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PERSPECTIVE

Porphyrins in troubled times: a spotlight on porphyrins and their metal complexes for explosives testing and CBRN defense

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Porphyrins are large π-aromatic systems that can complex metal ions from all across the periodic table. The resulting metalloporphyrins are readily tunable with regards to analyte detection properties, and constitute an important class of chemical sensors. In light of the current geopolitical situation and security concerns, we review the potential of porphyrins and their metal complexes for the detection of explosives and their use in chemical, biological, radiological and nuclear (CBRN) defense and set them in the context of up-and-coming security-related applications.

Introduction

No, porphyrins are not in trouble. If at all, the rapid growth of investigations in their synthesis, as (components of) functional materials, and use as test beds indicates a mature and healthy state of the field. A few decades ago, the situation might have looked different. Their synthesis was a cumbersome but manageable endeavor — at least in the hands of porphyrin chemists —, significant knowledge on their biosynthesis and natural function had been accumulated, and they found applications as dyes, in supramolecular chemistry, catalysis, and as photosensitizers. The field appeared mature and one was told that porphyrins are a 'dead dog' as a research topic. Yet, the many advances in organometallic chemistry and functionalization strategies,[1–4] Vogel's use of the annulene concept for macrocycle-modified porphyrinoids,[5] and broadly applicable and 'easy' synthetic methods, such as from Lindsey's laboratory,[6] have since given rise to a multitude of porphyrin(oids) with altered, conformationally flexible,[7,8] interconvertible,[9] and even antiaromatic[10] macrocycle frameworks. Thus, the 'porphyrin landscape' looks very different today, than in, say, 1989. Access to standard porphyrins is now simple, and they have branched out into many other areas of the chemistry world, ranging from tunable electro-optical or catalytic materials, as theranostic agents, and more. One is hard pressed to find an area of contemporary chemistry or materials research into which porphyrins have not entered.

As topics and interests in chemistry change with time, so does the world it is part of. When the senior author during his military service was looking across the Fulda gap, the situation was more black and white than today, but in a sense easier to deal with in terms of 'good' and 'evil'. The threats were known, as were the scenarios in which escalation might occur. Ultimately, this stabilizing bipolarity ended peacefully,[11] mutually assured destruction (MAD) was replaced by the immediate post-Cold War period with its mistaken promise for more predictable and stable times, and then followed by the decline of old — and rise of new major powers and global geostrategic shifts.[12] Today, many people consider the world a more fragmented, unstable, and dangerous place — troubled times.

While waves of terror,[13] power asymmetries, and global destabilization are nothing new in history — one may only think of the terror wave engulfing Europe in the late 19th and early 20th century — at the very least, the seeming level of threat and the perception of insecurity in many areas of daily life, multiplied by instant (fake) news, makes security one of the fundamental concerns at a personal level. Not only are traditional nation states engaged in the development and deployment of new (bio)chemical threats,[14] irrational rouge states and failed countries destabilize whole areas,[15] and franchised terror organizations and networks,[16] bent on asymmetric warfare, are also using the internet to crowdsource the weaponization of common chemicals and harmful organisms, and to disseminate the information necessary to use such agents.[17]

Countermeasures must be developed not only for domestic or industrial accidents, but also for deliberate mass casualty exposures in a diverse range of public settings. Likewise, the military and security forces charged with assuring public and (inter)national safety must be equipped with tools enabling them for mission success. This rapidly changing landscape of existing and emerging chemical threats has generated a need for a change in the scale and efficiency of countermeasure discovery and for counter-proliferation strategies.[18]

In light of the multifaceted uses of porphyrins for almost any application, their promising electro-optical properties and the many

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advances made in their synthesis and functionalization, we have therefore undertaken a study on the potential use of free base porphyrins and metalloporphyrins in security-related applications. For this, we have analyzed the literature with regard to studies using porphyrins for explosives and CBRN detection and related topics. First, we give a brief overview of current general strategies in these areas, outline the use of metalloporphyrins as sensors, and then look in more detail at their use in the title context.

State of the art explosives and CBRN detection

In the last decades, multiple factors like global politics, the ease of international travel, or the distribution of biological and chemical agents for industrial and domestic use, have contributed to an increased and ever more urgent need to address the dangers posed by conventional weapons, improvised explosive devices (IEDs), and weapons of mass destruction (WMD). These can bring death and significant harm to a large number of humans and human structures and range from chemical and biological hazards to radiological and nuclear threats. Such being the case, a pressing demand for innovative approaches to countermeasure the security threats derived therefrom has emerged.[19]

Explosives and chemical weapons are particularly suited for spectroscopy- and spectrometry-based detection.[14,20] This is based on a number of reasons, such as facile interaction with many chemical sensors (e.g., metalloporphyrins) and good detectability. This allows the use of more or less traditional analytical techniques (for example, colorimetrics, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, Raman spectroscopy, Fourier-transform infrared spectroscopy (FTIR), ion mobility spectrometry (IMS), and their derivatives) to be deployed. On the other hand, the electrical/electrochemical properties of metalloporphyrins are easily influenced by certain analytes, opening avenues in electronic engineering. Some of these approaches promise a range of advantages, including portability, low detection limits, high selectivity, the ability to qualify/quantify complex mixtures, affordability, and user-friendliness. However, at the same time, most are lacking one or another crucial feature and are characterized by high cost, large instrumentations, non-applicability in the field, long collection times, or large power consumption. As a result, the search for an all-in-one device suitable for multiple purposes continues.

A promising technology to circumvent some of these disadvantages is the colorimetric sensors array (CSA), a sensitive and highly practical, low-cost approach based on naked-eye detection of organic/inorganic analytes or infective agents and their products alike.[21] Other contributions have reached the realms of electrical engineering, material science, and nanotechnology, e.g., the ultratrace detection of dangerous analytes.[22] Additionally, artificial organs such as chemical noses[23] and tongues[24] may replace specially trained sniffer dogs and bees/wasps for explosive detection. Another new technology is based on amplifying fluorescent polymers that recognize and/or inactivate explosives, chemical warfare agents (CWAs), bacteria, fungi, and viruses thanks

to their unique physicochemical and binding properties.[25] Furthermore, detection of infectious agents and diseases, particularly in the light of possible biological warfare (BW) and bioterrorism scenarios, includes the whole range of mainly laboratory-based and clinical methodologies, but also a growing landscape of smart electrochemical, optical, and nanomaterial-based biosensors.[26]

On the other hand, recognition of nuclear and radiological agents often depends on registration of their (radioactive) decay products (i.e., through a dosimeter or Geiger–Müller tube). Naturally, this poses an elaborate challenge due to their instable and impalpable nature but a number of chemical sensors, devices, and strategies have been fabricated through an interplay of scientific and engineering disciplines. This involves, for example, metal–organic frameworks (MOFs) for radiation sensing[27] and bioremediation/sequestering,[28] or complexation of radionuclides by porphyrins[29] for decontamination and detection purpose (Fig. 1).
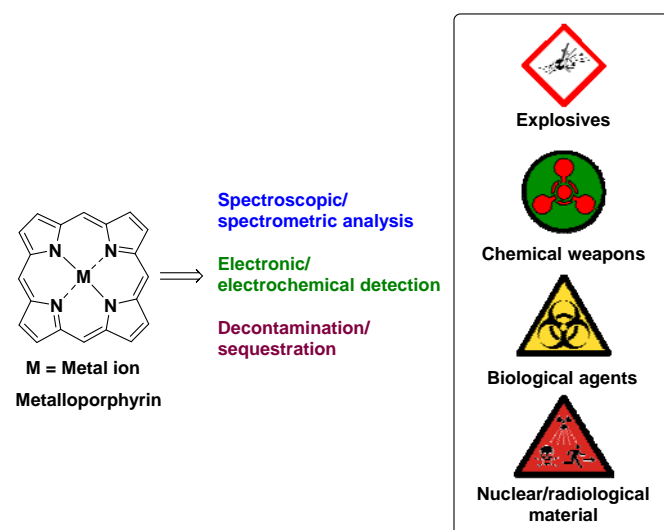

Fig. 1 Perspectives for metalloporphyrins in CBRN defense.

Metalloporphyrins as sensors

Basic properties and definitions

Porphyrins and porphyrinoids have functional prerequisites, structural features, and physicochemical properties that qualify them as receptors and sensors for ions and neutral molecules, such as protons, metal ions, and pollutants as well as many hazardous analytes.[23,30–34] This includes conventional threats (explosive materials) and extends well beyond 'standard' chemosensing, offering perspectives for CBRN defense.

Chelation of a central metal ion by a free base porphyrin to access metallated porphyrin-based sensors can be achieved through formation of a coordination complex with the four central nitrogen atoms (Fig. 2a).[35] In a typical setup, the properties of the metalloporphyrin change upon interaction with an analyte, and are translated into a signal, e.g., a color change or an electric signal by

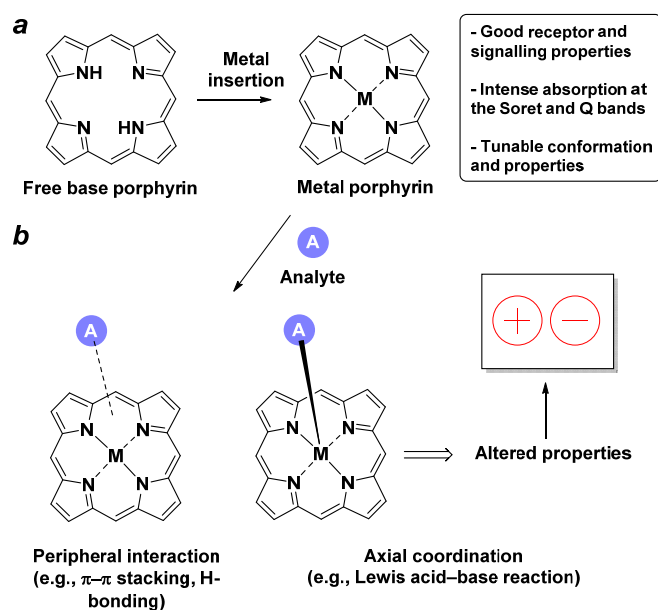means of a transducer, indicating the presence of a substrate (Fig. 2b).

Fig. 2 Basic properties of metalloporphyrins for use as sensors and schematic representation of analyte recognition: axial and peripheral binding.

