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# Probing the simulant behavior of PNPDPP toward parathion and paraoxon: A computational study

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ABSTRACT

The extreme toxicity of organophosphorus nerve agents and pesticides mandates to employ models or simulants in place of the actual compounds in the laboratory. The importance of simulants is known, however, their efficacy for direct comparison with the toxic organophosphorus compounds is not well documented. We have examined the potential energy surfaces (PES) for the alkaline hydrolysis of pesticides like paraoxon (diethyl 4-nitrophenyl phosphate), parathion (O,O-diethyl O-4-nitrophenyl phosphorothioate) and PNPDPP (4-nitrophenyl diphenyl phosphate), a simulant with MP2/6-311 + G*//B3LYP/6-311 + G* + $\Delta G_{solv}$ (HF/6-31 + G*) level of theory. The effect of aqueous solvation was considered with the Integral Equation Formalism Polarizable Continuum Model (IEF-PCM). The alkaline hydrolysis of these organophosphorus compounds reveals that the reaction proceeds through the attack of hydroxide ion at the phosphorus center to form a pentacoordinate intermediate. The calculated free energies of activation for the alkaline hydrolysis of paraoxon and parathion are in good agreement with the available experimental activation free energies. The computed results show that the reaction profiles for the alkaline hydrolysis of paraoxon, parathion and PNPDPP are largely similar; however, the rate of hydrolysis of parathion may be higher than that of paraxon and PNPDPP. Such difference arises due to the less electrophilic nature of the phosphorus atom of parathion molecule as observed in the charge analysis study. The conceptual DFT analysis also showed the similar trend for the alkaline hydrolysis of paraoxon, parathion and PNPDPP with hydroxide anion. This computational study provides a quantitative support toward the use of PNPDPP as a simulant for organophosphorus compounds, which cannot be used directly for the laboratory purposes.

## 1. Introduction

Several persistent chemicals such as paraoxon, parathion and chemical warfare compounds such as VX, sarin etc. are hydrophobic phosphorus (V) esters or phosphylating agents [1]. They can irreversibly react with the enzyme acetylcholinesterase (AChE), inhibiting its control over the central nervous system [1–3]. AChE catalyzes the ester hydrolysis of the neurotransmitter acetylcholine (ACh) to terminate synaptic transmission [4–6]. Inhibition of AChE occurs as a result of the phosphylation of the active serine residue with organophosphorus (OP) compounds [7–9]. Such AChE inhibition results in acetylcholine accumulation at cholinergic receptor sites, thereby excessively stimulating the cholinergic receptors. This can lead to various clinical disorders sometimes causes death. Remediation of such toxic contaminants therefore continues to be a challenge for research groups. In particular, chemical means of achieving efficient destruction of organophosphorus esters remains an active area of research. The easy hydrolysis of these toxic organophosphorus esters is one of the prime focuses in recent times [10,11]. Other detoxification methods have also been explored using oxidizing agents, photocatalysis, metal-catalyzed decomposition, enzyme degradation, and reduction [12–17].

Paraoxon and parathion are the compounds most often responsible for the poisoning of agricultural workers [18]. The extreme toxicity of these nerve agents mandates that most laboratory research utilizes models or simulants in place of these hazardous compounds [10,19]. Especially, many researchers use PNPDPP as a simulant to develop effective decontaminating reagents toward actual compounds [20–24]. PNPDPP has become the unauthorized standard simulant for phosphotriester hydrolytic reactions, since its introduction in 1969 [24]. Use of simulant allows ready comparison of kinetic data obtained with many different nucleophiles under varying reaction conditions due to its non-toxicity and the structural similarity with many organophosphorus (OP) compounds [21]. However, the literature lacks the comparative

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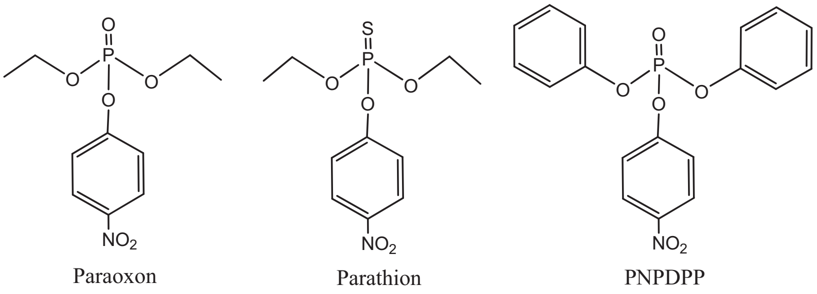

**Scheme 1.** Structures of organophosphorus compounds paraoxon, parathion and PNPDPP (simulant).

data for PNPDPP and other OP compounds to validate the use of former compound as simulant. This prompted us to examine the simulant behavior of PNPDPP toward paraoxon and parathion by exploring the alkaline hydrolysis of these compounds (Scheme 1). Generally, the selection of appropriate simulants for the hydrolysis will depend primarily on the presence of the bonds in the simulant compounds at which the hydrolysis reaction occurs in the original compounds. The best simulant will closely match the structure of the original compound and can potentially form the same or similar hydrolysis products [25]. The alkaline hydrolysis process of paraoxon, parathion and PNPDPP has been studied employing density functional theory (DFT) and Møller–Plesset (MP2) calculations. Further the reactivity trends have been examined with the conceptual DFT analysis.

