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Investigation of the Colorimetric Characteristics of VX in Squaraine-Based Solutions

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Abstract: Colorimetry is an important on-site detection method for organophosphorus compounds. *O*-Ethyl *S*-(2-diisopropylaminoethyl) methylphosphonothioate (VX) is recognized as one of the deadliest organophosphorus chemical agents, and the rapid on-site detection of VX is of great significance to public safety. In this paper, a squaraine derivative was synthesized as probe molecules, and the sensing characteristics of VX in a colorimetric solution system containing tetrabutylammonium fluoride (TABF) were studied with UV−Vis spectroscopy, nuclear magnetic resonance (^{1}H NMR), and mass spectrometry. The results showed that the binding of the thiol moiety of VX to the quaternary ring of the squaraine probe changed the molecular conjugation system, and that the rapid colorimetric detection of micro-trace VX was achieved based on color change before and after interaction with squaraine, enabling the detection limit of VX to be as low as 0.4 μg/mL. Moreover, the colorimetry method also possessed satisfactory sensitivity and could detect VX from other organophosphorus pesticides (e.g., parathion and dichlorvos), phosphorus-containing reagents (e.g., diethyl chlorophosphate and dimethyl methylphosphonate), a benzene series (e.g., toluene), and acid and base agents (e.g., acetic acid and triethylamine, respectively), which demonstrated that squaraine-based colorimetry could provide fast, on-site measurement results for VX detection. The strategy of this research could be extended as a common approach for the detection of other organophosphorus nerve agents or organophosphorus pesticides.

Keywords: squaraine; colorimetry; VX; mechanism

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1. Introduction

Squaraine compounds are a class of excellent functional dyes with unique D–A–D conjugated structures [1], extremely high molar extinction coefficients, and strong absorption and fluorescence emission in the visible and near-infrared regions [2,3]. The unique structural characteristics of squaraine dyes make them easy to be attacked by nucleophiles [4,5]. As colorimetric and fluorescent probes, squaraine dyes are used in the detection of proteins [6,7], small biological molecules [8,9], environmental pollutants [10], and metal ions [11–13].

Organophosphorus compounds represented by organophosphorus nerve agents and organophosphorus pesticides are extremely toxic to humans and animals. After entering the body, they can quickly interact with acetylcholinesterase, resulting in neurological disorders and endangering the life and safety of the body. *O*-Ethyl *S*-(2-diisopropylaminoethyl) methylphosphonothioate (VX) is one of the deadliest persistent organophosphorus nerve agents [14]. Human skin contact or the inhalation of VX can cause poisoning, and a lethal dose of VX can cause a person to stop breathing and die within minutes [15]. Currently, VX detection methods mainly consist of chromatography and chromatography–mass spectrometry [16,17], which can be employed for the qualitative and quantitative analyses of samples and have extremely high sensitivity. However, these methods usually require sophisticated and expensive instruments, and the operations are complicated and time-consuming; therefore, they are not appropriate for the on-site rapid detection of targets.

Consequently, determining a fast, simple, and cost-effective method for VX detection is still a challenge. Compared with traditional persistent nerve agent detection methods represented by chromatography and chromatography–mass spectrometry, colorimetry possesses the advantages of low cost and fast and simple operation [18–21] and is widely used for the rapid, on-site detection of organophosphorus compounds [22–25]. At present, most colorimetry methods used for VX detection have used gold nanoparticles and enzymes [18,19]. These sensing materials should be prepared in advance, and their selectivity is mediocre. Squaraine has excellent absorbance and has application prospects in the colorimetric detection of persistent organophosphate nerve agents. However, there are few reports on the use of squaraine as a probe for VX detection.

Most of the procedures for the colorimetric detection of VX with dyes have used F^- to react with VX at room temperature to quickly destroy the P–S bond [26,27]. The solubility of VX is extremely poor, and organic solvents are generally used to dissolve and sample VX. Therefore, it is necessary to use organic fluorine salts to react with VX because of the poor solubility of metal salts, such as sodium fluoride in organic solvents. As an organic base, tetrabutylammonium fluoride (TABF) is a good phase transfer catalyst with good solubility in both the organic phase and water that can be utilized as a facile fluoride source. In this paper, a squaraine derivative is synthesized as a probe molecule, and TABF is mixed with squaraine to prepare a colorimetric solution. A colorimetric method for VX detection is established, and the sensing features of VX in the solution are investigated using UV−Vis spectroscopy and nuclear magnetic resonance (^{1}H NMR). This study shows that the colorimetry method used for the detection of VX developed in this article can be used for the rapid on-site detection of microtrace VX. In addition, organophosphorus pesticides, phosphorus-containing compounds, a benzene series, and acid and base compounds have no effect on the colorimetric detection of VX. Therefore, these observed results demonstrate that this method has promising application in the field of organophosphorus compound detection.

