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Supramolecular Detection of a Sub-ppm Nerve Agent Simulant by a Smartphone Tool

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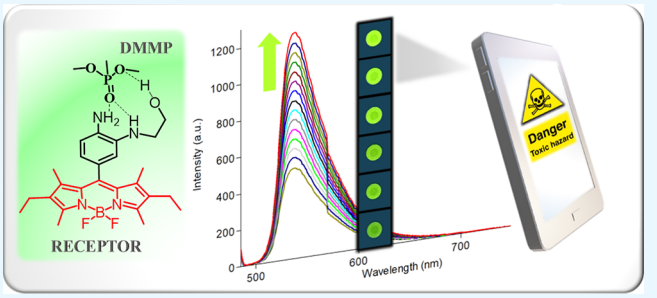
ABSTRACT: The widespread use of smartphones and related tools is extending their applications in several fields. Herein, we report a reusable smartphone coupled portable detection system for the sensing of sub-ppm level of a nerve agent mimic (dimethylmethylphosphonate) in the gas phase. The detection system is based on multiple hydrogen-bond interactions of the vapor analyte with an ad-hoc functionalized Bodipy chromophore scaffold. The multitopic approach used for the molecular recognition of DMMP leads to the highest binding constant values, high selectivity, and low limits of detection.



1. INTRODUCTION

Organophosphates (OP) nerve agents (NAs) are highly toxic derivatives, widely employed as herbicides, pesticides, and chemical weapons, known also with the name of Chemical Warfare Agents (CWAs), classified in G,V-type and the most recent Novichok (see Figure 1).[1]

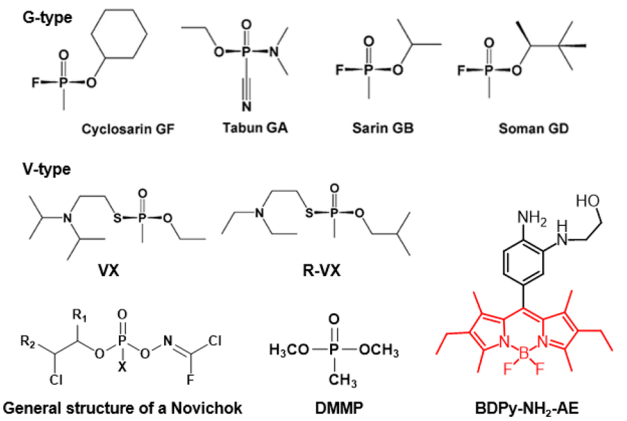


Figure 1. Chemical structures of organophosphorus nerve agents, DMMP simulant, and **BDPy-NH$_2$-AE** receptor.

Despite the production, stockpile, and use of NAs being forbidden, they are potentially accessible by terrorist groups and still represent a real threat to public safety and international security, posing a serious risk to the environment too.[2] A fast detection method of NAs both in solution and gas phase at very low concentration values is desirable for military and civilian safety. Due to the high toxicity of real NAs, their use for research purposes is strongly restricted and research activity in this field is conducted by using less poisonous NA simulants: less toxic organophosphates with comparable structures and properties.[3] In particular, dimethylmethylphosphonate (DMMP) has been demonstrated to be one of the best simulants of G series nerve agents.[4]

Current detection systems for NAs are mainly based on instrumental techniques such as mass and NMR spectroscopies,[5] having high sensitivity and selectivity, but their portability is limited due to the dimensions of the instruments. Optical-based sensing is a successful alternative, affording portability of the equipment, real time monitoring, and rapid and sensitive detection.[6] In this context, a number of fluorescent probes for NA detection have been developed based on the covalent interaction between functional groups anchored on a chromophore scaffold and the selected NA simulant.[7] Despite the high sensitivity levels reached with this strategy, in most cases, it presents relevant limitations, such as the non-reusability of the sensor after the first use and the low selectivity due to the nonspecific nature of the interactions involved. By contrast, the less explored supramolecular detection of NAs recently showed a number of advantages, including reversibility of the sensors and a higher selectivity due to the proper design of the receptor based on the chemical structure of the target NA.[8] The supramolecular approach