The pronounced dependence of porphyrin properties on their structures provides diverse possibilities for sensor design, including synthetic modifications, such as varying the coordinated metal or even altering the molecular skeleton. At the same time, macrocycle conformations and size can be tuned by the number and nature of peripheral substituents,[7,36] thus modulating ion selectivity and sensitivity. Additional features are their suitable photophysical properties, for instance, intense absorption at the Soret and Q bands, and red to near-infrared emission, thus providing straightforward optical and fluorescence detection methods. It is also interesting to note that porphyrin-based sensing materials often mimic the biological functions of the parent macrocycle (e.g., reversible binding of gaseous compounds, catalytic activation, and optical changes).[23]

The overall performance of a sensor is defined by a number of quantitative and qualitative properties, allowing a comparison among different devices.[37,38] The fundamental characteristic is the response curve, which is a plot of the sensor signal *versus* the analyte concentration. Sensitivity is defined as variation of a sensor signal with respect to variation of the substrate concentration. Another important feature is resolution, namely the smallest change in analyte concentration that can still be detected. It is dependent on the sensor signal's measurement error, and ultimately limited by the noise of the sensor signal .[39] Response curve, sensitivity, and resolution are mathematically coherent and a better sensitivity enables detection of the smallest concentration changes. Another crucial aspect to be considered is selectivity, which is defined by the capability of a sensor to preferentially bind the target when subjected to a mixture. Note that a sensor's signal is the combination of sensitivity and concentration; therefore, even

analytes with little sensitivity can give rise to large signals when their concentration is sufficiently high.[40]

Due to the plentitude of competing analytes present in the field, the quest of engineering highly selective receptor motifs is paramount. While low selectivity sensors give rise to ambiguous signals and can only really be used in an environment where the compounds in a sample are known beforehand, porphyrins stand as an important class of receptors that offer multiple possibilities for molecular design. They can facilitate multiple interactions and allow for tailoring of their physicochemical properties *via* macrocycle, central metal, and substituent modulation to specifically emphasize desired interactions, thus increasing selectivity.

Recognition, quantification, and monitoring of compounds for environmental and clinical use has undergone a vast technological evolution from gas chromatography–mass spectrometry (GC-MS), mass spectrometry (MS), atomic absorption spectroscopy (AA), and others to as far as quantum mechanical approaches.[41,42] This is due to the continuous expansion of the field and today, probably more than ever before, military- and security-related applications need to be addressed too. Therefore, contemporary porphyrin- and porphyrinoid-based chemical sensors exploit a broad spectrum of detection methods for gaseous substrates, such as NO_2,[43–46] CO_2,[47–49] and volatile organic compounds (VOCs),[46,50—58] as well as liquid phase analytes, for instance, NO in cells,[59,60] H_2O_2,[61–64] dopamine and other neurotransmitters,[65–69] explosives,[22,70–74] pollutants,[75–79] pharmaceutical and biological analytes,[80–84] ammonia and amines,[85–87] metal ions,[88–94] protons,[95–99] ascorbic acid,[100] and glucose (Fig. 3).[101,102] The tetrapyrroles used therein are often complexed by main group and transition metals from all across the periodic table, which is a crucial prerequisite for their performance. Intense research has also been dedicated to the development of porphyrin-based molecular oxygen sensors.[23,103]

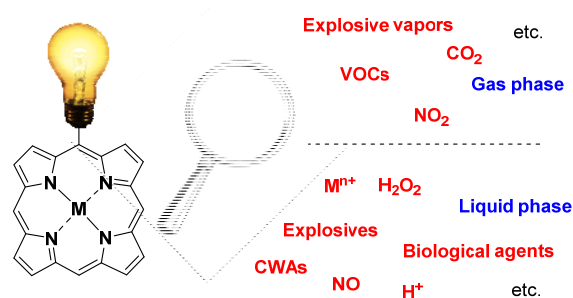
Fig. 3 Metalloporphyrins sense liquid and gas phase analytes through a range of interactions. The bulb represents a reporter group.

Metalloporphyrins as chemical noses and tongues

The selectivity of chemical sensors for gaseous and liquid compounds can be compared to that of the receptors of the olfactory and gustatory systems, which inspired research into artificial sensory organs.[104] Such being the case, a well-resourced library of chemical noses has been developed. Since the terminology used throughout the literature for such systems is sometimes missing integrity, chemical nose shall be defined here simply as a detector for gases and VOCs based on a chemosensor.[23]

This term is often used synonymously to electronic nose, which — in a strict sense — is only a subspecies of the former, where a chemosensor provides an electronic or electrochemical output.[105,106] On the other hand, the term optoelectronic nose describes a chemosensor that can be employed in a colorimetric sensor array.[107] By analogy, sensors working in liquid environments are known as chemical tongues.[24,108]

Typically, electronic noses consist of two units, namely a sensitive material with a site to host the recognition event and a transducer to convert this interaction into a signal. Among these are metal tetrapyrrole-doped composite materials for use as chemoresistors, which rely on a change in electrical resistance (R), upon chemical interaction with a substrate (Fig. 4a). On the other hand, analyte recognition in tetrapyrrolic optical sensors is accompanied by changes in the optical properties of the sensitive material, most practically, absorbance and fluorescence (Fig. 4b). This can be evaluated by irradiation and measuring attenuation of the incident radiation or by detecting the secondary radiation emitted. Absorbance changes, fluorescence quenching (turn-off), and fluorescence turn-on have been monitored to optochemically detect analytes of clinical, environmental, and security-related interest, including hydrochloric acid,[109,110] NO released by cancer cells,[59] pollutants,[75–79] and explosives,[69–74] to name a few, at high sensitivity (*vide supra*).
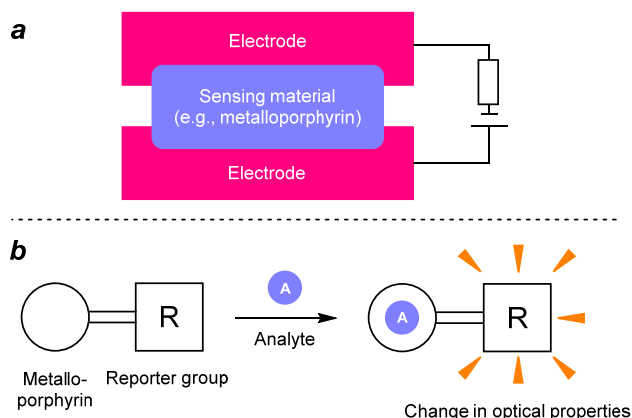

Fig. 4 Make up and working principles of tetrapyrrolic chemoresistors and optical sensors.

The potential and increasing use of metalloporphyrins for molecular recognition and beyond, e.g., explosives detection, and disease diagnostics, is not least due to their ability to detect a broader range of volatile fingerprints through variation of the complexed metal ion and the macrocycle substitution pattern.[111] While these are only selected examples to illustrate some working principles of chemical noses, it is beyond the scope of this perspective to discuss all contributions to the field in detail. Instead, more in-depth examinations of recognition and signaling mechanisms will be provided only where essential.

Recent developments on tetrapyrroles for chemical sensors have been summarized thoroughly by Paolesse and coworkers.[23] Notably, the groups of Paolesse and Di Natale have contributed significantly to the evolution of chemical noses by implementing

metallated porphyrins, both in terms of basic research[112–118] and potential applications, including breath testing,[119] and food analysis.[120] This again highlights how variation of the central metal in metalloporphyrins appears to be one of the most effective tools to design selective sensors.[112] Nevertheless, additional factors are equally important. Besides the molecular structure, recognition properties of porphyrinoid composite materials are highly dependent, for example, on the arrangement of the dye on a surface.[121]

Optoelectronic noses are particularly interesting because they provide convenient detection methods, and their evolution is proof of efficient and resourceful design. They are based on chemoresponsive dyes or fluorophores that contain a metal center or acidic, basic, or redox-active groups, to name a few, which react with analytes. Interaction with the substrate is preferably different from – and stronger than – simple physical adsorption, and a reaction results in a color change of the reflected or absorbed light. At the same time, the interaction center must be strongly coupled to an intense chromophore or fluorophore. These requirements are met by metallated porphyrins (Lewis acidic dyes), pH indicators (Brønsted acidic or basic dyes), and redox responsive dyes. The original optoelectronic nose was developed by Suslick and coworkers, and utilized porphyrins and their metal complexes as sensors for odor visualization,[122–124] bringing about the many advantages of porphyrin-metal complexes discussed earlier and since then, its scope has broadened continually.[125] In practice, in the simplest case, the CSA is digitally imaged before and during exposure to generate a difference map through digital subtraction, i.e., pixel by pixel of the image of the array before and after exposure with regards to red, green, and blue (RGB) values (Fig. 5).[111] This was applied to monitor explosives,[126,127] meat freshness,[128] pathogens,[129] and toxic industrial chemicals.[130]
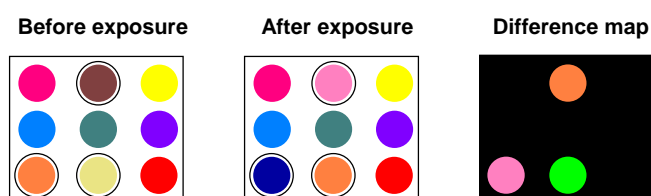

Fig. 5 Representation of a digitalized CSA before and after exposure. Through comparison, a difference map was generated. The individual spots represent chemoresponsive dyes (e.g., metalloporphyrins), some of which underwent a color change upon contact with metal ligating gases.[111]

In the past, various other groups have derived applications of, e.g., phthalocyanine/porphyrin metal complexes[85,131,132] and doped materials[85] in conjunction with spectroscopic methods for gas and VOC sensing, which were more or less inspired by Suslick's pioneering studies. The latest developments in CSA and fluorometric sensor array technologies for 'smell seeing'[123] applications have been reviewed in 2013.[125]

The paucity of comparable literature on porphyrinic artificial taste systems (chemical tongues) might be due to difficulties in finding arrays that, by analogy with taste receptors of the tongue, provide non-selective sensors endowed with sufficient cross-selectivity,

while operable in liquid media.[104] However, examples at hand again confirm the important role of a complexed metal ion in determining the performance of tetrapyrroles as taste sensors,[133] with potential applications including multicomponent testing of wines[134] and polluted water.[135]

Towards distortion-dependent free base porphyrin sensors

Many examples show how metallated tetrapyrroles are particularly suited for sensing and catalysis applications. At the same time, it is more challenging to apply their metal-free counterparts (free base porphyrins) in a similar way. This is due to the unavailability of the porphyrin core (i.e., the amine and imine groups) for small molecule recognition and activation, as they are shielded by the surrounding macrocycle. While there are reports on the use of free base porphyrins for sensing of VOCs,[57] water and ethanol,[136] and gases[43,46,137–141] based on optical changes resulting from alterations in the microenvironment of the porphyrin, only few cases invoke a specific tailoring of the porphyrin skeleton towards improved substrate binding, anion recognition,[142,143] pH sensing,[95,144,145] or chiral sensors.[146]