2. Materials and Methods

2.1. Reagents and Instruments

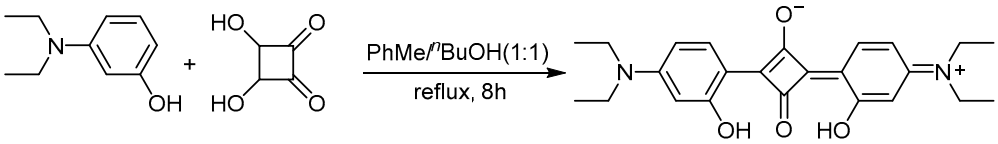
3,4-dihydroxy-3-cyclobutene-1,2-dione (98%) was obtained from Adamas Reagent Co., Ltd., Shanghai, China, and dimethyl methylphosphonate (DMMP) was obtained from Sun Chemical Technology (Shanghai) Co., Ltd. (China). Diethyl chlorophosphate (DCP) (97%) was purchased from Alfa Aesar (United States). Parathion and dichlorvos (DDVP) were received from MTstandard (Beijing, China). VX was received from the Laboratory of Analytical Chemistry, Research Institute of Chemical Defense (Beijing, China). Other chemicals of analytical grade were procured from Beijing Chemical Works (Beijing, China).

^{1}H NMR and mass spectra (MS) were measured with Brucker Advance 300 MHz $CDCl_3$ (δ = 7.26 ppm) and Agilent InfinityLab LC/MSD instruments, respectively. UV−Vis spectra were recorded with a Mettler Toledo UV5Nano Spectrophotometer.

2.2. Synthesis of Squaraine Probe (SP)

The synthetic route of SP is shown in Scheme 1. A total of 3.3 g of N, N-diethyl-m-hydroxyaniline (20 mmol) and 1.14 g (10 mmol) of 3,4-dihydroxy-3-cyclobutene-1,2-dione were added to a 250 mL dried solanum bottle. Then, 130 mL of mixed-solvent toluene and *n*-butanol (*V*:*V* = 1:1) was added. After evenly mixing, the mixture was stirred for reflux at 138 °C for 8 h. During the reaction process, the water produced by the reaction was removed with a water separator. After the reaction was complete, the mixture was filtered, and the solvent was removed. The residue was recrystallized in methanol and filtered, and the filter cake was rinsed with methanol three times. After vacuum drying, 1.6 g golden green solid was obtained with a yield of 40%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.09 (s, 2H), 11.39 (s, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 2H), 6.33 (dd, *J* = 9.2, 2.4 Hz, 2H), 6.13 (t, *J* = 2.9 Hz, 2H), 3.47 (q, *J* = 7.1 Hz, 8H), and 1.25 (t, *J* = 7.1 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.56 (s), 132.78 (s), 107.95 (s), 98.94 (s), 93.38 (s), 45.83 (s), 12.99 (s),

and 0.14 (s). MS (ESI) m/z: 409.2 $(M+H)^+$. ^1H NMR spectrum of SP in $CDCl_3$ is displayed in Figure S1.



Scheme 1. Synthesis of squaraine probe.

2.3. Establishment of Colorimetry

A method for determining the concentration of TABF in a colorimetric solution can be found in the Electronic Supplementary Information (ESI), and UV−Vis spectra and color changes of colorimetric solutions contented TBAF of different concentrations are shown in Figure S2 and Figure S3, respectively. Table S1 displays the absorbance change of colorimetric solutions, and the concentration of TABF in a colorimetric solution was determined to be 250 μg/mL. A series of 2 μg/mL SP colorimetric solutions (CH_2Cl_2, containing 250 μg/mL TBAF) was prepared, and the concentrations of VX contained in these colorimetric solutions were 0, 2, 4, 10, 40, 100, 150, 200, 400, and 500 μg/mL. This was followed by an observation of the color changes in this series of solutions with the naked eye. The UV−Vis absorption spectra of these solutions were measured with a Mettler Toledo UV5Nano Spectrophotometer, and the maximum absorbance was plotted as a curve.

