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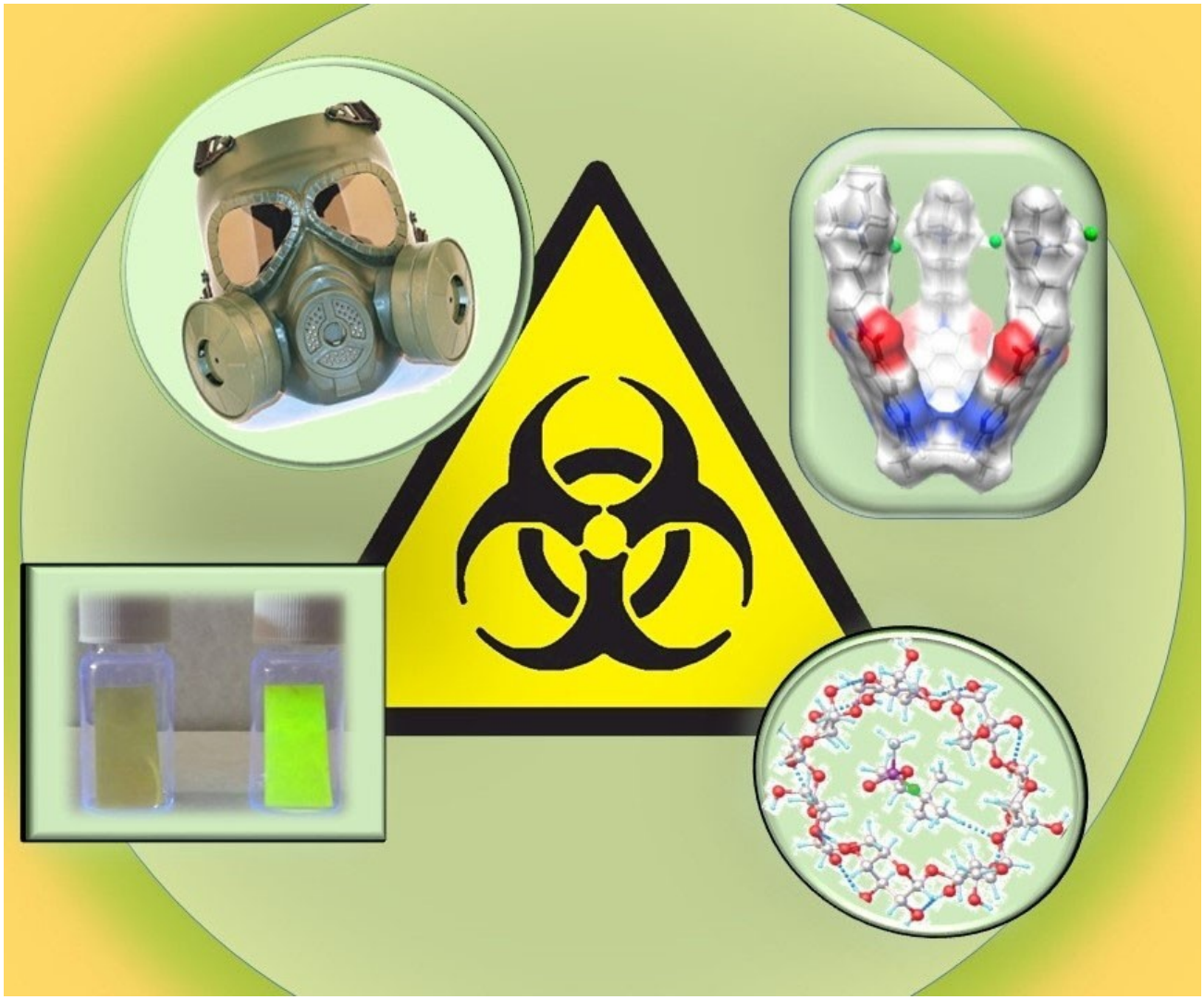
Supramolecular Sensing of Chemical Warfare Agents

Ester Butera,[a] Agatino Zammataro,[a] Andrea Pappalardo,[a, b] and Giuseppe Trusso Sfrazzetto*[a, b]



Chemical warfare agents are a class of organic molecules used as chemical weapons due to their high toxicity and lethal effects. For this reason, the fast detection of these compounds in the environment is crucial. Traditional detection methods are based on instrumental techniques, such as mass spectrometry or HPLC, however the use of molecular sensors able to change a detectable property (e.g., luminescence, color, electrical resistance) can be cheaper and faster. Today, molecular sensing of chemical warfare agents is mainly based on the "covalent approach", in which the sensor reacts with the analyte, or on the "supramolecular approach", which involves the formation of non-covalent interactions between the sensor and the analyte. This Review is focused on the recent developments of supramolecular sensors of organophosphorus chemical warfare agents (from 2013). In particular, supramolecular sensors are classified by function of the sensing mechanism: i) Lewis Acids, ii) hydrogen bonds, iii) macrocyclic hosts, iv) multi-topic sensors, v) nanosensors. It is shown how the supramolecular non-covalent approach leads to a reversible sensing and higher selectivity towards the selected analyte respect to other interfering molecules.

1. Introduction

Chemical weapons are a wide class of toxic molecules used, from global wars of the past century, also in terrorist attacks.[1] The use of these toxic chemical compounds, also called Chemical Warfare Agents (CWAs), previously used also as pesticides, is still current, as demonstrated by the recent international scenario.[2,3] For example, sarin gas was alleged to have been used in recent conflicts,[4a,b] and the Novichok group, one of the latest generation of CWAs, has recently been employed as a poison.[4c,5]

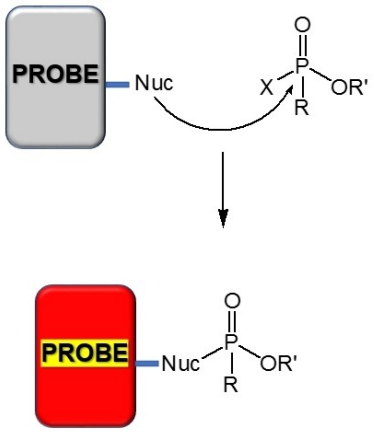
In general, a terrorist attack in which the CWAs are released in air or water can be due to a nebulization/vaporization,[6] or by solubilization in water.[7] In addition, CWAs can be also released in solid matrices, such as foods of other common objects. After the release on the environment, the first step is the fast detection of CWAs, followed by the adequate protocol of decontamination, such as acid/base catalyzed hydrolysis, metal-assisted decomposition, enzymatic hydrolysis or degradation inside MOF (metal-organic-framework) nanostructures.[8] Also at this step, sensing of these degradation or decontamination compounds is crucial to check for effective decontamination alongside initial identification.

Detection of CWAs can be performed by instrumental techniques, such as gas-chromatography, HPLC, MS and NMR methods.[9,10] These techniques show excellent sensibility and selectivity, however they are expensive in term of cost and time-analysis. In addition, the use in real field is precluded due to their sizes.

On the contrary, molecular probes are cheap, fast, easily performable, and economic. In general, a molecular sensor reacts or interacts by non-covalent interactions with the analyte, leading to a change of a measurable response (i.e., electrical, optical, magnetic response). In this context, CWAs detection can be performed by using two different approaches: the covalent and the supramolecular. In the "covalent approach", a covalent reaction occurs between sensor and analyte, leading to the formation of a new compound having different properties compared to the starting sensor (Scheme 1).[11]

In fact, the detection of an analyte based on spectroscopic techniques, such as UV-Vis or emission measurements, are fast and easy.[12,13] In this context, the covalent approach shows some limitations: low specificity for the analyte due to reaction with other analytes, thus leading to false-positive responses. In particular, in most cases, sensor contains a nucleophile moiety that reacts with the CWA due to the electrophilic nature of the P=O group. In the presence of other analytes also containing a similar electrophilic site (such as acyl chlorides or anhydrides) a similar reaction occurs thus leading to false positive. Furthermore, these sensors cannot be reused after the exposure to the analyte, due to the formation of an irreversible covalent bond.

In the last decade, a new sensing method based on the supramolecular interactions between sensor and analyte has been developed.[14] This strategy has been named as „supramolecular approach". The success of this approach can be ascribe to avoid the irreversible reaction between sensor and analyte, leading to the formation of non-covalent inter-



Scheme 1. Schematic representation of the "covalent approach" used for the detection of a generic CWA.

[a] *Dr. E. Butera, Dr. A. Zammataro, Prof. A. Pappalardo, Dr. G. Trusso Sfrazzetto*
Department of Chemical Sciences
University of Catania
Viale Andrea Doria 6, 95125, Catania (Italy)
E-mail: giuseppe.trusso@unict.it
[b] *Prof. A. Pappalardo, Dr. G. Trusso Sfrazzetto*
INSTM Udr of Catania
Viale Andrea Doria 6, 95125, Catania (Italy)

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actions between the species, thus obtaining reusable sensors. In addition, this approach minimizes the presence of other interfering analytes.