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exploits noncovalent interactions, such as hydrogen bonds,[9] inclusion within hydrophobic cavities,[10] and Lewis acid−base interaction.[11] Indeed, the recently explored multitopic supramolecular approach, which consists in the simultaneous involvement of more than one noncovalent interaction sites, has been demonstrated to be one of the most successful methods for NA detection, leading to higher binding constant values and higher selectivity.[12] In addition, the possibility of easily detecting the presence of NAs by a facile method, namely, a smartphone as a detector, leads to real-life applications of these detection systems. In this context, our research group recently developed a portable, fast detection method for sub-ppm concentrations of nerve agent simulant gas, exploiting a common smartphone.[13]

Nerve agent simulant gas sensing using an easily accessible tool, such as a smartphone, has barely been reported so far. Swager et al. developed wrapping single-walled carbon nanotube-based conductive systems for the sensing of NA simulants, exploiting covalent reactions between the receptor system and the selected analyte.[14] Smartphone-based fluorescence detection of OP nerve agents has been less studied. Indeed, fluorescence leads to high sensitivity, cheap starting materials for test-strip kit preparation, easy to use equipment, and a fast readout response accessible also to a nonqualified person. In particular, recently, Song et al. reported the detection of phosgene and mustard gas by means of a bifunctional quinoline-based fluorescent probe, exploiting a covalent reaction between the receptor and the analytes.[15] This system shows the advantage of using the fluorescence as an output but provides the covalent reaction between the sensor and analyte. Furthermore, Anslyn et al. used fluoride- and thiol-triggered self-propagating cascade covalent reactions to detect and quantify fluorine-containing G-series NAs and V-series NAs. The amplified fluorescence signal was exploited to develop a portable device able to perform the sensing using common cellular phone images and a proper color processing application.[16]

In this context, the first portable smartphone-based device, exploiting multitopic supramolecular interactions between a fluorescent receptor (BDPy-Di-NH_2) and the OP NA simulant in gas phase, has been recently reported by our group,[13] leading to good affinity for DMMP (log 6.60), moderate selectivity, and the possibility of restoring the starting probe after acid/base cycles. A Bodipy scaffold has been selected as a chromophore due to the high fluorescence quantum yields, easy synthetic protocols and functionalization processes, and high Stokes shift.[17] These compounds, in fact, have found many applications in the sensoristic field. However, this first prototype suffers from some limitations, such as low selectivity and lack of procedure for recovery based on acid/base cycles.

To improve the affinity and selectivity and restore the properties, in this work, a new fluorescent probe **BDPy-NH_2-AE** (Figure 1), bearing three different hydrogen bond donor groups, for the selective detection of DMMP in solution and gas phase via multiple hydrogen bond formation, is reported. The recognition properties of the new receptor toward DMMP in solution have been investigated by fluorescence titration, affording the binding constant value and the limit of detection. The multitopic approach leads to the highest binding constant value reported in the literature, to the best of our knowledge, and high selectivity for DMMP. Moreover, two-dimensional NMR measurements provided information on the geometry of the supramolecular complex. Finally, to obtain a portable solid device for real-time DMMP vapor sensing, a prototype has been developed, exploiting a standard smartphone camera and proper processing software. The new supramolecular sensor here reported represents an implementation of the previous one due to the presence of the ethanolamine arm. Indeed, exploiting the multitopic approach, the selectivity and the binding constant value are improved. In addition, also the recovery procedure has been improved due to the possibility of restoring the sensor by a simple thermal treatment.

2. MATERIALS AND METHODS

General experimental methods, procedure for fluorescence titration, determination of stoichiometry, and procedures for sensing using test strips and for the recovery of the device are described in detail in the Supporting Information.

