Solvolysis of organophosphorus pesticide parathion with simple and α nucleophiles: a theoretical study

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Abstract. Density functional theory (DFT) has been used to study the solvolysis process of the organophosphorus compound, O,O-diethyl *p*-nitrophenyl thiophosphate (Parathion, PTH) with α -nucleophiles [hydroxylamine anion (NH_2O^-), hydroperoxide (HOO^-) and simple nucleophile methylthiolate (CH_3S^-) in both gas and aqueous phases. Formation of a trigonal bipyramidal intermediate at the phosphorus center followed by elimination of leaving group is considered to be the major solvolyzed pathway through addition-elimination scheme. In this study, although there are two possible orientations for incoming nucleophiles with respect to the substrate, the present reaction mechanism is found to be independent of this relative orientation. The proposed addition-elimination mechanism has been first explored here. The results indicate that the α -effect is observed in presence of solvent. Free energy barriers for NH_2O^- and HOO^- are comparable and lower than that for the simple nucleophile, CH_3S^- . An important physical insight of this study is that there is a significant influence of the reaction medium on the nucleophilic reaction for solvolysis of PTH irrespective of the relative orientation of incoming nucleophile group.

Keywords. Parathion; α -nucleophiles; Solvolysis; DFT; potential energy surface; pesticide; softness; Fukui function.

1. Introduction

Parathion (PTH), an organophosphate (OP), is widely used as a pesticide to protect crops from insects.¹ OPs show significant toxicity towards mammalian organisms;^{2,3} they inhibit the activity of the enzyme acetylcholinesterase, which is involved in the transmission of nerve impulses through phosphorylation. On the other hand, increasing use of these insecticides contaminates the environment, particularly soil and ground water. Therefore, due to the high toxicity and bio-accumulation shown by these organophosphate compounds, many methods have been developed for their degradation.^{4,5} The methods available presently for the degradation OPs are homogeneous and heterogeneous hydrolysis,⁶ photolysis,⁷ photochemical degradation,⁸ biodegradation,⁹ the chemical treatments based on the use of nucleophiles^{4,5,9} or α -nucleophiles.^{10,11} However, some of these treatments may not be very efficient or are not

environment friendly due to the formation of products that have mild or acute toxicity.^{8,12} Some recent investigations pointed out that α -nucleophiles play an effective role in the degradation of the above type of toxic compounds.^{13,14} Several theoretical studies were also carried out for the thermal unimolecular decomposition,¹⁵ hydrolysis,^{16,17} α -nucleophilic destruction^{18,19} of such lethal agents and reported that α -nucleophiles are highly effective for decomposition of toxic OP pesticides under mild condition.^{20–24} As α -Nucleophiles bear non-bonding pairs of electrons at the position R to the nucleophilic center, their reactivity is greater than that would be expected on the basis of the pKa values.²⁵ Moreover, the high reactivity of α -Nucleophiles towards phosphorus makes them reagents of special interest for the destruction of nerve gases and other organophosphorus poisons.²⁶ But the origin of α -effect remains controversial till today.^{20,25,27–44} Earlier theoretical studies suggested that the origin of α -effect includes ground-state (GS) destabilization, transition-state (TS) stabilization, thermodynamic stabilization of products