To evaluate the colorimetry method's VX detection specificity, 4 mg/mL of organophosphorus pesticides (parathion and DDVP), phosphorus-containing reagents (DCP and DMMP), a benzene series (toluene), an acid (acetic acid), and a base (triethylamine) were added separately to colorimetric solutions containing 2 μg/mL SP and 250 μg/mL TBAF, and their absorption spectra were recorded with the same procedure as that used to detect VX. Meanwhile, to investigate the anti-interference of the colorimetry method, solutions containing 2 μg/mL SP, 250 μg/mL TBAF, and 10 μg/mL VX were treated with 1 mg/mL parathion, DDVP, DCP, DMMP, toluene, AcOH, and Et_3N, and their absorption spectra were measured with the same procedure used to detect VX.

All spectra mentioned above were measured one minute after the solutions were mixed.

2.4. Detection Mechanism

An SP solution containing TABF, a mixed solution of TBAF and VX, and a colorimetric solution containing SP, TBAF, and VX were prepared, followed by a determination of the mass spectrometry and ^1H NMR results of the three solutions.

3. Results

3.1. Colorimetry for VX Detection

As can be observed from Figure 1, the colorimetric solution without added VX was light blue, and the color of the solution gradually became lighter after adding VX. When the VX concentration reached 200 μg/mL, the solution was faded and almost transparent. Furthermore, the change in the UV−Vis spectra showed that the absorption peak of the solution at 644 nm decreased gradually with an increase in VX concentration (Figure 2a). It can be noted that the UV−Vis spectra still changed with a concentration of VX as low as 2 μg/mL. As the VX concentration increased to 400 μg/mL, the absorbance of the colorimetric solution at 644 nm hardly changed (Figure 2b).

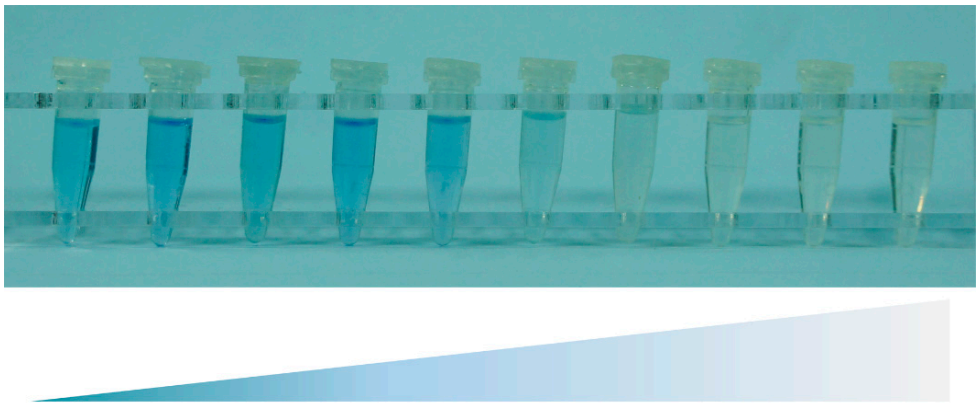


Figure 1. Change in color of the colorimetric solution. The concentrations of VX in the colorimetric solution were 0, 2, 4, 10, 40, 100, 150, 200, 400, and 500 μg/mL, respectively, from left to right. The gradient color bar represented the VX concentration and color change of the solution.

