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Review

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Tetraphenylethylene-Based AIE-Active Probes for Sensing Applications

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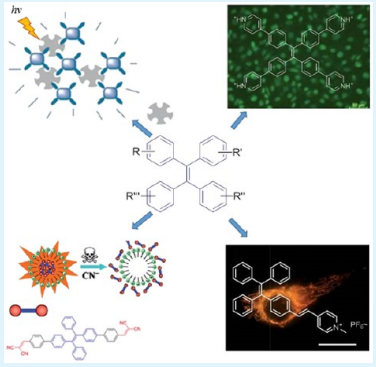
ABSTRACT: This Review provides a comprehensive analysis of recent development in the field of aggregation-induced emission (AIE)-active tetraphenylethylene (TPE) luminophores and their applications in biomolecular science. It begins with a discussion of the diverse range of structural motifs that have found particular applications in sensing, and demonstrates that TPE structures and their derivatives have been used for a diverse range of analytes such as such as H^+, anions, cations, heavy metals, organic volatiles, and toxic gases. Advances are discussed in depth where TPE is utilized as a mechano-luminescent material in bioinspired receptor units with specificity for analytes for such as glucose or RNA. The rapid advances in sensor research make this summary of recent developments in AIE-active TPE luminophores timely, in order to disseminate the advantages of these materials for sensing of analytes in solution, as well as the importance of solid and aggregated states in controlling sensing behavior.



KEYWORDS: *sensors, AIE-active luminophore, analytes, mechanoluminescent material, biosensor*

1. INTRODUCTION

One of the most remarkable abilities of fluorescence microscopy is that it can provide an insight into an understanding of the intracellular metabolism of live organisms. Fluorescence microscopy techniques not only allow imaging of unicellular organisms and individual cells from multicellular organisms, but also imaging of encapsulated cells in 3D arrays and ex vivo models. This fluorescence technique with the appropriate instrumentation offers cell-based screening of whole organisms, including bacteria, yeast, plants, flies, worms, fish, and mice.[1,2]

For mapping the total metal content in cells and organisms, fluorescence microscopy in combination with the supplementary analytical techniques offers scientists the opportunity to address fundamental questions about cellular metal homeostasis. In the recent years, luminophores which strongly emit in the aggregated and solid state have widely been studied for the functionalization of small objects such as cancer cells, indicating potential for use in practical biomedical applications. As such, the development of well-organized luminescent materials that display aggregation-induced emission (AIE) and solid-state emission is of interest not only from a technological perspective, but also in biological science.[3] The reason for this is that AIE-active molecules are useful for fluorescence microscopy which is an indispensable tool for cell and molecular biology, and is compatible with visualization of living specimens.

Since the concept was originally developed in 2001,[3] AIE behavior has attracted the continued attention of researchers, as the phenomenon is the opposite of the more common aggregation-caused quenching (ACQ)[4] encountered in conventional luminophores/fluorophores. The conventional ACQ effect occurs in porphyrins[5] and naphthalenediimides[6] due to aggregation in the condensed phase. The mechanism behind the AIE effect has been resolved, and is attributed to the restriction of intramolecular rotation (RIR).[7,8] This phenomenon is important because the luminophores are commonly used as solid films for real-world applications such as organic light-emitting diodes (OLEDs)[9] or aggregates with a high contrast for chemo-imaging and bio-imaging.[10,11] In the literature there have been various reports on the chemical, physical, and engineering approaches undertaken to study luminophore aggregation, which includes attachment of bulky alicyclics, encapsulation by amphiphilic groups or combining with polymers to achieve AIE-active luminophores.[12,13]

Among the AIE-active luminophores that have found utility as mechanoluminescent materials, tetraphenylethylene (TPE) derivatives have attracted significant attention due to their capability of self-organization,[14] and their ability to be conveniently incorporated into larger multicomponent assemblies with ACQ fluorophores. The functionalization of TPE can be undertaken with a receptor whose absorption and emission properties vary upon the binding of guests (anions and cations) in either polar or nonpolar solvents. Therefore, new AIE luminogens can be achieved through functionalization or decoration of TPE with receptor moieties, leading to a new AIE luminogen with a range of applications. For example, this