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and solvent effects.^{20,25,27–44} Interestingly, solvent effect is also contentious for the α -effect, whether it is intrinsic properties of the nucleophiles or solvent induced phenomenon.^{25,28–31,33,35,42–50} The gas phase reactions between various anions and OP compounds have been investigated using mass spectrometry^{51,52} in absence of solvents and these findings reported that α -nucleophiles show greater reactivity than normal nucleophiles. Biberbaum *et al.*²⁸ in their study of gas phase reaction between α -nucleophiles and alkyl chlorides using a tandem flowing afterglow-selected ion flow tube instrument concluded that the α -effect is not due to an intrinsic property of the anion, instead, it is due to the solvent effect. But this is in contradiction to other experimental and theoretical studies of McAnoy *et al.*,^{29,53} with gas phase α -effect. In an experimental study, DePuy *et al.*²⁸ reported that nucleophilicity of peroxide anion is similar to hydroxide in gas phase and the α -effect is not significant in the absence of solvent. These results motivated us to investigate solvent effects on α -nucleophiles as well as on simple nucleophiles (no α -effect). However, depending primarily on the alkylation or arylation state of OPs and the nature of nucleophile, different pathways¹⁹ of degradation were reported. It has been reported that the attack at the phosphorus center, SN2(P) is the sole reaction pathway⁵⁴ for the reactions of Paraxon and its sulfur analogue, Parathion. Another study of alkaline perhydrolysis of a model VX compound reported that all the hydrolysis reactions proceed through the phosphorus-centered pentavalent intermediate.^{29,55} There are two different types of α -nucleophiles and one simple nucleophile used for nucleophilic destruction. Among various α -nucleophiles, the (-N-O- type) α -nucleophiles, i.e., hydroxybenzotriazoles have been used recently for the solvolysis of organophosphate esters, which show faster rate of solvolysis for such toxic esters.⁵⁶ This finding motivated us to explore the solvolysis of PTH with NH_2O^- nucleophiles. Previous theoretical study⁵⁷ of solvolysis of VX using hydroxide and α -nucleophile hydroperoxide inferred that hydroperoxide is a better nucleophile compared to hydroxide as hydroperoxide solely produces non-toxic products. Therefore, we have taken HOO^- as a α -nucleophile for detoxification. Other type of simple nucleophiles, namely CH_3S^- and CH_3O^- were reported⁵⁸ theoretically for solvolysis of different type of phosphate triesters. Xia *et al.*⁵⁹ reported a detail theoretical study of the methanolysis of paraxon and analogous reactions with sulfur substituted at the key oxygen position. However, no theoretical work is available so far in the literature for the thiolysis of PTH by CH_3S^- . Earlier theoretical study⁶⁰ reported that there is a significant attack at

the phosphorus center of phosphate triesters having an aryl-derived leaving group by CH_3S^- nucleophile in gas phase.

In order to investigate the α -effect of the nucleophiles, we have performed a systematic computational study of the solvolysis reaction of PTH with α -nucleophiles (NH_2O^- , HOO^-) and simple nucleophile, CH_3S^- in both gas and aqueous phases. As the biological activity of molecules depends on the electronic structure of the active part of a compound and its conformation, we first performed a conformational analysis of PTH. As the nucleophilic attack at the phosphorous center ($\text{SN}_2@\text{P}$) is the important pathway for solvolysis of OP pesticides,^{19,29,54,55} a detailed study of these pathways has been discussed for these three nucleophiles for the solvolysis of PTH. In addition, a comprehensive analysis has been performed to know the reactivity of the three nucleophiles, NH_2O^- , HOO^- and CH_3S^- in the $\text{SN}_2@\text{P}$ reaction using conceptual density functional theory.

2. Computational details

To find out stable conformers of PTH, a molecular dynamics (MD) conformational search has been performed with an unconstrained MD trajectory using the Verlet velocity algorithm and NVE thermostat along with other default parameters in Gabedit V.2.3.8.⁶¹ The PM6 semi-empirical method, as implemented in MOPAC 2009,⁶² has been used to find the minimum conformational geometries. Twenty five representative minimum structures, which are selected from the rigorous conformational search for final validation of the conformational analysis, are studied by the density functional theory (DFT). The DFT, with the hybrid functional (M06-2X) of Truhlar and Zhao,⁶³ has been employed to fully optimize the geometries of all the molecular species involved in this study. The standard 6-31++G(d,p)⁶⁴ basis set is used for all the atoms. The theoretical level for this combination of method and basis set is denoted as M062X/6-31++G(d,p). The normal-mode analyses have been performed at the same level of theory for reactants and products as well as TS geometries, and the minima are characterized with no imaginary frequency, whereas the presence of one imaginary frequency is the characteristic of TS. To evaluate the zero-point vibration energy (ZPVE) and thermal corrections to the Gibbs free energy at $T = 298.15$ K, harmonic vibrational frequencies are calculated at the M062X/6-31++G(d,p) level. The first-order saddle points, which are the transition states that connect the equilibrium geometries, are obtained using the synchronous transit-guided quasi-Newton (STQN) method. A parallel intrinsic reaction coordinate (IRC) calculation with all transition states has been performed to confirm whether these transition states connect the right minima or not.^{65,66} Single-point energy calculation are performed on the M062X/6-31++G(d,p) optimized geometries at MP2/6-311++G(2d,2p) level.^{67–72} Unless stated otherwise, energy