2.1. Synthesis of BDPy-NH_2-AE. A total of 75.1 mg (0.175 mmol) of **BDPy-Di-NH_2** was solubilized in 10 mL of dry acetonitrile, and 150 μL of bromoethanol (2.11 mmol) was added to the as-prepared solution. The reaction mixture was stirred under N_2 at 80 °C for 2 weeks and monitored through TLC (silica gel:AcOEt/CH_2Cl_2 7:3). The solution was fully evaporated and subsequently separated using column chromatography (silica gel:AcOEt/CH_2Cl_2 5:5 + 5% CH_3OH), obtaining 18.7 mg of **BDPy-NH_2-AE** (yield 22.5%). ^{1}H NMR (500 MHz; acetone-d_6): δ 0.97 (t, J = 7.5 Hz, 6H), 1.26 (s, 6H), 2.33 (q, J = 7.5 Hz, 6H), 2.50 (s, 6H), 3.96 (m, 2H), 4.42 (q, J = 4.9 Hz, 2H), 7.11 (d, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H) ppm. ^{13}C NMR (125 MHz; DMSO-d_6): 149.4, 142.3, 133.8, 131.7, 128.7, 12.41, 126.26, 121.1, 117.1, 116.3, 59.3, 40.1, 12.4, 10.5, 8.22, 8.03 ppm. ESI-MS: m/z = 479.1 $[M + Na]^+$. Anal. calcd for $C_{25}H_{33}BF_2N_4O$: C, 66.09; H, 7.32; N, 12.33. Found: C, 66.05; H, 7.22; N, 12.28.

3. RESULTS AND DISCUSSION

The receptor moiety was designed to simultaneously recognize via H-bonds (i) the P—O and (ii) one of the methoxy groups of the DMMP simulant. In particular, ethanolamine displays the perfect geometry to perform such interactions with DMMP (see Figure 2). The calculated distance between H-donor groups in the ethanolamine arm (Figure 2b) matches the calculated distance between the H-acceptor groups in the DMMP (Figure 2c).

Here, we introduced an ethanolamine arm to increase the efficiency and selectivity for DMMP, exploiting the multitopic approach shown in Figure 2. The best way to obtain such a system is to introduce one ethanolamine arm to the previously

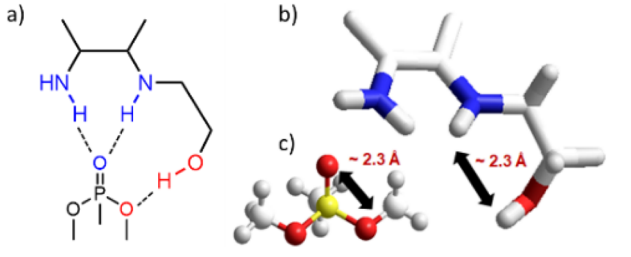

Figure 2. (a) Target interaction geometry between the receptor moiety and DMMP; (b) optimized structure of the ethanolamine chain linked to the chromophore scaffold (the chromophore is omitted for clarity) and calculated distances between H-donor groups; (c) optimized structure of the DMMP guest and calculated distances between H-acceptor groups.

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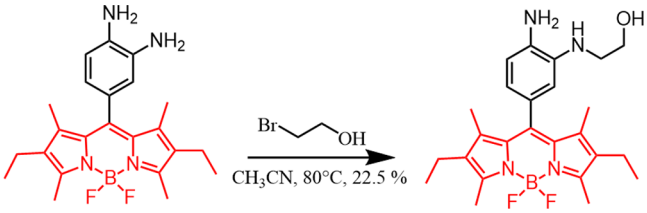
synthesized **BDPy-Di-NH$_2$** (see Scheme 1), through the functionalization of the meta-amine group with a bromoethanol chain (the meta-amino group is more nucleophilic if compared to the para; in addition, an ROE contact between the CH_2 protons of the ethanolamino arm and the CH_3 protons of the Bodipy core suggests the functionalization in the meta position).

Scheme 1. Synthesis of BDPy-NH$_2$-AE



In light of this, **BDPy-NH$_2$-AE** was synthesized starting from **BDPy-Di-NH$_2$**,[13] which after the reaction with a large excess of bromoethanol, was converted to **BDPy-NH$_2$-AE** (Scheme 1), as confirmed by ^{1}H and ^{13}C NMR spectroscopy and ESI-MS measurements (see the Supporting Information).

