Tetrahedron Letters 51 (2010) 1754–1757

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Dual colorimetric and electrochemical sensing of organothiophosphorus pesticides by an azastilbene derivative

Chandrima De [a], Tova A. Samuels [a], Tajay L. Haywood [a], Ginger A. Anderson [a,c], Keith Campbell [b,c], Kenneth Fletcher [b,c], Desmond H. Murray [b,c], Sherine O. Obare [a,*]

[a] Department of Chemistry, Western Michigan University, Kalamazoo, MI 49008, USA
[b] Department of Chemistry and Biochemistry, Andrews University, MI 49104, USA
[c] Building Excellence in Science and Technology (BEST), Berrien Springs, MI 49104, USA

ARTICLE INFO

Article history:
Received 28 December 2009
Revised 24 January 2010
Accepted 26 January 2010
Available online 1 February 2010

ABSTRACT

We have investigated the optical and electrochemical changes of the azastilbene, dimethyl-[4-(2-quinolin-2-yl-vinyl)-phenyl]-amine (DQA), with four organothiophosphorus (OTP) pesticides: ethion, malathion, parathion, and fenthion. Significant changes in UV–visible absorbance wavelength and in electrochemical signals indicate the effectiveness of DQA as an OTP sensor.

Development of molecular sensors that interact with organic environmental pollutants continues to be a timely area of research. For many years, detection of environmental pollutants has relied heavily on non-portable instruments and required technical expertise. However, molecular chemosensors that give visible color changes or electrochemical changes have the potential for on-site monitoring. Our approach toward designing small molecule chemosensors with dual signal transductions involves unprecedented use of donor–acceptor azastilbene sensors for toxic electrophilic organothiophosphates (OTP). We hypothesized that the photophysical and electrochemical properties arising from the electron-deficient azaaromatics π-conjugatively attached to an electron-rich styryl substructure[1–3] would lead to effective interaction with OTP compounds, thus making the azastilbene an effective chemosensor.

We report that the azastilbene derivative, dimethyl-[4-(2-quinolin-2-yl-vinyl)-phenyl]-amine (DQA), recognizes and reacts with the electrophilic organothiophosphorus (OTP) pesticides: ethion, malathion, parathion, and fenthion (Fig. 1). DQA–OTP interaction is characterized by optical and electrochemical changes at room temperature.

OTPs with a thiophosphoryl (P═S) functional group constitute a broad class of widely used insecticides. They are related to the more reactive phosphoryl (P═O) organophosphates (OPs), which include very lethal nerve agents and chemical warfare agents, such as, VX, Soman, and Sarin. Unfortunately, frequent use of OTP compounds in agricultural lands worldwide has resulted in their presence as residuals in crops, livestock, and poultry products and has further led to their migration into underground aquifers.[4–6] These compounds are highly toxic to human health and are powerful inhibitors of cholinesterase enzymes.[7] Current detection methods for OPs and OTPs include nuclear magnetic resonance (NMR) spectroscopy,[8] chromatography,[9] mass spectrometry[10], and a variety of other analytical approaches including enzymatic assays.[11–14] From a practical agricultural viewpoint, the above-mentioned approaches have limitations such as low sensitivity, lack of instrument portability, limited selectivity, difficulties in real-time monitoring, and operational complexity. In addition, in many cases, these tests are qualitative and may provide false-positive results. An alternative detection and analysis strategy begins with the design and synthesis of chemosensors that provide more than one signal transduction and thereby minimize false-positive signals.

To synthesize donor–acceptor azastilbene chemosensors we relied upon the single-step approach involving base-promoted condensation of donor-substituted aromatic aldehydes with methyl-substituted azaaromatics. Specifically, we developed and

