	-52.19	-41.17	-50.64	-50.22	-41.50	-50.84	-51.15
Van der Waals Energy	-13.48	-14.18	-15.15	-13.50	-13.73	-14.16	-13.53	-13.75	-14.20
Coulomb Energy	-17.32	-26.76	-27.81	-17.31	-26.63	-27.46	-17.35	-26.64	-27.61
Bond Energy	3.29	3.60	3.90	3.33	3.63	3.99	3.29	3.61	3.86
Angle Energy	3.98	4.76	5.34	4.03	4.81	5.42	3.98	4.77	5.27
Dihedral Energy	2.80	3.23	3.27	2.81	3.24	3.32	2.79	3.23	3.26
Molar Energy (bond+angle +dihedral)	10.07	11.60	12.51	10.17	11.68	12.73	10.06	11.60	12.39
Long Range	31.34	-33.68	-34.17	-31.34	-33.62	-34.06	-31.34	-33.62	-34.06
Enthalpy	-41.40	-51.48	-53.81	-40.78	-52.76	-54.35	-41.42	-53.13	-55.81

3.1.1 Density Simulation vs Experimental Density

Calculated densities for all three systems, estimated from NPT simulations are shown in Tab. 7.

Table 7. Density - NPT

DENSITY	**after 1million steps of 1fs.**		
Total 1ns	**500molecules**		
Substance	**A230**	**A232**	**A234**
EXPERIMENT (g/mL)	1.612	1.515	1.414
SIMULATION (NPT) (g/mL)	1.608	1.561	1.499
Difference (%)	-0.26	3.00	6.00

It is clear that density estimation with the current potential models is close to the ones stated in the literature by an acceptable margin of -0.26% (A230) to +6% (A234). This fact gave the clearance to proceed in further simulations in NVE ensemble to estimate the majority of properties in the particular liquid systems. Positive difference for A232 and A234 (3 and 6% respectively) could be attributed to the extra methyl groups in A232 (1 extra CH_3 group) and A234 (2 extra CH_3 groups).

3.1.2 ΔHvaporization

As mentioned before Heat of vaporization was calculated using Eq. (5)

$$\Delta H_{vap} = U_{vap} - U_{liq} + RT + \mathrm{C} \tag{5}$$

Where Uvap is the potential energy for a single molecule simulation (1μs) without periodic boundary conditions and Uliq is the potential energy for a 500-molecule system from the liquid system MD simulations (1ns). C stands for the correction term due to differences between calculated vibration energies and nonideal gas effects and in general and in this case is considered negligible. Results for 298K, 1atm are shown in Tab. 8.

Table 8. Heat of Vaporization

	ΔHvaporization (Kcal/mol)		
	A230	**A232**	**A234**
NVE	18.30	11.90	22.08

Results show a range of 12-22 kcal/mol approximately in the Heat of Vaporization from A230 to A234. In all three liquid systems ΔH_{vap} is positive, therefore vaporization is an endothermal process, requiring external energy to proceed. This might be attributed to the high (absolute values) potential energy values, that lead liquid systems to stability. Lower ΔHvap value in the case of A232 could be explained due to structural reasons, ie possible weaker intermolecular forces in certain site-site interactions.

3.1.3 Specific Heat (Constant Pressure) Cp

Specific Heat under Constant Pressure was calculates using the expression in Eq. 6

$$Cp = \frac{H(T+\varepsilon,P)-H(T-\varepsilon,P)}{2\varepsilon} \tag{6}$$

known and tested also as "the finite difference approrach" [25]. This method involves a set of two extra MD simulations in two temperatures. One above initial temperature by an amount of ε K and another below initial temperature by ε Kelvin.

In our study, initial temperature was 298K and ε was selected equal to 15K, in order to give significant difference in Enthalpy. As mentioned in the corresponding paper, this method involves higher times of simulation, so instead of 1ns simulations were carried out for 5ns to improve statistical accuracy for systems of 500 molecules. Results for 298K, 1atm are shown in Tab. 9.