The optical properties of the new receptor were investigated by means of UV−vis and fluorescence spectroscopy (see the Supporting Information). The emission profile of **BDPy-NH$_2$-AE** in chloroform solution shows an intense emission band centered at 545 nm, by exciting at 480 nm. The high Stokes shift observed makes **BDPy-NH$_2$-AE** a good candidate for fluorescence sensing application.

To explore the detection properties of **BDPy-NH$_2$-AE** toward DMMP, fluorescence titration was performed by adding progressive amounts of DMMP to a solution of the host. A remarkable increase in the emission intensity of the host was observed upon addition of the guest (Figure 3), probably due to the inhibition of the PET mechanism in the presence of DMMP. The Φ_F value of **BDPy-NH$_2$-AE** changes from 0.34 to 0.66 by addition of 1 equiv of DMMP.

Considering a recognition process with a 1:1 host/guest stoichiometry, as confirmed by Job's plot (see the Supporting Information), we calculated a logarithmic binding constant value of 7.56 (calculated by HypSpec 1.1.33),[18] which is the highest reported in the literature so far, concerning the noncovalent detection of DMMP.

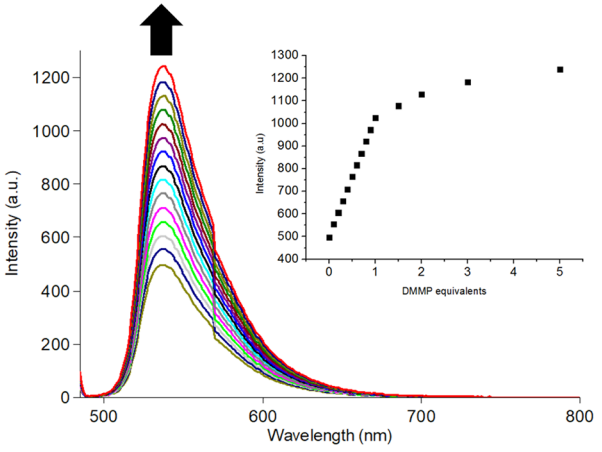


Figure 3. Fluorescence titration of **BDPy-NH$_2$-AE** ($CHCl_3$, 1×10^{-6} M, λ_{exc} = 480 nm) upon addition of increasing amount of DMMP in the range 0−5 equiv. The inset shows the calibration curve.

Sensitivity is an important parameter in the design of sensors for toxic contaminants. In the case of Sarin nerve agent, the toxicity level expressed in terms of LD_{50} is around a concentration of 2−6 ppm.[9a] Notably, the limit of detection (LOD) of **BDPy-NH$_2$-AE** toward DMMP, calculated through the standard deviation method (see the Supporting Information), is 296 ppt, which is confirmed by titration at low DMMP concentration values (see the Supporting Information, Figure S8), well below the hazardous concentration.

To shed light on the geometry of the supramolecular complex, a two-dimensional ROESY experiment of an equimolar solution of **BDPy-NH$_2$-AE** and DMMP in $CDCl_3$ was carried out (see Figure 4). As expected from the design process, ROE contacts were observed between the $-CH_2-$ group of the host and the methoxy group of DMMP, suggesting the formation of the supramolecular complex, which simultaneously involves three different hydrogen bond sites: (i) two bonds between the P—O group of DMMP and the amino groups of the receptor; (ii) the third one between the $-OCH_3$ of the guest and the OH group of the receptor.

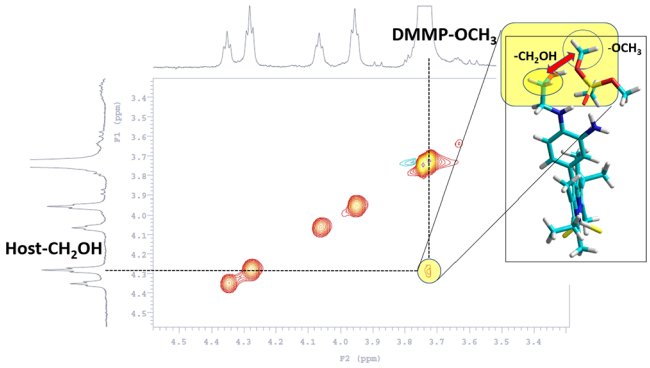


Figure 4. Details of the ROESY spectrum of **BDPy-NH$_2$-AE@DMMP** (1×10^{-3} M in $CDCl_3$). The inset shows the minimized structure (force field MM+) of the supramolecular complex, highlighting the functional groups involved in the ROE contacts.