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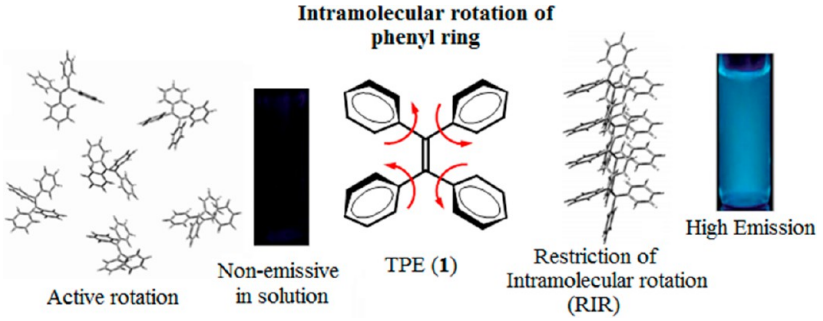

Figure 1. AIE phenomenon of the propeller-shaped luminogen TPE through RIR. Adapted with permission from ref 8. Copyright 2014 Royal Society of Chemistry.

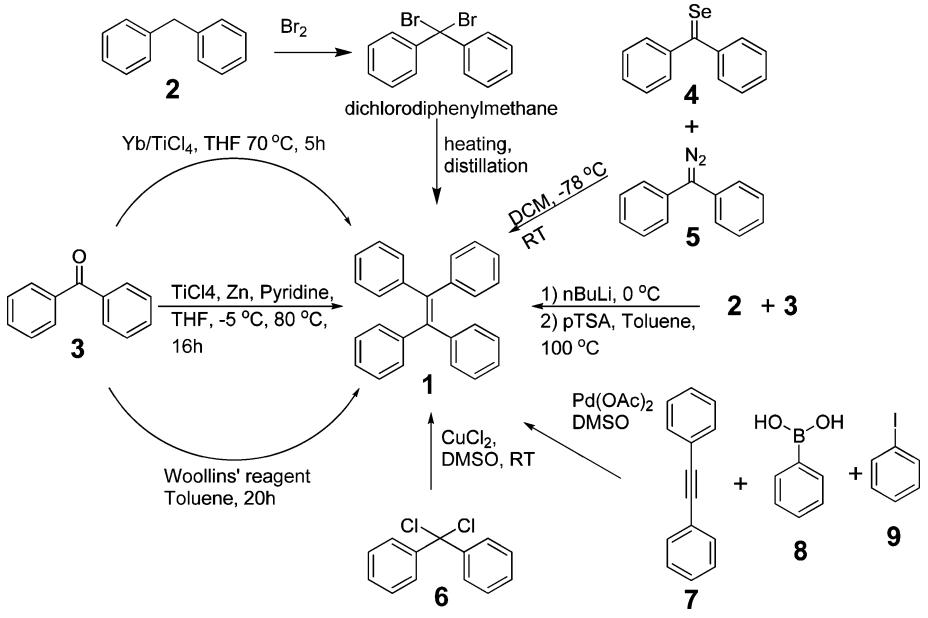

Figure 2. Synthetic routes for the preparation of the tetraphenylethylene (TPE, **1**).

strategy was used to functionalize TPE with anthracene (An), pyrene (Py), carbazole (Cz), and triphenylamine (TPA), generating a series of TPE−An, TPE−Py, TPE−Cz, and TPE−TPA AIE luminogens with very high fluorescence quantum yields of up to 100% in the resulting films.[15]

Designing luminogens as probes to monitor a biological process or as biological agents requires a detailed understanding of both the probe behavior and the analyte of interest. Although some luminogenic molecules can be used in their solubilized state, for example where only the pH or a small ion is to be monitored, a luminescence signal is often required when the probe is associated with a more complex target analyte.[16]

The majority of conventional probes may fail in terms of selectivity due to the troublesome ACQ effect, where molecules in aggregates quench the fluorescent emission. TPE derivatives that take advantage of the AIE effect may thus offer a new way to engineer bioprobe molecules, as TPE luminophores are nonfluorescent in the dissolved state in solution but become highly emissive in the aggregated and solid states. Taking advantage of this, various groups have used TPE and derivatives for various biological applications such as bioprobes,[17] chemosensors,[18] cell imaging, and cell labeling.[19] In this Review we focus on TPE derivatives and their applications in sensing a range of analytes such as pH, anions, cations, heavy metals, organic volatiles, toxic gases, and biomolecules (DNA, RNA, glucose, etc.). This Review begins with a summary of fundamental research efforts on the chemistry of AIE-active TPE molecules, with an emphasis on the most recent advances, leading to a description of key advances in the supramolecular chemistry and related sensing applications of TPE derivatives