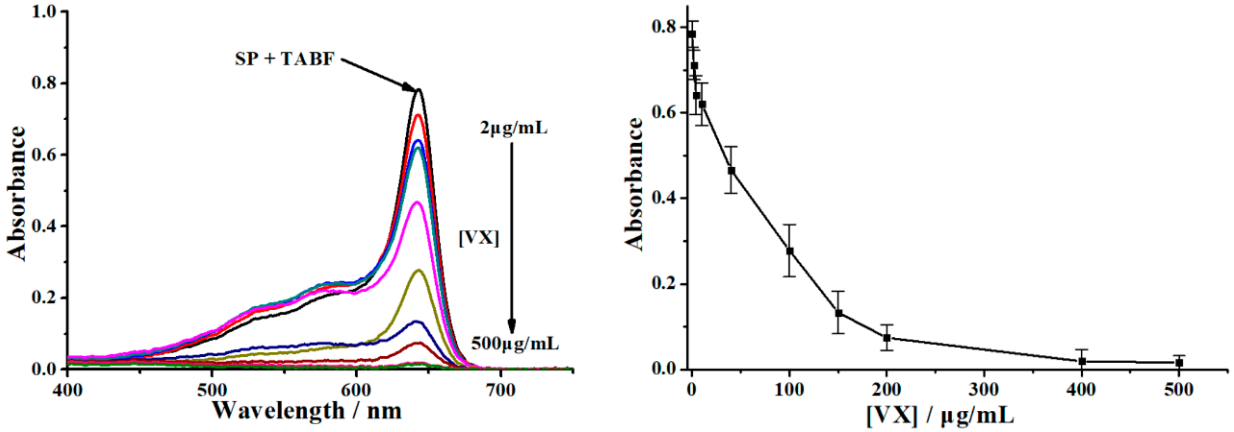


Figure 2. (**a**) UV−Vis spectra changes in colorimetric solution with increasing VX concentration; (**b**) curve of absorbance with VX concentration at 644 nm.

As displayed in Figure 3, a curve was obtained by plotting the rate of change in absorbance at 644 nm against the quadratic root of the VX concentration [VX]. On the ordinate, $(1 - {}_{\Delta}A/A_0) \times 100\%$ is plotted, where A_0 was the initial absorbance and ${}_{\Delta}A$ is the difference in the absorbance corresponding to before and after VX was added into the colorimetric solution, respectively. When the concentration of VX was in the range of 4~200 μg/mL, $(1 - {}_{\Delta}A/A_0) \times 100\%$ and [VX] showed a linear relationship, and the following relation was obtained:

$$(1 - {}_{\Delta}A/A_0) \times 100\% = 0.37523[\mathrm{VX}] + 19.79432 \ (R^2 = 0.9819, p < 0.00001, \mathrm{N} = 6).$$

The detection limit (DL) of 0.4 μg/mL was calculated using the following equation: DL = 3σ/k [28], where σ is the standard deviation of blank measurement, and k is the slope of the linear relationship between $(1 - {}_{\Delta}A/A_0) \times 100\%$ and [VX].

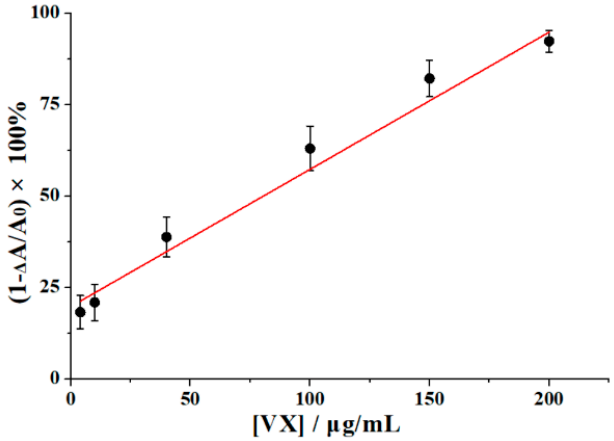


Figure 3. The calibration curve for VX detection using colorimetry.

3.2. Selectivity and the Anti-Interference Ability of Colorimetry

In this study, the specificity performance of the colorimetry method was also investigated by measuring the response of the colorimetry method to different interferents. Figure 4 shows the color changes in colorimetric solutions containing 2 μg/mL of SP and 250 μg/mL of TABF after the addition of 4 mg/mL of different of interferents. Meanwhile, their UV−Vis absorption spectra were also recorded. As can be seen from Figure 5, the absorbances of the colorimetric solutions were only slightly reduced, and the peak shapes did not change significantly after the addition of DMMP and toluene. The absorbance of the colorimetric solution was slightly reduced and changed to purple-red after the addition of DCP. After adding triethylamine (Et_3N) and DDVP, the absorbances of the solutions increased significantly, while Et_3N changed the color of the solution to blue and DDVP changed the color of the solution to purple-gray. Parathion and acetic acid (AcOH) both caused significant increases in the absorbance of the colorimetric solution system, in which the color changed to yellow-green after the addition of parathion, and AcOH made the colorimetric solution change to light emerald-green color. Colorimetry exhibited extremely different responses to all of the other organophosphorus pesticides, phosphorus-containing reagents, the benzene series, and the acid and base mentioned above compared with VX. Based on these facts, we can assume that the colorimetry method developed in this article was suitable for the selective detection of VX.