values reported herein include zero-point vibrational energy. The aqueous-phase calculations have been performed at the same level of theory similar to the gas-phase ones. The solvent effect has been taken into account by the conductor-like screening solvation model (COSMO),⁷³ as implemented in Gaussian 09.⁷⁴ All COSMO calculations in this study have been performed by using default choice of the Gaussian 09 program with the recommended standard parameters. In our previous study¹⁹ of nucleophilic degradation of fenitrothion by anionic nucleophiles, it has been reported that the COSMO model provides more appropriate information on energetics than the integral equation formalism polarized continuum solvation model (IEF-PCM)^{75–79} when compared with the experimental findings. Therefore, we have used the aqueous-phase energetics as well as geometric parameters of the COSMO model in successive discussions. All electronic structure calculations have been performed using the Gaussian 09 suite of quantum chemistry programs.⁷⁴

The reactivity descriptor, which is used in this work, is related to the local softness, $s(r)$, the global softness, S of the system⁸⁰ and the Fukui function,⁸¹ $f(r)$ by the following relation:

$$s(r) = f(r)S$$

Using the finite difference approximation, as proposed by Yang and Mortier,⁸² the compact form of Fukui functions of an atom k in a molecule with N electrons are,

$$f_k^+ = [q_k(N+1) - q_k(N)] \text{ for nucleophilic attack}$$

$$f_k^- = [q_k(N) - q_k(N-1)] \text{ for electrophilic attack}$$

where $q_k(N)$, $q_k(N-1)$, $q_k(N+1)$, are the electron population for the atom k in the neutral, cationic, anionic states of a system, respectively. The electron populations are evaluated at the neutral molecular geometry in both gas and aqueous phases. The Mulliken⁸³ charges calculated using the optimized geometries at M062X/6-31++G(d,p) level is utilized to compute f_k . The finite difference formula is used to calculate the global softness (S), i.e.,

$$S = 1/(IE - EA)$$

where, IE and EA are the first vertical ionization energy and electron affinity, respectively. IE and EA can be estimated from the Koopman's theorem⁸⁴ as the energy of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), respectively. Thus, S can be calculated from the following the expression,

$$S = 1/(E_{LUMO} - E_{HOMO})$$

The local softness of nucleophile and electrophile can be defined as,

$$s_k^- = S f_k^-$$

$$s_k^+ = S f_k^+$$

In our study, s^+ represents the local softness of the P atom in PTH and s^- represents the local softness of the O/S atom in nucleophiles. From the local version of the well-known hard

soft acid base (HSAB) principle of Gazquez⁸⁵ and Nguyen *et al.*,⁸⁶ and after a generalization by Ponti,⁸⁷ it emerges that the interaction between reaction partners is favored when it occurs through minimal $\Delta s(r)$, where,

$$\Delta s(r) = |s^+(r) - s^-(r)|$$

3. Results and Discussion

3.1 Conformational search of PTH

Low-energy conformations of molecular systems are found through conformational search by varying geometric parameters. Among the 25 selected conformers of **PTH**, the minima are finally optimized at M062X/6-31++G(d,p) level of theory. After DFT optimization, we get five lower-energy structures. The optimized geometries are shown in Figure 1, with the relative energies given in the parentheses. The lowest energy conformer found here is M1. The most stable ground state structures obtained by us are in good agreement with that reported previously by Ford-Green *et al.*,⁸⁸ who carried out the conformational search for PTH using DFT.

3.2 Reaction mechanisms: solvolysis of PTH

The nucleophilic substitution reactions for solvolysis of phosphotriesters compounds illustrate that substitution reactions mainly occur at phosphorus center through associative pathway.^{89,90} There are two possibilities in associative pathway: one is addition-elimination mechanism and other is direct displacement pathway. According to earlier results,^{16,17,55,91,92} the multistep pathway occurs in sarin, acephate, O,S-dimethyl methylphosphonothiolate (VX type model compound) and tabun, but paraoxon, parathion, fenitrothion and demeton-S appear to be hydrolyzed through direct displacement pathway. In contrast to these results, we have obtained only the multistep pathway for our systems, although several attempts have been made to find out the single step pathway. Previous theoretical work¹⁶ based on direct displacement type mechanisms was reported for the hydrolysis of a number of phosphotriesterase (PTE) substrates, but the solvolysis of parathion based on addition-elimination type mechanisms by α -nucleophiles has not yet been investigated theoretically. In the present investigation, the solvolysis of PTH is mainly due to the addition-elimination mechanism, involving the formation of trigonal bipyramidal intermediate and its further decomposition. The schematic representation of the aforesaid mechanism is as follows (Scheme 1).