Similar to sensing, catalysis requires binding of the substrate to the active center; thus, molecular engineering of the tetrapyrrole scaffold can be used to increase selectivity and sensitivity. Our research into conformational design of nonplanar porphyrins[7,36,147–149] and the availability of their nitrogen atoms for hydrogen bonding[150–152] led us to propose a model of bifunctional substrate activation for porphyrin-based organocatalysis.[153] Therein, macrocyclic out-of-plane saddle distortion[154] is a vital prerequisite to render free base porphyrins catalytically active. Following this, conformational control was exerted to provide porphyrins **2** with an exposed core for hydrogen bonding (distortion-dependent hydrogen bonding) and increased basicity.[155] While previously, all natural and synthetic catalytically active tetrapyrroles were dependent on the presence of a central metal ion, this allowed us to utilize highly substituted and *N*-methylated species **2** as bifunctional organocatalysts, opening a new functional role and offering future perspectives for sensor design through conformational control (Fig. 6).
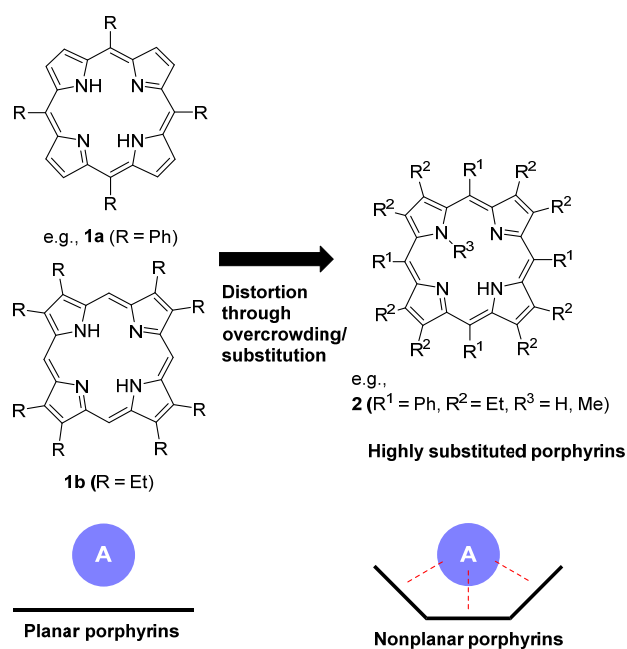

Fig. 6 Concept of distortion-dependent porphyrin sensors. The core of planar porphyrins **1** is unable to complex an analyte, while highly substituted, distorted analogues **2** are able to do so. This technique was successfully used in catalysis and application for sensing is highly encouraged.[118]

Porphyrins for explosives detection

There has been extensive research in the field of explosives detection, particularly in the context of recent military conflicts, and in the wake of terror attacks.[156,157] Particularly, the wide-spread use of improvised explosive devices (IEDs) presents a problem during military deployments and armed conflicts.[158,159] Increasingly, they are also used by terrorists to target government infrastructures, and common places alike. Therefore, the development of reliable detector systems to protect people and property from dangerous attacks is a priority. It is envisioned that the application of chemical sensors in this area will lead to more cost-effective, user-friendly, and compact devices. Additionally, they may need less manual attention, and could be deployed easily with low public visibility.

In this context, metal porphyrin-based systems offer rich opportunities for recognition of explosive molecules due to their tunable physicochemical characteristics and binding properties.[33] Accordingly, frequently used detection methods involve optical and electronic/electrochemical approaches utilizing 'plain' tetrapyrroles as well as advanced (electroactive) materials, including composites of porphyrin and mesoporous silica[160] or carbon allotropes.

An early study showed that sulfonic acid-substituted porphyrins change their absorbance and show fluorescence quenching in the presence of 2,4,6-trinitrotoluene (TNT), through formation of a 1:1 complex, as evaluated by a Stern–Volmer plot, providing detection down to 200 ppb.[161] Furthermore, aryl phosphonate- and phosphonic acid-functionalized free base and zinc porphyrins **3** were used for molecular recognition of TNT (≥ 5 ppb), where emission turn-off following intermolecular hydrogen bonding, π–π stacking, and axial coordination occurred (Fig. 7a).[162] The same

publication revealed that macrocyclic distortion upon protonation increased selectivity towards the explosive at nanomolar levels. Another generic study on the explosive sensing properties of Zn(II) porphyrins **4** was conducted by the group of Panda, where various substituted tetrapyrroles showed reduced emission in the presence of, e.g., TNT, 2,3-dimethyl-2,3-dinitrobutane (DMNB), 1,3,5,7-tetranitro-1,3,5,7-tetrazocane (HMX), and 1,3,5-trinitro-1,3,5-triazinane (RDX; Fig. 7b).[163]
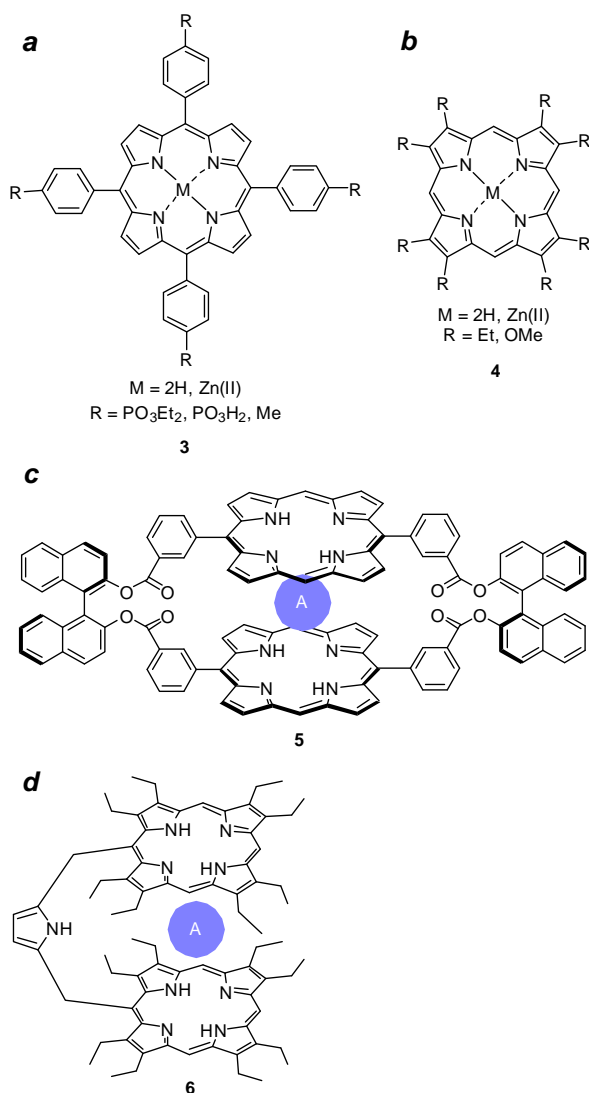

Fig. 7 Various porphyrins used to study the binding of nitroaromatic explosives. Functionalized free base and Zn(II) porphyrins **3**[162] and **4**[163] and chiral dimers **5**[164] and **6**.[72]

Recognition of 1,3,5-trinitrobenzene took place in the presence of chiral diporphyrin receptor **5**, when the guest was intercalated into a structural cavity via cooperative π–π -stacking (Fig. 7c).[164,165] Moreover, dimer **5** functioned as a naked-eye sensor, which can drastically reduce the need for specialized equipment and personnel, providing straightforward sensing for a potential application in the field.

Bisporphyrin **6** with a flexible diethylpyrrole bridge was able to encapsulate 2,4,6-trinitrophenol (picric acid, detection limit = 2.4

ppm; Fig. 7d).[72] Additionally, the host discriminated the target from other nitroaromatic compounds, and efficient electron transfer to the guest was observed. Selectivity to picric acid (≥ 18 ppb) was also realized with a Lewis acidic Zn(II) porphyrin carrying phenylmercury(II)chloride substituents, and the Stern-Volmer quenching constant and limits of detection (LODs) were determined to be among the best of small-molecular receptors for nitroaromatic explosives.[166]

Research on advanced porphyrin-based materials for the construction of optical sensors, such as free base-, Cd(II), and Zn(II) porphyrin-doped hierarchically structured porous silica films resulted in an improved sensitivity towards TNT (10 ppb) and 2,4-dinitrotoluene (DNT) vapors.[167,168] The results were superior to previously reported single modal films,[169–171] and the bimodal (macropore–micropore) structure of the material was believed to be responsible for the observed sensing performance as it provided facile diffusion of the analyte, high density of interaction sites, and a large surface area. Mesoporous silica was also covalently doped with carboxylic acid-substituted porphyrin **7** and applied as a chemosensor for TNT vapor (10 ppb, Fig. 8a).[172] In addition, quantitative detection of TNT (0.46 ppm) in aqueous media occurred using a complex of carboxylporphyrin **8** and MOF PCN-224.[74] This approach combined the advantages of the dye with the porous makeup of the MOF, leading to a fluorescent probe that benefited from a high surface area and an intrinsic open structure. Note that analyte complexation involved hydrogen binding with the porphyrin's central N-H groups (Fig. 8b).

An amine-modified electrospun nanofibrous film sensor based on a methoxyporphyrin and polystyrene showed sensitivity to ppb levels of TNT vapor and ppt levels of picric acid vapor.[173] Such being the case, an application for the construction of portable sensing devices at low cost was suggested. Similarly, trace amounts of TNT vapor as low as 10 ppb were detected by another nanofiber electrospun from zinc porphyrin polyimide **9** (Fig. 8c). The high surface area-to-volume ratio provided good gas accessibility and favorable fluorescence quenching behavior. On the other hand, a porous thin film on the surface of an optical fiber for vapor sensing of TNT and DNT traces (10 and 180 ppb, respectively) was constructed via 'click' chemistry of a vinyl-functionalized porphyrin.[73]

Merging synthetic methods and electronic engineering, libraries of devices for electric and electrochemical explosive detection have also been designed. This includes a polymeric porphyrin prepared through electropolymerization and deposited onto an electrode.[174] Detection of a range of explosives in aqueous solution was then investigated through differential pulse voltammetry (DPV). It was found that the doped electrode greatly enhanced the reduction of various explosives, such as TNT, DNT, N-methyl-N-(2,4,6-trinitrophenyl)nitramide (tetryl), and RDX with LODs down to 8 ppb. Furthermore, porphyrin nanoassemblies of Zn(II) and titanyl complexes of 5,10,15,20-tetrakis(4-pyridinyl)porphyrin were used as nanoelectronic sensors to detect H_2O_2 vapor (≥ 0.25 ppm),[175] and a membrane sensor for perchlorate potentiometric batch and flow injection analysis (FIA) was fabricated incorporating an In(III) porphyrin for the assay of fireworks and propellants.[176]
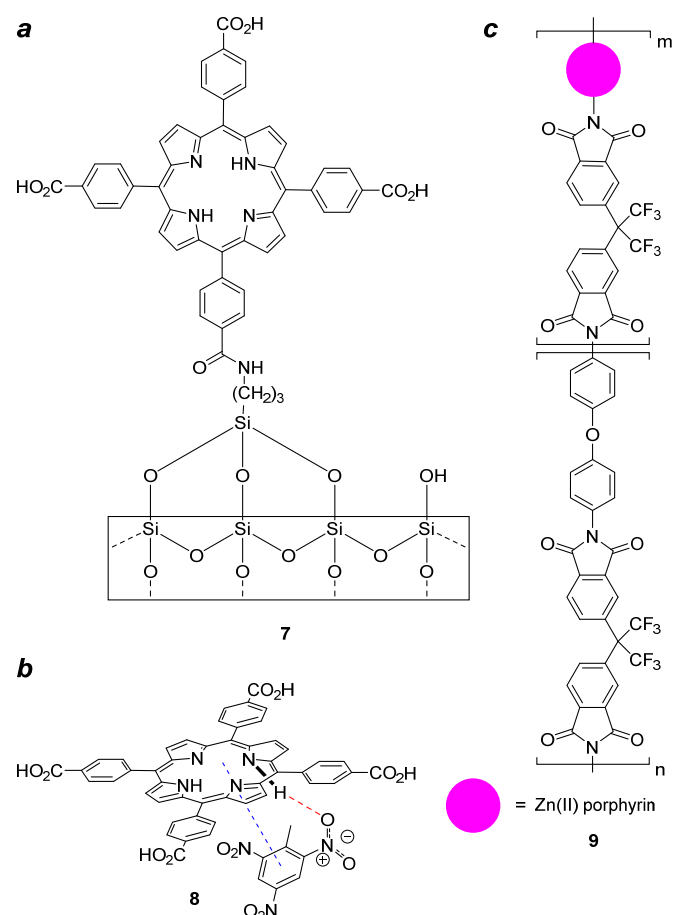
Fig. 8 Examples of porphyrins and their materials for optical explosive sensors. Porphyrin-doped mesoporous silica **7**,[172] complex of **8** and TNT (red dashed line = H-bond, blue dashed line = π–π stacking),[74] and zinc porphyrin polyimide **9**.[173]