This minireview aim to collect the recent developments on supramolecular sensing of CWAs, starting from 2013 up to nowadays. In fact, after the review of Sambrook and Notman, many progresses have been reported in this field. After a brief introduction on the chemical structure, classification and toxicity of CWAs, we focused our attention on different categories of supramolecular sensors, such as *i*) Lewis-Acid receptors, *ii*) receptors exploiting hydrogen-bonds, *iii*) macrocyclic hosts, i*v*) multitopic receptors and v) nanosensors. Although many nanosensors, based on graphene, nanoparticles or nanotubes, cannot be define as "supramolecular" receptors, they have been used in the non-covalent sensing of CWAs and some recent interesting reviews collected these applications.[15,16]

2. Classification of OP CWAs

CWAs include a wide range of compounds, such as blister agents, blood agents and organophosphorus nerve agents. From a chemical point of view, organophosphorus Chemical Warfare Agents (OP CWAs) are organic compounds, in which the P=O group is covalently linked to a good leaving group, and other two substituents. Today, OP CWAs can be classified into three main groups: G-type, V-type and, the most recent, A-type (also called Novichok) (Figure 1).[17–19]

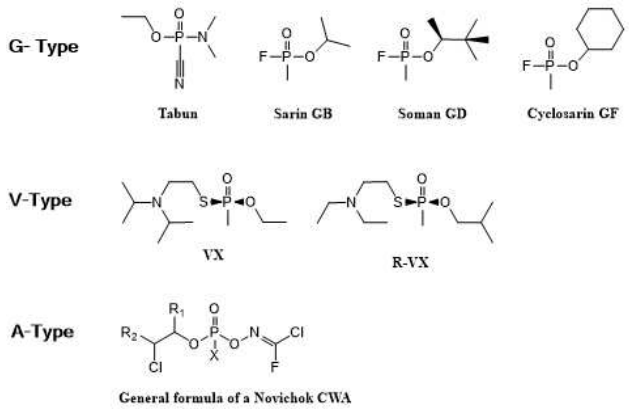


Figure 1. Chemical structures of G-type, V-type and general formula of A-type OP CWAs.

G-Type (German-agents) CWAs were developed starting from 1930s to 1940s, and include Cyanophosphoramidate,[20] Tabun (GA),[21] Sarin (GB),[22] Soman (GD)[23] and Cyclosarin (GF).[24]

V-Type (venomousagents) CWAs, discovered after World War 2, are methylphosphothioates and collect two compounds: VX[25] and RVX.[26] V-type compounds are less volatile respect to the G-type, so they are more persistent in the environment, thus more toxic. The use of OP CWAs for research activity is not permitted in many countries, thus researchers perform their activity, in terms of sensing and degradation studies, by using

Ester Butera was born in Palermo in 1997. She received her bachelor's degree in industrial chemistry in 2020, working on the synthesis of fluorescent BODIPY for pillar[5]arene derivates. She is currently working towards a master's degree in chemical sciences at the University of Catania, working on sensing of chemical warfare agent by supramolecular receptors.

Agatino Zammataro received his master's degree in organic and bioorganic chemistry at the University of Catania in 2019, working on functionalization of carbon quantum dots for nanomedicine application and photo releasing of drugs. Currently he is a PhD student at University of Catania in partnership with SIFI, working on proteomics studies for the treatment of eye diseases.

Prof. Andrea Pappalardo was born in Catania, Italy in 1974. After receiving his BS degree in chemistry and pharmaceutical technologies from Catania University in 1999, he continued his PhD study in Catania under the supervision of Prof. Gaetano Tomaselli. In 2004 he had a postdoctoral position at the Department of Organic and Biological Chemistry of the University of Messina under the supervision of Prof. Melchiorre Parisi. From 2015, he is a Professor at the Department of Chemical Science of the University of Catania. His research interests are focused on calixarene macrocycles and their use as receptors in the supramolecular host/guest chemistry.

Dr. Giuseppe Trusso Sfrazzetto was born in Catania in 1981. He received his master's gegree in 2007 and PhD degree in 2011 at the University of Catania working in the group of Prof. Gaetano Tomaselli on the synthesis and applications of new chiral cavitand hosts for the enantioselective molecular recognition of amino acid derivatives. From 2017, he is a researcher at the Department of Chemical Sciences of the University of Catania. His research interests are focused on supramolecular chemistry, molecular recognition and fuorescent sensors for important analytes.

Table 1. Physical properties of OP CWAs.[a]

	Vapor Pressure	Volatility	Odor	Solubility	Persistency
Tabun (GA)	0.037 mm Hg at 20 °C	576–610 mg/m^3 at 25 °C	Fruity	9.8 g/100 g at 25 °C	$T_{1/2}$ = 24–36 hours
Sarin (GB)	2.1 mm Hg at 20 °C	16,400–22,000 mg/m^3 at 25 °C	Odorless	Miscible	2-24 hours at 5–25 °C
Soman	0.40 mm Hg at 20 °C	3,060–3,900 mg/m^3 at 25 °C	Fruity; oil of camphor	2.1 g/100 g at 20 °C	Relatively persistent
GF	0.07 mm Hg at 25 °C	59 ppm	Odorless	3.7 g/100 g at 25 °C	Unknown
VX	0.0007 mm Hg at 20 °C	3–30,0 (10,5) mg/m^3 at 25 °C	Odorless	Miscible at < 9.4 °C "Slight" at 25 °C	2–6 days

[a] Adapted from reference [11] with permission from American Chemical Society.

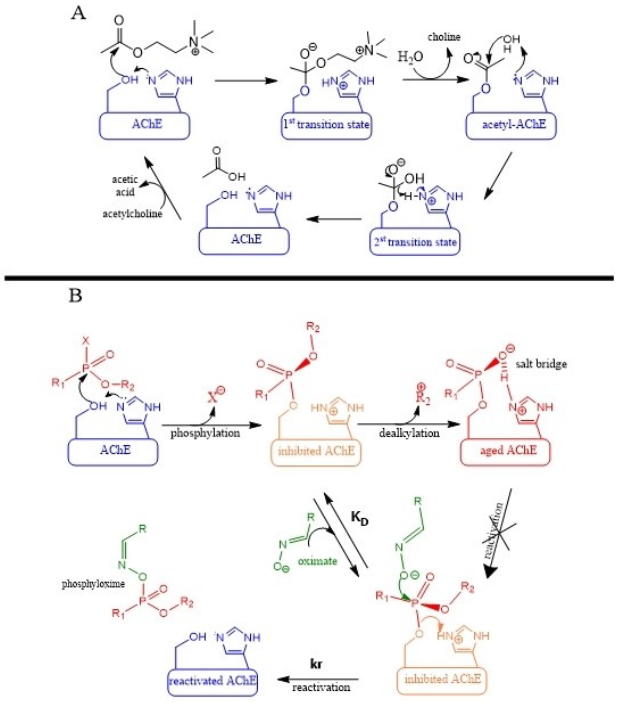
simulants, less toxic organic compounds having similar structure-geometric features with respect to the OP CWAs.[27] The reduced toxicity of the simulant is due to a less reactivity with the specific enzyme (acetylcholinesterase) due to the absence of the leaving group, characteristic of CWAs.

Table 1 reports the physical properties of the G and V-type of CWAs. The volatility at room temperature is similar to water, thus the dispersion by aerosol is the preferred way to spread these toxic compounds in the air. The stability of OP CWAs in the environment in normal conditions is defined as persistency. This is due to the combination of volatility and density, and is related to the chemical stability of the toxin upon the light and water exposure. As previously reported, V-type CWAs are more persistency respect to the G-type.

3. Toxicity

The lethality of OP CWAs is due to their ability to inhibit the enzyme Acetylcholinesterase (AChE). This enzyme, in physiological conditions, catalyze the hydrolysis of acetylcholine in the synapses (Scheme 2A): a serine, by the assistance of a histidine, acts as a nucleophile reacting with the carbonyl group of the substrate, leading to a tetrahedral transition state which, after reorganization, generates choline. The enzyme restores its catalytic structure by the presence of a water molecule, which, after deprotonation assisted by the histidine, attacks the acetylserine moiety leading to acetic acid and the pristine enzyme.