Nucleophilic attack on the P atom of PTH followed by the release of p-nitrophenol through the SN2-type reaction is consistent with the addition-elimination

Figure 1. Gas-phase-optimized geometries at M062X/6-31++G(d,p) level [(Relative energies in kcal mol⁻¹ are given the parenthesis)] for the most stable conformers of PTH with important geometrical parameters.

mechanism. Depending on the relative orientation of incoming nucleophilic group, there are two possible pathways. In the first pathway, proton of hydroxylamine and hydroperoxide and methyl group of CH_3S^- are in the opposite direction to the phosphoryl sulfur atom (C1 path), whereas in second pathway, it is positioned in the same way (C2 path). All possible pathways have been explored in both gas and aqueous phases. Interestingly, second pathway is not established for gas phase. To confirm this finding, we have scanned the potential energy surface (PES) (given in the Supplementary Information [SI]) in the gas phase for the P-Nu bond formation and it is observed that there is a steady increase in energy, having no local minimum or maximum that might suggest absence of any transition state. However, we have bestowed light on only one pathway where orientation of nucleophile is opposite to phosphoryl sulfur atom in the gas phase and established both pathways in the aqueous phase. To facilitate the identification of each stationary point, we adopt a nomenclature to characterize them in the following sections. In Figures 2 to 7, a, b, c in the entire species name indicate the nucleophiles NH_2O^- , HOO^- , CH_3S^- , respectively, and there are two pathways associated with two relative orientations in aqueous phase, one is named as C1_{aq} and other is C2_{aq}. The relative energies calculated at MP2/6-311++G(2d,2p) // M062X/6-31++G(d,p) level, relative

free energies and enthalpies calculated at M062X/6-31++G(d,p) level are given in Table 1.

3.3 Reaction of PTH with hydroxylamine anion (NH_2O^-)

First we have studied solvolysis mechanism of PTH with NH_2O^- in both gas and aqueous phases. The optimized structures are given in Figure 2 and the free energy profiles obtained from M062X/6-31++G(d,p) calculation are presented in Figure 3. All the coordinates associated with the stationary points and ΔE values calculated at M062X/6-31++G(d,p) are given in the SI.

In the first step of gas phase solvolysis, a reaction complex (RCa) is formed, having 38.0 kcal mol⁻¹ lower in free energy than the infinitely separated complex ($\text{PTH} + \text{NH}_2\text{O}^-$). Here, orientation of nucleophile is opposite to the phosphoryl sulfur atom. The RCa is stabilized through the formation of a hydrogen bond between the O atom of the nucleophile and H atom of both $-\text{OC}_2\text{H}_5$ moiety with distances of 1.93 and 1.94 Å. Free energy profile (Figure 3) shows that nucleophile attacks at the P center of PTH to form an intermediate, IMa, through a unique trigonal bipyramidal (TBP) transition state, TS1a, having activation energy (ΔE) of 6.9 kcal mol⁻¹ and activation free energy (ΔG) of 6.8 kcal mol⁻¹. Our calculated values of both ΔE

Scheme 1. Addition-elimination reaction mechanism for the nucleophilic solvolysis of PTH. reaction of solvolysis of PTH.

and ΔG are comparable with that reported⁹² for the alkaline hydrolysis of paraoxon ($\Delta E = 8.7$, $\Delta G = 8.6 \text{ kcal mol}^{-1}$), methyl parathion ($\Delta E = 8.7$, $\Delta G = 8.8 \text{ kcal mol}^{-1}$) and fenitrothion ($\Delta E = 9.0$, $\Delta G = 9.3 \text{ kcal mol}^{-1}$) at MP2/6-311++G(2d,2p) // B3LYP/6-31+G(d) level of theory. In the next step, -OAr group is eliminated from IMA, which is a penta-coordinated intermediate with a unique trigonal bipyramidal structure, to form the product, Pa, situated $73.9 \text{ kcal mol}^{-1}$ below in free energy profile, *via* the transition state, TS2a, having activation free energy of $0.7 \text{ kcal mol}^{-1}$. The vibrational mode of the single imaginary frequency of TS2a corresponds to the complete rupture of the P-O bond. This value is also comparable to the earlier reported results⁹² for alkaline hydrolysis of paraoxon, methyl parathion, fenitrothion. The reason for this lower energy barrier is due to utmost similarity in structure between IMA and TS2a and it is consistent with the previous studies of paraoxon hydrolysis.⁹² In addition, from the enthalpy values, it is observed that formation of Pa is also exothermic in nature.