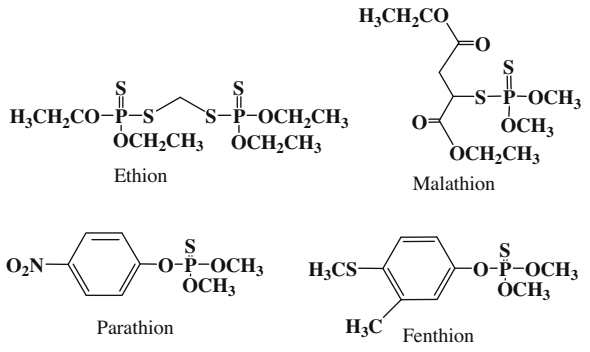


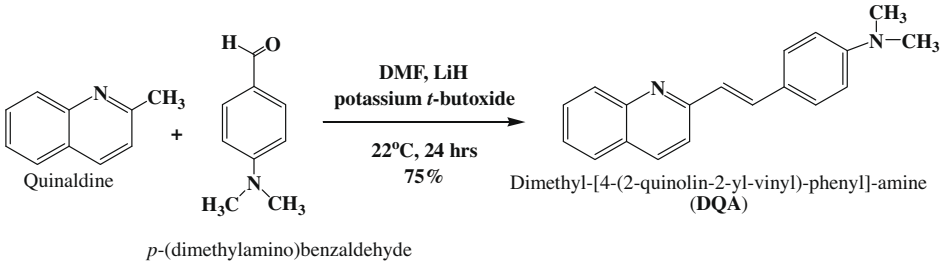
Figure 1. Chemical structures of ethion, malathion, parathion, and fenthion.

* Corresponding author. Tel.: +1 269 387 2923; fax: +1 269 387 2909.
E-mail address: sherine.obare@wmich.edu (S.O. Obare).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.01.100

utilized an improved method based on an earlier report involving the synthesis of cyanostilbenes.[15–17] Thus, DQA was made in 75% yield by room temperature condensation of a 1:1 quinaldine and 4-(dimethylamino)benzaldehyde mixture (Scheme 1). Excess potassium *t*-butoxide base was used along with lithium hydride which ensured a dry non-protic reaction medium.

The interaction of DQA with ethion, malathion, parathion, and fenthion was studied by (1) UV–visible absorbance spectroscopy and (2) cyclic voltammetry. A solution of DQA in acetonitrile absorbs at 385 nm which is assigned to intramolecular charge transitions from the dimethylamine nitrogen to the quinaldine nitrogen.[1] Changes in the UV–visible absorbance spectrum of DQA with each pesticide were measured by titration studies. In each case, 3 mL of 2.4×10^{-5} M solution of DQA in acetonitrile was placed in a 1×1 cm quartz cuvette having a 24/40 attachment. Two microlitres aliquots of each pesticide solution was added to the DQA solution in increments less than or equal to 1 equiv by mole ratio of DQA as indicated in Figure 2. A septum was used to seal the solution after the addition of each aliquot of OTP pesticide, and then the UV–visible absorbance was measured. As shown in Figure 2a, an increase in ethion concentration to a solution of DQA in acetonitrile resulted in the decrease in the UV–visible absorbance intensity at 385 nm, and was accompanied by the formation of two new peaks at 325 nm and at 500 nm. Similar behavior was observed in the case of malathion, except two new peaks which arise at 330 nm and 505 nm as shown in Figure 2b. In both cases two isosbestic points were observed at 340 nm and 425 nm for ethion, and at 335 nm and 430 nm for malathion.



Scheme 1. Synthetic scheme for DQA.