AChE inhibition, due to the presence of OP CWAs which interact with the serine–histidine–glutamate triad in the active site (Scheme 2B),[28] causes the accumulation of acetylcholine, saturating the muscarinic and nicotinic receptors, leading to cholinergic crisis.[29] As reported in Scheme 2B, OP CWA is attacked by the serine, in a similar mechanism with respect to those observed with acetylcholine, leading to the elimination of the leaving group of the starting OP CWA. Also in this case, the enzyme is covalently bounded in a tetrahedral transition state.[30] However, the reactivation of the enzyme is more difficult, because the histidine, necessary to activate a water molecule able to restore the initial enzyme, is busy in a salt-bridge with the anionic form of the adduct enzyme-CWA obtained after dealkylation (aged-enzyme). Thus, the hydrolysis of the aged-enzyme is extremely slow (from hours to days).[31] The reaction of dealkylation can be avoided by the presence of an oximate, acting as an antidote, which by nucleophilic attack



Scheme 2. (A) Mechanism of hydrolysis of acetylcholine by the enzyme AChE; and (B) mechanism of AChE inhibition by OP CWAs, aging, and reactivation by oximate. Adapted from reference [28] with permission from the American Chemical Society.

leads to phosphyloxime, reactivating the enzyme.[32,33] As demonstrated by the reaction reported in Scheme 2B, the treatment with the antidote must be done as soon as possible, to avoid the formation of the aged-enzyme. This time, also called as "aging time" is in the range of few minutes for Soman, hours for Sarin or days for VX and Tabun.[34–36]

Table 2 shows the toxicity levels of the common OP CWAs. The LD_{50} values are in the milligram range for all OP CWAs. VX is the most dangerous, in fact a drop of liquid VX on the skin is potentially lethal. Furthermore, 2 ppb of nebulized VX are toxic. The exposure to OP CWAs can lead to broad clinical effects, related to muscarinic transmitters inhibition (salivation, lacrimation, urination, defecation, diaphoresis, gastric emesis, bronchorrhea, bronchoconstriction and bradycardia). Furthermore, the inhibition of nicotinic transmitters can lead to more severe effects, such as weakness and facial paralysis. Also lethal effects can be occurred.

Table 2. Toxicity values of some OP CWAs.

	LD_{50}[a] [mg/person]	LC_{50}[b] [ppm]	LCt_{50}[c] [mg×min/m^3]	IDLH[d] [ppm]
Tabun (GA)	1	2	100–400	0.03
Sarin (GB)	1.7	1.2	50–100	0.03
Soman	0.35	0.9	25–70	0.008
GF	0.03	Unknown	Unknown	Unknown
VX	0.01	0.3	5–50	0.002

[a] Dose required to kill 50% of those exposed; [b] concentration required to kill 50% of those exposed; [c] concentration-time product that is lethal to 50% of those exposed and reflects toxicity by inhalation route; [d] concentration of toxin in air that is "immediately dangerous to life and health". Adapted from reference [11] with permission from the American Chemical Society.

4. Sensing by Supramolecular Approach

Due to the progress of Supramolecular Chemistry in the last decades, today Supramolecular Organic Chemists can design and synthesize artificial receptors able to selectively recognize analytes, thus obtaining high binding constants, low limits of detection and high selectivity. These three parameters are essential for an efficient sensor. In addition, the formation of non-covalent interactions can lead to the possibility to restore the starting receptor, thus obtaining a reusable sensor. The target of this minireview is to analyze the OP CWAs sensors focusing on the non-covalent interactions at the base of their sensing mechanism. The goals of the supramolecular approach are multiple:

i) Reversibility: due to the formation of low energy interactions between receptor (host) and analyte (guest), by the appropriate external stimuli, such as temperature or solvent, is possible to break the supramolecular host-guest complex, recovering the starting sensor.

ii) Selectivity and false-positive responses: the formation of an equilibrium between free-sensor and analyte-sensor can prevent the irreversible interaction with other analyte (false-positive responses), widespread in the covalent approach. In fact, a chemical reaction between the sensor and the analyte is poorly selective. By the contrast, the possibility to design the most appropriate supramolecular receptor for the desired analyte and, in particular, the possibility to tune the binding constant affinity values by choosing the appropriate non-covalent interactions, can lead to a more selective sensor.

iii) Multi-topic approach: the possibility to recognize the selected analyte by exploiting more than one site of the sensor leads to higher binding constant values, and reduces the possibility to obtain a false-positive response, due to the low probability that other molecules, different from the selected analyte, satisfy the same chemical-geometric requirements. This approach leads to higher selectivity, if compared to the "classic" sensors, higher association constants and a lower limit of detection.

iv) Fast-response: in general, non-covalent interactions are instantaneous, thus the sensing by using this approach is faster, compared to many chemical reactions that can occur in minutes or hours.

4.1. Sensing by Lewis Acids

The non-covalent recognition by Lewis Acid-Base interactions exploits the ability of a metal ion (Lewis Acid) in the sensors backbone to interact with the P=O group of OP CWAs (Lewis Base), by accepting the lone pair of oxygen atom of OP CWAs.

The interaction of Ln^{3+} ions with the P=O group was well studied during the last decades.[37] Sensing by using these complexes is based on the "disruption of an antenna effect",[38] by the presence of the analyte. This effect can be due by the chelating action of the analyte towards the metal ion, leading to a non-emissive complex (Figure 2, left) or by the interaction of the analyte with the ligand of the lanthanide, leading to the loss of the metal ion and the change of the spectral characteristics (Figure 2, right).

Sambrook and co-workers described the synthesis and sensing application of two lanthanide complexes, containing Eu(III) and Tb(III), to recognize Sarin in organic solvent.[39] By UV-Vis titrations, they calculated for Sarin binding constant values of $3.80\times10^4\ M^{-1}$ and $4.10\times10^4\ M^{-1}$ by using Eu(III) and Tb(III), respectively. Similar binding association values have been calculated also for DMMP (dimethylmethylphosphonate) and DCP (diethylchlorophosphate), two of the most common used CWAs simulants. The sensing mechanism invoked by the authors is merely to ascribe to a dynamic (collisional) excited state quenching mechanism (Figure 1, down), due to the absence in the CWA tested of a second site able to chelate the Ln^{3+}.[40]

On the contrary, a static quenching mechanism is involved (Figure 2, left) in the bodipy fluorescent sensors obtained by Martìnez-Manez and coworkers.[41] These sensors contain Eu(III) or Au(III) as metal ions, and are selective towards V-Type CWAs respect to the G-Type. Furthermore, the presence of the bodipy moiety allows to follow the sensing event by emission spectroscopy and by naked eyes. Binding constant values calculated for Eu(III) or Au(III) complexes with Demeton (a phosphorothioate V-Type simulant) are ca. $7.94\times10^6\ M^{-1}$ and $5.01\times10^6\ M^{-1}$, respectively, with a limit of detection of 12.89

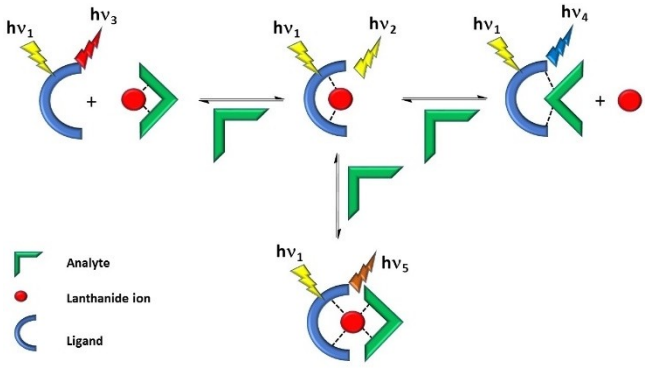


Figure 2. Sensing mechanisms by the antenna effect.

and 9.08 ppm. The higher affinity with the Au^{3+} ion is to ascribe to the higher affinity of gold cation for sulfur atom (present in the Demeton). The selectivity towards V-Type CWAs has been demonstrated by using G-Type simulants, also in large excess respect to the sensors.

The first example of Salen-metal complex able to interact with OP CWAs has been reported by Atwood and coworkers.[42] In particular, the authors demonstrated by ESI-MS measurements the interaction of Sarin and Soman with the aluminum metal center by a Lewis Acid-Base interaction, after proper activation of the receptor by the acetate anion. Although this detection system is not practical, this work paved the way for the synthesis of new metal-salen complexes, able to be easily monitored (vide infra).

Our research group synthesized the first metal-salen complex able to recognize DMMP, both in solution than onto a solid device (Figure 3A and B, respectively).[43]

The metal center, acting as a Lewis acid, is represented by the uranyl cation (UO_2^{2+}). Recognition event has been monitored by ^{1}H NMR and UV-Vis spectroscopy, obtaining a binding constant value of 2.24×10^4 M^{-1}. This receptor has been further functionalized in order to be covalently anchored onto a silica solid support, obtaining a real device for sensing application. Detection of DMMP by this solid device has been monitored by UV-Vis and XPS measurements. Notably, detection limit has been estimated in 6 ppm by XPS experiments, and the recovery of the solid device was tested by exposing the solid sensor to acetonitrile at 70 °C for 10 minutes. Reusability of the device

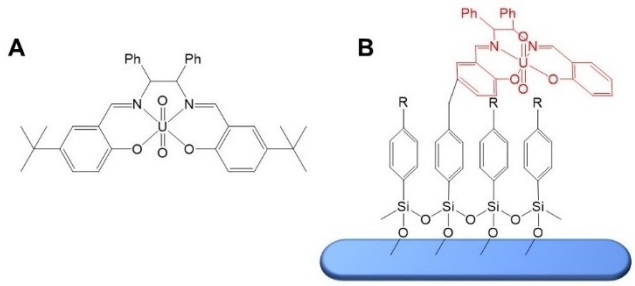


Figure 3. A) Uranyl-salen complex for DMMP recognition is solution; B) schematic representation of the solid support, containing uranyl-salen complex covalently anchored.