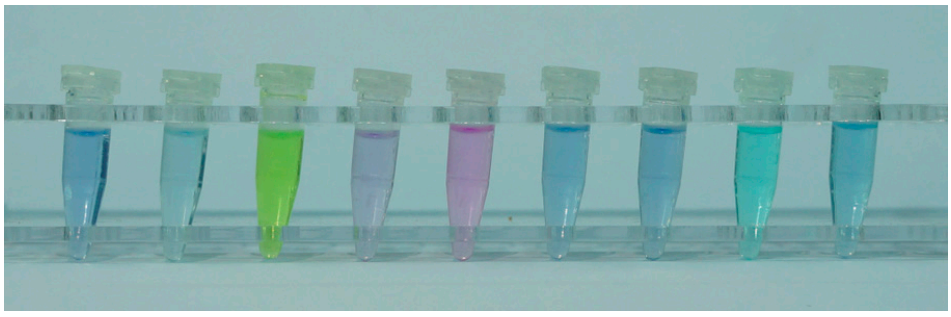


Figure 4. The color changes in the colorimetric solution before and after the addition of different interferents. From left to right, blank, 50 μg/mL of VX, and 4 mg/mL of parathion, DDVP, DCP, DMMP, toluene, AcOH, and Et_3N.

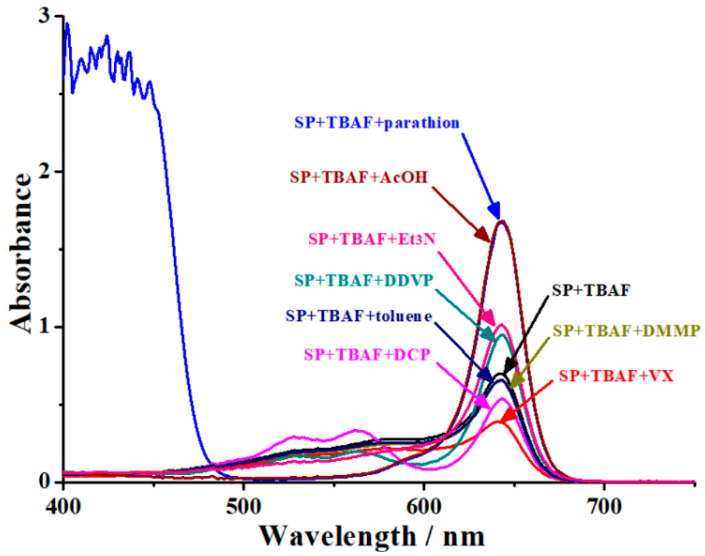


Figure 5. UV−Vis spectra changes in colorimetric solutions after the addition of different interferents.

To examine whether the colorimetry method developed in this article could maintain the sensing of VX under the potential competition of interferents, its anti-interference capability was studied. Parathion, DDVP, DCP, DMMP, toluene, AcOH, and Et_3N were added at the 100 equiv. of VX. As shown in Figure 6, DDVP, DCP, and AcOH had slightly noticeable effects on the detection of VX, which increased the *A* of the colorimetric solutions and lowered the calculated concentrations. The other interferents did not appear to interfere significantly with the detection of VX. It can be concluded that the colorimetry method could still detect VX in the presence of the 100 equiv. of these different interferents; however, its quantitative detection was, unfortunately, interfered. Therefore, the influence of interferents such as DDVP, DCP, and AcOH on the detection results should be taken in account when performing colorimetry.

