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Short communication

Real nerve agent study assessing pyridyl reactivity: Selective fluorogenic and colorimetric detection of Soman and simulant

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ABSTRACT

Herein, a chemical probe is tested with live agents for the purpose of benchmarking fluorescent pyridyl-containing systems with actual nerve agents and simulants together. The molecule showed selective fluorogenic and colorimetric detection of Soman (GD) and its simulant over other G-series nerve agents and their simulants. ^{1}H and ^{31}P NMR spectroscopy and TD-DFT calculations help reveal the origin of the colorimetric and fluorogenic changes in the reacted system.

1. Introduction

Reliable and mature analytical methods of detecting volatile nerve agent species include such techniques as ion mobility spectrometry, mass spectrometry, multinuclear NMR spectroscopy, and enzyme-based sensing [1–4]. These methods provide accurate and precise results; but, with some exceptions they are not practical *'real time'* and point-of-contact small molecule-based methods for the battlefield and accident scene. For this reason, colorimetric and fluorogenic sensing methods continue to be pursued vigorously. They involve various advantages [5–7]. Fluorogenic and chromogenic sensors, for the detection of nerve agents are required to be convenient, real-time, matrix compatible, sensitive and selective. Various fluorogenic and colorimetric sensors for nerve agents, often used with the unaided eyes, have been reported [6–21]. The issue of selectivity is a vital issue and this relates to kinetic and thermodynamic driving forces. Simulants of nerve agents, *e.g.*, diethyl chlorophosphate (DCP) for Sarin/Soman (GB/GD) and diethyl cyanophosphonate (DECP) for Tabun (GA), are frequently used in reports due to the extreme toxicity of the actual nerve agents (Fig. 1). When probes are used with live agents, they can allow for a better understanding of the basic science of these systems. Only a few probes have been treated with real nerve agents [18–21] and are able to discriminate among *G*-series nerve agents. When there is discrimination between two species, it is important to understand the underpinnings that different phosphates/phosphonates may impart to the system. Also, addressing the origin of the change in photophysical properties is eventually necessary.

Pyridyl is a truly ubiquitous motif [22]. The pyridiyl group was chosen for the detection of nerve agents as a nucleophile in the system; the 4-N position is the most accessible/available position in solution to any species (Solvents, molecule, M^{n+}, H^{+} and electrophiles). Thus, it being ubiquitous means that the group is also liable to bind to a wide range of substances. Because of this, it is important to pinpoint the "window of opportunity" a phosphate/phosphonate group has in competing in binding and giving a reliable and sensitive signal. Herein, we address phosphonate attack at the pyridyl moiety. The *meso*-Pyridyl-BODIPY system (***m*-**Py-BOD, Fig. 1) showed the selective detection of GD and its simulant over other *G*-series of nerve agents and their simulants.

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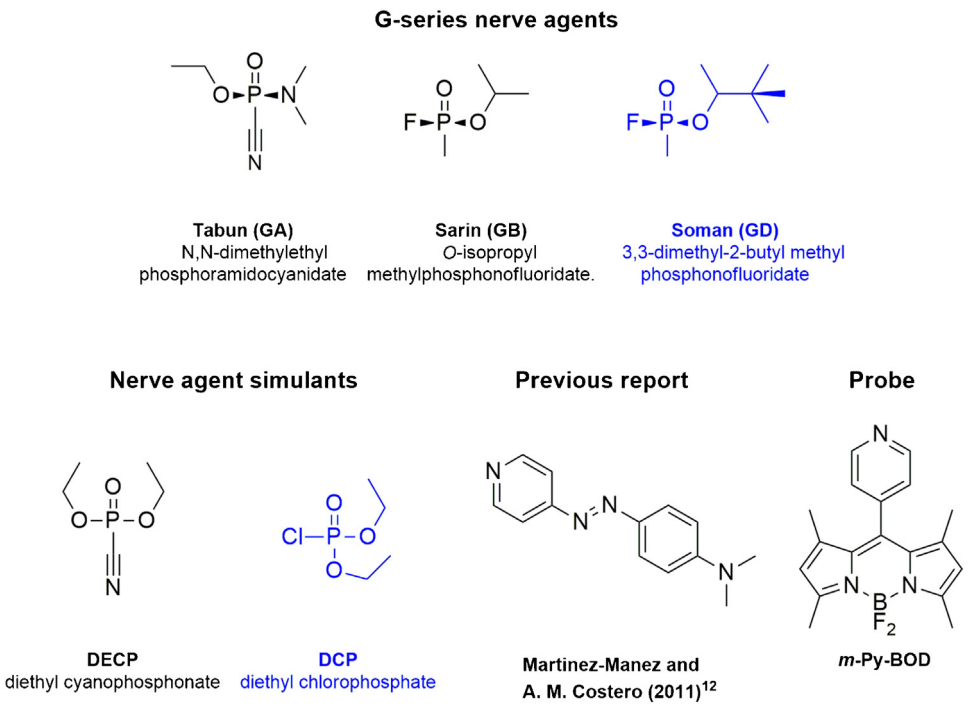

Fig. 1. Structure of chemical warfare nerve agents (*G*-series), simulants, the probe ***m*-**Py-BOD, and reported probe by Costero and Martínez-Máñez et al.

