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Theoretical prediction on the hydrolysis rate of the new types of nerve agents: A density functional study

Md Al Mamunur Rashid [a], Byounghwak Lee [b], Kwang Ho Kim [a], Keunhong Jeong [b,*]

[a] Clean Energy Research Center, Korea Institute of Science and Technology, Seoul 02792, South Korea
[b] Department of Physics and Chemistry, Korea Military Academy, Seoul 01805, South Korea

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ABSTRACT

Although the hydrolysis mechanism of the nerve agents, which is the main decontamination pathway, has been studied experimentally and theoretically, the reliable theoretical prediction method for the hydrolysis rate is not studied yet. Furthermore, after the CWC (Chemical Warfare Agent) list is updated, Novichok candidate structures can be more than 10,000 structures, for which it is not possible to perform the experiment for all of them for synthesizing and getting the hydrolysis rate. Therefore, developing a reliable theoretical method for hydrolysis rate prediction is crucial to prepare for the forthcoming usage of new types of nerve agents. Herein, by using DFT (Density Functional Theory), we successfully developed a new method of predicting the hydrolysis rate on nerve agents by investigating the electrophilicity index (EI) of the various A-, V-, and G-series nerve agents and found a suitable correlation with the experimental hydrolysis rate. Among the several DFT methods, wb97xD predicts the EI with the lowest % deviation of the studied nerve agents. Our results show that EI can be a good indicator to predict the hydrolysis rate of the anticipated nerve agents. Based on the result, we predicted the hydrolysis rate on another type of Novichok candidates, which could be the firm basis for developing a decontaminant and antidote with much fewer experimental efforts on new types of nerve agents.

1. Introduction

Chemical warfare agents (CWAs) are the most destructive, toxic, and lethal chemicals used in the twentieth century [1–4]. After World War I, a large quantity of these agents was disposed of in the oceans [5], without keeping in mind how could it be dangerous for sea life and their dependent species [6,7]. Among the four classes of CWAs [8,9], the most hazardous CWA, for terrorist activities, are nerve agents, which are classified as the G-series, which includes G- [tabun (GP), sarin (GB), soman (GD), and cyclosarin (GF)] and V-series, of which the most well-known is VX, and VR. Another novel class of nerve agents, referred to as Novichok agents, were also synthesized in the 1970s, which are A-230, A-232, and A-234 [10]. These deadliest nerve agents strongly inhibit the activity of cholinesterase [11], highly detrimental to both target and non-targeted organisms [12,13], and a threat to human as these chemicals were used not only in warfare but also in acts of terrorism [14–16]. These nerve agents are considered the most toxic substances amongst CWAs ever synthesized [17–19]. Although there is an updated CWC list on those materials [20]. [20], very little reliable information on their physicochemical, electronic, or other properties [7].

The A-series Novichok nerve agents first alerted the world after the assassination attempt against Sergei Skripal being exposed to a Novichok agent A-234 [21,22]. More recently, another Novichok agent was used against Alexei Navalny in 2020 [23]. The nerve agents can inactivate the central nervous system enzyme, which is responsible for the breakdown of the neurotransmitter acetylcholine; thus, leading to rapid and severe adverse effects on the environment, animals, and humans, resulting epilepsy, and inability to concentrate, etc. [24,25]. Although the Skripal poisoning motivated to research on the chemical structure, synthesis, toxicity, deployment, detection, and destruction of these nerve agents, unfortunately, there is still little information on the detection, neutralization, and poisoning treatment. Thus, from a social security perspective, further investigation of various properties of nerve agents, including toxicity, reactivity, and hydrolysis is crucial.

The scientific literature on nerve agents is incomplete and sometimes contradictory [6,26]. Only a handful of experiments have been performed on the nerve agents until now due to these compounds' unavailability [19,27,28]. Thus, researcher focused on theoretical investigation to obtain information about the various properties of these

* Corresponding author.
E-mail addresses: doas1mind@kma.ac.kr, doas2mind@berkeley.edu (K. Jeong).