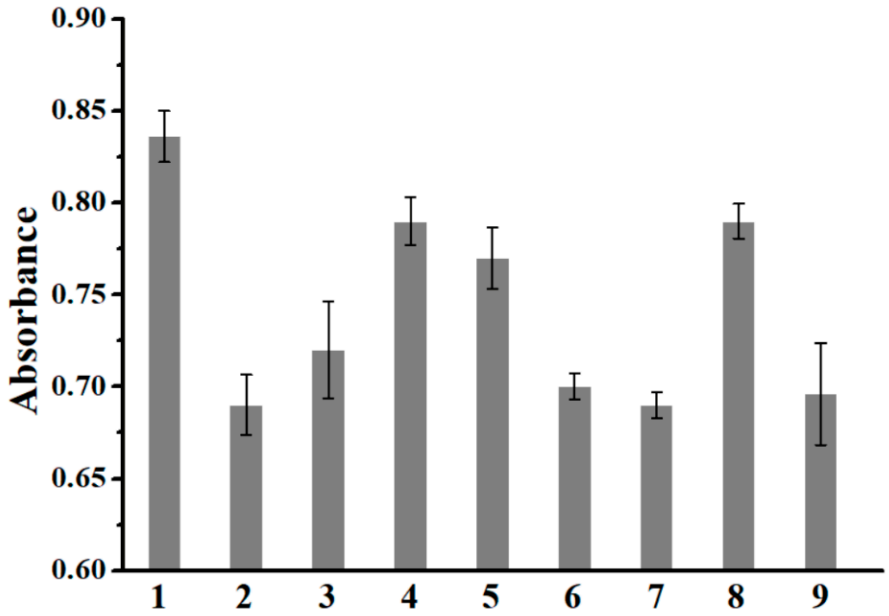


Figure 6. Absorption of colorimetric solutions (1), colorimetric solution containing VX (2), and colorimetric solution containing VX mixed with the 100 equiv. of interferents (parathion (3), DDVP (4), DCP (5), DMMP (6), toluene (7), AcOH (8), and Et_3N (9)) at 644 nm.

3.3. Mechanism for the Colorimetric Detection of VX

The addition of only VX to the colorimetric solution did not lead to color change, while the presence of TABF led to a change in the UV-Vis spectrum. To further investigate the response mechanism of the colorimetry method, the ^{1}H NMR spectra of the SP (Figure 7a), TBAF (Figure 7b), VX (Figure 7c), the mixture of the SP with TBAF (Figure 7d), the mixture of the SP with VX (Figure 7e), the mixture of TBAF with VX (Figure 7f), the mixture of the SP with TBAF, and VX (Figure 7g) were compared. When the SP was mixed with TBAF (Figure 7d), the proton signal H_a (12.14 ppm) in the hydroxyl part of the SP disappeared, the proton signal H_b (7.93 ppm) on the benzene ring adjacent to the hydroxyl group was significantly split, and the proton signal on the benzene ring away from the hydroxyl group became more complex. When the SP was mixed with TBAF and VX (Figure 7g), the proton signal on the benzene ring changed significantly compared to the SP mixed with TBAF and shifted to higher fields at 7.54 ppm.

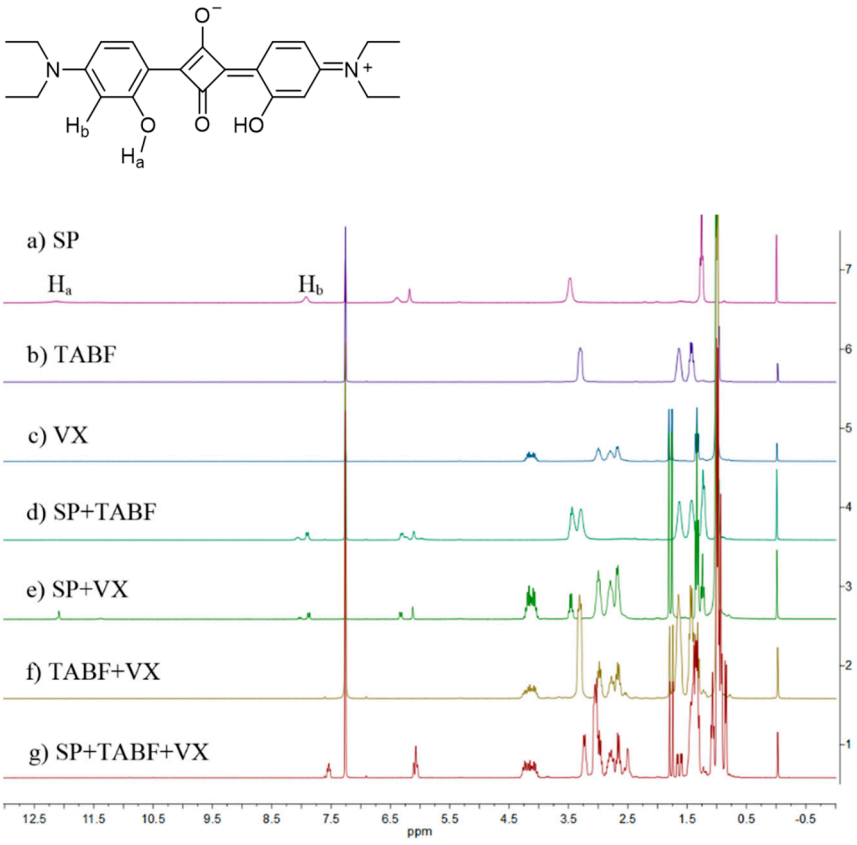
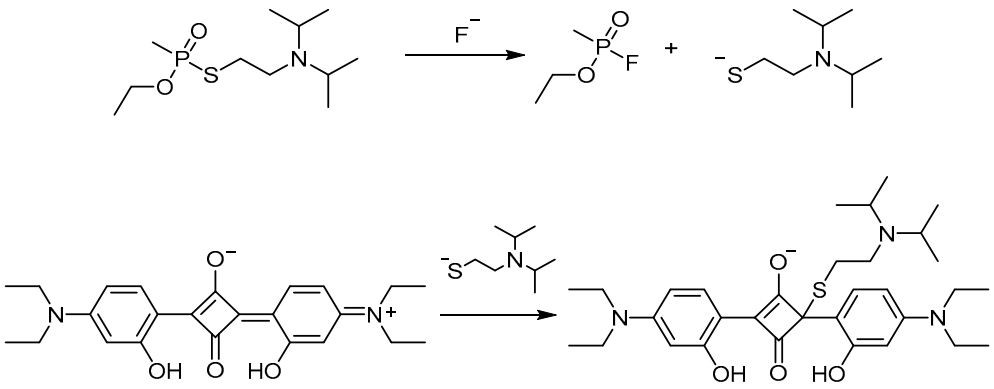