Research into advanced materials produced miniaturized and low cost sensor platforms of organic materials and this has been discussed in the light of environmental and security applications by the group of Rao.[177] Specifically, organic field effect transistors (OFETs) made up of polymer and Cu(II) porphyrin demonstrated high selectivity and ultratrace sensitivity to explosive vapors of TNT, RDX, and dinitrobenzene associated with the high permeability and roughness of the film that was prepared.[178,179] Similar results were achieved using OFET composites of poly(3-hexylthiophene) and functionalized polysiloxane as an organic layer and Cu(II)TPP, with excellent sensitivities (< 70 ppt for RDX and < 100 ppt for TNT).[180]

The attractive electrical properties of some carbon allotropes were also exploited by various groups, which led, for example, to composites of carbon black and Co(II), Cu(II), and Zn(II) complexes of 2,3,7,8,12,13,17,18-octaethylporphyrin (**1b**, OEP).[181] These were utilized in thin film chemiresistive architectures to detect ammonia (30 ppm), TNT (LOD *ca.* 30 ppt), and common organic vapors. Furthermore, chemiresistors of single-walled carbon nanotubes (SWCNTs) and transition metal complexes of 5,10,15,20-tetraphenylporphyrin (**1a**, TPP) have been used in VOC sensing and applications in environmental monitoring, the security sector, and healthcare diagnostics were suggested.[182] A coating based on

diamond nanoparticles functionalized with the cationic porphyrin (5,10,15,20-tetrakis(4-methylpyridinium)porphyrinato)zinc(II) tetrachloride for surface acoustic wave (SAW) transducers was investigated by Chevallier *et al.* for detection of DNT vapor.[183] The nanodiamonds offered a stable porous matrix to immobilize the dye, with the resulting sensor having a high sensitivity of typically 120 Hz per ppb, a LOD of 1 ppb, and an enhanced response as opposed to undoped porphyrin.

Functionalization of carbon nanotubes (CNTs) with 5-(4-hydroxy)-10,15,20-triphenylporphyrin led to a sensor film that gave a good electrochemical response towards 1,3-dinitrobenzene (LOD = 2.0 ppb).[70] This was due to the synergistic interplay of the CNTs and the tetrapyrrole, providing endemic preconcentration of the explosive on one hand, and forming π donor–acceptor complexes with a high electron transfer rate on the other. Comparison with a range of non-porphyrin explosive sensors shows that the LOD of the porphyrin/CNTs film used herein was superior to systems based on, e.g., mesoporous carbon materials (LOD = 25 ppb), ionic liquid–graphene hybrid nanosheets (IL–GNs, LOD = 4 ppb), composites of molecularly imprinted polymers (MIP) and multi-walled carbon nanotubes (MWCNTs, LOD = 25 ppb), and a molecularly imprinted monolayer (MIM)–gold nanoparticles glassy carbon electrode (GCE, LOD = 13 ppb).[70]

Similarly, 5,10,15,20-tetrakis(4-pyridyl)porphyrin-substituted graphene facilitated the electrochemical sensing of ultratrace amounts of TNT (0.5 ppb), DNT (1 ppb), 1,3,5-trinitrobenzene (1 ppb), and 1,3-dinitrobenzene (2 ppb).[22] Here, underlying synergistic effects from the adsorptive properties of the porphyrin and the large electroactive surface area, in addition to fast charge-transfer of graphene contributed to highly sensitive and reproducible detection.

Along with such closely application-related molecular recognition studies, basic research has been carried out on the physicochemical properties and underlying detection mechanisms of porphyrin-based sensors. For example, this includes theoretical studies on the DNT detection of a self-cleaning iron porphyrin by Warnick *et al.*[184] Calculations described the reaction between the substrate and oxygen, catalyzed by the tetrapyrrole's iron core: oxygen is bound to the metal and then removed by reaction with another equivalent of DNT, restoring the porphyrin (Fig. 9). In addition, the nonlinear absorption (NLA) properties and excited state dynamics of an 2,3,7,8,12,13,17,18-octamethylporphyrin in the presence of explosive molecules (TNT, RDX, and 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (CL-20)) were investigated by Anusha *et al.*, which revealed increasing NLA coefficients and shorter first excited state decay times in the presence of the analytes.[185]

It was also found that porphyrins may aid the degradation or, in contrast, the stability of explosive materials. In one example, an iron-containing cytochrome P450–flavodoxin fusion enzyme catalyzed the reductive denitration of RDX, offering perspectives for porphyrins on the interface of biotechnology and the security sector, especially bomb disposal.[186,187] Early steps in the degradation of TNT by carboxyl- and sulfonate-appended porphyrin

have been identified by UV-vis and fluorescence spectroscopy.[188] At room temperature, complexation occurred *via* formation of hydrogen bonds between the pyrrolic nitrogen atoms and a substrate nitro group, while hydrophobic interactions prevailed at elevated temperature.
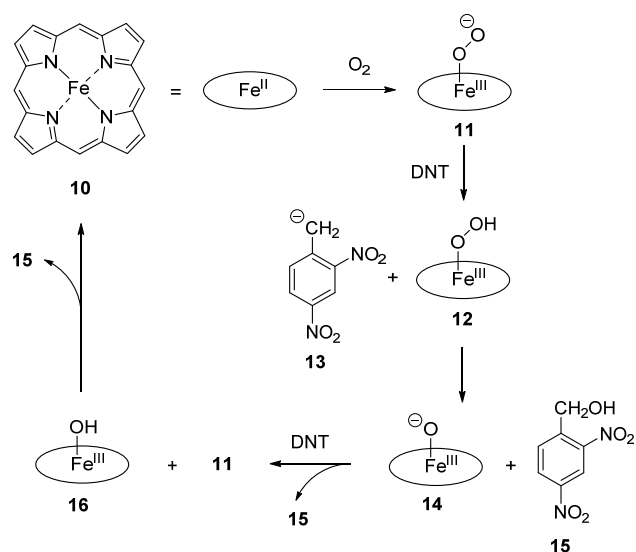

Fig. 9 Theoretical mechanism of the catalytic degradation of DNT by (porphyrinato)iron(II) **10** in the presence of oxygen. After oxidation to **11**, H-transfer from DNT to the porphyrin occurs, forming **12**. Subsequent hydroxylation of the anion **13** yields **15** and tetrapyrrole **14**. This is followed by reaction with another equivalent of DNT to give the hydroxylated catalyst **16** and dehydroxylation eventually restores **10**.[184]

The thermodynamic stability of 2,2-bis[(nitrooxy)methyl]propane-1,3-diyl dinitrate (PETN), another explosive with high brisance that was used, for example, in the 1980 Paris synagogue bombing, was enhanced *via* doping with an iron porphyrin.[189] This is an early step towards the use of porphyrins to enhance the stability of energetic materials for safe use and IED disposal. Additionally, optical sensors made of free base and metallated porphyrin–enzyme complexes have been discussed by Johnson-White and Harmon with an emphasis on antiterrorism and international security.[190]

Porphyrins for CBRN defense

The threat of CBRN agents and WMDs is addressed by intergovernmental organizations in the form of weapon treaties and disarmament agreements on one hand, and first responders, troops, and researchers on the other. Narrowing this topic down to the share of natural scientists, a number of approaches have emerged both in the laboratory and in clinical environments. This includes research into new antidotes, early warning systems, real-time sensors, and decontamination methods. Many approaches are based on reactive chemical compounds and physical or chemical interactions and once again, metalloporphyrins stand as an important class due to their remarkable and tunable catalytic competence, complexation abilities, and optical/photophysical properties.

Defense against chemical agents

As an infamous class of neurotoxic and pesticidal agents, organophosphates and derivatives,[191] e.g., sarin **17**, and VX **18** pose a significant threat as CWAs[192] and environmental toxins. On the other hand, vesicants, including mustard gas **19**/sulfur mustards and nitrogen mustards, are cytotoxic and cause the formation of harmful blisters on exposed skin and in the lungs (Fig. 10a).[193] Both types have a history which dates back to the early 19th century and consequently, methods to sense and decontaminate these agents have gained significant interest.[194] Due to their extreme toxicity, models or simulants are often employed in place of the actual compounds.[195]
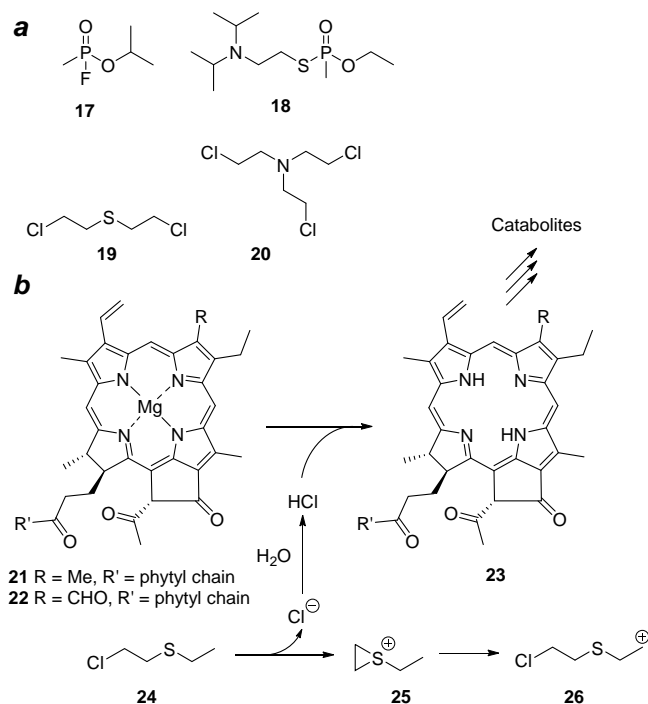

Fig. 10 a) Structures of the nerve agents sarin **17**, and VX **18** and the vesicants mustard gas **19** and nitrogen mustard HN3 **20**. b) Sulfur mustard analogue **24** undergoes intramolecular S_N1 reaction to give **25** by eliminating chloride. The intermediate reacts further to form carbocation **26**, a fluorescence quencher. Additionally, chlorophyll *a* and *b* (**21** and **22**) are demetallated by hydrochloric acid from breakdown of **24**. Follow-up reactions of pheophytin **23** eventually lead to non-fluorescent catabolites.[197]