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nerve agents [22]. However, investigations of the hydrolysis reactions of the nerve agents are crucial to ensure the proper utilization of the nerve agents [29–31], and to establish the fast decontamination methods to decrease the threat for the environment and human security [32–34]. Thus, the easy hydrolysis of these nerve agents is a prime focus of many studies in recent times [34,35]. Ramasami calculated the enthalpy and energy changes for hydrolysis and solvolysis of A-234 [22]. Imrit studied the hydrolysis mechanism of A-234 using DFT, finding that the water molecule attack at the acetoamidine center is thermodynamically favored compared to the hydrolysis at the phosphinate center [36]. Hadad performed a computational study of the five nerve agents, named as soman (GD), VX, VR, paraoxon, and tabun, and showed the exothermicity behavior with nucleophiles [37]. Ganguly did a DFT study regarding the solvolysis of GB and found a profound effect of α-nucleophiles on the process of sarin compared to alkaline hydrolysis [38].

While several groups investigated the mechanism of the hydrolysis reaction of the nerve agents theoretically from a different viewpoint such as reaction pathway, transition state structure, activation energy, conformer of the transition state structure, etc., however, the hydrolysis reactions under basic conditions, have not been investigated in detail in the viewpoint of nucleophilic activity. Patterson performed a DFT study regarding the solvolysis of a CWA named VX, with the two nucleophiles hydroxide and hydroperoxide, where they found that the hydrolysis reaction has been considered to attack only one nucleophile, but the two nucleophiles (hydroxide and hydroperoxide) no longer display the same preference for initial attack [31]. Thus the explanation of the experimental hydrolysis through the reaction mechanism or activation energy is not always trustworthy. Although even the involvement of nucleophiles is crucial for hydrolysis, very few studies have investigated the nucleophilic chemistry during the hydrolysis of the nerve agents, which also lacks proper information such as prediction of experimental hydrolysis rate, proper activation energy, factors affecting the hydrolysis rate, etc. However, the electrophilicity index (EI), which measures the reactivity towards the nucleophile [39], can be a good indicator for the proper explanation, as well as prediction of the hydrolysis process for the nerve agents. If we can explore the EI, we will know how EI can be vulnerable to many other nucleophiles in the hydrolysis rate during the hydrolysis reaction. Unfortunately, there are not many papers that investigated the EI regarding the nucleophile and the hydrolysis rate. This inspired us to investigate the hydrolysis rate of the nerve agents in relation to EI.

Recently, Harvey experimented with the hydrolysis reactions of the conventional nerve agents, including Novichok agents, under neutral conditions and in the presence of enzymes and compared them with common G- and V-series nerve agents at 25°C and a pH of 7.2 in 50 mM bis-tris-propane, and they concluded that the hydrolysis rates of Novichok agents were much slower than that of GB and slower than that of VX under neutral conditions [28]. In this contribution, we analyzed their experimental hydrolysis rate (see ESI) compared to theoretically calculated EI to predict the hydrolysis rate of the studied nerve agents (Fig. 1). Here, we performed quantum chemical calculations using density functional theory (DFT) to investigate how EI can predict the hydrolysis rate of nerve agents. We found a good correlation between hydrolysis rate and EI, which can be used to predict the hydrolysis rate for future nerve agents. We believe that this study will give shed light on predicting the hydrolysis rate of the upcoming nerve agents.

2. Methods

All the calculations were performed using Gaussian 16 package unless otherwise stated [40]. Initially, the nerve agents were optimized using the B3LYP/6–311++G(d, p) [41] level of theory. Harmonic vibrational frequency calculations were confirmed with no imaginary frequency of the optimized structures. One imaginary frequency was found for the transition state structures. Activation energies were