One of the main advantages of the supramolecular approach in the sensing field is the possibility of simultaneously involving several interaction sites of the host and guest, thus increasing the selectivity. With the aim of testing the cross selectivity of the receptor toward DMMP, also in competition with other common analytes present in the environment, the emission spectra of a $CHCl_3$ solution of **BDPy-NH$_2$-AE** were recorded before and after exposure to air (standard composition: 24000 ppm water, 400 ppm CO_2, 5 ppm NO, and 10 ppm CO) for 5 min, without observing any change in the emission profile (Figure 5). Similar results were obtained after exposure to an excess (10 equiv) of triethylphosphine (Et_3P), triphenylphosphine (PPh_3), phosphocholine (Pho-Ch, used as a phosphocholine chloride calcium salt tetrahydrate simulant of V-series), acetone, and methanol. Meanwhile, after the addition to the same **BDPy-NH$_2$-AE** solutions of 1 equiv of DMMP, a strong increase in the emission intensity was observed, confirming the strong cross selectivity of this new receptor toward this specific NA simulant. We tested also other OP compounds having similar structure with respect to DMMP. In particular, diethyl methyl phosphonate (DEMP), triethyl phosphate (TEP), and tributyl phosphate (TBP) have been tested. **BDPy-NH$_2$-AE**

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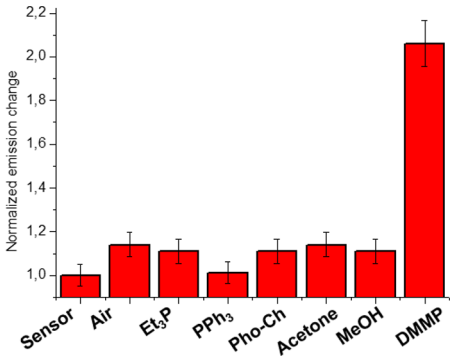

Figure 5. Selectivity tests: normalized emission change of **BDPy-NH$_2$-AE** solution (I/I_0, 1×10^{-6} M in $CHCl_3$, λ_{ex} = 480 nm, λ_{em} = 540 nm) after exposure to air (bubbled for 5 min), other competitive guests (10 equiv), and DMMP (1 equiv).

shows a similar response to DMMP due to the presence of similar supramolecular recognition sites (see the Supporting Information, Figure S10). These results confirm the validity of the supramolecular method. Indeed, by designing a complementary host to the target analyte, we obtained a remarkable selectivity, avoiding the risk of possible false positive response. Furthermore, as shown in Figure 4, the noncovalent interactions between **BDPy-NH$_2$-AE** and DMMP can be also invoked with real phosphate-containing nerve agent compounds. In fact, as reported in Figure S11 (see the Supporting Information), all these chemical compounds show a P—O group covalently bound to two substituents with H-bond acceptor atoms (oxygen, in most cases, sulfur, nitrogen, or halogen). This aspect makes **BDPy-NH$_2$-AE** a good candidate for the detection of real NAs.

Once the high performance of **BDPy-NH$_2$-AE** in detecting ppt levels of DMMP in solution was evaluated, we explored the possibility of obtaining a solid portable device for the sensing of DMMP vapor at different concentrations. To this aim, a prototype was developed. In particular, silica RP$_{18}$ was selected as a proper solid support, suitable to reduce the possible interaction with the fluorescent receptor as well as with DMMP vapor. The solid sensor was realized by dropping 1 μL of a **BDPy-NH$_2$-AE** solution (1 mM in CH_2Cl_2) on the solid support and then exposing it to progressively increasing concentrations (0−450 ppm) of DMMP vapor in a closed vial (volume 23 mL).