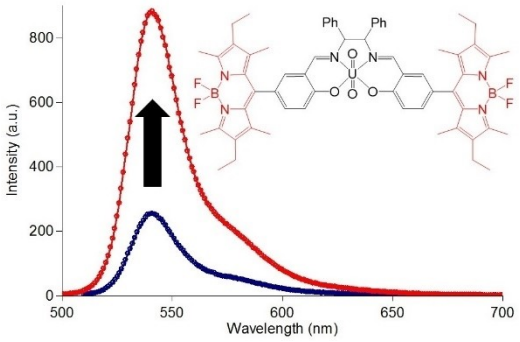


Figure 4. Fluorescence response of the fluorescent Uranyl-salen complex (showed in the inset) to DMMP.

was confirmed for 4 cycles, also demonstrating the robustness to the thermal treatments. Selectivity was tested in real atmospheric condition, in the presence of 24000 ppm of water, 400 ppm of CO_2, 5 ppm of NO and 10 ppm of CO.

Very recently, we functionalized the uranyl-salen backbone with a strong fluorophore (Bodipy), thus obtaining the first fluorescent uranyl-receptor for supramolecular recognition of DMMP.[44] Due to the presence of bodipy moieties (inset of Figure 4), molecular recognition can be monitored by fluorescence titration, finding a binding constant value of $K = 1.86\times10^7$ M^{-1}. This fluorescent uranyl-sensor shows a strong *turn-on* response in emission (Figure 4), with good selectivity in the presence of acetone and other common analytes contained in air, thus ideal for real sensing applications.

Encouraged by these results, we synthesized oligo-metal-salen receptors, to enhance the recognition properties of the metal-salen receptor.[45] In this contribution, we changed uranyl-metal ion with Zn^{2+}, due to the similar Lewis Acid-Base recognition properties previously demonstrated.[46] In particular, we synthesized and characterized by ^{1}H NMR, GPC and NMR-DOSY measurements, three oligomers containing Zn^{2+}, having different length (6, 8 and 12 repetitive units, respectively). By fluorescence titrations, we founded that the longer oligomer, containing 12 Zn-salen units, shows a higher binding constant value for DMMP ($K = 4.90\times10^5$ M^{-1}) respect to shorter oligomers ($K = 7.24\times10^4$ M^{-1} and $K = 9.55\times10^4$ M^{-1} for the oligomers with 6 and 8 Zn-salen units, respectively), demonstrating that the synergistic cooperation of multiple sites leads to higher affinity for OP CWAs.

Recently, Ward and co-workers reported the application of a luminescent sensor containing two different lanthanide metal ions (Ir and Eu) for a qualitative luminescent assay for the detection of OP CWAs.[47] This sensor has been previously demonstrated to be selective for VO (a simulant of V-series), with a ratiometric change of the luminescence in the presence of VO, and a $K = 7.0\times10^4$ M^{-1}.[48] The test strip was prepared by dropping this sensor onto a Whatman paper, then the analytes have been dropped onto the sensor deposited and responses were detected under UV lamp after 1 minutes, 4 minutes and 1 hours. Although the emission responses of the sensor to the different analytes are difficult to rationalize, the authors demonstrated the possibility to realize a real prototype for the detection of OP CWAs under UV excitation.

4.2. Sensing by Hydrogen Bonds

Hydrogen bond represents probably the most important non-covalent interaction in the field of Supramolecular Chemistry.[49] Due to its high geometric constrain between donor and acceptor atoms, and to the relative high energy with respect to other non-covalent interactions, hydrogen bond can be used to tune and regulate the geometry and the stability of a supramolecular complex. In addition, by proper change of the solvent, this interaction can be formed or disrupted.

Our research group studied three different oximes (Figure 5A) having the ability to interact with DMMP in solution

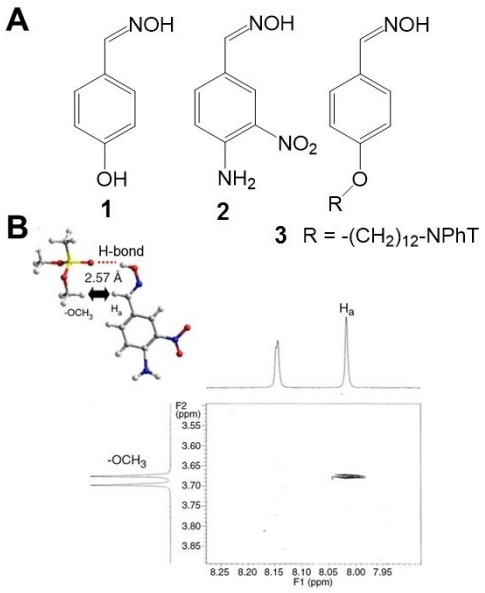


Figure 5. A) Chemical structure of oximes studied in the molecular recognition of DMMP via hydrogen bond, B) Details of T-ROESY of the supramolecular complex (hydrogen bond and ROE contact are marked). Adapted from reference [50] with permission from Springer.

through the formation of hydrogen bond.[50] This ability was investigated by NMR and UV-Vis spectroscopy. During a UV-Vis titration between oximes and DMMP, it was possible to observe in all cases a progressive decrease in absorbance at 264 nm, by addition of increasing quantities of DMMP: this phenomenon was interpreted assuming an interaction between the oxime group and DMMP which causes an alteration of π–π^* transition.

Binding constant values are higher for the complexes with the oximes **1** and **3** ($K = 2.0\times10^3\ M^{-1}$ and $2.9\times10^3\ M^{-1}$, respectively), with respect to the complex with the oxime **2** ($K = 1.0\times10^2\ M^{-1}$). These differences are due to the effect of the substituent on the aromatic ring: the presence of the electron-accepting NO_2 group decrease the efficiency of the hydrogen bond formation, which was confirmed by ^1H NMR measurements in CD_3CN, following a downfield shift of the oxime proton by the addition of DMMP. Also, ^{31}P NMR titration suggested the interaction between oxime and DMMP, by the progressive downfield shift of the phosphorous signal. Moreover, TROESY experiments support the proposed supramolecular geometry (Figure 5B).

Kim and co-workers used DFT computational method to calculate structures and binding energies of 1:1 complexes between DMMP and 13 thiourea derivatives.[51] The supramolecular complexes between these thioureas and DMMP were also studied experimentally. In general, more highly crystalline is the receptor, the lower the binding efficiencies are. In particular, the possibility to establish two intermolecular hydrogen bonds between thiourea derivatives and DMMP is the principal driving force in the supramolecular complexes formation.

In order to obtain new host systems, Gale and co-workers synthesized negatively and neutral charged ditopic receptors (Figure 6).[52] Binding abilities of these receptors were measured by using both anions (such as chloride anions) and CWAs (such as DMMP, Soman and pinacolyl methylphosphonate). It has been shown that groups such as urea, thiourea and boronic acid, through the formation of hydrogen bonds, are able to coordinate both anions and neutral molecules, as previously reported by the same research group.[53] However, it has been demonstrated that hosts have a higher affinity for neutral guests than negatively charged ones, because the negative charge on the coordinated system reduces the anionic affinity. In particular, by NMR titration, the authors demonstrated the efficient recognition of Soman with a binding constant value of $1.5\times10^3\ M^{-1}$, by using urea receptor containing BF_3^- in meta position (Figure 6B). Due to the oxobasicity and negative charge of phosphates such as $H_2PO_4^-$, in the complexes that are obtained through the formation of hydrogen bonds, there is a greater tendency to favor anionic hosts than neutral species. To reverse this trend, negatively charged hosts were used in this study, in fact they are less similar to negatively charged guests due to electrostatic repulsion, however, allowing the recognition of the neutral host. These systems paved the way for the realization of sol-gel supramolecular receptors of CWAs (vide infra).

Kumar and co-workers have synthesized a fluorescent chemical probe capable of sensitively and selectively detecting toxic anions and CWAs simulant (Diethyl cyanophosphonate DCNP, a Tabun simulant) through chromogenic and fluorogenic variations (Figure 7).[54]

Detection studies were also carried out on solid surfaces, in the gas phase and in a spiked soil sample, in order to verify the concreteness of this sensing system in real life scenarios. The authors found a limit of detection of 270 mM by using naked eyes. The chromogenic and fluorogenic detection of tabun mimic, in addition to being selective and sensitive, has also proved to be not affected by the presence of interfering species sulfonyl chlorides, thionyl chloride, anhydrides and acid chlorides.

