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A Chromogenic Probe for the Selective Recognition of Sarin and Soman Mimic DFP**

Sameh El Sayed,[a, b, c] Lluís Pascual,[a, b, c] Alessandro Agostini,[a, b, c] Ramón Martínez-Máñez,*[a, b, c] Félix Sancenón,[a, b, c] Ana M. Costero,*[a, d] Margarita Parra,[a, d] and Salvador Gil[a, d]

The synthesis, characterization and sensing features of a novel probe **1** for the selective chromogenic recognition of diisopropylfluorophosphate (DFP), a sarin and soman mimic, in 99:1 (*v*/*v*) water/acetonitrile and in the gas phase is reported. Colour modulation is based on the combined reaction of phosphorylation of **1** and fluoride-induced hydrolysis of a silyl ether moiety. As fluoride is a specific reaction product of the reaction between DFP and the –OH group, the probe shows a selective colour modulation in the presence of this chemical. Other nerve agent simulants, certain anions, oxidant species and other organophosphorous compounds were unable to induce colour changes in **1**. This is one of the very few examples of a selective detection, in solution and in the gas phase, of a sarin and soman simulant versus other reactive derivatives such as the tabun mimic diethylcyanophosphate (DCNP).

The use of chemical warfare agents (CWA) in terrorist attacks has led to increasing interest in the study of these lethal chemicals.[1] Among CWA, nerve agents are especially dangerous because they are capable of interfering with the action of the nervous system. More specifically, their primary mode of action is the inhibition of acetylcholinesterase enzyme resulting in acetylcholine accumulation in the synaptic junctions hindering muscles from relaxing and causing serious toxicity.[2] From a chemical point of view, nerve agents belong to the organophosphonate family.

The easy fabrication of nerve gases and their indiscriminate use by certain nations and by terrorist groups have increased the efforts of the scientific community toward the detection and remediation of these deadly chemicals.[3] Currently, the most used methods for monitoring the presence of nerve agents are based on the use of biosensors,[4] ion mobility spectroscopy,[5] electrochemical methods,[6] micro-cantilevers,[7] photonic crystals[8] and optical fiber arrays.[9] Recently, as an alternative to these instrumental methods, the development of fluorogenic and chromogenic probes has gained increasing interest.[3b,10] Chromogenic systems are especially appealing because there are few techniques as simple as visual detection and they allow rapid and sensitive detection to the naked eye in situ or at site without any sample pre-treatment. However, in this field there are relatively few examples of selective probes for the detection of nerve gases.[11] Usually in these studies, nerve gas simulants such as diethylcyanophosphate (DCNP), diisopropylfluorophosphate (DFP) and diethylchlorophosphate (DCP) are used (see Figure 1). These compounds show similar reactivity to real nerve agents, that is, sarin, soman and tabun, but lack their severe toxicity (see Figure 1).

Most of these reported probes make use of the electrophilic reactivity of nerve gases with suitable nucleophiles.[12] However, these reactions are in most cases unspecific and usually the probes display the same optical response to all nerve agents.[13] In this context, it has been indicated that the design of rapid methods for the individual signalling of nerve agents is of importance. In this respect, even though the emergency response protocol is similar for sarin, soman and tabun, there is evidence that some antidotes are effective only for certain nerve gases indicating the importance of distinguishing one specific agent within this family of deadly compounds.[14] In this field, there are very few examples of probes capable to selectively discriminating DCNP[11a] and DFP[11b] as model compounds for tabun and sarin/soman, respectively.