Figure 3 represents the PES of the reaction mechanisms of PTH with NH_2O^- at M062X/6-31++G(d,p) level in the aqueous phase. Here, two alternative pathways are discussed. Both pathways are started from the same substrate but orientation of incoming nucleophile is different. Figure 2 shows a significant structural difference between RCa-C1aq and RCa-C2aq complexes. But nucleophilic attack occurs in both the stationary points *via* TS1a-C1aq and TS1a-C2aq to form an intermediate IMA-C1aq and IMA-C2aq, respectively. The ΔE and

ΔG values for both TS are almost similar but lower than the gas phase values. This is probably due to more α -effect of the nucleophile in the solvent. In both pathways for two relative orientations, the product formation is exergonic in nature (ΔG of Pa-C1aq = -23.3 and ΔG of Pa-C2aq = $-22.9 \text{ kcal mol}^{-1}$). The normal-mode analysis and the IRC calculation confirmed that both transition states are well connected by the intermediate and product. The aforementioned reaction mechanisms are in good agreement with the addition-elimination mechanism in spite of different orientation of incoming nucleophilic group. As the activation energy barrier for elimination of leaving group is lower compared to addition of nucleophile group, the formation of TBP intermediate is the rate-limiting step and this outcome agrees well with the previous results.⁹²

3.4 Reaction of PTH with hydroperoxide anion (HOO^-)

Hydroperoxide anion is also an efficient α -nucleophile for solvolysis of PTH and it follows the similar type mechanism as described above for NH_2O^- . The optimized stationary points and free energy profile for both phases are presented in Figure 4 and Figure 5, respectively. Figure 5 shows reactant complex (RCb), which is located $36.9 \text{ kcal mol}^{-1}$ below the reactants (PTH + HOO^-), transforms further into intermediate, IMb, *via* a TBP geometric transition state, TS1b, having activation energy (ΔE) of $7.6 \text{ kcal mol}^{-1}$ and activation free energy (ΔG) of $7.4 \text{ kcal mol}^{-1}$. These values are

Table 1. Relative energies (ΔE) calculated at MP2/6-311++G(2d,2p) // M062X/6-31++G(d,p) level of theory and ΔH and ΔG calculated at M062X/6-31++G(d,p) level for all the species involved in the reactions.

Gas				Aqueous			
Species	ΔE	ΔH	ΔG	Species	ΔE	ΔH	ΔG
PTH + NH_2O^-	0.0	0.0	0.0	PTH _{aq} + NH_2O^- aq	0.0	0.0	0.0
RCa	-37.6	-49.6	-38.0	RCa-C1 _{aq}	-2.8	-1.5	8.1
TS1a	-30.7	-45.8	-31.2	TS1a-C1 _{aq}	1.9	0.2	11.7
IMa	-55.1	-72.8	-58.7	IMa-C1 _{aq}	-16.7	-22.7	-9.1
TS2a	-55.3	-71.7	-58.0	TS2a-C1 _{aq}	-17.0	-22.8	-8.4
Pa	-71.5	-86.3	-73.9	Pa-C1 _{aq}	-31.8	-34.2	-23.3
				RCa-C2 _{aq}	-2.5	-1.1	8.6
PTH + HOO^-	0.0	0.0	0.0	TS1a-C2 _{aq}	2.2	0.3	13.3
RCb	-36.3	-49.1	-36.9	IMa-C2 _{aq}	-17.4	-23.4	-8.4
TS1b	-28.7	-43.4	-29.5	TS2a-C2 _{aq}	-17.6	-23.5	-8.2
IMb	-53.2	-70.5	-55.9	Pa-C2 _{aq}	-32.0	-34.6	-22.9
TS2b	-52.1	-67.5	-54.3	PTH _{aq} + HOO^- aq	0.0	0.0	0.0
Pb	-59.1	-73.7	-61.6	RCb-C1 _{aq}	-3.8	-2.3	7.9
				TS1b-C1 _{aq}	1.3	-0.3	11.5
PTH + CH_3S^-	0.0	0.0	0.0	IMb-C1 _{aq}	-11.3	-16.5	-2.2
RCc	-25.4	-34.6	-23.6	TS2b-C1 _{aq}	-10.8	-15.2	-1.4
TS1c	-18.9	-29.8	-16.6	Pb-C1 _{aq}	-24.1	-25.1	-13.8
IMc	-26.2	-35.9	-24.0	RCb-C2 _{aq}	-3.3	-1.8	8.1
TS2c	-26.3	-35.9	-23.3	TS1b-C2 _{aq}	1.0	-0.9	12.2
Pc	-41.4	-49.3	-39.0	IMb-C2 _{aq}	-14.3	-19.1	-4.4
				TS2b-C2 _{aq}	-11.6	-16.0	-1.3
				Pb-C2 _{aq}	-21.1	-23.4	-11.6
				PTH _{aq} + CH_3S^- aq	0.0	0.0	0.0
				RCc-C1 _{aq}	-4.4	-1.5	6.7
				TS1c-C1 _{aq}	6.8	7.1	18.7
				IMc-C1 _{aq}	1.8	3.6	15.2
				TS2c-C1 _{aq}	3.5	4.6	17.1
				Pc-C1 _{aq}	-15.2	-11.6	-1.9
				RCc-C2 _{aq}	-3.4	-1.3	9.4
				TS1c-C2 _{aq}	8.1	8.0	20.2
				IMc-C2 _{aq}	2.6	4.5	17.5
				TS2c-C2 _{aq}	3.0	4.6	18.3
				Pc-C2 _{aq}	-12.3	-9.2	-0.5