In one study, detection and quantification of organofluorophosphonates — or, more specifically, of their fluoride ions, which were produced upon catalytic hydrolysis — was developed using a polymeric membrane containing Al(III) porphyrin and a chromoionophore for optical sensing with excellent sensitivity (e.g., LOD = 0.1 ppm for diisopropyl fluorophosphate).[196] Another approach towards an ultrasensitive fluorometric sensor for sulfur mustard was pursued by *Kaur et al*., who investigated the quenching effect of mustard gas analogue **24** on chlorophyll fluorescence (Fig. 10b).[197] In this study, breakdown of the macrocycles **21** and **22** and coordination of **26** to the tetrapyrroles led to altered emission, and immobilization of the dye in a porous matrix fabricated by a sol–gel process, further enhanced selectivity (LOD = $7.68 \cdot 10^{-16}$ M). This is yet another intriguing and possible application of natural chlorophyll derivatives in materials science.[198]

Staying with biological materials, optical detection of dimethyl methylphosphonate could be achieved using a sulfonate-substituted porphyrin–plant-esterase complex.[199] Here, the system provided a decrease in absorbance intensity in the presence of the CWA simulant as observed in solution (LOD = 90 ppt) as well as in an immobilized state (LOD = 0.45 ppb). Consequently, applications as rapid warning systems and for field analysis were suggested. Furthermore, a number of organic chemical warfare agent degradation products could be detected using a tetra-phenylsulfonic acid-substituted porphyrin as probe.[200] This was achieved using indirect laser-induced fluorescence and capillary electrophoresis. Because of the high intensity of the incident light emitted by a violet laser diode and the ability to accurately focus the light on the capillary, the technique provided low LODs down to 9 ppb.

In another study by Harmon, porphyrin–enzyme complexes were subjected to, e.g., cholinesterase inhibitors, and displacement of the macrocycles from the active site occurred, with LODs down to 2 ppb.[201] This changed the tetrapyrrole's microenvironment and ultimately, resulted in spectroscopic detection of the analyte. Interestingly, the high sensitivity was explained on the base of nonlinear optics (NLO) and multi-photon absorption; areas of research for which porphyrins are especially suited.[202]

Recognition of cyanide as a toxic inorganic analyte by 2-iminothiolane-substituted Cu(II) porphyrin on a cellulose film was realized through an absorbance loss that appeared upon complexation of CN^- (LOD = 1.5 ppb), with similar results achieved for myoglobin.[203] Cyanide is an inhibitor of the enzyme cytochrome c oxidase and a strong cytotoxin. Even though there is no confirmed information on this substance being utilized in CWAs, reports have indicated its use in the Iraq–Iran war and against the Kurds in the 1980's.[204,205]

Catalytically active iron and manganese tetraarylporphyrins 27 were successfully exploited for the hydrogen peroxide oxidation of sulfur mustard model compounds 30, with the aim being to design catalytic systems for decontamination of CWAs (Fig. 11a).[206] Similarly, a nanocrystal of porphyrin-containing Zr(IV) MOF 37 acted as a dual-function catalyst to simultaneously detoxify two CWA simulants, namely dimethyl 4-nitrophenylphosphate (34, paraoxon analogue) and 2-chloroethyl ethyl sulfide (24, mustard gas analogue; Fig. 11b).[207] Deactivation involved hydrolysis and oxidation to nontoxic products 33, 35, and 36 via a pair of pathways catalyzed by 37 that efficiently adsorbed the substrates and facilitated diffusion to catalytically active sites. Note that the sulfur atom in 24 was photochemically oxidized by singlet oxygen ($^1O_2$) generated by the tetrapyrrole, and a comparable photooxidation was previously reported by Liu et al.[208] In a further study on nerve agent degradation, a catalytically active Al(III) porphyrin carrying very bulky residues was integrated into a porous organic polymer (POP) for use in the degradation of 4-nitrophenyl diphenyl phosphate.[209] Interestingly, best catalytic activity arose after supercritical CO_2 processing to afford POPs with large pores and a large pore volume.
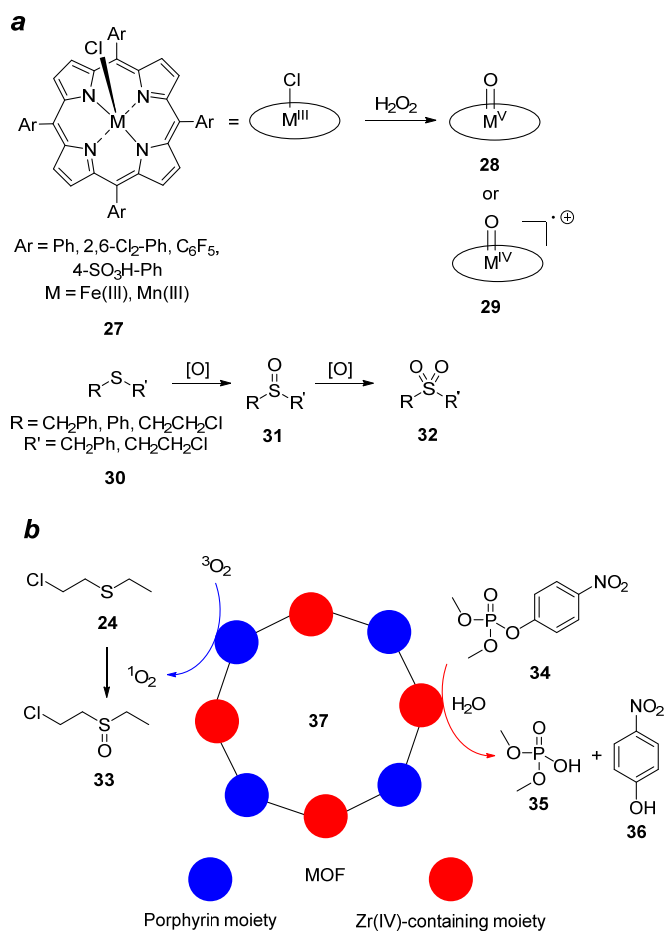

Fig. 11 a) Fe(III) and Mn(III) porphyrins 27 catalyzed oxidation of mustard analogues 30 to sulfoxides 31 and sulfones 32. The presumed catalytically active species 28 and 29 formed upon hydrogen peroxide oxidation.[206] b) Schematic representation of porphyrin-based Zr(IV)-containing MOF 37 that was used to simultaneously detoxify 24 and 34. $^1O_2$ oxidation of 24 yielded sulfoxide 33 and hydrolysis of 34 generated 35 and 36.[207]

Increasingly, porphyrinoids, as opposed to true 24-macrocycle atom porphyrins are used in sensing. For example, a comparative study on the Mn(III)–organophosphonate binding properties of an A_2B type metallocorrole and an A_2B_2 type metalloporphyrin with nerve agent models was conducted by Kim et al., and spectroscopic methods as well as DFT geometry optimizations were employed to elucidate some characteristics, such as association constants of the complexes formed.[210] Spectroscopic experiments also provided an insight into the noncovalent association of the nerve agent substitute diisopropyl methylphosphonate with symmetric and unsymmetric Zn(II) porphyrins, suggesting that interaction took place via coordination of the metal center to the analyte's phosphoryl oxygen atom.[211] A good understanding of the binding situation in complexes of detoxifying agents and their substrates is also important to tailor CWA countermeasures with optimal efficiency.

While the above discussed results mainly aid the detection of toxic compounds and the development of preventive measures, emerging studies suggest porphyrins as promising candidates for pre-exposure prophylaxis and post-exposure treatment.

Specifically, the development of a reactive topical skin protectant for troops against percutaneous CWAs based on porphyrin is noted.[212] Intriguingly, it has been evidenced that treatment of rats with a catalytically active (5,10,15,20-tetrakis(*N*,*N*-diethylimidazolium-2-yl)porphyrinato)manganese(III) compound (AEOL 10150) reduced inflammation and oxidative stress due to inhalation of a sulfur mustard model.[213,214]

Defense against biological agents

The potential of biological warfare (BW) and bioterrorism is an unsettling reality of 21st century life, with the possibility to use biological warfare agents (BWAs) in a bioterrorist attack posing a global cause for concern. We do not need to look much further than 2001, where the mailing of letters containing anthrax spores to various locations within the U.S.A. brought the frightening realization that bioterrorism is not simply a hypothetical or past danger, but a real and present-day threat.[215] Potential BWAs include bacteria, fungi, viruses, spores, and toxins.[216] Upon dissemination through air, water, or contamination of food/surfaces, highly infectious and toxic substances have the potential to cause a high degree of lethality within military personnel and the civilian population. Furthermore, antibiotic resistance remains one of the biggest health crises facing our world today, with the emergence of bacterial strains resistant to all known antibiotics already presenting a major challenge.[217,218] As such, the potential to weaponize antibiotic resistant strains of common microorganisms in BW or bioterrorism poses an even higher threat. With no security screening in place for common species, these agents may be considered near-ideal biological weapons with the possibility not only to cause highly infectious diseases and potential death among the masses, but also to remain largely undetected until large-scale contamination and infection has occurred. Therefore, countermeasures with the ability to detect and deactivate potential biological weapons are highly sought.[219–221]

Antimicrobial photodynamic therapy (PDT) or photodynamic inactivation (PDI), involving the use of a photosensitizer (PS) and visible light to generate reactive oxygen species (ROS) to destroy microorganisms,[222] may provide a versatile approach, to which microorganisms cannot acquire resistance to.[223] Although discovered over 100 years ago for its ability to kill microorganisms,[224,225] PDT is gaining renewed interest in recent years due to the rise of antibiotic resistant strains of common pathogens (Fig. 12).
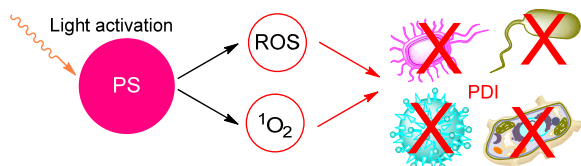

Fig. 12 Principle of PDT/PDI. A PS (e.g., metalloporphyrin) is activated *via* light, which results in ROS and $^1O_2$ formation. These species can destroy biological agents, such as bacteria and their endospores, fungi, viruses, and toxins.

PDT targets lipids, nucleic acids, and proteins in microorganisms, with such biomolecules forming major components of all potential BWAs.[216] Thus, in theory, PDT can be used as an approach to deactivate all known classes of biological threats. Commonly used PSs in PDT are, amongst others,[226] porphyrins and their metal complexes and herein, we review the potential of porphyrins to deactivate BWAs.