Following our interest in the design of chromogenic probes for the potential discrimination of nerve agents,[15] we report herein probe **1** (see Figure 1) which is able to display a highly selective chromogenic response, both in solution and in gas phase, in the presence of DFP (a sarin and soman mimic) versus other simulants and organophosphates. Probe **1** (see Supporting Information for details of its synthesis) contains two reactive subunits, that is, a nucleophilic hydroxyl moiety and a silyl ether group. The underlying sensing idea is that phosphorylation of the hydroxyl moiety of probe **1** by DFP would yield the phosphate derivative **3** and the release of

[a] *S. El Sayed, L. Pascual, Dr. A. Agostini, Prof. R. Martínez-Máñez, Dr. F. Sancenón, Prof. A. M. Costero, Prof. M. Parra, Prof. S. Gil*
Centro de Reconocimiento Molecular y Desarrollo Tecnológico (IDM)
Unidad Mixta Universidad Politécnica de Valencia
Universidad de Valencia (Spain)

[b] *S. El Sayed, L. Pascual, Dr. A. Agostini, Prof. R. Martínez-Máñez, Dr. F. Sancenón*
Departamento de Química, Universidad Politécnica de Valencia
Camino de Vera s/n, 46022 Valencia (Spain)
E-mail: rmaez@qim.upv.es

[c] *S. El Sayed, L. Pascual, Dr. A. Agostini, Prof. R. Martínez-Máñez, Dr. F. Sancenón*
CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN)

[d] *Prof. A. M. Costero, Prof. M. Parra, Prof. S. Gil*
Departamento de Química Orgánica, Universitat de València
Dr. Moliner 50, 46100 Burjassot, Valencia (Spain)
E-mail: ana.costero@uv.es

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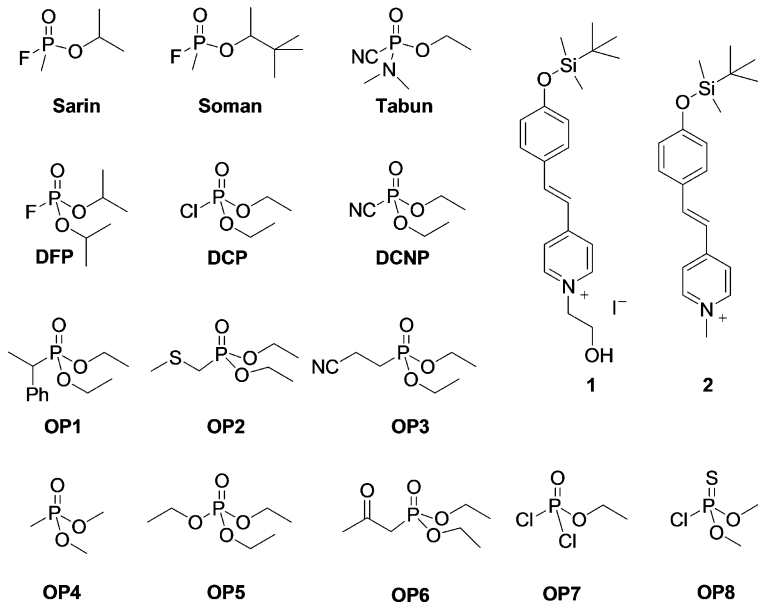
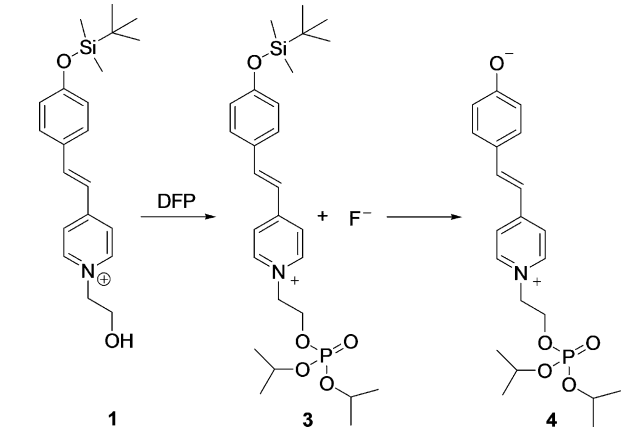


Figure 1. Chemical structures of nerve agents sarin, soman, tabun, their simulants (DFP, DCP and DCNP), selected organophosphates (OP1–OP8) and compounds **1** and **2**.