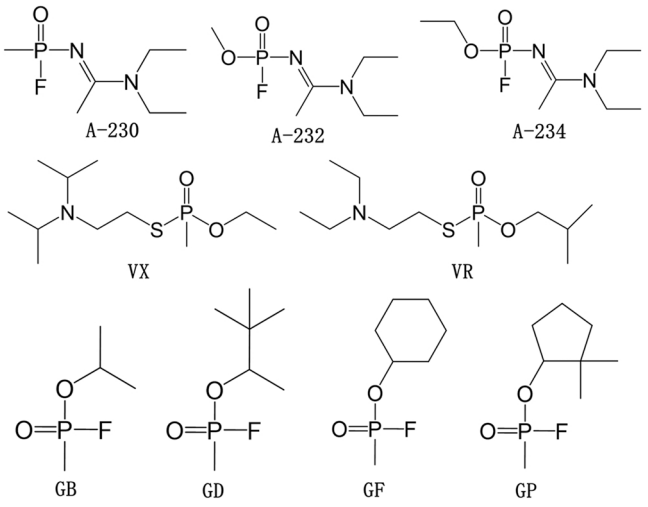

Fig. 1. Chemical structures of the studied A-, V-, and G-series nerve agents.

obtained from the transition state calculations. IRC (Intrinsic Reaction Coordinates) calculations for all the transition state structures were performed at the same level. Single point energy calculations were performed with M062X/6–311++G(d, p) [4] and MP2/6–311++G(d, p) [42] level of theory based on the optimized and transition state structures of B3LYP functional. To introduce the solvent effect, the solvent H_2O with a polarizable continuum model (PCM) [43] was used throughout the calculations for all the nerve agents. All the electronic structural properties were calculated in the solvent phase from the optimized geometries using the B3LYP/6–311++G(d, p) method. The electronic properties were obtained mainly by using Multiwfn software [44]. Later, the EI was calculated from the optimized geometries by using five different DFT functionals such as M062X, APFD, PBE, BMK, and wb97xD, with the same 6–311++G(d, p) basis sets in the same solvent phase via UCA-FUKUI program [45]. The lipophilicity property (AlogP98) of Novichok candidates were determined using the Discover Studio 2022 software package (Accelrys Software, Inc., San Diego, CA, United States).

3. Results and discussions

3.1. Activation energy analysis

The optimized structures of the V-, A-, and G-series nerve agents have been shown in Fig. 2 (Fig. 2). The optimization has been done by using B3LYP/6–311++G(d, p) in the aqueous conditions as the efficiencies of S_N2 reactions are influenced by solvent effects in the H_2O [46,47]. During the hydrolysis with OH^-, the P-F and P-S bonds break, in the case of A-, G-series, as well as V-series, respectively [48]. As our concern was not to depict the hydrolysis reaction mechanism of the nerve agents, we have focused only on the activation energy of the first step of the hydrolysis which has been listed in Table S1. For the comparison, we have calculated the activation energies of the nerve agents with two DFT methods, B3LYP and M062X, as well as the MP2 method. It is seen that the activation energy calculated by M062X is lower than that of the other two methods (see Table S1). Although the first step of the hydrolysis reaction is generally considered the rate-determining step because the energy of transition state on rate-determining step is kinetically the highest energetic number to overcome to go further for overall reaction [48], it is worth noting that we did not find any correlation between the experimental hydrolysis rate [28] and the calculated activation energy of the hydrolysis reaction of the nerve agents.