Table 9. Specific Heat under Constant Pressure (Cp)

	A230	**A232**	**A234**
Cp (J/K)	396.25	434.22	462.58

We note that there is a rather expected increase in Specific Heat Capacity by increasing Molecular Mass from A230 to A232 and then A234.

3.2 Self Diffusion and Dipole Moment

3.2.1 Self-Diffusion Coefficient

Self-Diffusion Coefficient for each molecule was calculated using Einstein's formula (Eq. 7) in NVE enselmbe Simulations:

$$\mathrm{Ds}=\lim_{t\to\infty} \frac{1}{6}\frac{\partial(MSD)}{\partial t} \tag{7}$$

Where MSD equals Mean Squared Displacement.

A graph for A230 Mean Square Displacement in 298K, 1atm for 1ns is shown in Fig. 4. Fig. 4 shows explicitly that simulation has converged and when least squares polynomial fit is applied to data, R^2 convergence factor is equal to 0.9968. Same results occurred for all three substances, so Self-Diffusion Coefficient was calculated in all liquids.Results for 298L, 1atm are shown in Table 10.

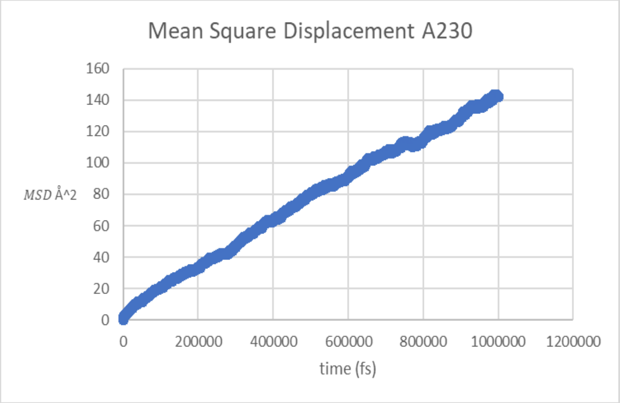


Fig. 4. Mean Square Displacement of A230.

Table 10. Self-Diffusion Coefficient

Diffusion Coefficient		**(m2/s)**
Obtained using MSD Data		**NVE 1ns**
A230	**A232**	**A234**
$0.230*10^{-09}$	$0.138*10^{-09}$	$0.144*10^{-09}$

As it is easily noted from Tab. 11, Self Diffusion Coefficient is similar for A232 and A234, due to minor differences and quite different from the one of A230, possibly due to the presence of extra bulky Methyl Group(s).

3.2.2 Dipole Moment

Dipole moment was calculated in a cell containing a single molecule without periodic boundary conditions with timestep 0.5 fs and total time of simulation 500ns in order to achieve high statistical accuracy. The same single molecule simulations were employed to calculate Uvap ie the potential energy of a single isolated molecule, used in the calculation of Heat of vaporization. Averages were taken over Eq. 8 and the scalar part of the calculation is presented in Tab. 11.

$$\mu = \sum_i q_i r_i \tag{8}$$

Table 11. Dipole Moment

	Dipole Moment for a single molecule		
	A230	**A232**	**A234**
Dipole Moment (Debye)	4.234	5.181	5.956

Differences in calculated Dipole Moments show that adding an extra (or two in the case of A234) Methyl Groups increases the calculated dipole moment, possible due to the fact that positively charged Methyl Groups are added to the positive end of the molecule.

3.3 Structural Properties

In this section intermolecular liquid structure in all molecular liquids studied, will be discussed. Radial Pair Distribution Functions (rPDFs) are a versatile and powerful tool for the study of chemical substances, and have many applications in materials science, physics, chemistry, and biology. Radial pair distribution functions (rPDFs) are a common tool in structural analysis and are often used to determine the spatial arrangement of atoms or molecules in a solid, liquid, or gaseous state. In other words, it gives information about the local arrangement and density of the particles in a material. Furthermore, provide information on the structural and bonding characteristics of chemical substances, such as the coordination number, bond length, and bond angle distribution. Specifically, radial Pair Distribution Functions (rPDF) are going to be presented for selected molecular sites for A230, A232 and A234 molecules in comparison. Plots exhibit function $G_{ab}(r)$ versus distance. This function represents probability of presence of atom(site) b of molecule j in distance r from atom(site) a of molecule i. rPDFs were calculated for distances equal to the cut-off radius of the MD Simulations, 14Å. This distance was split to 250 segments, so resolution of display is equal to 0.056Å.