Figure 7. ^{1}H NMR spectra of the SP (**a**), TBAF (**b**), VX (**c**), the mixture of the SP with TBAF (**d**), the mixture of the SP with VX (**e**), the mixture of TBAF with VX (**f**), and the mixture of the SP with TBAF and VX (**g**).

A proposed mechanism is illustrated in Scheme 2, in which a fluoride anion reacts with VX to generate a thiolate fragment. The thiolate anion initiates a nucleophilic attack on the electron-deficient central four-membered squaric acid ring in the SP. Then, the nucleophilic attack of the thiolate fragment breaks the conjugation in the SP and induces color fading.

Subsequently, the mixture of the SP with TBAF and VX was subjected to MS analysis. As can be seen from Figure 8, the positive ion peak at 162.2 for the hydrogenation of the thiol portion of VX was found in the MS of the positive ionization of the mixture. However, as can be seen from Figure S4, the hydrogenation of the thiol portion of VX was not found in the MS of the positive ionization of the mixture of the SP and VX, indicating that the P–S bond of the VX was broken to produce a thiol fragment in the presence of TABF.



Scheme 2. The proposed mechanism of MS in the colorimetric detection of VX.

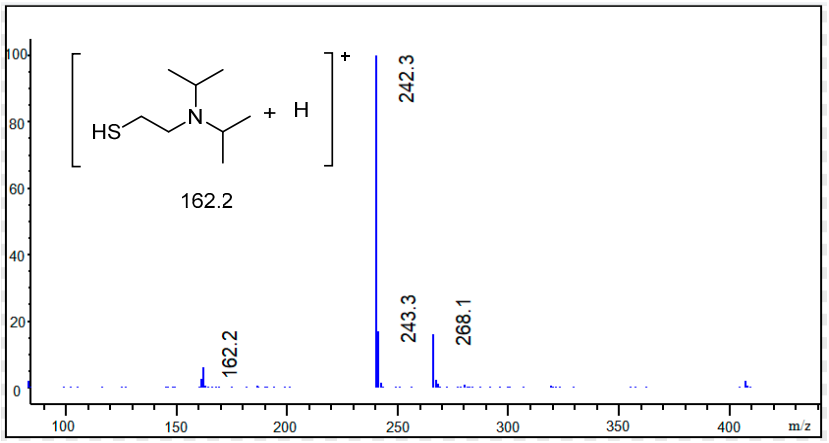


Figure 8. MS of the VX thiol fraction in the mixture of the SP with TBAF and VX.