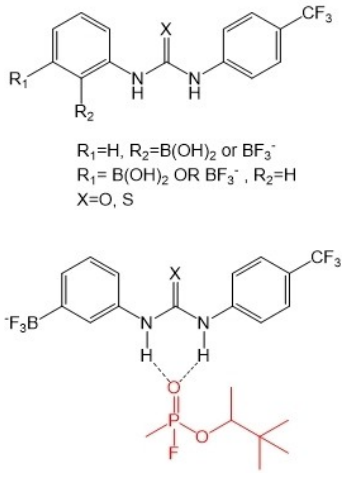


Figure 6. A) urea and thiourea ditopic receptors synthesized by Gale and co-workers; B) supramolecular complex proposed.

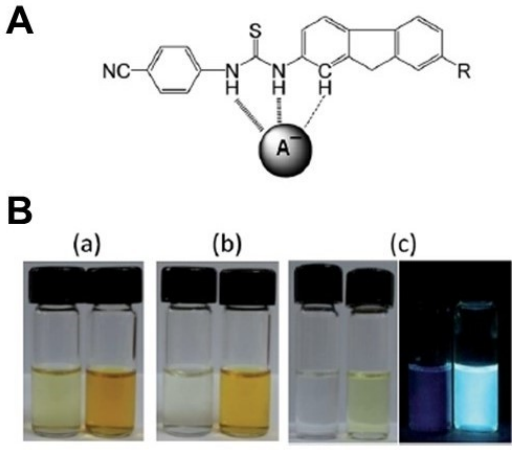


Figure 7. A) Chemical structure of sensor and supramolecular complex with DCNP; B) Chromogenic response of receptor 2 with DCNP (a) in spiked soil sample. (b) in gas phase (c) minimum detection limits of DCNP with 2 with naked eye and its response under UV lamp (365 nm). Adapted from reference [54] with permission from the Royal Society of Chemistry.

Song and co-workers performed interaction studies between thiourea derivatives (TU) and DMMP, by ^{1}H NMR titrations and DFT calculations.[55] As previously reported, thiourea functionality is able to form H-bonds with different types of guests including CWAs, promoting self-aggregation. Notably, in this study, also the gas phase adsorption of low concentration of simulant (12 ppm) was observed through a quartz crystal microbalance (QCM) (Figure 8A), also demonstrating the possibility to remove the simulant from the sensor (Figure 8B).

Several thioureas differently substituted on the nitrogen atom were synthesized, analyzing the characteristics necessary for the sensing of the nerve agents (Figure 8C). It has been seen how the presence of a benzyl group as a substituent, although it has an acidity and a lower ability to donate hydrogen bonds than an aryl group, plays an important role in the recognition of the nerve agents. Through NMR and DFT data, it was shown how, thanks to these characteristics of the substituent, the self-aggregation of the thiourea molecules was successfully reduced

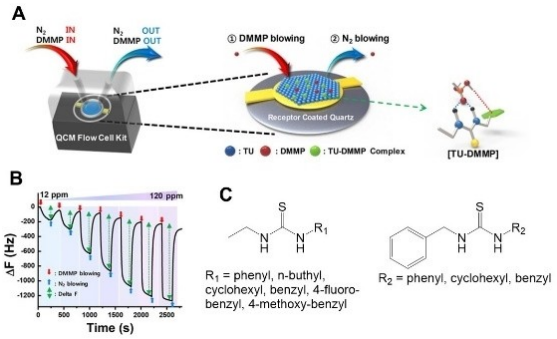


Figure 8. A) Schematic diagram of the QCM measurement setup; B) representative QCM response curve with TU 4 on increasing concentrations of DMMP from 12 to 120 ppm; C) chemical structures of thiourea derivatives. Adapted from reference [55] with permission from the American Chemical Society.

and the presence of a CH-π interaction allowed to strengthen the bond between host and guest. In phenyl derivatives, through ^{1}H NMR titrations and non-linear regression analysis, it was possible to highlight a stronger strength of the H bond donor favored by auto aggregation, while in the case of substituted benzyl, the interaction with DMMP was more favorite. It was possible to reveal the importance of the interaction between the π electrons of the *N*-benzyl group and the CH of DMMP through DFT calculations. This study, therefore, made possible to emphasize how self-aggregation should be avoided and, in reverse, favor the CH-π interaction, to allow a better detection of organophosphates.

Supramolecular gels are an interesting class of gels able to form the gel-system by exploiting supramolecular interactions.[56] In particular, stimuli-responsive supramolecular gels show potential applications as supramolecular sensors, due to the ability to change physical properties in the presence of a specific analyte.[57,58] Supramolecular recognition of OP CWAs by these systems is mainly due to the possibility to form or disrupt hydrogen bonds with the OP CWAs (or simulant), leading to the disassembly of the supramolecular gel structure.

Following the OP CWAs recognition studies based on the hydrogen bond formation, Gale and co-workers realized a new OP CWAs sensing method based on the perturbation of the supramolecular gel structure based on a tren-based tris-urea by the presence of the nerve gas, exploiting the formation of hydrogen bonds.[59] It has been shown that the time required for gel formation is related to the structure and concentration of the gelator, the type of solvent and the concentration of simulant used. For low concentrations of gelator and high concentrations of DMMP, longer gelation times are obtained, also due to the formation of hydrogen bonds between urea and simulant. The authors studied the response also in the presence of the nerve agent Soman (GD): it causes longer times to form the gel and lower concentrations of GD are required to totally prevent the formation of the gel. The response of the system to the nerve agent is found to be more sensitive compared to DMMP. Similar supramolecular gels were also used for the degradation of OP CWAs.[60–62]

Recently, Ward and co-workers developed a coordination cage able to interact with OP CWAs simulant by the formation of hydrogen bonds.[63] This coordination cage forms a hydrophobic cavity with an internal volume of ca. 400 Å^3, ideal for guests having a volume of ca. 220 Å^3. For this reason, this host is selective for DIMP (Diisopropyl methyl phosphonate), with a $K = 3.90 \times 10^2$ M^{-1}, with a 1:1 stoichiometry. The driving force of the recognition event is the formation of a hydrogen bond network between the hydrogen-bond donor atoms of the host and the P=O group of the simulant. Furthermore, a crucial role is played by the match of the internal volume of the cavity and the dimensions of DIMP.

4.3. Sensing by Macrocyclic Hosts

The ability to synthesize organic molecules having a hydrophobic cavity able to accommodate different molecules inside

paves the way to create "artificial enzymes". In fact, the hydrophobic cavity can be compared to the active site of the enzyme. Inspired by the AChE, synthetic organic chemists developed in the last decade different hosts, able to recognize OP CWAs inside their cavity.

In this context, Badjić and co-workers play a crucial role in the international scenario. In fact, by using modular basket-like hosts, supramolecular recognition of OP CWAs has been performed also in water (Figure 9).[64]

The inclusion of OP CWAs simulant (DMMP) into the basket cavity in water is mainly due to the hydrophobic effect.[65] Complexation was monitored by ^{1}H NMR titration, finding a binding constant value of $3.21\times10^2\ M^{-1}$, also confirmed by accurate DFT analysis. Calorimetric measurements confirmed that the inclusion of the simulant into the basket is favored both by enthalpic and entropic contributions. By increasing the size of the guest, binding affinity values decreased due to the steric hindrance between guest and the cavity. Furthermore, the authors invoked an induced-fit mechanism due to the possibility of the basket host to flex in order to accommodate the methyl group of DMMP.

Badjić and co-workers functionalized the basket host with three alkyl ammonium groups, in order to obtain an amphiphilic host able to self-assemble in water into nanometric unilamellar vesicles having dimension of ca. 350 nm. This system is able to include dimethyl phenylphosphonate (DMPP) into the basket cavity, with a binding constant affinity of $1.97\times10^3\ M^{-1}$.[66] Recognition event was monitored by ^{1}H NMR, ESI-MS, calorimetric and DLS measurements. In particular, DLS highlights that the sensing of DMPP induces a phase transition of the vesicles into nanoparticles, thus obtaining a stimuli-responsive material.

In addition, Badjić and co-workers demonstrated by calorimetric measurement that, depending on the nature of the simulant, the different host-guest complex can lead to nanoparticles or larger vesicles.[67] Different guests have been studied, both aliphatic and aromatic, having different sizes. The highest binding constant value was $6.04\times10^3\ M^{-1}$ with the bigger aromatic guest. Moving into aromatic anionic guests, the affinity increases leading to an association value of $6.61\times10^4\ M^{-1}$. In particular, in the presence of neutral simulant, the vesicles (having a diameter of ca. 350 nm) include the guest leading to nanoparticles having a diameter of ca. 250 nm.

On the other hand, with anionic simulants, the supramolecular system evolves into larger vesicles having a diameter of ca. 750 nm. Notably, the interconversion between the different supramolecular nanostructures is reversible and selective (Figure 10).