Among the extensive collection of site-site Radial Pair Distribution Functions (rPDFs) for the under-study molecules, several were selected for presentation in the present paper. Selection of RDFs were based in those exhibiting attractive nature between intermolecular sites. Also the P-P rPDF is presented, in order to show an approximate image of how the whole molecules come close to each other, since P is close enough to Centre of Mass (COM) for all three substances (approximately 1Å is the average distance of Center of Mass to Phosphorus Atom in A230, A232 and A234. P-P rPDF is shown in Fig. 5.

In Fig. 6, rPDFs of P with F2 and Cl2 are shown. The obvious conclusion from the study of these three graphs is that there exists a first coordination sphere around P atom, with halogen atoms from neighbouring molecules, at distances of 3.5-4.5Å. The scheme is similar in all three substances under the present study.

In the two graphs in Fig. 7, rPDFS of Carbon group C1 are shown, namely with F1 and F2 atoms. From these two rPDFs it is obvious that since Methyl Groups are attached to the C1 group (A232 and A234 case), C1 group is hindered by the large Methyl Group, thus being difficult for other molecules' site/atoms to approach. This explains the decrease in the size of the corresponding peak as well as the shift to greater distance from the center group.

In graphs in Fig. 8, rPDFs of sp2 hybridized Carbon atom vs selected other atoms are displayed. Notice that C= atom has a flat bond geometry, which makes this atom accessible to several other molecules' atoms.

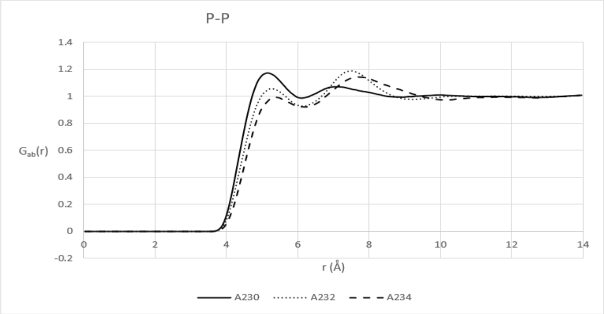


Fig. 5. site-site rPDF P-P (approximation of COM-COM).

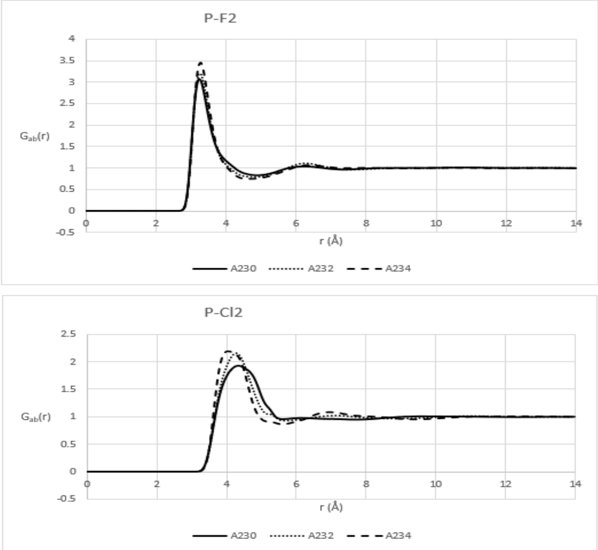


Fig. 6. P-X rPDFS.