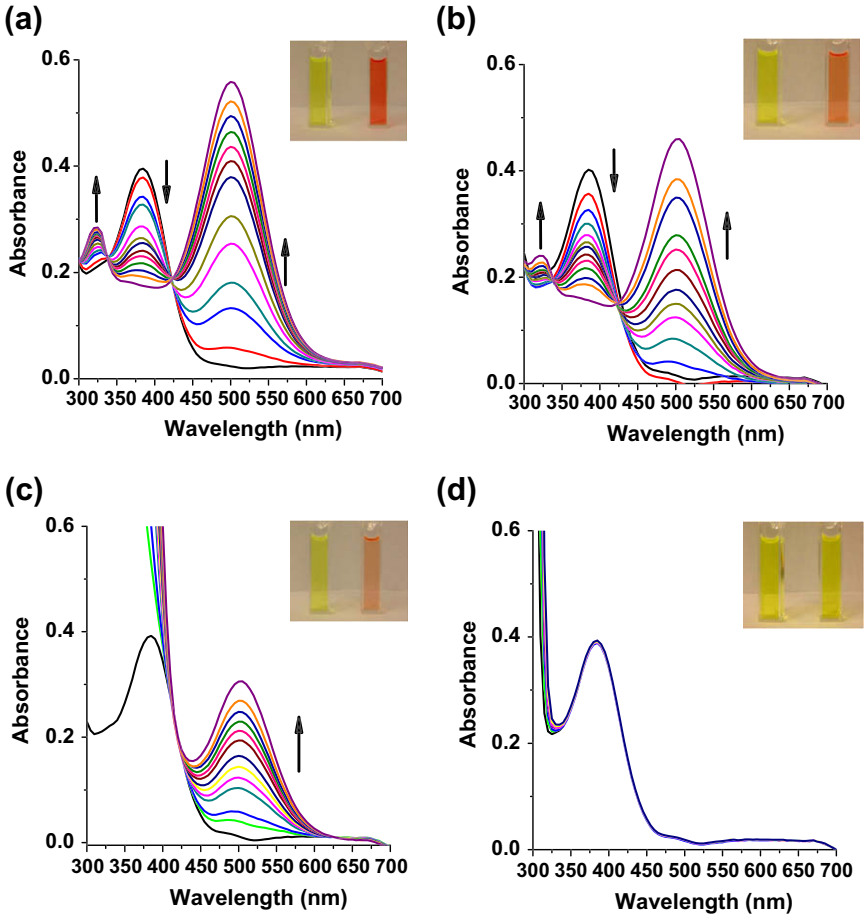


Figure 2. Changes in the UV–visible absorbance of DQA [2.4×10^{-5} M] upon binding to OTP pesticides: (a) titration with ethion; (b) titration with malathion; (c) titration with parathion; (d) titration with fenthion. In each case the direction of the arrow indicates concentration of 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 μM.

Furthermore, we observed that the titration of parathion to a solution of DQA in acetonitrile did not result in the quenching of the 325 nm peak, however, a new peak at 505 nm formed and increased in intensity with an increase in parathion concentration as shown in Figure 2c. On the other hand, the addition of fenthion to the DQA solution did not show any notable changes in the original absorbance of DQA as shown in Figure 2d.

At the end of the DQA titrations with ethion, malathion, and parathion, the color of the solution had changed from yellow to red-orange, orange, and peach-orange, respectively. The same color changes in DQA were also observed when saturation concentrations of OP pesticides were added. No color change was observed when fenthion was added to DQA.

Changes in the UV–visible absorbance spectrum show that DQA is efficient in distinguishing between the four OP pesticides and result in different colored solutions with different λ_{max} values. The method of continuous variation was used to determine the stoichiometry of DQA with ethion, malathion, and parathion.

In each case, it was found that a 1:1 DQA–OTP complex was formed. Based on the 1:1 stoichiometry, binding constants were calculated to be $6.5 \times 10^4\ M^{-1}$, $1.1 \times 10^4\ M^{-1}$, and $0.2 \times 10^4\ M^{-1}$ for ethion, malathion, and parathion, respectively.

^{1}H NMR spectroscopy was also used to monitor the interaction between DQA and the OTPs. The addition of either ethion, malathion or parathion to a CD_3CN solution of DQA in concentrations less than and up to 1 equiv of DQA was recorded. In each case, the chemical shifts of the protons closest to the quinaldine nitrogen in DQA shifted downfield with gradual addition of the OTP. Addition of more than 1 equiv of the OP gave no further NMR changes. This observation confirmed the 1:1 stoichiometry of DQA with the OTPs, and also indicated that the quinaldine nitrogen had a higher affinity for the OTPs relative to the dimethylamine nitrogen (see Supplementary data).

Computational calculations were conducted to determine the nucleophilicity of the two nitrogen atoms by analysis of DQA's electrostatic potential. The supporting information section shows the data collected from a structure that was optimized at the B3LYP level of density functional theory. The data revealed that the electrostatic potential at the quinaldine nitrogen is higher relative to the dimethylamine nitrogen.

Furthermore, it is well known that the reactions of electrophiles (e.g., protons and metal cations) with 4-dimethylamino styrylazaaromatics occur exclusively at the 'ring' (pyridyl, quinolinyl) nitrogen. This generally results in the formation of the corresponding quaternary pyridinium and quinolinum salts. It is thus reasonable to assume that electrophilic phosphorus reactants will also react preferentially at the azaaromatic 'ring' nitrogen.