Furthermore, Badjić and co-workers synthesized a dual-basket host, having two cavities in opposite directions, containing six alanine residues that improve the water solubility.[68] This receptor is able to include guests into the two cavities in allosteric fashion, miming the behavior of some enzymes. The simulants used in this work have been chosen by depending on the steric hindrances, in analogy respect to VX and Soman. The authors found that, in the presence of VX-simulant, the host recognizes one single guest molecule, with a binding constant value of $1.45\times10^4\ M^{-1}$ calculated by calorimetric measurements. However, in the presence of a smaller guest, simulating Soman, the two cavities can accommodate one single guest for each cavity, with two binding constant values of $7.91\times10^3\ M^{-1}$ and $2.37\times10^3\ M^{-1}$, respectively.

Cragg and co-workers reported the ability of β-cyclodextrins to recognize Soman by hydrophobic effects.[69] The use of these macrocyclic hosts as receptors towards OP CWAs has been previously reported,[70] however, in this work, experimental and computational methods have been developed to shed light on the inclusion complexes of Soman and cyclodextrin. The authors demonstrated the formation of the supramolecular

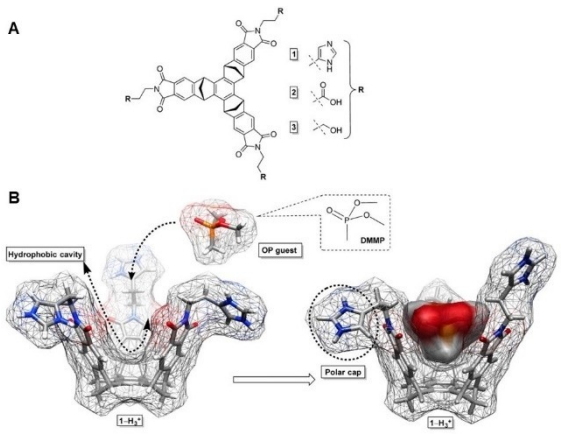


Figure 9. A) chemical formula of modular basket hosts; B) 3D structures of the interaction between host and DMMP. Adapted from reference [55] with permission from the Royal Society of Chemistry.

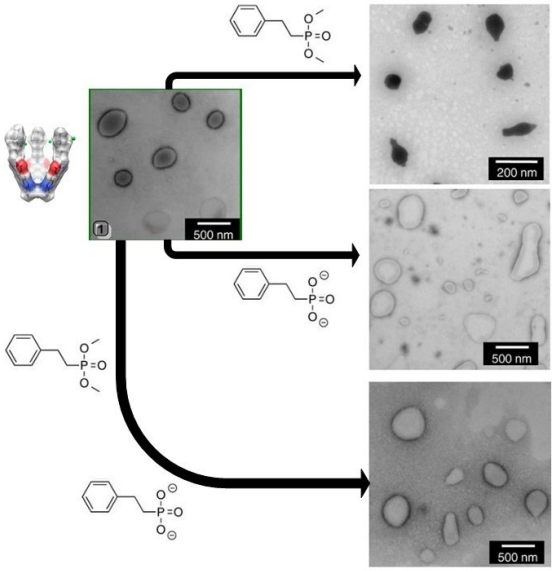


Figure 10. TEM images of basket amphiphilic (1.0 mM in H_2O). Top: TEM image of basket amphiphilic (1.0 mM in H_2O) containing neutral guest (20.0 mM). Middle: TEM image of a solution of host (1.0 mM in H_2O) containing anionic guest (20.0 mM). Bottom: TEM image of a solution of basket (1.0 mM in H_2O) obtained after a successive addition of neutral and anionic guests (20.0 mM of each). Adapted from reference [67] with permission from the American Chemical Society.

complex by ^{1}H, ^{19}F and ^{31}P NMR measurement in D_2O, with a 1:1 stoichiometry and a binding constant value of $2.07\times10^{3}\ M^{-1}$. Computational studies conducted with the four stereoisomers of Soman confirmed the recognition ability of β-cyclodextrin is due to the hydrophobic effects and to the formation of hydrogen bonds (Figure 11). Computational studies, combining semi-empirical and DFT methods, were carried out also to predict IR spectra of CWAs and their simulants, also predicting the inclusion complexes into cyclodextrins.[71]

Sambrook and co-workers studied also the ability of *p*-sulfonatocalix[n]arenes (n = 4 and 6) to recognize Soman in water.[72] Binding affinity values, calculated by NMR titrations, are low with both calixarene derivatives (calix-4 shows a K = 75 M^{-1}, while calix-6 shows a K = 10 M^{-1}).

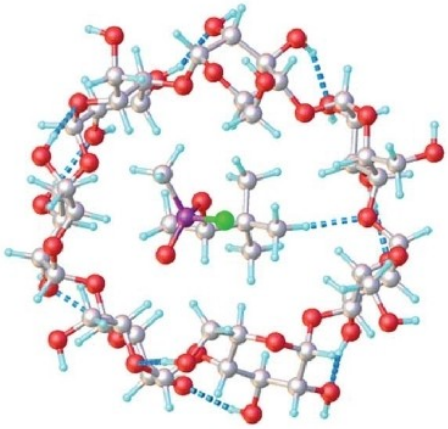


Figure 11. Supramolecular complex between b-cyclodextrin and one of the isomers of soman. Reproduced from reference [69] with permission from the Royal Society of Chemistry).

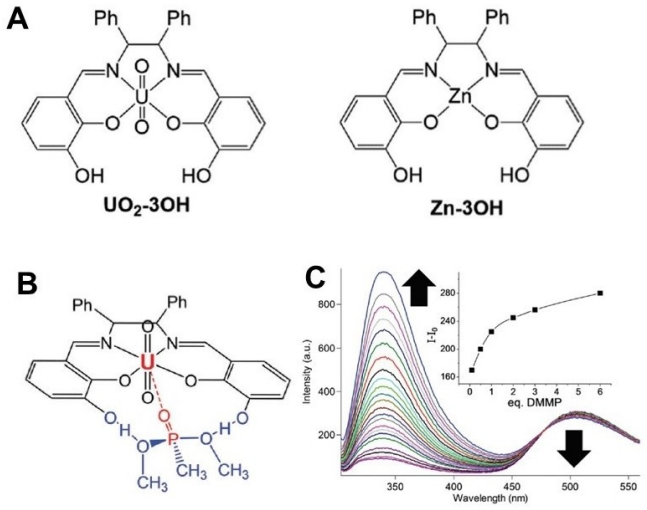


Figure 12. A) Chemical structures of receptors employed in the Multi-topic approach for DMMP sensing; B) supramolecular complex proposed; fluorescence titration by using Zn-complex showing a ratiometric response. Adapted from reference [73] with permission from the Royal Society of Chemistry.

4.4. Sensing by a Multi-Topic Approach

The possibility to establish more than one interaction between a receptor and the target analyte leads to an increase of the binding constant value. In addition, for the reason previously mentioned, also the selectivity improves due to a more specific host-guest interaction. This approach has been defined as multi-topic, and requires a precise design of the receptor, starting from a chemical-geometric analysis of the target analyte.

Based on these considerations, our research group developed the first multi-topic receptors for DMMP, exploiting the formation of a Lewis Acid-Base interaction assisted by the formation of two hydrogen bonds.[73] In particular, we synthesize two metal salen complexes (M = UO_2^{2+} and Zn^{2+}, respectively) bearing two hydroxyl group in 3-3′ positions of the salen backbone (Figure 12A). After ^{1}H NMR titrations and TROESY experiments, we demonstrated that the metal center interacts with the P=O group of DMMP, in addition, following the chemical shift of DMMP signals, the hydroxyl groups of the receptors interact *via* hydrogen bonds with the $-OCH_3$ groups of the guest, as showed in Figure 12B. The binding constant value, calculated by UV-Vis titration, of the supramolecular complex between receptor UO_2–3OH and DMMP is $8.51\times10^{4}\ M^{-1}$, 4-fold higher respect to the receptor without OH groups in 3-3′ positions.[43] In addition, the sensing properties of the Zn-3OH receptor can be monitored by emission spectroscopy, with a binding constant value of $1.10\times10^{5}\ M^{-1}$. Notably, Zn-receptor shows a ratiometric emission response[74] after the addition of DMMP, with a large stokes shift (> 50 nm, Figure 12C). Selectivity experiments confirmed the success of the multi-topic approach due to the selective response of Zn-3OH toward DMMP, also in the presence of the common analyte contained in the atmospheric air.

Starting from a geometric analysis of DMMP, and in particular considering the possible interaction sites (the P=O group as Lewis Base center and $-OCH_3$ as hydrogen bond acceptors), we designed two new fluorescent sensors, having a naphthylamide core (as a chromophore) bearing one or two ethanolamine arms (as chelating groups) (Figure 13A).[75] DMMP recognition was evaluated by fluorescence titration, with binding constant values of $3.47\times10^{3}\ M^{-1}$ and $1.05\times10^{4}\ M^{-1}$ with Naphthyl-Mono-AE and Naphthyl-Di-AE, respectively. These data highlighted the role of ethanolamine arms to stabilize DMMP *via* multiple interactions. Selectivity was confirmed by following the emission response of the sensors after the exposure to DMMP, in the presence of the common analytes contained in air. The chelating mechanism by multi-topic approach (Figure 13B) was supported by ^{1}H NMR titrations, following the chemical shift changes of NH and OH protons in the receptor. Furthermore, also ESI-MS and TROESY experiments supported the formation of the supramolecular host-guest complex.