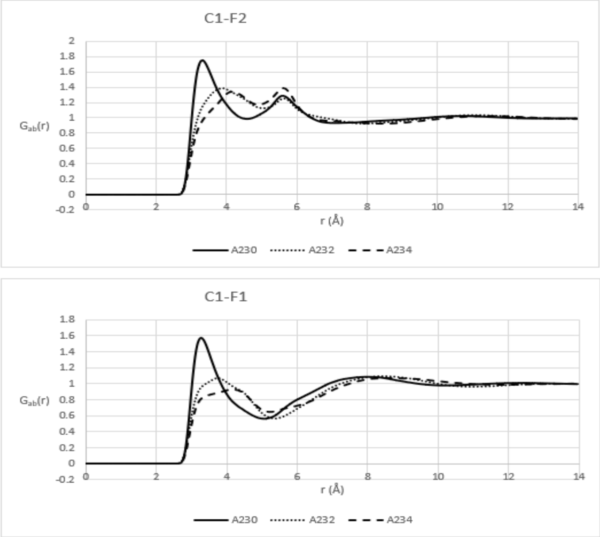


Fig. 7. C1 (C-P) rPDFs.

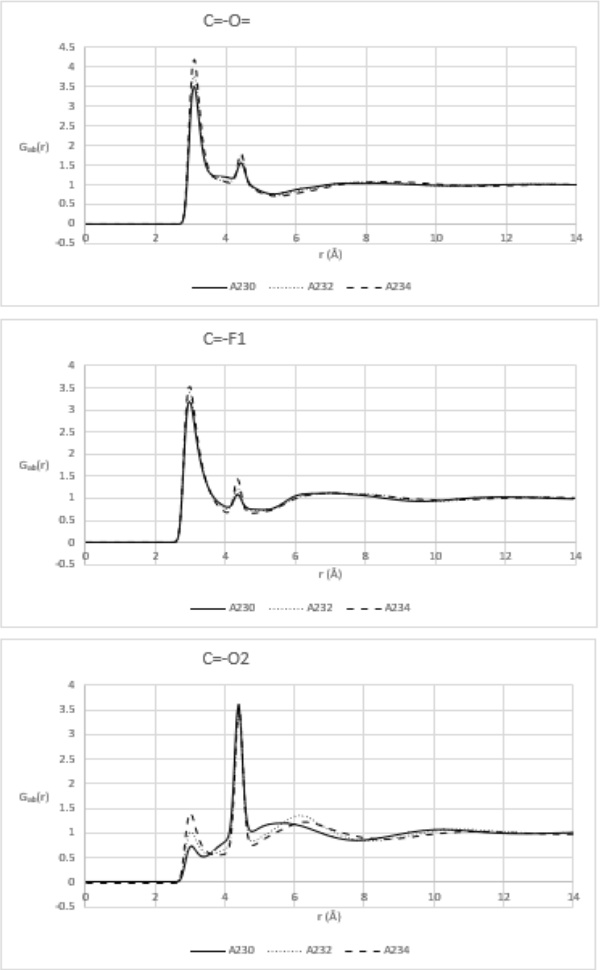


Fig. 8. rPDFS of sp2 Carbon atom vs double-bond O, F1 and O2.

In Fig.8 graphs, it is straightforward that there exists a well-defined attraction among sp2 hybridized Carbon atom and three atoms with partial negative charge, specifically “double bonded” Oxygen atom, Fluorine atom attached to Phoshporus and Oxygen atom that connects P atom to the Carbon-Chlorine group in the positive end of the molecule. This is probably due to the easily allowed approach to the sp2 Carbon, because of its flat geometry in terms of atom-atom bonding. Moreover, a distinct C(sp2)-O2 second rPDF peak, much higher in intensity than the first one may be explained due to the position of the O2 atom (among large groups of atoms).

In the graphs of Fig. 9 an interesting phenomenon is being presented. We notice from the decrease in first peak max, followed by an increase in second peak max from A230 to A232 and then A234 that stereochemistry plays a major role in intermolecular structure. Namely, the extra methyl group(s) in A232 and A234 lead to more molecules being “pushed” to the second coordination sphere, since Fluorine atoms (the ones connected directly to P atom) are more keen to keep away from the particular carbon atom, due to the ajacent extra methyl groups.