Exploiting the optical properties of this receptor, which displays a strong fluorescence emission when irradiated with wavelengths in the UV range (356 nm), we observed the change in the emission intensity of the supported receptor as a function of DMMP vapor concentration (Figure 6a), showing a sort of linearity in the range 0−14 ppm DMMP, thus suggesting the potential use in the real detection of NAs (fluorescent carbon nanoparticles were used as a control test). The procedure comprises the use of a dark chamber having a lamp irradiating at λ 365 nm. A standard smartphone can be used to acquire pictures of the test strip. Finally, data processing by means of Fiji software[19] was able to perform a cross-sectional analysis of the pixel intensity expressed in grayscale, thus affording the correlation reported in Figure 6b.

Another remarkable advantage of the supramolecular approach over the classic covalent one is the possibility of restoring the sensor due to the noncovalent nature of the interactions involved.

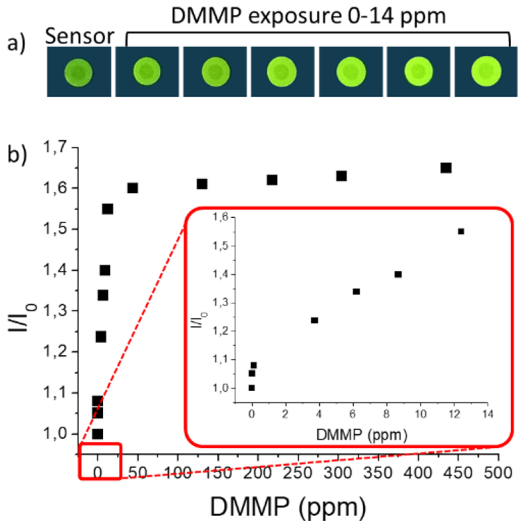

Figure 6. (a) Pictures of the **BDPy-NH$_2$-AE** sensor deposited on a silica RP$_{18}$ support under a UV lamp (356 nm) before and after exposure to DMMP gas in the range 0−14 ppm (solution of DMMP in CH_2Cl_2 at different concentrations, exposed to the supported sensor for 1 h at 50 °C in a 23 mL closed vial). (b) Normalized fluorescence intensity (I/I_0, where I and I_0 are the gray channel emission values of the probe and control, respectively) as a function of DMMP gas concentration in the range 0−450 ppm. The inset shows the linear correlation in the range of 0−14 ppm DMMP.

To evaluate this possibility, recovery tests were performed, exploiting the effect of the temperature on the supramolecular complex. In particular, as previously demonstrated,[12] the increase in the temperature leads to the breaking of the hydrogen bonds between ethanolamine arms and DMMP. Figure 7b shows the possibility of reusing **BDPy-NH$_2$-AE** at least three times, although with a loss of efficiency.

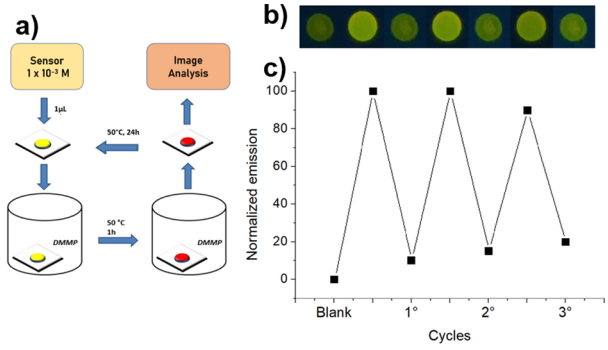

Figure 7. (a) Schematic representation of the thermal cycle; (b) pictures of the **BDPy-NH$_2$-AE** sensor deposited on a silica RP$_{18}$ support under a UV lamp (356 nm) before and after each thermal cycle; (c) normalized fluorescence intensity of **BDPy-NH$_2$-AE** ($I - I_0$, where I is the gray channel emission values defined as those described in Figure 6 of the probe after each adsorption cycle and I_0 is the initial emission of the probe).