All energies are in kcal mol⁻¹.

comparable with previously reported results⁹² of alkaline hydrolysis of organophosphorus pesticides. In the next step, a bond cleavage is occurred in the TS, TS2b, (activation free energy (ΔG), 1.6 kcal mol⁻¹) to form the product, Pb. IRC calculation for the corresponding TS confirms the formation of final product via complete breaking of the P-O bond.

In case of aqueous phase, two possible pathways are explored. Both the reactant complexes, RCb-C1_{aq} and RCb-C2_{aq} are lower in free energy in the energy profile, and nucleophilic attack occurs irrespective of orientations of the PTH and forms unique trigonal bipyramidal intermediate structures through the TS1b-C1_{aq} (ΔG = 3.6 kcal mol⁻¹) and TS1b-C2_{aq} (ΔG = 4.1 kcal mol⁻¹), respectively. Next in the elimination process of leaving

group, -OAr is eliminated to form the product complexes, Pb-C1_{aq} and Pb-C2_{aq} via the transition state, TS2b-C1_{aq} and TS2b-C2_{aq}. The IRC calculation for both the TS corroborates with the leaving of -OAr group through the intermediate and the product complex. Here, formation of the intermediate is rate-determining step and ΔE values for corresponding TS is lower in aqueous phase compared to gas phase due to more α -effect in solvent.

3.5 Reaction of PTH with methanethiolate anion (CH_3S^-)

In contrast to the above-mentioned α -nucleophiles, CH_3S^- is also an efficient simple nucleophile for the

Figure 2. Optimized geometries with important parameters in the gas and aqueous phases obtained at M062X/6-31++G(d,p) level for all the species involved in the reaction of parathion with NH_2O^- . All bond lengths and angles are in Å and ($^\circ$), respectively.

detoxification of PTH and other organophosphate esters. The optimized geometries in gas and aqueous phases are given in Figure 6 and the potential energy profiles obtained from M062X/6-31++G(d,p) calculation are presented in Figure 7.

An adduct (RCc), with $23.6 \text{ kcal mol}^{-1}$ lower in free energy with respect to isolated reactants, is formed during the initial nucleophilic approach towards PTH in gas phase. The RCc once formed transforms into another intermediate, IMc, through a TBP geometric

Figure 3. Free energy profile for the reaction of parathion with NH_2O^- at M062X/6-31++G(d,p) level of theory in gas (black color line) and aqueous (violet and cyan color lines) phases. C1 (violet line) and C2 (cyan line) correspond to the relative orientation in aqueous phase.

transition state, TS1c, having activation energy (ΔE) of $6.5 \text{ kcal mol}^{-1}$ and activation free energy (ΔG) of $7.0 \text{ kcal mol}^{-1}$. After surmounting the transition state, TS1c, the intermediate, IMc, a penta-coordinated intermediate with a TBP structure, is formed. In the very next step, p-nitrophenol can be eliminated from IMc to form the product, Pc, via the transition state, TS2c, having activation free energy of $0.7 \text{ kcal mol}^{-1}$. The vibrational mode of the single imaginary frequency of TS2c corresponds to the breaking of P-O bond. The greater similarity between intermediate and transition state structures is responsible for lowering of the free energy barrier.