Bacteria Multidrug-resistant infections present a major problem, especially among immunocompromised hospital patients and open wound or burn victims in military personnel.[227,228] Among these, methicillin-resistant *Staphylococcus aureus* (MRSA) is a gram-positive bacterium that can cause severe infection in humans. Inactivation of *S. aureus* with porphyrin-based PDI has been explored, with photo-induced killing of the bacteria being strongly dependent on the PS concentration and delivered dose/light illumination time.[229] A recent study by Winkler and coworkers demonstrated photodynamic inactivation of clinically-derived multidrug-resistant *S. aureus* isolates using the tetrapyrrole chlorin e_6 (**38**, Ce6; Fig. 13).[230] A 5-log colony-forming unit (CFU) reduction in cell viability was displayed in all isolates following preincubation of the cells with the PS **38** in the dark and subsequent illumination by red light. Mamone *et al.* used a porphyrin bearing four basic amino groups **39** to mediate complete eradication of *S. aureus* in the planktonic state and a 3-log CFU reduction in *S. aureus* biofilms.[231] Such a result is of importance, given that biofilm-associated diseases account for nearly 80% of infections in humans.[232] Korchenova *et al.* studied the effect of free base porphyrins (e.g., **40a**) *versus* zinc(II) metalloporphyrins (e.g., **40b**) on photodynamic inactivation of MRSA.[233] Further examples of (metallo)tetrapyrroles for PDI of *S. aureus* have been reported. Notably, an early study by Maisch and coworkers showed that the 5,15-substituted dication **41** was capable of killing multiple logs of MRSA.[234]

Similarly, a study by Vecchio *et al.* showed that antimicrobial PDT using a zinc phthalocyanine (RLP068/Cl) could kill MRSA and accelerate wound healing in a mouse model of infected skin abrasion.[235] In one of the first studies in this context, Griffiths *et al.* in 1997 demonstrated PS concentration-dependent killing of MRSA using a sulfonated Al(III) phthalocyanine (AlPcS2).[236]

Another multidrug-resistant infection is that of *Acinetobacter baumannii*, an opportunistic pathogen, which represents a growing problem particularly in severe burn and wounds suffered by soldiers in combat.[237] It was shown that topical PDT using a covalent conjugate between chlorin e_6 and polyethylenimine was highly effective in inactivating *A. baummanii* burn infections in mice, infected using multidrug-resistant clinical isolates from an injured U.S. solider deployed to Iraq.[227] Porphyrins and their analogues have also been reported to be capable of inactivating multiple other bacteria, such as *Pseudomonas aeruginosa*[238] and *Escherichia coli*.[229]
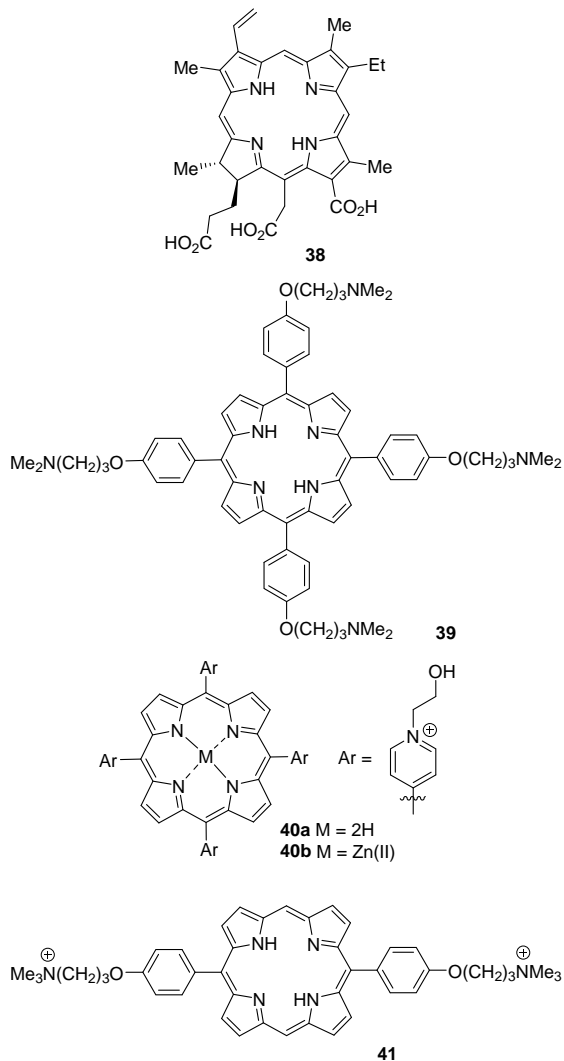
Fig. 13 Selection of tetrapyrrole PSs against *S. aureus*.

Bacterial endospores *Bacillus anthracis* is a gram-positive endospore-forming bacterium and the causative agent for anthrax disease in humans. It is extremely well-suited for use as a biological weapon, and in fact, weaponization has been accomplished in the past by such bioweapons programs as those of the United Kingdom, the U.S., and Japan.[216] The deadly nature of *B. anthracis* is attributed to its ability to form endospores: forming in response to unfavorable environmental conditions, the spores are highly resilient and capable of surviving extreme temperatures and low-nutrient conditions. This renders them very difficult to destroy by means of heat, radiation, or antibiotic/antimicrobial agents and as such, *B. anthracis* remains a major bioterrorism threat.[239] While inactivation of vegetative cells is relatively easy, annihilation of bacterial endospores remains a major challenge. A past study has implicated the use of light-activated porphyrin-based formulations as a potential treatment against *B. anthracis* spores.[240] Testing the effect of amine-modified protoporphyrin IX **42** and **43** (TMPyP4), Banerjee *et al.* showed that treatment with a combination of the PS and germinants (L-alanine and inosine) in the presence of light

decreased spore viability by as much as 4.5 log units, with **43** being more effective (Fig. 14).
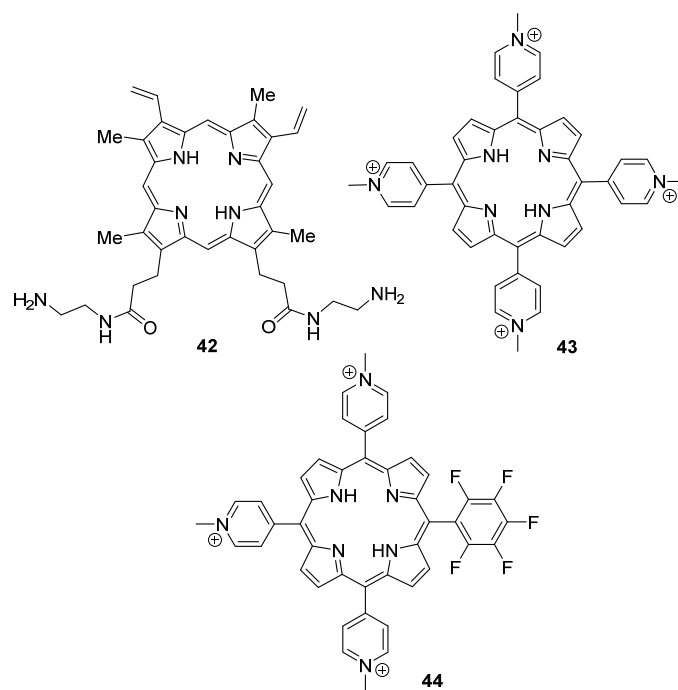

Fig. 14 Porphyrins that were successful in PDI of *B. anthracis*-, *B. cereus*-, and *B. atrophaeus* endospores.

Bacillus cereus and *Bacillus atrophaeus* are closely related species to *B. anthracis* and are often used as simulants for the latter due to the high biohazard risk associated with it.[216,241] Utilizing *B. cereus,* Oliveira *et al*. published a study showing a reduction of 3.5 log units after 4 min of irradiation of tricationic **44** that carried a pentafluorophenyl group.[241] In a similar study, Maisch and coworkers observed PDI of *B. atrophaeus* spores through intense pulse light and **43** in a total treatment time of 10 s.[242]

Fungi The most deadly of the primary fungal pathogens in humans is that of *Coccidioides immitis*.[243,244] As such, it is the only fungal species listed as a potential biological warfare agent amongst the Select Agents of bioterrorism under U.S. law. It produces spores, with exposure having the potential to cause profound pulmonary disease and further dissemination *via* the bloodstream. Although there have been no reports of deactivation of its spores using PDT, successful PDI of related fungal species has been achieved, suggesting that this may be a viable approach against *C. immitis* as well.[216] For example, Junqeira and coworkers published the use of a cationic nanoemulsion of a zinc phthalocyanine to induce PDI of biofilms produced by *Candida* spp., *Trichosporon mucoides*, and *Kodamaea ohmeri*.[245] A more recent study demonstrated high microcidal activity of *N*-ethylpyridinium zinc porphyrin **45**-decorated CdTe quantum dots (QDs) when photoactivated against *Candida albicans* (Fig. 15).[246]
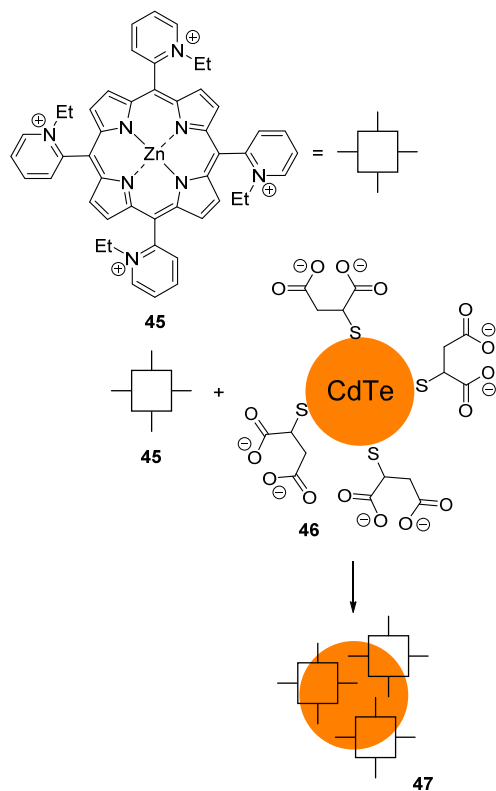
Fig. 15 Schematic representation of composite PS **47** fabrication based on Zn(II) porphyrin **45** and mercaptosuccinic acetate-stabilized CdTe QDs **46**.[246]

Viruses Ebola is a filovirus classified as a Centers for Disease Control and Prevention (CDC) category A bioterrorism agent.[247–249] Infection can cause acute and serious illness, i.e., Ebola virus disease (EVD) in humans and is often fatal if untreated. A recent study by Wang *et al*. showed that a conserved guanine-rich sequence is present in the L gene of the Ebola virus, with the sequence tending to fold into a G-quadruplex RNA structure.[250] The study demonstrates the ability of TMPyP4 **43** to inhibit L gene expression at the RNA level, concluding G-quadruplex RNA stabilization may represent a new therapeutic strategy against EVD.