2. Results and discussion

The pyridyl group readily undergoes reaction with electrophilic centers. A very important electrophilic species is the central phosphorus in organophosphorus compounds; such reaction results in distinct electronic changes which impact the probe. How the probe works with real agents is an important objective for this research. The change of absorbance and emission were expected as a result of substitution reactions with CWAs. *meso*-Pyridyl-BODIPY (***m*-**Py-BOD) is an important intermediate which has been previously used in electrochemical and photophysical property studies, or in the synthesis towards other BODIPY-based research objectives in fluorescence [23–25]. It is an important starting point because of its simplicity. Furthermore, pyridyl-BODIPY has not yet been studied as a probe for the detection of chemical nerve agents or mimics. Here, we rely on previous reports of Royo et al. [12].

Preliminary studies of ***m*-**Py-BOD with nerve agent *simulants* were first performed. DCP and DECP were added in the presence of ***m*-**Py-BOD (10^{-5} M, acetonitrile). Changes observed were both optical (from yellow to pink) and fluorescent (diminishment) in ***m***-Py-BOD solution with DCP to give **DCP-*m*-Py-BOD** (Fig. 2a and b). On the other hand, DECP did not give any changes in both colour and fluorescence emission. To rule out that the potentially competing protonation of pyridyl moiety quenched the fluorescence, ***m***-Py-BOD (10^{-5} M) was tested with DCP (10^{-3} M) in two types of buffer solution; PBS (10 mM, pH 7.2) and HEPES (10 mM, pH 7.4). The changes of absorbance were not exactly the same as with previous results in acetonitrile. The intensities of absorbance were reduced after addition of DCP, but the red-shift in the absorbance maximum was not observed (Fig. S6a and b). On the other hand, the fluorescent changes of the two buffer solutions showed very similar features showing 'turn-off' signal (Fig. S6b and b).

Titrations with ***m*-**Py-BOD and nerve agent simulants were carefully studied. As a result of titrations with simulants, the maximum absorption peak was shifted from 499 to 505 nm. Emission intensity gradually decreased upon addition of DCP. The limit of detection was found to be 3.36 μM (Fig. S5). As expected, DECP was not able to effect any color change (Fig. S8). Often, test paper can be used as a reliable and relevant testing surface. Here, for potential application of ***m*-**Py-BOD, filter paper (125 mm, Whatman™) was used to visualize colour and fluorescence changes. The paper was soaked in a ***m*-**Py-**BOD** solution (10^{-5} M, acetonitrile) and then dried. A drop of DCP (10^{-1} M, acetonitrile) was placed on the paper. As seen in Fig. 2, colour and fluorescence changes were observed. The decrease in fluorescence was still slightly vague, due to the interference of the section revealing bright fluorescence; but, at the centre of the spot testing zone, the change was clear (Fig. 2c–f).

m*-**Py-BOD was then tested with real nerve agents (GA, GB and GD). The absorbance spectra and images under UV- lamp irradiation of ***m*-**Py-BOD with *G*-series nerve agents were obtained. The experiments were performed under the same conditions as alluded to above, except here, real nerve agents were used instead of DCP. Among the three *G*-series nerve agents, ***m*-**Py-BOD showed a distinct UV–vis absorbance change ($\lambda_{ab,max}$ from 499 nm to 508 nm) and fluorescence intensity decrease (under UV-lamp irradiation, λ_{ex} = 365 nm) in the solution of ***m-Py-BOD with GD (**GD-*m*-Py-BOD**) *only* (Fig. 3c and d). However, GA and GB did not show absorbance changes (Fig. 3a and b).

To understand the change of colour and diminution of fluorescence at the atomic level, the structure of reacted ***m*-**Py-BOD with DCP was sought. DCP was exploited to confirm the structure of reacted ***m*-**Py-BOD with ^{1}H and ^{31}P NMR spectroscopic analysis. ^{31}P NMR spectral peaks of DCP showed singlets at ~4.1 and −12.8 ppm; the peak at ~−12.8 ppm was assigned to the form of the hydrolysate [10]. After reaction between DCP and ***m*-**Py-BOD, the main singlet peak at ~4.1 ppm was upfield-shifted to ~0.4 ppm in the ^{31}P NMR spectrum (Fig. S4). Additionally, proton peaks at the pyridyl moiety were downfield-shifted slightly from 7.38 to 7.49 nm (Fig. S3). Based on NMR spectra, the pyridyl moiety in DCP undergoes nucleophilic substitution at the phosphorus.

A density functional theory (DFT) and time-dependent density functional theory (TD-DFT) calculation of ***m*-**Py-BOD with DCP and GD binding was conducted to obtain optimized geometries, electronic level distributions, etc (Figs. 4 and S7 and Table