2. AIE-ACTIVE TPE LUMINOGEN

The nonplanar TPE molecule is a propeller-shaped AIE-active luminogen bearing four phenyl rings around a central C═C double bond that is nonemissive in the dissolved state, mainly due to RIR, but is highly fluorescent in solid and aggregated states.[8] Nonluminescence of TPE in solution is due to the free rotation of the four phenyl rings, which provides a nonradiative relaxation pathway for excited electrons. In aggregates and the solid state, the intramolecular rotation of these phenyl rings are inhibited, preventing nonradiative relaxation, and resulting in strong photoluminescence as illustrated in Figure 1.

3. GENERAL SYNTHESES

In 1888, Boissieu described the first synthetic method to form TPE (**1**, see Figure 2),[20] which involved bromination of diphenylmethane (**2**) to give dibromodiphenylmethane, followed by heating, distillation, and recrystallization from benzene to obtain **1** in reasonable yield. Wang et al. reported the most common method for the preparation of **1** by using a simple

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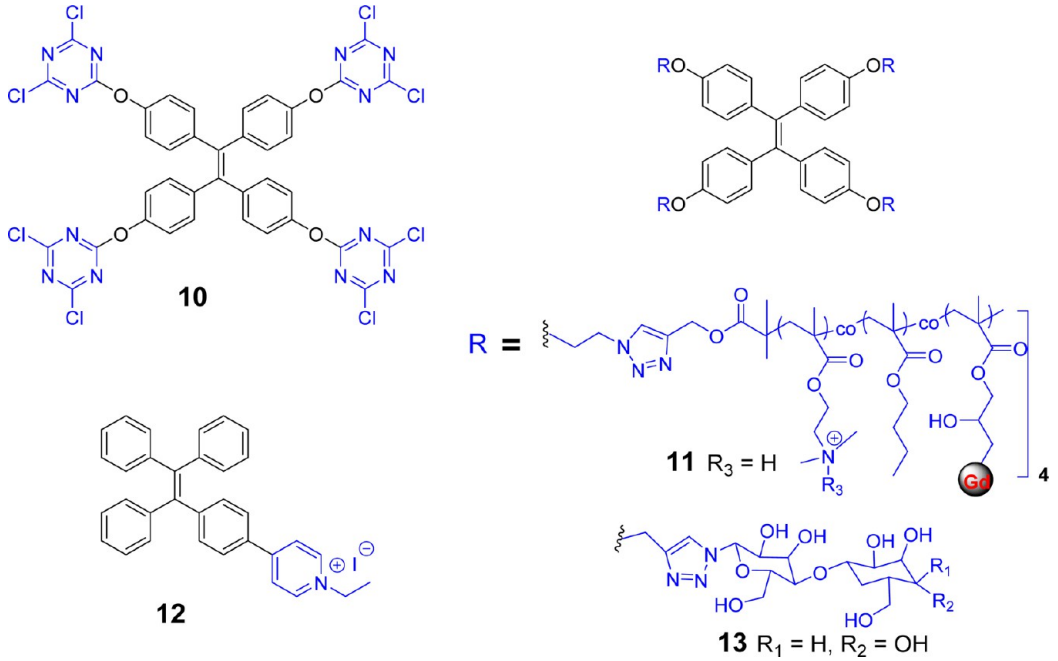

Figure 3. TPE derivatives used for infectious disease sensing.

Knoevenagel condensation reaction. Typically, the reaction of *n*-BuLi with **2** at 0 °C followed by the addition of benzophenone (**3**) to form a tertiary alcohol, followed by dehydration using *p*-toluenesulfonic acid (pTSA), gives a white solid in 84% yield.[21] McMurry coupling is another widely used method in which $TiCl_4$ and Zn powder are used in dry THF at −5 °C to mediate the reductive coupling of **3** with 70% yield.[22] This method has been utilized to synthesize both symmetrical and asymmetrical TPE derivatives. Woollins et al. reported the synthesis of **1** in 100% yield by heating 2 equiv of ketone in toluene in the presence of Woollins's reagent.[23] Similarly, the use of ytterbium in combination with $TiCl_4$ in THF,[24] and a Heck reaction using a phosphapalladacycle catalyst,[25] were also shown to be very effective routes for the production of TPE in ∼99% yield. In another report, Otura et al. described the reaction of selenobenzophenone (**4**) with diphenyldiazomethane (**5**) in DCM at −78 °C to afford a 76% yield of **1**. Furthermore, they have shown that the reaction of benzophenone hydrazone with diselenium dibromide using triethylamine at room temperature gives TPE in 81% yield.[26] Tezuka et al. reported copper-catalyzed self-coupling of dichlorodiphenylmethane (**6**) in DMSO at room temperature to obtain **1** in 97% yield.[27] Another approach to synthesize TPE in 75% yield is by the double arylation reaction of diphenylacetylene (**7**) using phenylboronic acid (**8**) and iodobenzene (**9**) in the presence of palladium(II) acetate ($Pd(OAc)_2$) in DMSO.[28]