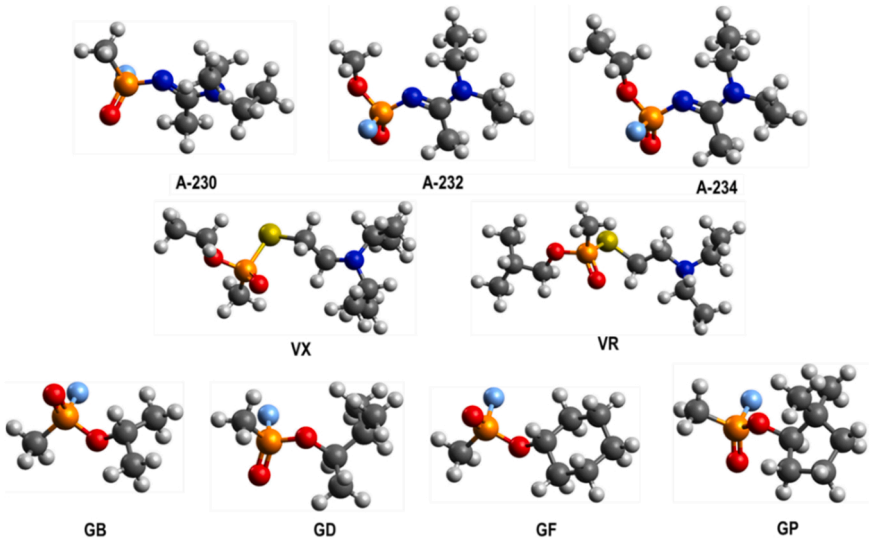

Fig. 2. Optimizes structures of the A-, V-, and G-series nerve agents using B3LYP/6–311++G(d, p) level of theory in H_2O solvent.

3.2. Electrophilicity Index analysis

Various electronic structure properties of the nerve agents have been calculated by using B3LYP/6–311++G(d, p) and listed in Table S2. Interestingly, we did not find any meaningful correlations of the experimental hydrolysis rate with the theoretically calculated electronic structure properties except the EI. Thus, to find the most reliable level of theory the EI has been calculated by using five more DFT methods such as M062X, APFD, PBE, BMK, and wb97xD with the same 6–311++G(d, p) basis sets in solvent H_2O. Fig. S1 represents the logarithmic value of the experimental hydrolysis rate vs negative logarithm of EI of the studied nerve agents using six DFT methods with 6–311++G(d, p) basis sets (Fig. S1). The circular red dot indicates the logarithmic experimental hydrolysis rate whereas the other dots represent the negative logarithmic value of EI of the nerve agents using six DFT methods. It is observed from Fig. S1 that the calculated EI show an almost linear relationship with the experimental hydrolysis rate of the nerve agents (Fig. S1). Since the EI values varied for various DFT methods, we have successfully normalized the experimental hydrolysis rate, as well as the calculated EI values for the quantitative analysis. Although all the EI values show almost similar trends, the EI calculated by the wb97xD method showed the least deviation with the experimental hydrolysis rate compared to other DFT methods. Thus, in order to discuss the electrophilicity pattern of the nerve agents clearly, we have only plotted the normalized logarithmic value of experimental hydrolysis rate vs normalized negative logarithmic EI value of the nerve agents using wb97xD/6–311++G(d, p) level of theory, which has been shown in Fig. 3 (Fig. 3). However, the calculated normalized EI value of the other DFT methods vs the normalized experimental hydrolysis rate has been shown in the ESI (Fig. S2). In Fig. 3, the triangular open dot indicates the normalized negative logarithmic value of the calculated EI done by the wb97xD method (Fig. 3). Similar to the experimental hydrolysis rate, the G-series shows a higher EI compared to the V-series and A-series, whereas the A-series nerve agents show the lowest value of EI. We have also classified the nerve agents into three different regions. The yellow, gray, and purple region represent the A-series, V-series, and G-series nerve agents. In the case of A-series Novichok agents, the EI shows almost similar to the hydrolysis rate of A-234 which is close to zero. With increasing the hydrolysis rate from 38 % to 52 % for A-232 to A-230, the EI increases up to 5 %. Similar behavior has been observed in the case of other DFT methods for the A-series Novichok agents (Fig. S2). We additionally analyzed the possible reason on the discrepancy of the hydrolysis rates among A230, A232, and A234. Additional calculation

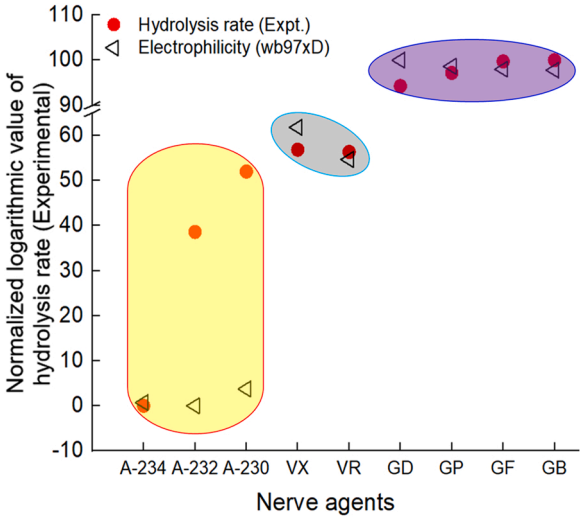

Fig. 3. Normalized logarithmic value of hydrolysis rate (Experimental) vs normalized negative logarithmic value of Electrophilicity index of the nerve agents calculated by wb97xD/6–311++G(d,p) level of theory in solvent H_2O.