Molecules that provide optical and electrochemical signals are ideal for exploitation in developing sensors that offer dual signal transductions. Cyclic voltammograms were acquired using a BAS CV50 electrochemical workstation using glassy carbon as the working electrode, a platinum wire as the counter electrode, and Ag/AgCl as the reference electrode. The electrolyte was a 0.1 M solution of tetrabutylammonium hexafluorphosphate ($TBAPF_6$). DQA was found to have a formal potential (E^0) at 860 mV versus Ag/AgCl. Changes in the electrochemical waves of DQA with 1 equiv of the pesticides ethion, malathion, parathion, and fenthion, were measured as shown in Figure 3. In the case of ethion, malathion, and parathion, the DQA–OTP complex formed had significantly different redox characteristics relative to DQA. The DQA/ethion complex showed three redox waves at $E_{1/2} = -875$ mV versus Ag/AgCl, $E_{1/2} = -500$ mV versus Ag/AgCl, and $E_{1/2} = +500$ mV versus Ag/AgCl.

The cyclic voltammogram of the DQA/malathion complex was also different relative to that of DQA; in this case two waves at $E_{1/2} = -1498$ mV versus Ag/AgCl and $E_{1/2} = -870$ mV versus Ag/

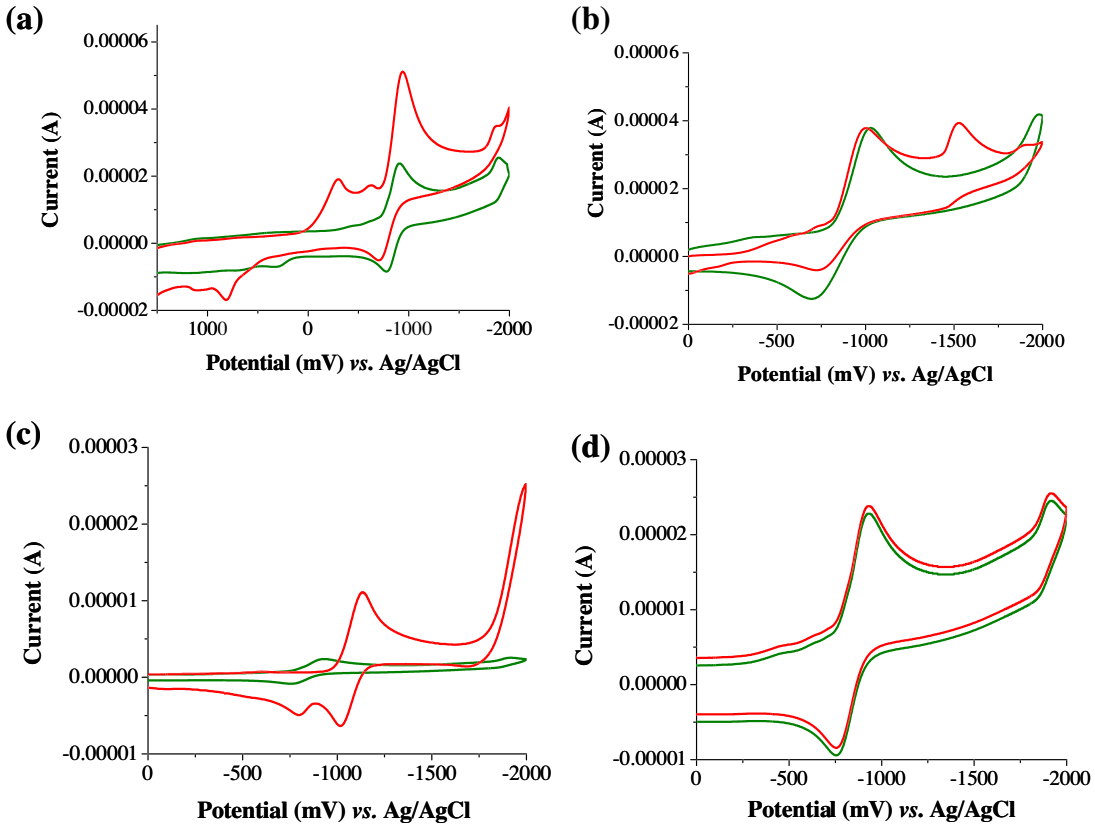


Figure 3. Cyclic voltammograms of DQA before and after the addition of (a) ethion, (b) malathion, (c) parathion, and (d) fenthion.

AgCl corresponding to DQA–malathion complex were observed. The formation of a DQA/parathion complex also demonstrated significant changes in the redox behavior ($E_{1/2}$ = −1072 mV vs Ag/AgCl, $E_{1/2}$ = −773 mV vs Ag/AgCl) in comparison to DQA. As expected, there were no changes in the redox behavior of DQA with the addition of fenthion.