The chromogenic response of probe **1** was also tested against certain anions (F^-, Cl^-, Br^-, I^-, HCO_3^-, HPO_4^{2-}, OH^-, CN^-, N_3^-, NO_3^-, SO_4^{2-} and citrate), oxidant species (H_2O_2 and $S_2O_3^{2-}$) and other organophosphorous compounds (**OP1**–**OP8**, see Figure 1) in 99:1 (*v*/*v*) water/acetonitrile. The results observed in the presence of nerve agent simulants, F^- anion and organophosphates are shown in Figure 3 (for the response of other selected anions and oxidant species see Supporting Information). Of all chemicals tested, only fluoride anion (in addition to DFP) was able to induce a chromogenic response. Competitive studies were also carried out, and in all cases mixtures of DFP with other anions, oxidants or organophosphorous derivatives resulted in a chromogenic signal similar to that obtained for DFP alone (see Supporting Information).

The mechanism of the chromogenic response was assessed by ^1H, ^{31}P NMR and MS studies. In the ^1H spectrum of **1**, there was a characteristic triplet centred at 3.83 ppm, which corresponds to the methylene group directly connected with the hydroxyl



Scheme 1. Mechanism of the chromogenic response with DFP.

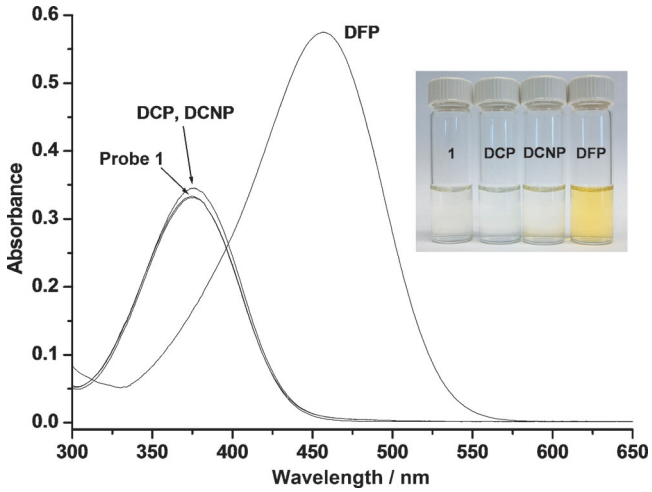


Figure 2. UV/Vis spectra of probe **1** (1.0×10^{-5} mol L^{-1}) in 99:1 (*v*/*v*) H_2O/CH_3CN at pH 8.0 in the presence of 10 equiv DFP, DCP or DCNP. The inset shows a photograph of the color changes observed upon addition of DFP, DCP and DCNP to solutions of probe **1**.

a fluoride anion that would hydrolyse the silyl ether[16] moiety, generating a coloured phenolate derivative (see **4** in Scheme 1). Both reactions, and therefore colour modulation, are expected to occur only in the presence of the sarin and soman simulant DFP.

In a first step, the response of **1** was tested with nerve agent simulants in 99:1 (*v*/*v*) water/acetonitrile solutions buffered at pH 8.0. Probe **1** is colourless and shows an intense absorption band centred at 374 nm. Upon addition of 10 equivalents of DFP, a remarkable change was observed with the appearance of a new band at 465 nm, which resulted in a colour modulation from colourless to yellow (see Figure 2). Addition of DCP and DCNP induced negligible changes in both colour and the band at 374 nm. Moreover, from further titration experiments of **1** with DFP, a remarkable limit of detection (LOD) of 5.4 ppm in 99:1 (*v*/*v*) water/acetonitrile was determined (see Supporting Information for details).

moiety that was shifted downfield to 4.34 ppm upon addition of DFP. Moreover, the ^{31}P NMR spectrum of DFP (in [D_6]DMSO) showed a sharp doublet at 11.0 ppm ($J_{PF}=967$ Hz) that progressively disappeared upon addition of increasing quantities of probe **1**, together with the growth of a new singlet at −1.54 ppm ascribed to the formation of a phosphate moiety. In addition, MS studies confirmed the formation of phenolate **4** upon reaction between probe **1** and DFP (*m*/*z* calculated for [**4**+H^+]: 533.08, found: 533.30). These facts clearly pointed to a DFP phosphorylation of the hydroxyl moiety and the subsequent fluoride-induced hydrolysis of the silyl ether group as the mechanism of the chromogenic response observed.