4. BIOSENSORS

In studies of biological systems, it is difficult to develop chemosensors of high sensitivity and selectivity due to the complexity and the high salt concentration of natural organisms. Infectious diseases pose a significant challenge to human health due to bacterial contamination of food, water, and air. One of the most common bacterial infections affecting humans, which causes intestinal and extra-intestinal problems such as diarrhea, food poisoning, and urinary tract infections, is due to *Escherichia coli*.[29] Therefore, early-stage treatment for these infections would be beneficial to arrest the progression of the diseases. Traditional urine pathogenic bacteria culture analysis suffers from various drawbacks such as low sensitivity and a time-consuming procedure with tedious steps, which means it is not a valid approach for the rapid screening of susceptible patients. To detect urinary tract infections, lipopolysaccharide (LPS) is widely used as a biomarker,[30] and LPS in clinical detection methods relies on the enzymatic limulus amebocyte lysate (LAL) assay. The LAL assay is very sensitive but is highly dependent on key conditions such as pH and temperature.[31]

In this regard, Lei et al.[32] described the LPS analysis of urine samples using the fluorescence turn-on technique. It is important to note that LPSs are highly negatively charged due to the phosphorylated glucosamine sugars and the two 2-keto-3-deoxyoctonate units, allowing them to be efficiently coupled to positively charged luminophores. Based on this observation, Zhao and colleagues reported for the first time the use of electrospun fibrous mats with a conjugated TPE fluorophore (**10**, Figure 3) as a turn-on fluorescent sensor for detection of *E. coli*.[33] They have also fabricated test strips based on mannose-conjugated PSMA fibers after exposure to *E. coli* of different concentrations. This method provides a potential device for visual detection of bacteria concentrations as low as 102 CFU/mL^{-1} in a matter of minutes. The selectivity of the sensor toward *E. coli* was confirmed by adding bovine serum albumin, glucose, or both of them into the bacterial suspension, which led to no significant changes in the fluorescence intensity, confirming selectivity.

A star-shaped four-arm amphiphilic copolymer dual-modality sensing probe (fluorescence and MR), bearing AIE-active TPE core moieties (TPE-*star*-P(DMA-*co*-BMA-*co*-Gd), **11**) was designed and used detection of bacteria in aqueous media.[34] The fluorometric and MR imaging modes exhibited detection limits of $\sim 8.5 \times 10^5$ and $\sim 5 \times 10^3$ CFU mL^{-1} for Gram-negative bacteria *E. coli* cells, respectively. Importantly, high selectivity was observed for bacterial in the presence of human red blood cells. More recently, an AIE-active TPE luminophore was prepared bearing a cationic pyridinium moiety (TPEPyE, **12**), which was soluble in water but formed aggregates upon binding to

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negatively charged LPS, leading to fluorescence turn-on.[35] The TPEPyE-based luminophore was able to detect LPS in artificial urine samples with good selectivity and nanomolar sensitivity with a detection limit of ca. 370 pM (3.7 ng/mL) in PBS buffer. TPEPyE **12** is also able to discriminate between Gram-positive bacteria (*Staphylococcus aureus*) and Gram-negative bacteria (*E. coli*).