The observed DQA–OTP reactions can be explained by Lewis acid–base or nucleophile–electrophile interactions between the quinaldine nitrogen and the OTP phosphorus. While a significant amount of work has been reported on phosphoryl transfer reactions,[18,19] much less is known about thiophosphoryl transfer reactions. One common mechanistic pathway for phosphoryl transfer reactions is via concerted $S_N2(P)$ processes in which a nucleophilic attack on phosphorus leads to expulsion of the leaving group. In these S_N2 scenarios, the reaction rate for the thiophosphoryl transfer is expected to be highly dependent on the leaving group. This in turn will affect the binding constant of the incoming nucleophile. This interpretation is consistent with our results since, for example, it is known that the *p*-nitrophenolate anion of parathion is a much better, more stable leaving group than the phenolate anion of fenthion. Thus, parathion has a stronger binding constant than fenthion to DQA.The interaction of DQA with each OP pesticide relies on the stability of the leaving group—the more stable the OP leaving group, the more likely it will dissociate upon interaction with the nucleophilic DQA quinaldine nitrogen.

In summary we have shown that the azastilbene DQA is effective in the detection of OTP compounds, which is important for both environmental and homeland security applications.

Acknowledgments

S.O.O. gratefully acknowledges the National Science Foundation CAREER program for financial support under grant CHE 1005456. The authors wish to acknowledge partial financial support under U.S. Army Grant No. W911QY-07-1-0003. T.A.S. thanks the Eastman Kodak Foundation for the Dr. Theophilus Sorrell doctoral fellowship administered by NOBCChE. T.L.H. thanks the American Chemical Society Project SEED program for support at Western Michigan University. G.A., K.C., K.F. and D.H.M. acknowledge the National Science Foundation and the American Chemical Society PRF for financial support under Grants CHE 0316532 and 40092-B4, respectively.

Supplementary data

Supplementary data (detailed synthetic procedures, ^{1}H NMR and computational data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.100.

References and notes

1. Wang, S. L.; Ho, T. I. *Chem. Phys. Lett.* **1997**, *268*, 434.
2. Bahner, C. T.; Pace, E. S.; Prevost, R. *J. Am. Chem. Soc.* **1951**, *73*, 3407.
3. Wang, L.-Y.; Chen, Q.-W.; Zhai, G.-H.; Wen, Z.-Y.; Zhang, Z.-X. *Dyes Pigments* **2007**, *72*, 357.
4. Zhang, H.; Wang, S.; Zhou, Z.; Pan, C.; Zhang, J.; Niu, W. *Phosphorus Sulfur* **2008**, *183*, 280.
5. Salas, J. H.; Gonzalez, M. M.; Noa, M.; Perez, N. A.; Diaz, G.; Gutierrez, R.; Zazueta, H.; Osuna, I. *J. Agric. Food Chem.* **2003**, *51*, 4468.
6. Gilliom, R. J. *Environ. Sci. Technol.* **2007**, *41*, 3408.
7. Walker, B. J. Organophosphorus Chemistry. Penguin Library of Physical Sciences: Chemistry, 1972.
8. Ross, R. T.; Biros, F. J. *Anal. Chim. Acta* **1970**, *52*, 139.
9. Black, R. M.; Muir, B. *J. Chromatogr., A* **2003**, *1000*, 253.
10. Steiner, W. E.; Klopsch, S. J.; English, W. A.; Clowers, B. H.; Hill, H. H. *Anal. Chem.* **2005**, *77*, 4792.
11. Evtugyn, G. A.; Budnikov, H. C.; Nikolskaya, E. B. *Analyst* **1996**, *121*, 1911.
12. Mionetto, N.; Marty, J. L.; Karube, I. *Biosens. Bioelectron.* **1994**, *9*, 463.
13. Russell, A. J.; Berberich, J. A.; Drevon, G. E.; Koepsel, R. R. *Annu. Rev. Biomed. Eng.* **2003**, *5*, 1.
14. Trojanowicz, M. *Electroanalysis* **2002**, *14*, 1311.
15. Takahashi, K.; Okamoto, T.; Yamada, K.; Iida, H. *Synthesis* **1977**, 58.
16. Wheeler, O. H.; de Pabon, H. N. B. *J. Org. Chem.* **1965**, *30*, 1473.
17. Becker, K. B. *Synthesis* **1983**, 341.
18. Ko, H. J.; Park, T. H. *Biol. Chem.* **2006**, *387*, 59.
19. Allen, K. N.; Dunaway-Mariano, D. *Trends Biochem. Sci.* **2004**, *29*, 495–503.