The aqueous phase reaction of PTH with CH_3S^- passes through the formation of two different rela-

tive orientations of reactant complex, RCc-C1_{aq} and RCc-C2_{aq}. But nucleophilic attack at P center occurs in both the stationary points via TS1c-C1_{aq} and TS1c-C2_{aq} to form the intermediates, IMc-C1_{aq} and IMc-C2_{aq}, respectively. The ΔG values for both TS are 12.0 and $10.8 \text{ kcal mol}^{-1}$ but higher than the gas phase values. This is probably due to the fact that the ionic nucleophile is more stabilized in solvent than in gas phase. In the elimination step, the leaving group $-\text{OAr}$ is eliminated from both intermediates having orientations through TS2c-C1_{aq} and TS2c-C2_{aq} to form solvolyzed products. The normal-mode analysis and the IRC calculation confirmed that both transition states are well connected between the intermediate and product structures. The afore-mentioned reaction mechanisms are in

Figure 4. Optimized geometries with important parameters in the gas and aqueous phases obtained at M062X/6-31++G(d,p) level for all the species involved in the reaction of parathion with HOO^- . All bond lengths are in Å.

good agreement with addition-elimination mechanism in spite of the orientation of different incoming nucleophilic group. Moreover, the first step of nucleophilic

attack is the rate-determining step. As CH_3S^- is a simple nucleophile, there is no possibility of any enhanced nucleophilic effect like other α -nucleophiles. Though

Figure 5. Free energy profile for the reaction of parathion with HOO^- at M062X/6-31++G(d,p) level of theory in gas (black color line) and aqueous (violet and cyan color lines) phases. C1 (violet line) and C2 (cyan line) correspond to the relative orientation in aqueous phase.

CH_3S^- is a simple nucleophile, it also shows multistep addition-elimination pathways.

3.6 Reactivity trend of three nucleophiles

We now discuss about the nucleophilic reactivity based energetic and conceptual parameters values. Nucleophilicity can be correlated by comparing the rate determining transition state structure for different nucleophiles. It is clear from Table 1 that the first transition state of nucleophilic attack is the rate determining state

in both gas and aqueous phases. The calculated ΔG value for TS1c is $0.4 \text{ kcal mol}^{-1}$ lower compared to the corresponding transition state TS1b and $0.2 \text{ kcal mol}^{-1}$ higher than the TS1a in gas phase. But from these relative energetic values (ΔG), the trend in reactivity cannot be predicted in gas phase. In case of aqueous phase, ΔG is similar for TS1a-C1_{aq} and TS1b-C1_{aq} but both are lower in ΔG than TS1c-C1_{aq}. The order of reactivity for nucleophilic attack for C1_{aq} can be predicted from the aqueous phase energetics data and it is $\text{NH}_2\text{O}^- \approx \text{HOO}^- > \text{CH}_3\text{S}^-$, whereas in case of C2_{aq}

Figure 6. Optimized geometries with important parameters in the gas and aqueous phases obtained at M062X/6-31++G(d,p) level for all the species involved in the reaction of parathion with CH_3S^- . All bond lengths are in Å.

pathway, ΔG value for $\text{TS1b-C2}_{\text{aq}}$ is lower than that of $\text{TS1a-C2}_{\text{aq}}$ and $\text{TS1c-C2}_{\text{aq}}$. Hence, reactivity trend should be $\text{HOO}^- > \text{NH}_2\text{O}^- > \text{CH}_3\text{S}^-$. So, the reactivity trend is different in aqueous phase and it may be concluded that there is significant enhancement of α -effect for α -nucleophiles in aqueous medium compared to simple nucleophiles. But the reasonable values of ΔE ,

ΔH and ΔG suggest that the proposed mechanism for the solvolysis of PTH in both phases is realistic.

Conceptual DFT analysis (by means of electron density as the fundamental property) has been performed to find the trend of reactivity of α -nucleophiles and simple nucleophiles with PTH in both phases and try to correlate it with the reactivity trend obtained from ΔH and

Figure 7. Free energy profile for the reaction of parathion with CH₃S⁻ at M062X/6-31++G(d,p) level of theory in gas (black color line) and aqueous (violet and cyan color lines) phases. C1 (violet line) and C2 (cyan line) correspond to the relative orientation in aqueous phase.