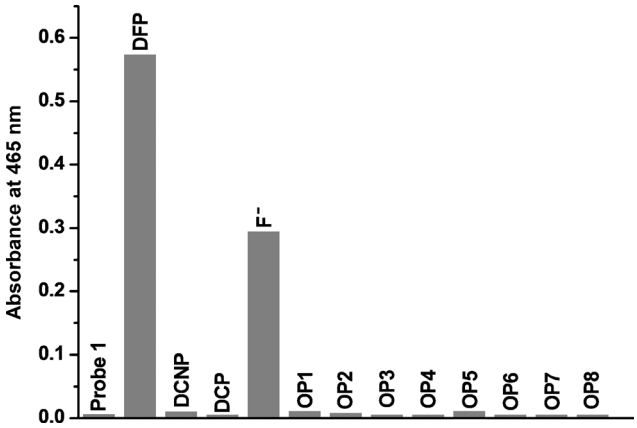


Figure 3. Absorbance at 465 nm of probe **1** (1.0×10^{-5} mol L^{-1}) in 99:1 (*v*/*v*) H_2O/CH_3CN at pH 8.0 solutions in the presence of 10 equiv DFP, DCP, DCNP, F^- or organophosphates (OP1–OP8).

Additionally, the central role played by the hydroxyl moiety in **1** was assessed by testing the analogous derivative **2** (see Figure 1) under similar conditions. 99:1 (*v*/*v*) water/acetonitrile solutions (pH 8.0) of probe **2** were colourless and showed an absorption band at 350 nm. However, addition of DFP, DCNP and DCP induced negligible changes in the band indicating that the presence of the hydroxyl moiety in probe **1** is crucial to observe a final chromogenic response.

In order to focus our research to a more potential application, we moved a step further and developed studies using probe **1** to design test strips for the colorimetric detection of DFP in solution and in the gas phase. To check this possibility, a polyethylene oxide film containing 0.1% **1** and 1% Cs_2CO_3 was prepared. In a typical assay, the polymer containing probe **1** was either exposed to 99:1 (*v*/*v*) water/acetonitrile solutions of DFP, DCP and DCNP or placed in a container containing the simulants as gases at different concentrations. A similar colour change in the presence of DFP in aqueous solution was observed when using the polyethylene oxide membranes containing **1**. Moreover, Figure 4 shows that this colour change is a selective response to DFP that is detected with the naked eye in air at concentrations of about 10 ppm; the other simulants DCP and DCNP did not induce colour changes even at concentrations of 50 ppm in air. Further, it was also confirmed that these membranes containing probe **1** were not affected by the presence of vapours of other potential interferents such as the organophosphorous **OP1**–**OP8** derivatives.

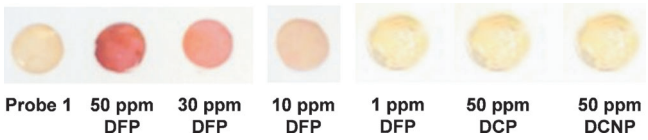


Figure 4. Polyethylene oxide membranes containing probe **1** after exposure to vapors of DCP, DCNP or DFP at different concentrations.

To summarize, we report herein the synthesis, characterization and sensing features of a new probe **1** for the selective chromogenic recognition of DFP (a sarin and soman mimic) in 99:1 (*v*/*v*) water/acetonitrile and in the gas phase. Colour modulation was due to the combined reaction of phosphorylation of **1** and fluoride-induced hydrolysis of a silyl ether moiety. As fluoride is a specific reaction product of the reaction between DFP and the –OH group, the probe shows a selective colour modulation in the presence of this chemical. Other nerve agent simulants, certain anions, oxidant species and other organophosphorous compounds were unable to induce colour changes in **1**. This is one of the very few examples of a selective detection, in solution and in the gas phase, of a sarin and soman simulant versus other reactive derivatives such as DCNP (a tabun mimic).

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Keywords: chromogenic probe · diisopropylfluorophosphate · nerve agents · sarin · soman

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