## 2. Computational methodology

A thorough conformational search was performed with the Macromodel program using MMFFs force field for paraoxon, parathion and PNPDPP [26–30]. Conformational search was performed with the random variation of all the rotatable bonds and combining the Monte Carlo conformational search (MCMM) algorithm [31,32] using 5000 Monte Carlo steps. Energy minimizations were performed with the Polak–Ribiere conjugate gradient (PRCG) method [33], which involves the use of first derivatives with the default convergence criterion 0.05 kJ/mol Å. Sorted all found conformations according to energy. Conformations whose relative energy was within 50 kJ/mol with respect to lowest energy structure were stored. The ensuing conformations were clustered based on torsional RMS using XCluster approach [34,35]. Based on the minimum separation ratio, two representative conformations in each case were chosen from this clusterization procedure. The selected conformations from the conformational families were stored for further higher level DFT calculations. The lowest energy conformations obtained at DFT calculations were considered to model the alkaline hydrolysis process. We have modeled the alkaline hydrolysis process by employing MP2/6-311 + G*//B3LYP/6-311 + G* + $\Delta G_{\text{solv}}$ (HF/6-31 + G*) composite level of theory which was chosen based on the bench marking of methods (please see Section 3).

All geometries involved in the alkaline hydrolysis processes were optimized using the B3LYP [36–38] density functional and the 6-311 + G* basis set. Harmonic frequency calculations at the same level were used to validate the stationary points and to estimate thermodynamic corrections. Intrinsic reaction coordinate (IRC) calculations were performed to connect all the transition states with their corresponding minima [39,40]. Single-point electronic energies were obtained at the MP2/6-311 + G* [41,42] level of theory. Free energies of solvation in water were determined at the HF/6-31 + G* level of theory using the Integral Equation Formalism Polarizable Continuum Model (IEF-PCM) [43] along with the UFF topological model [44], which places an explicit sphere on every atom. Energies reported in this study are free energies obtained from normal mode analysis with the harmonic approximation and no statistical simulations were carried out. All quantum chemical calculations were performed using Gaussian 03, Revision E.01 and Gaussian 09, Revision B.01 programs [45].

For conceptual DFT calculations, the local softness $s(r)$ can be obtained as

$$s(r) = f(r)S \tag{1}$$

where $S$ is the global softness of the species and $f(r)$ is the so-called Fukui function [46]. Within a finite difference approximation, combined with the idea of integrating the Fukui function over atomic regions, one finds the condensed Fukui functions for nucleophilic and electrophilic attack on atom A having $N$ electrons with Eqs. (2) and (3), respectively.

$$f_A^+ = q_A(N_0 + 1) - q_A(N_0) \tag{2}$$

$$f_A^- = q_A(N_0) - q_A(N_0 - 1) \tag{3}$$

where $q_A(N_0)$, $q_A(N_0 + 1)$, and $q_A(N_0 - 1)$ are the atomic populations for atom A in the neutral molecule and its corresponding anion and cation, respectively. For calculating the condensed Fukui function $f_A$, natural population charge analysis (NPA) [47] was performed on optimized geometries of $OH^-$ and OP compounds at the recommended B3LYP/6-31 + G(d,p) level of theory [36,48]. The global softness $S$ is given by the finite difference approximation.

$$S = \frac{1}{I - A} \tag{4}$$

where $I$ and $A$ represents the ionization energy and the electron affinity, respectively. For calculating global softness, one can apply Koopmans' theorem [49] (assumption of frozen orbitals), approximating $I$ by the energy of the highest occupied molecular orbital ($\varepsilon_{\text{HOMO}}$) and $A$ by the energy of the lowest unoccupied molecular orbital ($\varepsilon_{\text{LUMO}}$).

$$S = \frac{1}{\varepsilon_{\text{LUMO}} - \varepsilon_{\text{HOMO}}} \tag{5}$$

Further, the local softness for nucleophile and electrophile can be calculated with Eqs. (6) and (7), respectively.

$$s_A^+ = S f_A^+ \tag{6}$$

$$s_A^- = S f_A^- \tag{7}$$

In the present study, $s^+$ indicates the local softness of oxygen of nucleophiles and $s^-$ the local softness of phosphorus of sarin.

According to HSAB principle and in analogy with earlier work by Gázquez [50] and Geerlings et al. [51] and its generalization by Ponti [52], the preferred reactivity between the reaction partners can be based on the difference in local softness $s(r)$ of the interacting parts (atoms, functional groups) of these reaction partners should be minimal for most favorable interactions.

$$\Delta s(r) = |s^+(r) - s^-(r)| \tag{8}$$