ΔG values. The computational procedure to calculate these values has already been described in the Computational Details section. The calculated values for Fukui function (f) and local softness parameters (s^+ and s^-), the differences (Δs) of s^+ and s^- are presented in Table 2.

In the gas phase, the increasing order of Δs values is as follows: $\text{HOO}^- < \text{NH}_2\text{O}^- < \text{CH}_3\text{S}^-$. Therefore, the conceptual DFT results clearly infer that the reactivity of HOO^- is greater than that of NH_2O^- and CH_3S^- for the SN2@P attack on PTH, based on addition-elimination

Table 2. Global Softness (S), Local Softness (s^+ and s^-) and Fukui Function (f) for the α -nucleophiles (NH_2O^- , HOO^- , CH_3S^-) and Parathion, reactivity (difference in Local Softness (Δs) between parathion and α -Nucleophile) are calculated using Mulliken charge at M062X/6-31++G(d,p) level in the gas as well as in aqueous phase (in parentheses).

Species	S	F	s^+ and s^-	Δs
NH_2O^-	7.726 (4.206)	-0.567 (-0.565)	-4.381 (-2.377)	5.690 (2.301)
HOO^-	6.072 (3.722)	-0.643 (-0.657)	-3.904 (-2.448)	5.213 (2.372)
CH_3S^-	6.628 (4.141)	-0.879 (-0.928)	-5.826 (-3.843)	7.135 (3.767)
PTH	3.945 (4.057)	0.332 (-0.018)	1.309 (-0.075)	

mechanism. However, the increasing order of Δs values in aqueous phase is as follows: $\text{NH}_2\text{O}^- < \text{HOO}^- < \text{CH}_3\text{S}^-$ and it indicates that the reactivity of NH_2O^- is greater than that of HOO^- and CH_3S^- for the $\text{SN}_2\text{@P}$ attack on PTH. In addition, the computational analyses performed for the solvolysis of PTH suggest that the overall process seems to be a delicate balance between nucleophilicity and stabilization of intermediates and transition state. It may be concluded that other than the nucleophilicity of nucleophiles, reaction medium as well as electronic and structural factors could also be important to govern the rate of solvolysis of PTH. So, the reactivity trends for simple as well as α -nucleophiles for the $\text{SN}_2\text{@P}$ reactions with PTH through addition-elimination mechanism have been established.

4. Conclusions

The gas and aqueous phase reactions of the α -nucleophiles (NH_2O^- , HOO^-) and simple nucleophile (CH_3S^-) with neutral PTH have been studied in detail, theoretically. Mechanistic studies bestow light on the solvolysis reactions of PTH, based on multistep addition-elimination pathways which pass through the trigonal bipyramidal intermediates at phosphorus center. The reaction mechanism is independent of the relative orientation of the attacking nucleophile. The rate-determining step of multistep mechanisms appears to be associated with formation of an intermediate. The free energy barrier is lower for α -nucleophiles in aqueous phase compared to gas phase, indicating that the α -effect is significant in presence of solvent; but the results obtained for simple nucleophile is reverse. It is probably due to the stabilization of ionic nucleophiles by solvent. There is no significant α -effect in gas phase reactions for α -nucleophiles compared to simple nucleophiles. Moreover, the conceptual DFT analysis shows that the order of reactivity for all nucleophiles is different in aqueous phase compared to gas phase. After summarizing the

results, it is worth mentioning that the order of reactivity of nucleophiles based on forward activation energy barriers contradicts the conceptual DFT results in gas phase but it corroborates well in aqueous phase. Therefore, the most plausible explanation for the above fact is that the nucleophilicity and ability of leaving-group are important to determine the efficiency of nucleophilic reaction and it can be influenced by the medium of the nucleophilic reaction, electronegativity, stabilization of the transition states, intermediates, *etc.* In addition, these results are supported well by the previous⁹³ findings, which reported that the assessment of α -effect by conventional way can be ambiguous due to some controversial results obtained for gas phase reaction for the chosen α -nucleophiles compared to simple nucleophiles. We hope this work will serve as a reference for investigating the intrinsic reactivity of these types of compounds and can provide some useful information for further experimental and theoretical studies.

Supplementary Information (SI)

Relative energies, Cartesian coordinates of all optimized geometries are given in the Supplementary Information., which is available at www.ias.ac.in/chemsci.

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