The primary virulence factor of cholera is chloera toxin (CT), which is also a bacterium target. Hu et al. reported the synthesis of an AIE-active TPE derivative bearing four lactose moieties (**13**) by reacting propargyl-attached TPE with azido-functionalized lactose using a copper(I)-catalyzed "click reaction".[36] The lactose functionality was chosen to improve the water solubility and biocompatibility, as well as to provide binding sites for CT (Figure 4). Upon addition of CT into an aqueous solution of **13**,

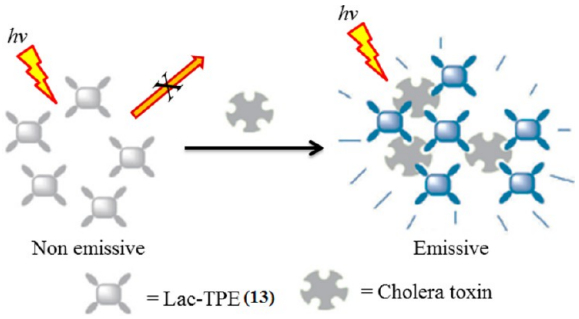

Figure 4. Graphical representation of fluorescence "turn-on" assay for CT with **13** based on the AIE effect for cholera toxin. Adapted with permission from ref 36. Copyright 2011 Wiley-VCH.

the fluorescence intensity significantly increased due to RIR of the phenyl groups in the aggregated state of **13**, which blocks the nonradiative pathway of **13**. This probe can detect CT in aqueous media with the detection limit as low as 1.0 μM.

DNA/RNA sensing is of significant importance in fundamental biological and biomedical research including clinical disease diagnostics, drug discovery, and gene delivery, to name a few.[37] Among the methods of sensing/translation of DNA, fluorescence turn-on sensing has become prominent because of its outstanding selectivity, ultrasensitivity, and real-time viability, attracting significant attention for sensing of DNA/RNA.[38] However, few of the reported nucleic acid dyes have exhibited very low sensitivity and selectivity in water, and some suffer from drawbacks such as being a biohazard.[39]

Nevertheless, traditional nucleic molecules such as ethidium bromide (EtBr), DAPI, TOTO, and Hoechst-like fluorescent dyes only functioned with double-strand DNA (dsDNA) through intercalation or groove binding,[40,41] and they failed to bind with single-strand DNA (ssDNA) due to the absence of the secondary structure in ssDNA as illustrated in Figure 5a. Recently, Tang et al. developed a series of TPE derivatives as "switch-on" DNA probes for real-time monitoring of DNA folding using AIE of TPE derivatives.[42,43] On the basis of the AIE principle, "light-up" DNA chemosensors were developed by Ding et al., who used TPE-modified molecules with one, two, three, and four triazole-[12]aneN_3 recognition sites, which acted as efficient nucleic acid "light up" and condensing agents.[44] Complete retardation of plasmid DNA was achieved at concentrations of 25 μM (**14**; Figure 6), 8 μM (for **15** and **16**), and 4 μM (**17**) and these compounds showed better sensitivity toward longer DNA, with compound **17** showing promising performance.

Wang et al. designed and synthesized the TPE derivatives **18** and **19** incorporating diaminopurine, a base analogue that can pair with other DNA bases, and can be used as a fluorescence indicator−displacement sensor for DNA detection.[45] Hydrogen-bonding or electrostatic interactions are the driving force for the interaction between DNA for **18** or **19**, which lead to the aggregation of TPE-based compounds, causing fluorescence enhancement. Moreover, these probes show highly selectivity for poly deoxyadenylic acid over other polynucleotides. TPE can be also functionalized with thymine, another base analogue that can pair with DNA through hydrogen bonding, to develop a new compound, TPE-T (**20**), which was used as a fluorescence biosensor for differentiating between ssDNA and dsDNA as shown in Figure 5b.[46]

The Liu group synthesized the propeller-structured BTPETTQ based on a donor−acceptor−donor (D-A-D) design using two TPE units as an electron donor and 4,9-di(5-bromothiophen-2-yl)thiadiazoloquinoxaline as an electron acceptor to for photoacoustic imaging with a good photothermal conversion efficiency (40%).[47] BTPETTQ exhibits very good NIR absorption and weak fluorescence, and a high photoacoustic signal in solution for molecular species. Furthermore, BTPETTQ contained in a polymeric matrix also gives an excellent photoacoustic signal, which is better than that obtained with widely used gold nanorods. BTPETTQ was also shown to be effective for photothermal therapy, i.e., the effective killing of HeLa cells upon NIR (808 nm) laser irradiation. Thus, the D-A-D design based on AIE-active TPE demonstrated the great potential of compounds with propeller structures for photoacoustic imaging and photothermal therapy applications. However, one limitation is that their solubility in water is very low.