In Fig. 9 we observe the rPDFs of the common Methyl Groups in A232 and A234 (attached to Carbon group C1). From the study of 5 graphs in Fig. 10 it is obvious that Methyl Groups in A232 and A234 attached to the first Carbon group (C1) have an exact similar behavior in terms of rPDFs, ie position of max/min and magnitude of $G_{ab}(r)$. An explanation for this fact is that there exists a similar stereochemistry environment from the Methyl point of viewin both molecules (A232 and A234).

Position of first Max/Min, corresponding Intensity of G(r) and coordination number for the aforementioned rPDFS are shown in Tab. 12 for CK model.

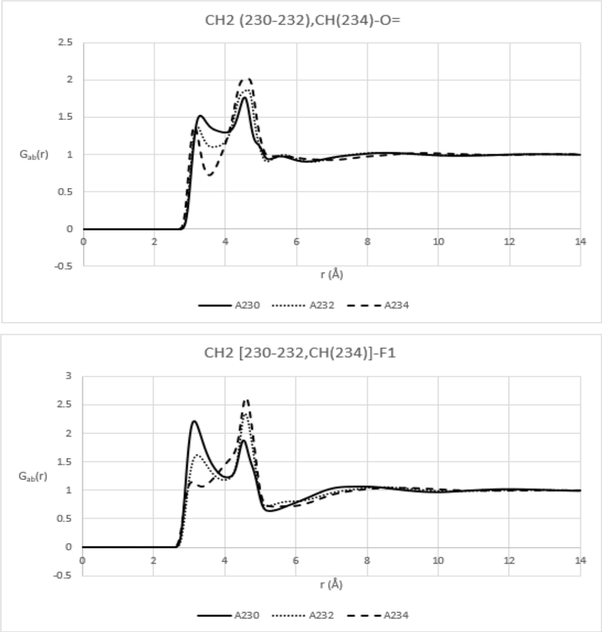
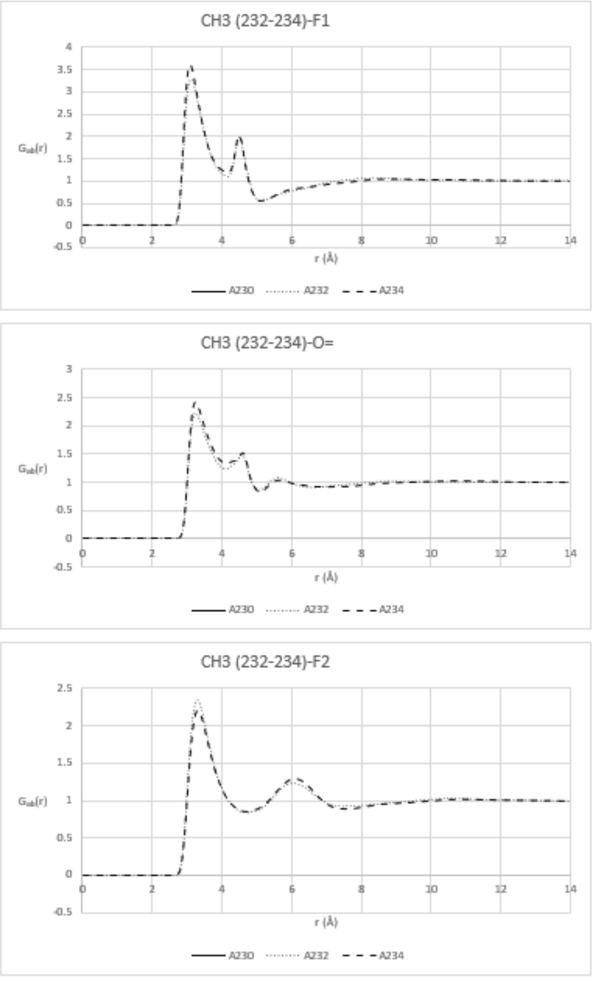


Fig. 9. rPDFS of CH2 (A230, A232) and CH(A234) groups, attached to the Cl2 atom versus O= and F1 atom.