on the atom-type partition coefficient (AlogP98) is carried out, it indicates that the A234 (0.921) is much more lipophilic than the others (A232: 0.573, A230: 0.233), which explains that the nucleophiles may be less accessible to the electrophilic center of Novichok agents (phosphorus) in aqueous circumstance. Although the deviation between the hydrolysis rate and EI is higher for these two Novichok agents, however, the predicted trend is the same. For V-series nerve agents, it is seen in Fig. 3 that with decreasing the hydrolysis rate from VX to VR, the EI also shows a decreasing pattern (Fig. 3). In Fig. S2, although all the calculated EI value are showing the similar decreasing pattern from VX to VR, however, the deviation of the EI values compared to the hydrolysis rate are larger (Fig. S2). The EI value calculated by BMK shows the lowest deviation whereas the EI calculated by B3LYP shows the highest deviation. For the G-series nerve agents, as the hydrolysis rate are observed as an increasing order from GD to GB, all the EI calculated by several DFT methods can predict the experimental hydrolysis rate smoothly as their values are close to each other (Fig. 3 and Fig. S2). Thus it can be said that the calculated EI can predict the hydrolysis rate of the G-series more accurately rather than that of A- and V-series nerve agents. Another observation is that the hydrolysis rate of G-series is higher than

V- and A-series. The calculated EI also shows higher value than that of V- and A-series. Similarly, the hydrolysis rate of A-series is lower than V- and G-series. The calculated EI of the A-series are also lower. This ensures that the calculated EI can accurately predict the hydrolysis rate of different series of nerve agents.

3.3. Suitable DFT method

As it is observed in Fig. 3 and S2 that the calculated EI shows the deviation of the % normalized value regarding various DFT methods (Fig. 3 and Fig. S2), we have compared the %deviation of the normalized EI value resulted from the six DFT methods to investigate which method can predict the hydrolysis rate of the nerve agents more accurately. The %deviation of the EI, of the studied nerve agents from the experimental hydrolysis rate, calculated by six DFT methods has been represented in Fig. 4 and listed in Table S3 (Fig. 4). In case of A-series Novichok agents, the deviation is <1 % for A-234. However, for A-232 and A-230, the % deviation of EI is higher which is 38.5 % and 49 %, respectively for all the DFT methods. For V-series nerve agents, the %deviation varies significantly based on the DFT methods. B3LYP shows the highest deviation (~20 %) and wb97xD shows the lowest deviation (5 % for VX and 1.6 % for VR) of the EI value for predicting the hydrolysis rate. For G-series nerve agents, the deviations are ~2 % for all the methods except for GD, which shows ~5 % deviation for most of the DFT methods. In summary, it can be successfully concluded that for predicting the hydrolysis rate of the nerve agents theoretically from the EI value, wb97xD is the most suitable method among the studied DFT methods.

3.4. Prediction of upcoming nerve agents

Based on the previous study, we developed a novel theoretical method for predicting the hydrolysis rate, which is most crucial information for developing antidote and decontaminant. Therefore, we used the developed method to predict the hydrolysis rate on new compounds, which have not been experimentally studied. Therefore, we have calculated the EI of the two other nerve agent candidates, mentioned as A and B (see Fig. 5) whose side chain is composed of guanidine derivative (different class from previous ones) and whose experimental hydrolysis rate is still unknown, by using wb97xD/6–311++G(d, p) level of theory, as this method shows the best result compared to other DFT methods. Based on our theoretical result, as A and B should be similar as the A-series nerve agents, it can be said that the hydrolysis rate of A and B will be lower than that of V-series nerve agents and significantly lower than that of G-series nerve agents. To the best of our knowledge, this is the first case to predict the hydrolysis rate on Novichok candidates.