Recently, we reported on the synthesis of the first water-soluble TPE derivative bearing four sulfonate functional groups on the core as a sodium salt, and demonstrated its AIE characteristics by adding various organic solvents into an aqueous solution of the compound. This phenomenon is the reverse procedure of traditional AIE-active TPE derivatives. The water-soluble SO_4-TPE was shown to be weakly emissive in water, but emits strongly upon addition of THF which caused aggregation.[48]

In this direction, Dong et al. synthesized three water-soluble TPE derivatives functionalized with trimethylamine of varying side-chain lengths, and demonstrated their optical properties under a range of conditions. The study clearly showed that the quantum yield of TPE upon aggregation in the presence of heparin varies with the length of the side chains.[49]

In 2014, the Tang group synthesized two fluorene-based fluorescent TPE probes for heparin detection.[50] In their study, they revealed that the AIE-active fluorene-based TPE derivative shows a performance than the ACQ probe used for heparin detection in terms of sensitivity and selectivity, with a detection limit of 10 nM. This study showed the potential for an AIE-active probe to monitor heparin during surgery or therapy.

We recently reported on the synthesis of (TPy-TPE, **21**), a tetrapyridinium derivative of TPE that is water soluble due to being cationic, and was used as a fluorescent visualizer for cell imaging and also as a DNA marker in a stoichiometric ratio (Figure 7).[17] This derivative was shown to be superior to standard dyes such as EtBr as it did not suffer from bleed through problems, which was attributed to a narrow fluorescence window of emission. The TPy-TPE luminogen was also shown to be nontoxic to cells at ~15 μM concentration, as no damage was

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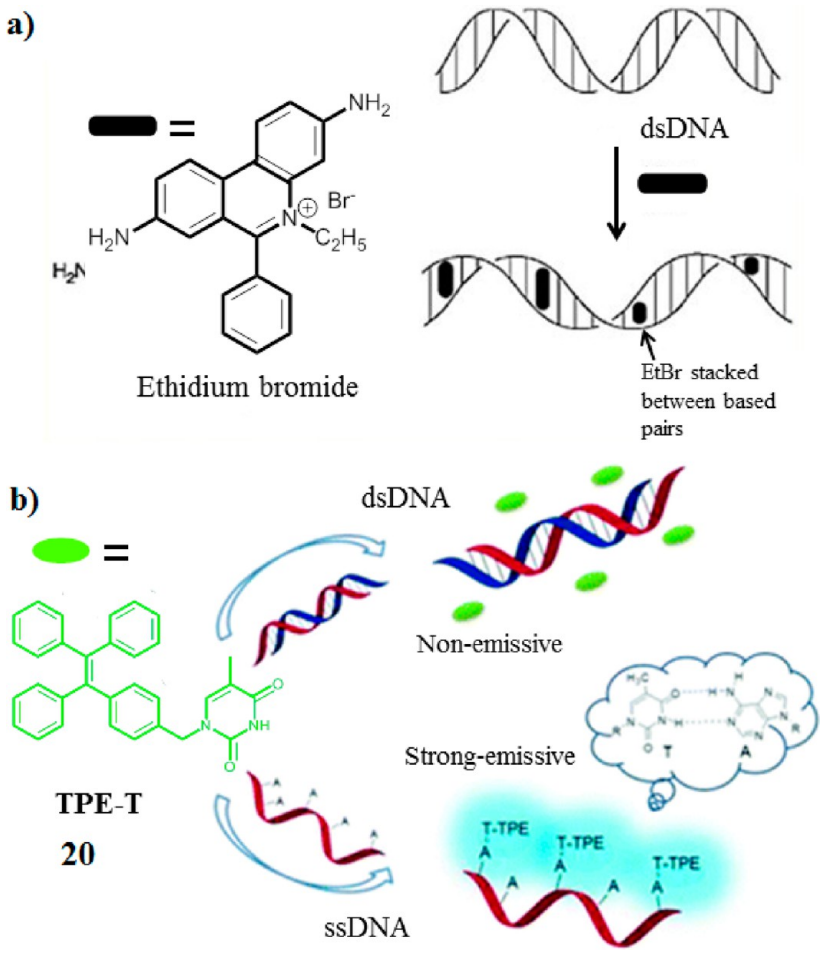

Figure 5. Illustration of the binding mechanism to ssDNA and dsDNA using (a) a conventional fluorescent dye (EtBr) and (b) the new compound TPE-T (**20**).