A negative ion peak at 569.2 of the SP bound to the thiol fragment was found in the MS of the negative ionization of the mixture of the SP with TBAF and VX. The mechanism of the colorimetry method for the detection of VX should be that the presence of TABF broke the P–S bond of VX, releasing the thiol fragment (Figure 9). Since the four-membered ring of the SP was highly electron deficient, an additional reaction of the thiol fragment with the SP subsequently occurred, which led to a disruption in the p–π conjugate structure of the SP and resulted in changes in the UV−Vis spectra and color of the SP.

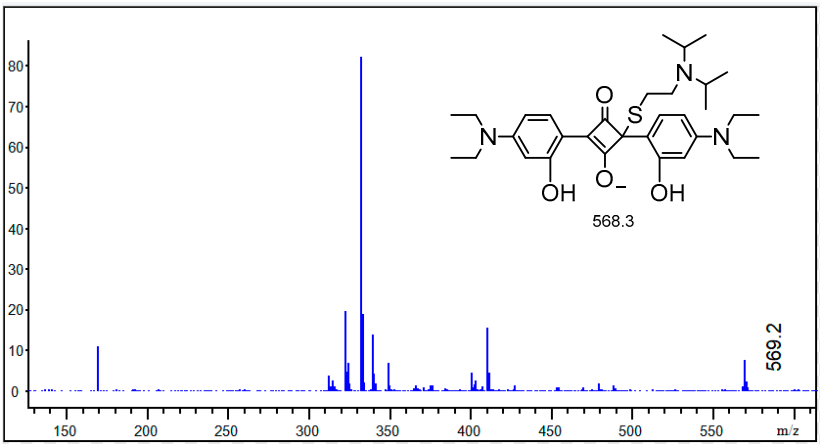


Figure 9. MS of the adducts of the SP and VX thiol in the mixture of the SP with TBAF and VX.

4. Conclusions

In this article, a colorimetric squaraine probe (SP) was prepared, and a colorimetry method for the detection of the organophosphorus nerve agent VX in a colorimetric solution that mixed the SP and TABF was established. The sensing characteristics of VX in the colorimetric solutions were studied using UV-Vis spectroscopy. The results showed that the absorbance levels of the colorimetric solutions decreased with increasing concentrations of VX, and the method exhibited good linearity between the rate of change in absorbance at 644 nm and [VX] in the range of 4~200 μg/mL. Furthermore, the colorimetry method could detect VX in the presence of the 100 equiv. of interferents, such as other organophosphorus pesticides, phosphorus-containing reagents, a benzene series, and an acid and base. ^{1}H NMR and MS studies revealed the mechanism of the colorimetric detection method. VX produced a thiol fragment in the presence of TABF; then, the thiol fragment bound to the four-membered ring of squaraine, which changed the D–A–D structure of the SP and caused color fading. Compared with previous fluorescence and colorimetric detection methods reported in the literature, the colorimetry method developed in this paper possessed a lower DL of 0.4 μg/mL. More importantly, it did not require the toxic metal ion of Hg^{2+} for color recovery [29]. Even compared with other squaraine-based colorimetric methods for the detection of organophosphorus nerve agents, the colorimetry method had a similar satisfactory sensitivity [30]. It should also be noted that, compared with the addition of VX, the absorption spectra of the colorimetric solutions changed significantly after the addition of parathion, DDVP, and DCP, which indicated that the colorimetric solution was also valuable for the detection of other organophosphorus compounds. Based on this, colorimetric arrays for different targets should be developed in the future.

The colorimetry method proposed in this article can be used for the rapid detection of VX; moreover, it provides a probable approach for the detection of organophosphorus nerve agents and pesticides, metal ions, and many other targets of interest in the fields of homeland security, environmental monitoring, and public health. This research also provides a technical basis and reference for promoting the development of new, on-site colorimetric methods, which have important supporting significance for the detection of various harmful substances.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemosensors11020137/s1, Figure S1: ^{1}H NMR spectrum of SP in $CDCl_3$; Figure S2: UV-Vis spectra changes in colorimetric solutions with TBAF contents of different concentrations; Figure S3: Color changes in colorimetric solutions; Table S1: Absorbance changes in colorimetric solutions; Figure S4: MS of the SP with VX.

Author Contributions: Conceptualization, B.D.; data curation, S.G.; formal analysis, L.G.; investigation, W.C., L.G. and F.H.; project administration, J.X. and L.C.; methodology, B.D. and F.H.; resource, J.X. and L.C.; supervision, W.C.; validation, S.G.; Writing—original draft, B.D.; writing—review and editing, S.G. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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