The limit of detections for f both receptors is 1 ppm, with an instantaneous response, and a Stokes shift of ca. 160 nm, ideal for real applications. Test strip was performed for Naphthyl-Di-AE (Figure 13C–E). In particular, a filter paper

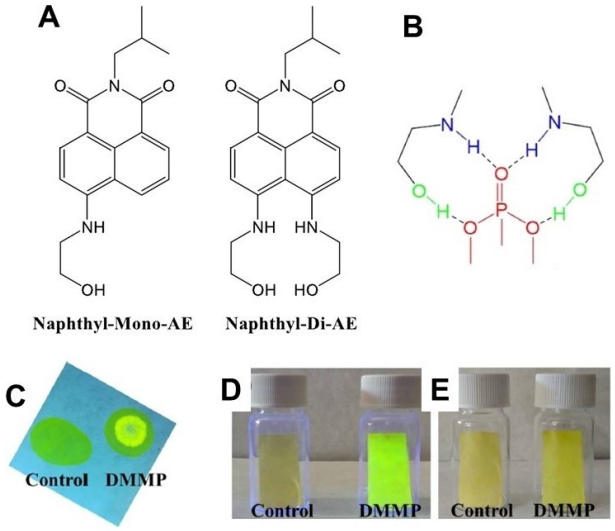


Figure 13. A) Chemical Structures of Naphthyl-mono-AE (Left) and Naphthyl-di-AE (Right); B) Multitopic proposed recognition mechanism based on ^{1}H NMR measurements; Test Strip with solution (C) and vapors (D). Adapted from reference [75] with permission from the American Chemical Society.

adsorbed with the sensor is able to detect 1 mL of DMMP (Figure 13C), in addition, also vapors of DMMP (40 ppm) can be detected under UV-Vis lamp (Figure 13D) and sunlight (Figure 13E).

Recently, two nanoscopic evolutions of Naphthyl-di-AE have been developed. In particular, carbon nanoparticles have been covalently functionalized with Naphthyl-di-AE[76] and ethanolamine chelating groups, obtaining two different nanosensors for the supramolecular recognition of DMMP. The covalent linking between Naphthyl-di-AE and carbon nanoparticles has been characterized by NMR and XPS spectroscopies. Recognition studies performed by UV-Vis spectroscopy established a binding constant with DMMP of $3.55\times10^{5}\ M^{-1}$, with high selectivity and a limit of detection of 0.16 ppm. Encouraged by these exciting results, we optimized the structure of nanoparticles, by direct functionalization with the chelating ethanolamine arms onto the nanoparticle surface.[77] These nanoparticles, having a diameter of ca. 16 nm, have been characterized by NMR, AFM, XPS and TEM spectroscopies. Notably, molecular recognition of DMMP was performed in water, due to the excellent solubility of these nanoparticles, finding a binding constant value of $2.88\times10^{6}\ M^{-1}$, and a limit of detection of 0.39 ppt. The multi-topic approach leads to an excellent selectivity, also in the presence of other phosphorous compounds. These nanoparticles have been dispersed onto alumina gel foil, obtaining a solid device for practical test strip. In particular, the nanosensor is able to detect progressive amounts of vaporized DMMP, leading to an increase of emission (Figure 14A). Quantification of the emission leads to a calibration curve, having a linear trend at low ppm of DMMP (Figure 14B). The validity of the supramolecular approach permits us to restore and reuse the device 7 times, without loss of efficiency (Figure 14C).

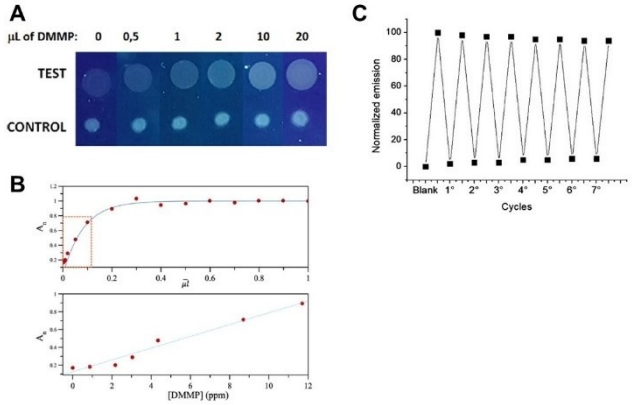


Figure 14. A) Test strip vapors: fluorescence response of carbon nanoparticles to increased amounts of vaporized DMMP; B) best fit of the experimental data obtained by image analyses; C) recovery tests. Adapted from reference [77] with permission from the American Chemical Society.

Our research group used the supramolecular approach also to detect phosphocholine, a simulant of VX. In particular, this analyte contains a P=O (Lewis base) and an alkylated nitrogen. Thus, the strategy was to design a supramolecular receptor having the proper distance between a Lewis acid center able to interact with P=O, and a hydrophobic cavity able to include the alkylammonium group (Figure 15A).[78] A quinoxaline cavitand, bearing a Zn-salen moiety, was synthesized and tested by fluorescence titration as receptor for the phosphocholine sensing (Figure 15B). Binding constant value calculated in chloroform was $1.15\times10^{7}\ M^{-1}$, with a detection limit of 2.31 ppb. The success of the supramolecular approach was confirmed also by the high selectivity of this receptor towards phosphocholine, respect to the common analytes contained in the air, but also with respect to the simulant of G-CWAs. In fact, these organophosphorus compounds do not contain the alkylated nitrogen, characteristic of V-serie.

4.5. Sensing by Nanosensors

Supramolecular recognition of OP CWAs can be performed also by using nanodevices, exploiting one or more non-covalent interactions.

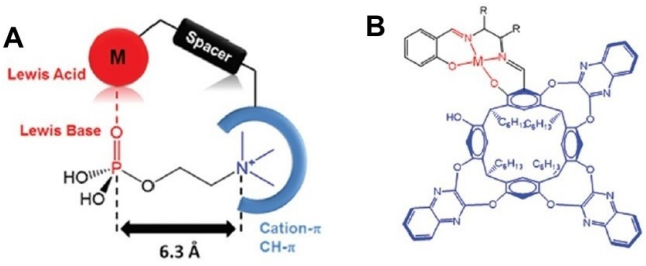


Figure 15. A) (a) design of the supramolecular receptor; (b) chemical structure of the metal-salen cavitand (M=Zn, R=H). Reproduced from reference [79] with permission from the Royal Society of Chemistry.

Li and co-workers used photonic cavities and optical resonator based on dielectric materials. This system can change the resonance frequencies of photonic cavities by function of their surroundings.[79] The selective sensing is due to the formation of hydrogen and halogen bonds between the CWAs simulant (methyl salicylate, MeS) and the nanobeam surface, containing fluoroalcohol polysiloxanes polymer (Aditol). The presence of the simulant can be monitored by using a probe laser to measure the shift of optical resonance of the nanobeam surface. The system was exposed to different concentration of MeS gas, from 240 to 1200 ppb for 240 s, obtaining a limit of detection of 1.5 ppb.

Che and co-workers developed hydrogen bond self-assembled nanofiber based on perylene diimide derivate (PDI), able to selectively detect DCP.[80] In particular, PDI contains a benzyl alcohol group, able to strongly interact with DCP by hydrogen bond. In normal conditions, this system self-assembly into nanofibers (Figure 16). After photoexcitation at 455 nm, these nanofibers can be weakened.

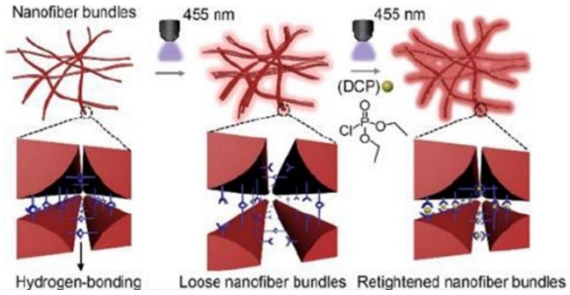


Figure 16. Assembling and disassembling of nanofibers. Reproduced from reference [80] with permission of the Royal Society of Chemistry.