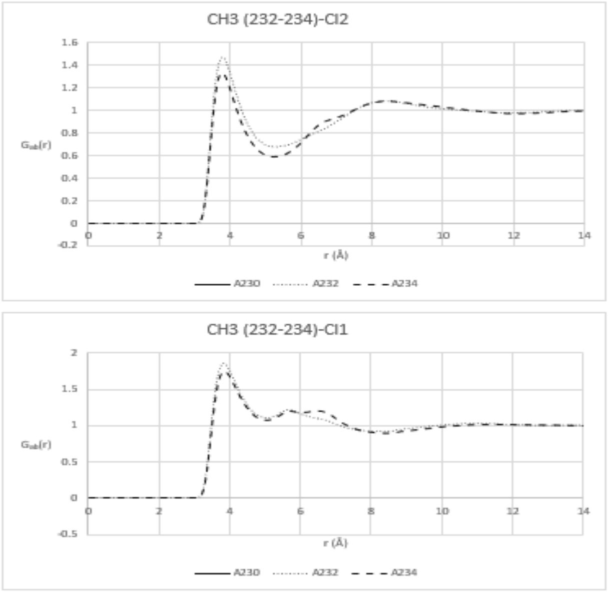


Fig. 10. Common Methyl Group CH_3 of A232 -A234 rPDFS.

From data in Tab. 12 and the fact that each molecule contains only a single Phosphorus atom, we can conclude that a micro-cluster structure exists in all three liquid systems. Integration results do not show a clear 3-4 molecules clusters but rather combinations of 2, 3, 4 and possibly more molecules clusters. Smaller numbers of molecules in the cases of A232 and A234 may be due to the fact that the latter molecules include one and two extra Methyl groups respectively.

Note that F1 marks the Fluorine atom attached to the Phosphorus atom in each molecule, F2 and Cl2 the fluorine and chlorine atoms attached to the sp2 Carbon atom (attached to the Nitrogen atom) and Cl2 the chlorine atom at the other end of the molecule, attached to Carbon group. Additionally, C1 is the carbon group attached to the O next to P atom and O= is the oxygen atom attached with double bond to the Phosphorus atom and O2 is the oxygen atom bonded to Phosphorus and Carbon group simultaneously. Finally, CH2 (A230,A232) and CH(A234) denote the Carbon group where Cl2 is attached to.

In overall, studying the results and the graphs of available rPDFs we may assess that there is a strong interaction between center of each molecule (P atom) with the Cl2 atom in the negative end of the molecules, as well as a strong attraction between the flat sp2 Carbon atom C= and the F1 and O= atoms located in the centre of the Novichok molecules. This suggests an inverted possible structure with the middle of the molecule exhibiting strong intermolecular attraction to the negative end of another molecule (F1-C=-Cl1) and vice versa. However, this is not the only case of attraction in the particular molecular systems. Specifically, in the A232 and A234 systems another strong attraction rises, the one between the common Methyl group CH3 of A232 and A234 and the central F1 and O= atoms, bonded to the Phosphorus central atom. All the above suggest a complex structure with strong intermolecular forces, forming a network of molecules, bearing a rather distinct preference in orientation.

The above results of rPDFs will be used and compared with the future obtaining results from X-ray, diffraction, or scattering experiments that represent the probability of finding a pair of particles at a given separation distance, relative to the number of particle pairs at that separation in a chemical substance.

Table 12. CK model rPDF results.