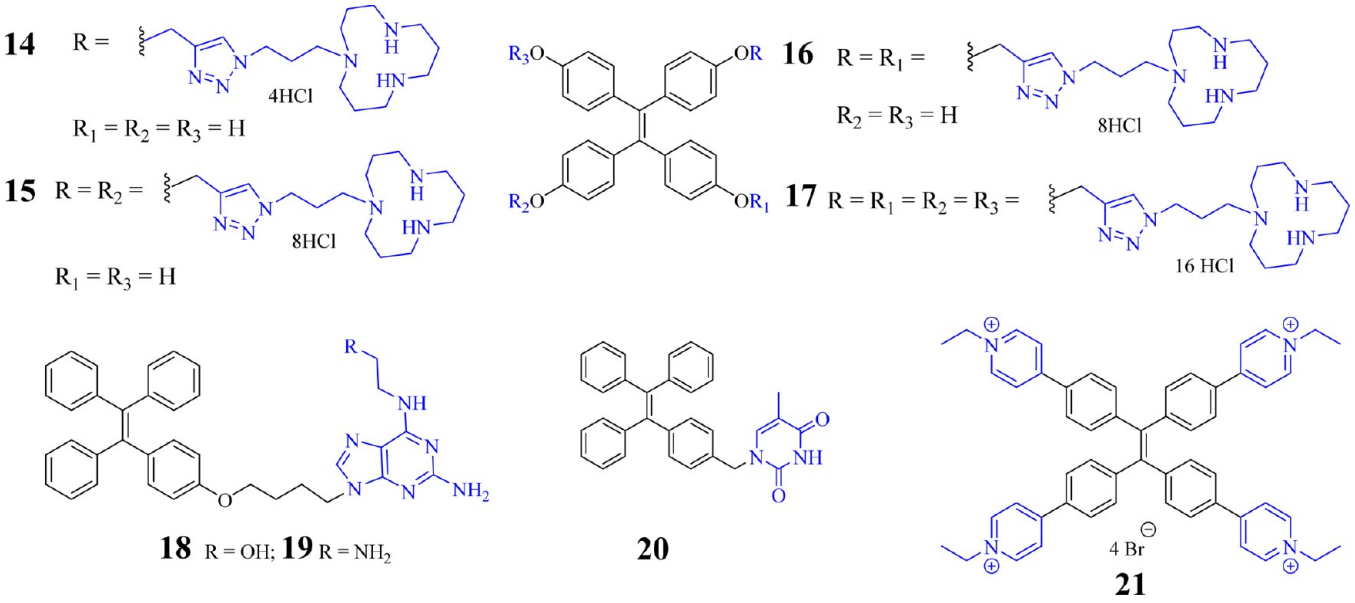

Figure 6. TPE-based compounds for detection and sensing of biological molecules such as DNA/RNA.

observed on cell membranes, which makes it a promising biocompatible material. The simple synthetic protocol used to prepare this dye makes it very promising for future cell imaging studies and for use as a DNA marker.

TPE derivatives are not only used as probes for detection of DNA, they can also conjugate with DNA to act as fluorescent biosensors. Min et al. synthesized the TPE-DNA conjugate (**22**) for ultrasensitive one-pot microRNA detection to overcome