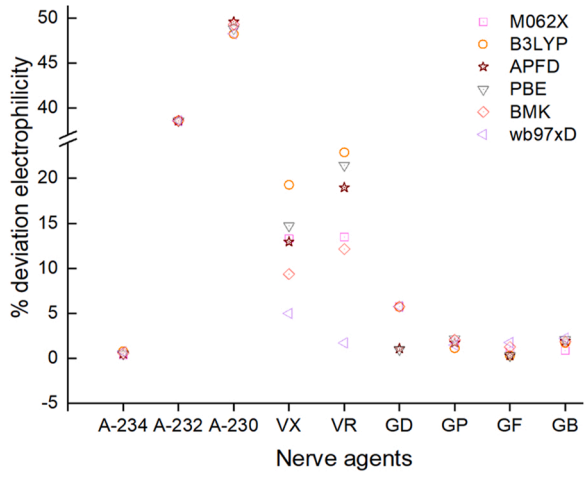

Fig. 4. % deviation of Electrophilicity index of several DFT methods with respect to experimental hydrolysis rate of the studied nerve agents.

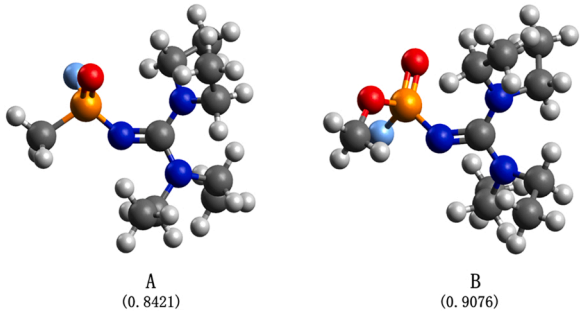

Fig. 5. : Optimizes structures of the two A-series nerve agents. The parenthesis value represents the electrophilicity index calculated by wb97xD/6–311++G (d, p) level of theory.

Therefore, from this study, our developed theoretical method using the EI, mathematical process, and DFT method (wb97xD/6–311++G(d, p)) can be a good indicator for predicting the hydrolysis rate of the other forthcoming nerve agents.

4. Conclusion

In this study, we successfully developed a theoretical method to predict hydrolysis rate of nerve agent and predict on new types of nerve agents. To do that, we theoretically calculated the EI of the A-, V- and G-series nerve agents by using six DFT methods and predicted the experimental hydrolysis rate of those nerve agents after reasonable mathematical process. To find and compare with any other methods, we also calculated the activation energy, which has been mostly considered, and several electronic structure properties of the nerve agents and did not find any correlation with the experimental hydrolysis rate. We found a logarithmic correlation of the experimental hydrolysis rate with the negative logarithmic calculated EI value of the studied nerve agents in the circumstance of various nucleophiles. Compared to other DFT methods, the EI value calculated by wb97xD method is more suitable for predicting the hydrolysis rate of the nerve agents. Thus it can be said that EI can be a very good indicator for the predicting of the hydrolysis rate of the future nerve agents. To apply its method on new materials (A and B), we performed on the new types of nerve agents, which does not have experimental data, and theoretical results predicted that its hydrolysis rate should be almost same with A-series. Even though CWC list is updated, exact structures of fourth generation nerve agents are not known yet. Further, experimental study has a big obstacle to study on hydrolysis properties. Therefore, this successfully established theoretical method could be a firm basis for developing decontaminant and antidote with much less experimental efforts. Moreover, further theoretical investigations on various chemo-physical properties are required in this field to cope with the usage of new types of nerve agents during terror or war in near future.

CRediT authorship contribution statement

Md Al Mamunur Rashid: Writing – original draft, Methodology, Investigation, Software, Visualization, Resources. **Byounghwak Lee:** Methodology, Investigation. **Kwang Ho Kim**: Writing – review & editing, Project administration, Funding acquisition. **Keunhong Jeong**: Conceptualization, Validation, Supervision, Writing – review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.toxrep.2022.12.001.

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