	A230		**A232**		**A234**	
	First Max	**First Min**	**First Max**	**First Min**	**First Max**	**First Min**
	r(Å), G_{ab}(r) n_{ab}	**r(Å), G_{ab}(r) n_{ab}**	**r(Å), G_{ab}(r) n_{ab}**	**r(Å), G_{ab}(r) n_{ab}**	**r(Å), G_{ab}(r) n_{ab}**	**r(Å), G_{ab}(r) n_{ab}**
P-P	5.18 1.17 1.10	6.13 0.99 2.75	5.29 1.05 0.97	6.19 0.92 2.27	5.35 0.99 0.81	6.19 0.92 1.88
P-F2	3.22 3.07 0.36	4.90 0.83 2.14	3.28 3.20 0.41	4.80 0.79 1.77	3.28 3.46 0.37	4.90 0.76 1.66
P-Cl2	4.34 1.93 1.06	5.63 0.96 3.30	4.28 2.16 0.93	5.63 0.93 2.87	4.06 2.20 0.58	5.57 0.87 2.40
C1-F1	3.28 1.57 0.25	5.12 0.56 1.60	3.78 1.08 0.44	5.40 0.57 1.66	4.06 0.92 0.48	5.25 0.64 1.27
C1-F2	3.33 1.75 0.32	4.56 0.99 1.52	3.89 1.38 0.62	5.01 1.22 1.87	4.17 1.35 0.72	4.90 1.17 1.47
C=-O=	3.05 3.40 0.24	4.17 1.17 1.40	3.11 3.77 0.32	4.12 1.09 1.20	3.11 4.18 0.31	4.12 1.05 1.12
C=-F1	3.00 3.20 0.31	4.06 0.80 1.23	2.94 3.37 0.22	4.06 0.75 1.10	3.00 3.52 0.27	4.06 0.67 0.98
C=-Cl2	4.45 1.48 0.89	7.92 0.92 8.56	4.68 1.41 1.03	7.76 0.96 7.22	4.96 1.29 1.14	8.93 0.94 9.72
CH2(A230,A232) CH(A234)-F1	3.16 2.21 0.30	4.06 1.22 1.21	3.22 1.62 0.22	3.95 1.18 0.79	3.11 1.14 0.12	3.33 1.07 0.22
CH2(A230,A232) CH(A234)-O=	3.28 1.52 0.21	4.00 1.30 0.88	3.22 1.37 0.15	3.61 1.10 0.39	3.11 1.37 0.10	3.56 0.72 0.29
CH3(A232-A234)-F1			3.11 3.28 0.32	4.17 1.09 1.44	3.11 3.60 0.32	4.17 1.18 1.34
CH3(A232-A234)-O=			3.28 2.23 0.28	4.12 1.24 1.09	3.28 2.42 0.27	4.00 1.35 0.99
CH3(A232-A234)-F2			3.28 2.33 0.30	4.73 0.84 1.61	3.33 2.21 0.30	4.73 0.85 1.40
CH3(A232-A234)-Cl1			3.84 1.85 0.44	5.07 1.10 1.92	3.84 1.75 0.42	5.01 1.08 1.57
CH3(A232-A234)-Cl2			3.78 1.48 0.31	5.24 0.68 1.53	3.78 1.34 0.25	5.24 0.59 1.21

4. Conclusions

New models of Novichok agents (A230, A232, A234) incorporating atomic flexibility provide agents models that are consistent with modern parameter sets for the simulation of synthetic molecules and have been shown to be necessary for accurate descriptions of condensed phases. The techniques employed in the present study include, rigid molecule model creation, energy minimization, partial charge estimation with eQeQ method and combining interatomic potential parameters from previous computational studies.

The present models have been tested against experimental data for thermodynamic properties and shown to be highly accurate.

The existence of a high quality A230, A232, A234 model, that is consistent with the LAMMPS all-atom parameter sets for synthetic molecules, allows for the possibility of simulating many interesting systems.

Additionally, the all-atom model presented here allows comparison with structural data from neutron scattering experiments that probe the heavy atom - hydrogen atom structure within the fluid.

We wish that research presented in the present paper might be a small block in the array of efforts against the threat of CWAs and that it may facilitate researchers to their inquiry for treatment of CWAs and in antidote research as well. This was the most and higher goal of our efforts, in a hope for a society ridden of the threat of CWAs.

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We would like to thank Emeritus Prof. J. Samios (University of Athens) for many useful comments and carefully reading of the manuscript. The CPU time of the GRID Computing Center, which is located at the International Hellenic University (IHU), at Kavala Campus (Greece) is also gratefully acknowledged.

Data and software availability

For all MD simulations LAMMPS version 29-Sept-2021 Stable was used. LAMMPS is open-source software distributed under the GNU General Public License Version 2. Procedure followed is described in detail in section "SIMULATION DETAILS" in the present paper.

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