Dengue virus (DENV) and yellow fever virus (YFV) both belong to the genus *Flavivirus* and their inactivation has also been demonstrated using metalloporphyrins. Miranda *et al*. investigated their inactivation using three metalloporphyrins: heme derivative **48a** and the cobalt- and tin complexes of protoporphyrin IX (**48b** and **49**; Fig. 16).[251] This revealed the marked ability of the metallated porphyrins to inactivate both DENV and YVF, weakening its ability to infect and to induce a cytopathogenic effect on host cells. These results indicate that metalloporphyrins are potential therapeutics for direct use against DENV and YFV, and good models to design novel antiviral drugs.[252]

Smallpox is an acute, contagious disease caused by *Variola* viruses, and one of the most devastating diseases known to humanity. It has been used as a BWA during World War II and American, British, and Japanese scientists engaged in research to weaponize the agent, while the Soviet biological weapons program also produced a stockpile of weaponized smallpox.[216,253,254] In present times there is

concern that smallpox may have been acquired by other governments or terrorist organizations for possible use in a BW or bioterrorism attack.[255] While smallpox has been successfully eradicated worldwide through a collaborative global vaccination program, the threat may still remain.[256]
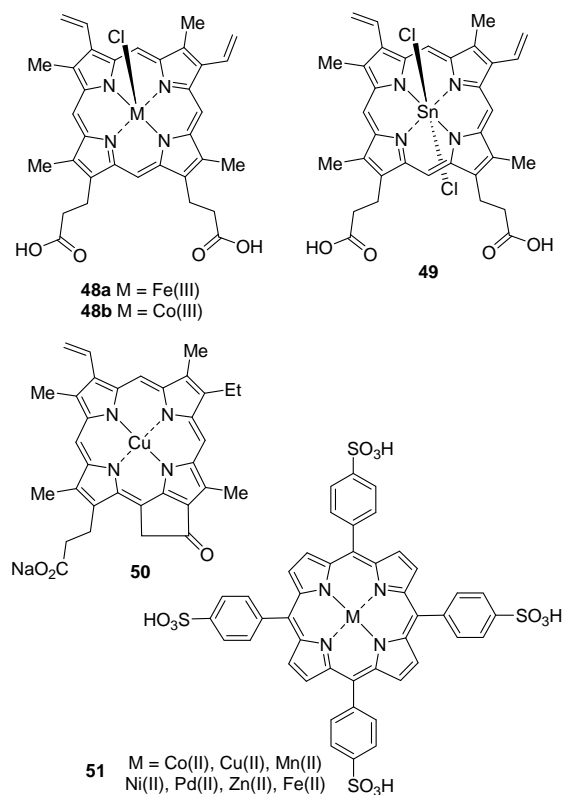

Fig. 16 Porphyrins tested for inactivation of *Flaviviridae*.

Variola variants belong to a family of enveloped DNA viruses, and while there are no reports of porphyrins inactivating smallpox specifically, there are reports of the use of tetrapyrroles against comparable enveloped viruses. A study by Guo *et al*. showed that a number of tetrapyrroles have broad antiviral activity against *Hepadnaviridae*, *Flaviviridae*, *Filoviridae*, and *Arenaviridae*.[257] In particular, a copper phytochlorin **50** was reported to alter the structure of Hepatitis B virus (HBV), extracellularly disrupting the virion envelope structure and subsequently, destroying viral nucleic acid. In addition, Vargas *et. al*. demonstrated the antiviral photo-inactivation of human immunodeficiency virus (HIV-1) using a series of phenylsulfonated Co(II), Cu(II), Mn(II), Ni(II), Pd(II), Zn(II), and Fe(II) porphyrins (**51**).[258]

Toxins Toxins and virulence factors secreted by microorganisms can be inactivated by PDI — one of the few antimicrobial treatments capable of doing so — since the ROS produced during PDI are able to denature them. The ROS can also attack functional groups of a toxin susceptible to oxidation, rendering the substance inactive.[216] A study by Okochi *et al*. used porphyrin–globotriose hybrids, e.g., **52** to effectively induce target-selective photodegradation of verotoxin-1, an exotoxin produced by enterohemorrhagic *E. coli* (EHEC; Fig. 17).[259] A more recent study by Bartolomeu and

coworkers investigated the effect of PDT on the virulence factors of *S. aureus*.[260] Using the tetraiodide of **43** as PS, the study concluded that all strains could be effectively inactivated through PDI. Furthermore, PDI was found to not only inactivate the microorganisms, but also to induce degradation of released virulence factors. These findings were accompanied by the observation that all of the *S. aureus* strains investigated did not develop resistance to the PDI treatment.
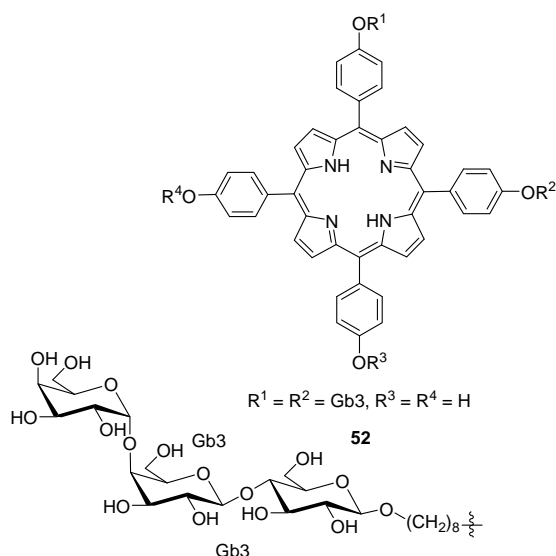

Fig. 17 Porphyrin–globotriose hybrid **52** used for photodegradation of verotoxin-1.[259]

Defense against radiological and nuclear agents

The uncontrolled radiation exposure following a nuclear bomb explosion or a nuclear power plant accident presents a significant threat to our world. This is only too evident from the devastating effects following the atomic bombings of Hiroshima and Nagasaki during World War II, and the 1986 Chernobyl and 2011 Fukushima Daiichi nuclear disasters. Ionizing radiation can have a profound effect on the human body, damaging cells and tissues, and results in radiation poisoning, mutations, cancer and death.[261]

All elements of the actinide series are radioactive, releasing energy upon nuclear decay. Thus, actinides can be considered as materials for nuclear/radiological warfare, particularly uranium and plutonium, which have been used in weapons in the past. A vast amount of enriched uranium and plutonium has been created worldwide through the production of WMDs and the harnessing of nuclear energy for electricity. Additionally, the widespread use of depleted uranium munitions on the battlefield creates medical effects.[262] Aside from the obvious concerns associated with stockpiling and transporting such elements, the potential for arms proliferation and the threat of a terrorist 'dirty bomb' attack have made the possible release of radiological material into the environment a frightening prospect.[263] As such, methods for their fast and accurate detection are needed.

Porphyrins are recognized as cation complexing agents *par excellence*,[35] which is particularly true for the late transition metals and is elaborated further when using expanded porphyrinoids.[264]

There also exist some examples of them binding actinides, and in the following we briefly discuss the potential of tetrapyrroles as sensors for radioactive/radiological substances, as well as their ability to mitigate biological damage by ionizing radiation.

Sensors for radioactive material Porphyrins have the ability to bind actinide cations and two common types of complexes have been observed: 1:1 coordination systems and 2:1 sandwich/double-decker complexes.[264] As early as 1987, Girolami *et al*. reported the synthesis and crystal structure of a 1:1 uranium porphyrin, namely the dichloro(5,10,15,20-tetraphenylporphyrinato)uranium(IV) THF solvate (**53**; Fig. 18).[265] Shortly thereafter, thorium and uranium porphyrins **54** of the sandwich type were synthesized as well.[266–268]
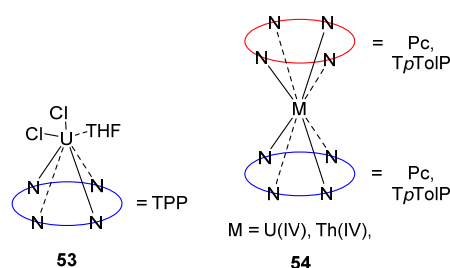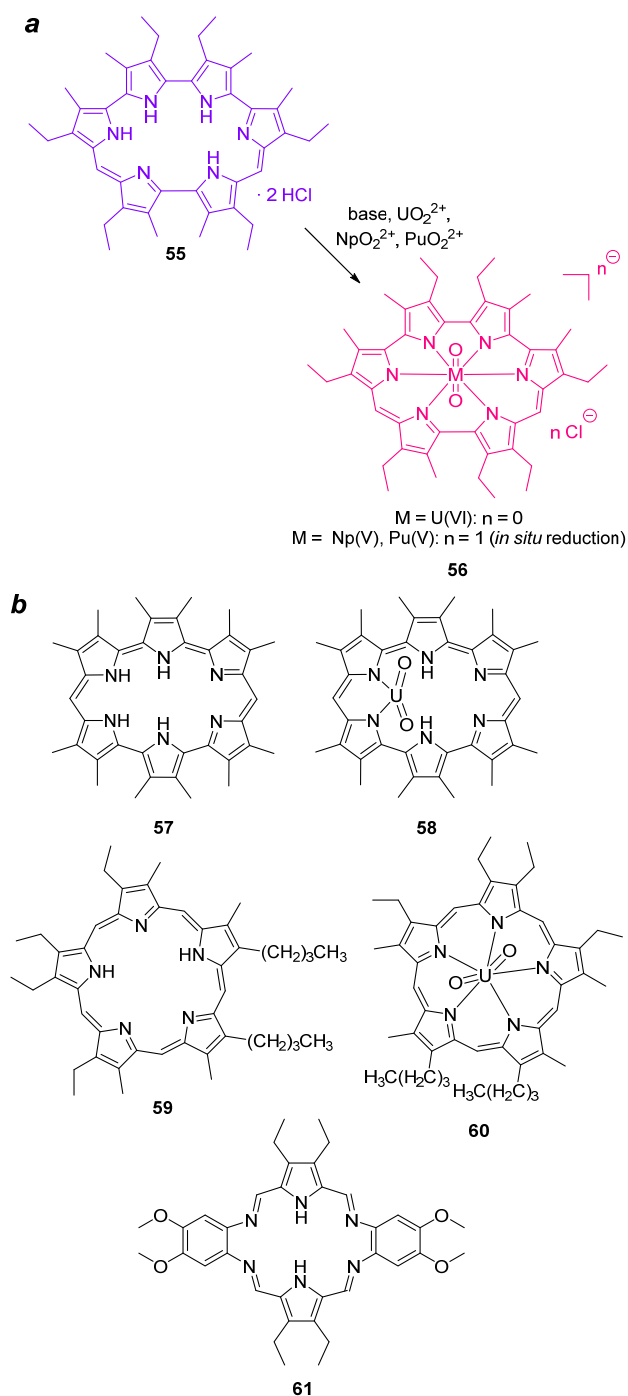

Fig. 18 Common structural motifs of actinide porphyrins. U(IV) compound **53** is a sitting-atop (SAT) complex, where the metal ion is 'sitting' on the porphyrin plane,[265] while **54** illustrates a square antiprism; Pc = phthalocyaninato, TPP = 5,10,15.20-tetraphenylporphyrinato, T*p*TolP = 5,10,15,20-tetrakis(*p*-tolyl)phenylporphyrinato.[266–268]

Aside from their ability to bind and potentially extract actinides from radiologically contaminated environments, porphyrins and related molecules may find application as sensors for radioactive material. Notably, Sessler *et al*. showed the potential of an expanded porphyrin, specifically the isoamethyrin-based macrocycle **55** as a naked-eye colorimetric actinide sensor (Fig. 19a).[269] The macrocycle provided detection of uranyl, neptunyl, and plutonyl species, undergoing a dramatic color change upon metal complexation. A later study involved the analysis of UO_2^{2+}, NpO_2^{2+}, and PuO_2^{2+} coordination by several expanded tetrapyrrole derivatives, including amethyrin **57**, isoamethyrin **55**, pentaphyrin **59**, and others (Fig. 19b).[270] These colorimetric studies revealed that **55** and **57** seemed to carry an inherent selectivity for neptunium, while the related Schiff base alaskaphyrin **61** coordinated plutonium preferentially. Such features may lead to portable and user-friendly actinide-specific sensors in the near future.

