



The number of conformers explains the high toxicity of novichok agents

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Abstract In this work, molecular modelling, by semi-empirical (PM6) method is employed to study Novichok A-230 and Novichok A-234, in order to verify, by comparison of parameters, what is the reason (or reasons) for such much higher toxicity of novichok in comparison with VX. Taking into account the obtained results, is proposed that a higher polarity, combined with a minor number of conformers implies in a minor amount of possible linkages to acetylcholinesterase, explaining why Novichok A-230 and Novichok A-234 are so more highly toxic than VX.

Keywords Semi-empirical, Novichok A-230, Novichok A-234, VX

Introduction

In march, 04, 2018, an ex-Russian spy, Sergei Skripal, 66, and his daughter Yulia, 33, were poisoned in Salisbury, England[1], provoking a diplomatic crisis between England and Russia.

It was proved that Skripal and his daughter were poisoned with novichok. In Russian novichok means "newcomer" and such name applies to a group of advanced nerve agents developed by the Soviet Union in the 1970s and 1980s.

Both, VX and novichok agents are "nerve agents". Many newspapers and television news channels have said that "novichok is several times more toxic than VX". In fact, one of them (A-230) is reportedly five to eight times more toxic than VX.

In the present work, molecular modelling, by semi-empirical (PM6) method is employed to study Novichok A-230 and Novichok A-234. VX is also modelled by the same approach, for comparison. Such study is performed in order to verify, by comparison of parameters, what is the reason (or reasons) for such much higher toxicity of novichok in comparison with VX.

Methodology

The molecular modelling of VX (Figure 1) and two novichok agents (A-230) and A-234) were performed by using Spartan 16 [2] (Semi-Empirical, PM6). The SE-PM6 approach was chosen taking into account its minor computation time consuming and its reliability, as verified for PtF₆ [3].

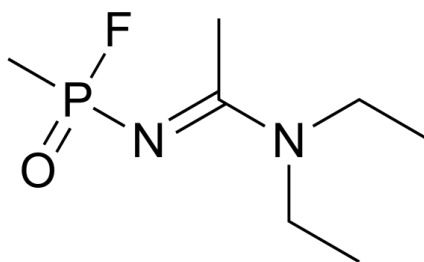


Figure 1: Structural formula of novichok A-230



Novichok agents exerts their action very rapidly, penetrate through the skin and respiratory system. Novichok A-232, for example, exceeds effectiveness of soman by 10 times and of VX by 5 to 8 times [4].

The proposal of the described “modelling experiment” was to shown/to verify if some of the calculated parameters could be used as a QSAR indicator of such higher activity of novichok agents.

Results and Discussion

The calculated parameters for VX, Novichok A-230 and Novichok A-234 agents are summarized in Table 1.

Table 1: Physicochemical properties and parameters calculated for VX, Novichok A-230 and Novichok A-234 (Semi-empirical, PM6)

Property/Agent	VX	Novichok A-230	Novichok A-234
$\Delta_g H_f^0 / \text{kJmol}^{-1}$	-779.06	-721.23	-962.55
Point group	C ₁	C ₁	C ₁
E _{homo} /eV	-7.90	-9.21	-9.27
E _{lumo} /eV	0.03	0.89	0.68
Dipole moment/D	0.84	5.01	5.14
PSA/A ²	23.694	23.079	30.557
Polarizability	63.22	55.22	57.43
Ovality	1.56	1.39	1.45
HDB	0	0	0
HBA	4	2	3
Conformers	6561	54	486
ZPE/ kJmol ⁻¹	883.58	567.25	645.40
S ^o /JK ⁻¹ mol ⁻¹	681.56	518.88	585.46

As can be verified from Table 1 data, both, Novichok A-230 and Novichok A-234, exhibits dipole moments much higher than that exhibited by VX.

Furthermore, both, Novichok A-230 and Novichok A-234 (specially the former) have a much minor number of conformers, if compared with VX.

Hence, can be concluded, by comparison, and for the investigated warfare chemical agents, that a minor number of conformers, associated with a high dipole moment could be, as a first attempt, associated with a higher biological/poisoning activity.

Like other organophosphate compounds, Novichok agents bind acetylcholinesterase preventing degradation of acetylcholine and producing the cholinergic or muscarinic toxidrome [5].

Taking into account the obtained results, can be stated that a minor number of conformers implies in a minor amount of possible linkages to acetylcholinesterase, explaining by this way, why Novichok A-230 and Novichok A-234 (Figures 1 and 2) are so much toxic than VX.

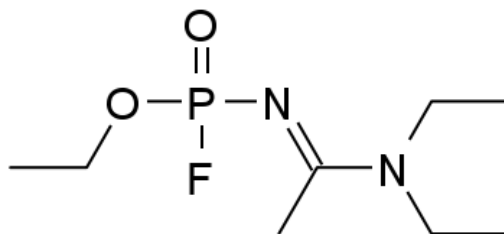


Figure 2: Structural formula of novichok A-234

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