This sensor represents the supramolecular receptor for CWAs simulant having, to the best of our knowledge, the highest binding constant affinity value in solution. As suggested also by 2D NMR experiments, this is probably due to the presence of ethanolamine arm that assists the recognition property of DMMP by the multitopic approach. Notably, the recognition of the CWAs simulant leads to a strong turn-on

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Table 1. Comparison between Analytical Parameters of Smartphone-Based Nerve Agent Sensors[a]

Ref.	Analyte	Approach	Response	LOD solution	LOD smartphone detector	Selectivity	Reusability
14b	DCP/ DFP	Covalent	Chemiresistive signal	Not reported	28 ppb	Selective towards DCP and DFP	Irreversible
15	SM/Phos	Covalent	Fluorescence (*turn-on*)	14 ppb Pho 70 ppb SM	Notreported	Selective to Phosgene (tested in solution)	Not tested
16	DFP/ DSM	Covalent	Chromaticity change	Not reported	0.17 ppm (DFP) 0.38ppm (DSM)	Not tested over other contaminants	Not tested
13	DMMP	SupramolecularlogK=6.60	Fluorescence (*turn-off*)	9.47 ppt	535 ppm	Slightly selective towards DMMP.	5 cycles(acid/base cycle)
Current work	DMMP	SupramolecularlogK=7.56	Fluorescence (*turn-on*)	296 ppt	0.79 ppm	Selective response to DMMP over other contaminants and OPs	3 cycles(thermal treatment cycle)

[a]DCP (diethyl chlorophosphate); DFP (diisopropyl fluorophosphate); SM (sulfur mustard); Phos (phosgene).

fluorescence emission response, ideal for sensing application. Furthermore, the multitopic approach leads also to a higher selectivity toward DMMP if compared to the previous receptor.[13] The higher efficiency of this new sensor is also demonstrated on the solid state, leading to the possibility of detecting sub-ppm values of DMMP in vapor phase, with a linear response under ca. 14 ppm. This represents a real novelty if compared to the other smartphone-based supramolecular sensors of CWAs.[13] In addition, the possibility of restoring the solid sensor by the use of temperature is a clear improvement with respect to the previous system, in which acid/base cycles were required.

Table 1 reports the comparison of **BDPy-NH$_2$-AE** with other nerve agent sensors reported in the literature so far, which use a smartphone as a detector. Interestingly, most of the sensors listed below exploit the covalent approach,[14−16] limiting the reversibility of the process. In particular, analytes bearing good living groups such as DFP, DCP, SM, and Pho are involved in covalent interactions with the receptor moiety of the sensor. The current work and our previous one[13] are the only two examples of supramolecularly driven nerve agent simulant gas detection via a smartphone. Taking advantage of the multisite noncovalent interactions, **BDPy-NH$_2$-AE** displays a remarkable binding constant value, almost 1 order of magnitude higher (10-fold) if compared to the previous sensor obtained. Furthermore, **BDPy-NH$_2$-AE** exploits the turn-on of fluorescence signal to detect NAs, leading to a simple hardware setup with respect to a chemiresistive response. In this work, the limit of detection (LOD) value in solution is lower if compared with the SM and Pho sensors.[15] Notably, with a smartphone, the LOD is under ppm value, improving the sensitivity of the other supramolecular sensor, with a performance in line with the covalent sensors.[4b16] The advantages of **BDPy-NH$_2$-AE**, also with respect to our previous sensor, are (i) the higher binding constant affinity due to the presence of multiple interaction sites; (ii) the turn-on emission response to the presence of DMMP; and (iii) the possibility of reusing the device, restoring the sensing properties with an easy methodology (thermal treatment).

4. CONCLUSIONS

A new BODIPY-based fluorescent probe able to selectively detect DMMP vapor in solution and gas phase is here reported. The ease of synthesis and the remarkable optical response make this new compound suitable for application in real sensing of toxic OP nerve agents. The unprecedented binding affinity and limit of detection toward the DMMP nerve agent simulant have been observed. The development of an easy-to-use (using a standard smartphone) solid device provided a functional and rapid detection of ppm level of DMMP vapor.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c03759.

Detailed experimental procedures, fluorescence measurements, HypSpec plot, determination of stoichiometry, procedure for sensing using test strips and recovery (PDF)

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Notes

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