A more recent study by Ho *et al*. reported on the use of a porphyrinoid-containing nanoparticle for ppb detection of uranium *via* photoacoustic imaging.[271] Interestingly, the nonaromatic porphyrin analogue used herein underwent aromatization upon binding of uranyl. On the other hand, Hayes *et. al*. published that direct sensing of UO_2^{2+} and other actinides was achieved by tethering an isoamethyrin derivative to a fiber surface,[272] while incorporation into TentaGels has been described as well.[273] Such *in situ* experiments are particularly important for the development of new methods to decontaminate water, especially in conjunction with water-soluble metal-chelating tetrapyrroles.
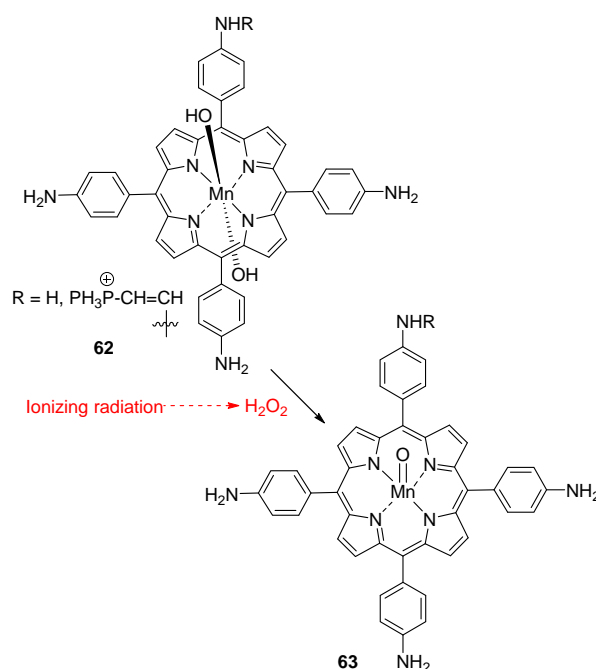
Fig. 19 Some expanded porphyrins and their actinide complexes. a) Isoamethyrin **55** was applied as a naked-eye colorimetric sensor for uranyl where formation of **56** resulted in a color change from violet to purple.[269] b) Alaskaphyrin **61** as well as macrocycles **55**, **57**, **59** and their metal complexes **56**, **58**, and **60** were among those studied by Sessler and coworkers for complexation of UO_2^{2+}, NpO_2^{2+}, and PuO_2^{2+}.[269,270]

Furthermore, Shu *et al*. demonstrated that carboxylporphyrin-terminated poly(*N*-isopropylacrylamide) was a highly sensitive and selective thermoresponsive fluorescent sensor for uranyl traces.[274] Zeyada and coworkers constructed an Au/Fe(III)TPP/porous silicon/Al heterojunction diode and studied the effect of γ irradiation on the electrical properties of the sensor.[275] Several parameters were found to be influenced by the irradiation dose,

suggesting this metalloporphyrin-based device may have an application as a γ-ray detector.

Mitigators for radiation damage Endothelial cells, DNA, and organelles are damaged on exposure to ionizing radiation. Such being the case, Vorotnikova and coworkers synthesized a family of compounds, which possess superoxide dismutase (SOD)-, catalase-, and peroxidase-like activity.[276] A range of manganese porphyrins acting as SOD/catalase mimetics were successfully tested for their ability to prevent apoptosis of epithelial cells after exposure to ionizing radiation *in vitro*. Future animal studies aim to show whether these compounds have the potential to protect against the effects of radiation, for example, due to a radiological accident or a terrorism scenario.

Ionizing radiation is known to cause overproduction of H_2O_2 in mitochondria with the concomitant induction of programmed cell death.[277] In this context, Stoyanovsky *et al*. tested the ability of manganese-containing porphyrin **62** to clear mitochondria of hydrogen peroxide, and it was found that in embryonic mouse cells, it reacted with the harmful compound, resulting in reduced mitochondrial apoptosis induced by γ rays (Fig. 20).

Fig. 20 Oxidation of manganese complex **62** by overproduced H_2O_2 (due to exposure to ionizing radiation) in mitochondrial environment yields **63**.[277]

Conclusions and outlook

All of these examples show that porphyrins, and their metal complexes in particular, as well as a number of related macrocycles,[278] offer rich opportunities for the development of portable yet high performance detectors in the light of anti-terrorism measures and beyond. This includes attractive applications stretching from the recognition, stabilization, or even disposal of nitroaromatic compounds and other explosives to as far

as the assay of fuels and propellants for security-related applications and the private sector.

Efforts have been made towards inexpensive porphyrinic CWA sensors for use by first responders and military personnel. Research has also been carried out on the binding and breakdown of toxic agents, ultimately providing a better understanding of substrate–porphyrin interactions. In addition, approaches towards prophylaxis and post-exposure treatment against CWAs using (metallated) porphyrins have emerged. Overall, this area is somewhat more developed in terms of practical applications compared to the BW arena.

Yet, there is high potential of metalloporphyrins and related macrocycles against infectious agents, microorganisms, and their products, and while past research has already provided a better understanding of such agents and their interaction with PSs, an ever-growing need to develop new countermeasures remains. This includes refinement of traditional approaches alike to outsmart the rapidly adapting and evolving landscape of BWAs to ensure global security.

Such new approaches will, as we have indicated, inevitably be carried out at the interface of natural science, engineering, medicine, and beyond to produce high-performance, cost-efficient, and compact devices that can hopefully easily be deployed by non-specialized personnel with low environmental impact.[279] At the same time, up-and-coming technologies for the military and the private sector may span from the use of tetrapyrroles in dosimeters,[280] in electromagnetic interference shields,[281] as pressure sensitive lumiphores,[282] and radar-absorbing materials to as far as NLO[202] for laser defense and PDT for battlefield sterilization, to name but a few. These and many other applications can only be envisioned due to the remarkable and tunable properties of porphyrins and their tight interplay with complexed metal ions.

We have also pointed at the potential of porphyrins for the defense community and for detection of radioisotopes and their decay products. It has been highlighted how tetrapyrroles and their metal complexes can be exploited as sensors for radioactive species and ionizing radiation. On the other hand, it is emerging that they are capable of counteracting the damage caused upon exposure to such species. Altogether, their catalytic activity, well developed chemistry, ability to mimic natural processes, and to complex almost any metal nominates them as facile candidates for decontamination and therapeutic use.

In light of the promising initial results outlined here for many areas of explosives detection and CBRN defense, the rising demand for new molecules and materials for the detection of — and against warfare agents justifies research into novel metalloporphyrins.

Lastly, a comment on research investments and spending. A reviewer suggested elaborating on governmental spending levels in this area. However, it is difficult to obtain detailed information on government budgets for research into security-related sensor technologies, CBRN defense, and similar to draw an international comparison. Still, a number of representative examples can provide insight into the level of governmental spending and interest in these areas. For example, in 2017, the Science and Technology Directorate (S&T), a component within the U.S. Department of Homeland Security (DHS), invested $962 million in research and development (R&D). This funded, for example, the development of countermeasures against chemical and biological threats, protection of infrastructure and transportation systems from explosives, etc.[284a] At the same time, the Domestic Nuclear Detection Office (DNOD), another child agency of the DHS, invested $63 million in R&D. The 2018 budget request for the Defense Advanced Research Projects Agency (DARPA), an agency of the U.S. Department of Defense (DoD), contains $30.2 million for 'basic photon science', including spectroscopy of CWAs, a total of $13.0 million for BW defense, $24.3 million for 'functional materials and devices' to detect, e.g., explosives, and $24.2 million for 'chemical processing for force protection', involving, for example, the development of new remediation systems for CWAs on site.[284b] Even more significantly, the 2015–2018 call for 'Fundamental Research to Counter Weapons of Mass Destruction' from the DoD and the Defense Threat Reduction Agency (DTRA) has a funding level of $ 500 million.[284c]

On the other hand, the EU-funded framework program Horizon 2020 has an estimated total budget of €1.7 billon (2014–2020) for a call 'Secure Societies', which funds research into, e.g., methods to detect weapons, explosives, and toxic substances.[284d,e] All these figures account for major governmental – let alone the private sector – investments and add further gravitas to the brisance of the topic. Clearly, research active countries see this as a societal challenge and major task for scientists. Researchers should engage in work for 'secure societies' and the budget figures point to a science-driven revenue stream that promotes a safe and healthy existence. Perhaps one can go as far as to say that ethical and conscientious scientists will never engage in the development of new threats or WMD[285] but also have a duty to actively counteract them through R&D.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Author group photo

(MK, CP, MOS; left to right)

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Marc Kielmann, M.Sc., studied chemistry (B.Sc.) and medicinal and natural product chemistry (M.Sc.) at the Gottfried Wilhelm Leibniz Universität Hannover after his military service in the German Air Force. During his master's degree, he did research on ferrocene/ferrocenium chemistry under the supervision of Prof. Dr. Holger Butenschön and remained faithful to intensely colored compounds thereafter. He is currently a 3rd year Ph.D. student at Trinity College Dublin, where he works on the synthesis of nonplanar porphyrins for use as organocatalysts and sensors.

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Caroline Prior is a final year Medicinal Chemistry student in Trinity College Dublin. She is currently carrying out her research project in the Senge group on bisporphyrin arrays as metal-free anion sensors. Her research interests include the synthesis of porphyrins as potential sensors, as well as for medical applications.

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Mathias O. Senge, Dipl.-Chem., M.A., Dr rer. nat., F.T.C.D., did serve in the early 1980s in the (West) German Luftwaffe and then studied chemistry and biochemistry in Freiburg, Amherst, Marburg, and Lincoln. After a Ph.D. from the Philipps Universität Marburg (1989) and postdoctoral studies with K. M. Smith at UC Davis he received his habilitation in Organic Chemistry in 1996 from the Freie Universität Berlin. From 1996 on he was a Heisenberg fellow at FU Berlin and UC Davis and held visiting professorships in Greifswald and Potsdam. In 2002 he was appointed Professor of Organic Chemistry at the Universität Potsdam and since 2005 holds the Chair of Organic Chemistry at Trinity College Dublin. He was the recipient of fellowships from the Studienstiftung des Deutschen Volkes, the Deutsche Forschungsgemeinschaft, and Science Foundation Ireland (Research Professor 2005–2009). His interests are synthetic organic chemistry, the (bio)chemistry of tetrapyrroles, photobiology and photomedicine, photoactive materials, structural chemistry, and history and philosophy of science.

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