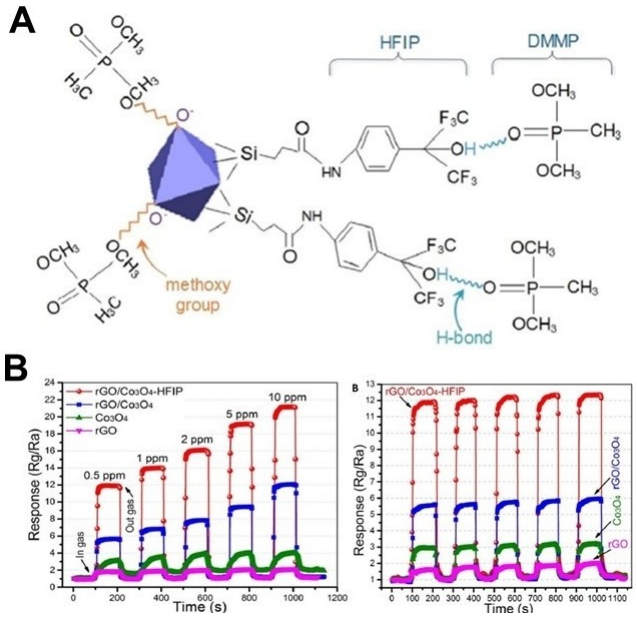


Figure 17. A) Mechanism of DMMP detection by functionalized Co3O4; B) Dynamic response curves at working temperature and recycling test. Reproduced from reference [81] with permission of Wiley-VCH.

During the irradiation, the fluorescence intensity decreases in the first 5 minute due to the break of hydrogen bonds, thus increasing the space between nanofibers. In the presence of DCP, the emission increases due to the formation of supramolecular interactions between P=O group of DCP and the benzyl groups of PDI. Although the enhanced fluorescence was not reversible, multiple detection of DCP can be performed. In addition, calculated limit of detection was 15 ppb. Notably, selectivity was confirmed also in the presence of common organic solvents and water.

Wang and co-workers functionalized micro-nano octahedral Co_3O_4, which was deposited on a layer of reduced graphene (rGO) with hexafluoroisopropanol (HFIP). This system was used to perform the detection of DMMP (Figure 17A).[81] The sensing material produces a change in the resistance due to absorption of gas molecules through hydrogen bonding, and the starting system can be restored on air, for multi-cycles sensing (Figure 17B). Selectivity towards other common solvents has been evaluated, with a limit of detection of 0.5 ppm.

Ameloot and co-workers created a system in which the electrodes were coated with a metal-organic framework (MOF UiO-66-NH_2), measuring the presence of DMMP by contact potential difference (CPD).[82] This nanosystem is reversible, with a limit of detection of 0.3 ppm in 1.9 minutes of response time. Molecular simulation suggested the recognition by hydrogen bonds.

Kumar and co-workers have synthetized single walled carbon nanotube (SWCNT) functionalized with 4-(Hexafluoro-2-hydroxy isopropyl)aniline (HFiP-1) as sensor for DMMP vapors.[83] In particular, the hydrogen bond between DMMP and benzyl alcohol anchored onto SWCNT increases the resistance of SWCNT (Figure 18). The selectivity was successfully tested by using hexane, toluene, benzene, ethanol, dichloromethane and water as competitive guests, with a limit of detection of 2.4 ppm. After the detection, nanosensor can be restored with N_2 flow.

The same benzyl alcohol has been used by Rao and co-workers.[84] In particular, they functionalized a gold coated quartz crystal microbalance (QCM) sensor with graphene- *p*-hexafluoroisopropanol phenyl (HFIPP-GR), thus obtaining a nanosensor able to detect DMMP by hydrogen bond. The reversible detection of DMMP was performed by QCM's oscillating frequency variation, with a limit of detection of 5 ppm. The authors demonstrated the selectivity of the nanosensor in the presence of other common organic solvents.

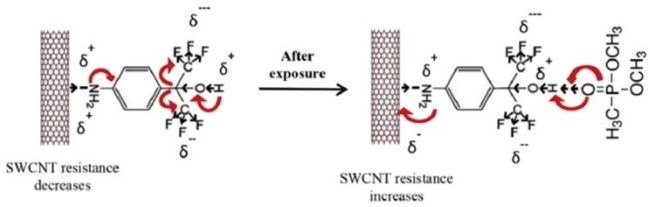


Figure 18. Interaction between SWCNT-HFiP1 and DMMP. Reproduced from reference [83] with permission from Elsevier.

Kwon and co-workers developed chemiresistive gas sensors using polypyrrole bearing carboxyl groups in order to detect DMMP *via* hydrogen bonding.[85] They measured the concentration of DMMP through the variation of sensor's resistance, with a limit of detection of 0.5 ppb. In addition, the electrical signal was absent when no DMMP vapors were exposed to the nanosensor. Selectivity was tested by using common solvents, such as chloroform, ammonia, acetic acid, butane, acetone, methanol and naphthalene.

Sayago and co-workers developed a DMMP sensor based on graphene oxide (GO).[86] In particular, GO interacts with DMMP *via* hydrogen bonds through carboxylic and hydroxyl groups present on the GO surface. The limit of detection for DMMP is 9 ppb, with good selectivity also in the presence of NO_2, NH_3 and CO.

Swager and coworkers developed copolymer-based detection platforms bearing a colorimetric unit able to change UV-Vis spectrum and color in the presence of CWAs simulant (DCP).[87] Copolymers were obtained by ring-opening metathesis polymerization (ROMP) and contains a triphenyl alcohol moiety, able to react with the simulant (Figure 19).

Notably, copolymer instantly responds to simulant vapors, and can be regenerated using NH_4OH. These systems can be exploited to create protective clothing, as the nerve agents are easily absorbed by the skin: through the presence of these materials in the fabric it is possible to create a protective barrier against any exposure to toxic agents, whose interaction would cause a mechanic change of the material itself. These systems show low detection limits (1–8 ppm) with 30 sec. of exposure time.

5. Conclusions and Future Perspectives

From the starting pioneering research, supramolecular chemists synthesized and developed many new organic compounds having today a wide range of applications in the real life. In this context, detection of Chemical Warfare Agents is crucial, in particular due to the recent international scenario. Molecular sensors, more practical respect to instrumental techniques such as mass spectrometry or HPLC, can be classified by function of the interaction with the CWA. Sensors which react with the organophosphorus CWA by the covalent approach, show high sensitivity (with low limit of detection values), however can be led to false-positive responses, due to the possibility to react with other molecules. This problem can be overcome by supramolecular sensors, which interact by non-covalent interactions with the selected target OP CWA. The possibility to tune the affinity for the OP CWA, by changing the non-covalent interactions, allows to obtain a more selective sensor. In addition, the non-covalent nature of sensor-CWA complex (host-guest complex) leads to the possibility to restore the initial sensor, thus obtaining a reusable device. These aspects have been highlighted in this review. Supramolecular sensing of OP CWAs can be performed by using mainly three non-covalent forces: *i*) Acid-Base Lewis interactions, *ii*) hydrogen bonds and *iii*) hydrophobic interactions due to the presence of a macrocyclic host. The use of one of these interactions permitted to obtain efficient sensors, demonstrated by high binding constant values and excellent selectivity. However, the opportunity to form supramolecular complexes by using multiple non-covalent interactions (multi-topic approach) permitted us to obtain more efficient sensors, in particular in term of selectivity. In fact, the possibility to avoid false-positive response is crucial to obtain real sensors to be used in real life.

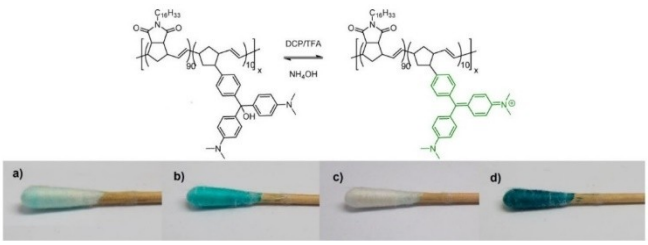


Figure 19. Polymer adsorbed on a cotton tip (a) responds rapidly to DCP (b) and TFA (d) vapors and can be regenerated upon exposure to vapor from an aqueous NH_4OH solution (c). Reproduced from reference [87] with permission from the American Chemical Society.

A crucial point in the research and development of OP CWAs sensors is the use of simulants. Research studies by using real OP CWAs are not permitted in most of cases for security reasons. Simulants show geometric and chemical features similar to the OP CWAs, but possess less toxicity due to the absence of a good leaving group. This similarity between simulants and OP CWAs has been recently criticized, in particular by Sambrook. In fact, by using cyclodextrin receptors, the simulants used did not match with the behavior of Soman, in particular simulants show binding constant values two order of magnitude lower than Soman.[69] Taking into account these data, the choice of simulant must be carefully evaluated, strictly considering geometric requirements between functional groups involved in the supramolecular recognition.

In order to obtain real practical devices, also demonstrating the success of the supramolecular approach, sensors should be validated in term of selectivity, reversibility and possibility to realize a prototype. In particular, the ability to detect trace of OP CWAs in air or solution (ideally water) by a test strip or solid device containing the sensor immobilized or adsorbed onto a solid support, is crucial to start a scale-up process. Selectivity towards OP CWAs should be evaluated by comparing real interfering analytes contained in the real matrix (atmospheric gases, molecules present in the water) rather than organic solvents available only in laboratory. Reversibility should be also evaluated, demonstrating the robustness of the sensor and the efficiency of the supramolecular approach.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: chemical warfare agents · host-guest systems · noncovalent interactions · sensors · supramolecular chemistry

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