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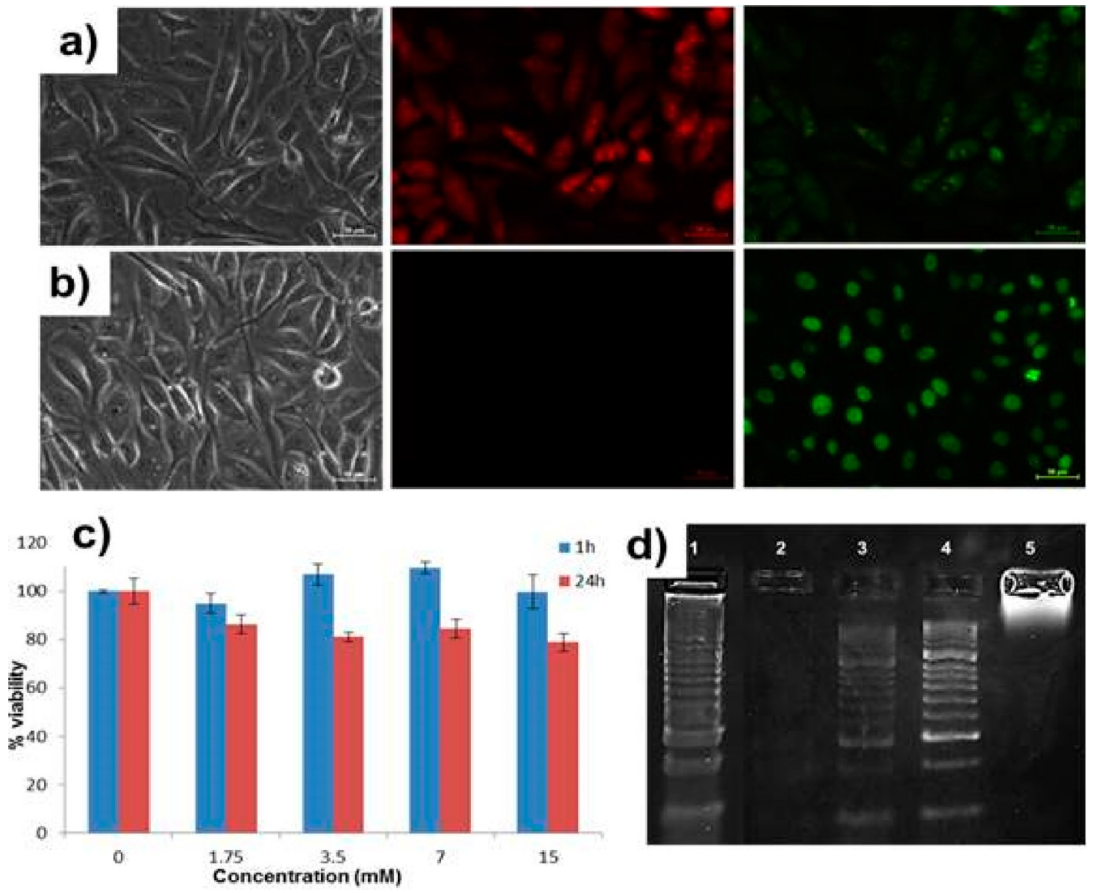

Figure 7. Cellular imaging, cytotoxicity, and DNA binding ability of luminogen **21**: (a) propidium iodide (PI)-stained (red), bleed-though (green), and unstained (left) cells; (b) PC-3 cells (left) stained with **21** (green) do not bleed through in the red channel (middle); (c) dose- and time-dependent cytotoxicity in PC-3 cells; and (d) 1, DNA marker stained with EtBr, 2, DNA marker with no stain, 3, DNA marker stained with 1 μM luminogen, and 4, DNA marker stained with 5 μM **21** with no DNA sample proteins in the cell membrane. The scale bars in (a) and (b) are 50 μm. Adapted with permission from ref 17. Copyright 2016 Royal Australian Chemical Society.

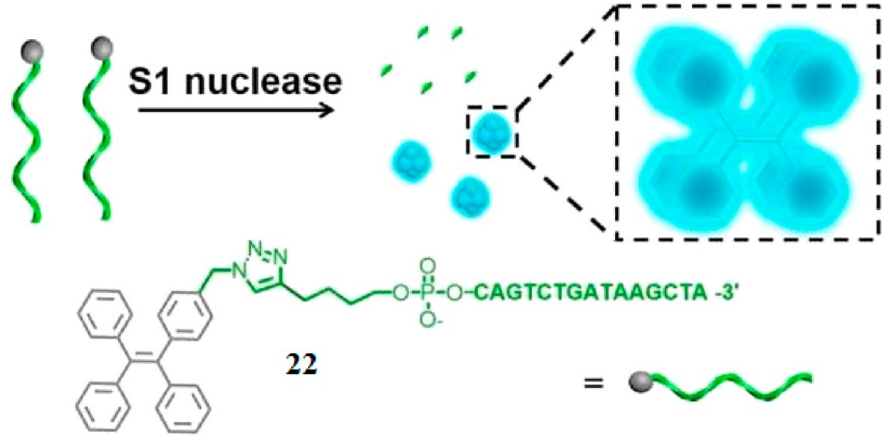

Figure 8. Mechanism for ultrasensitive one-pot microRNA detection by TPE-DNA conjugate **22**. Adapted with permission from ref 51. Copyright 2015 American Chemical Society.

limitations in microRNA detection (Figure 8).[51] The high specificity of the proposed assay is suitable for the direct detection of microRNA from bladder cancer patients using their urine samples. More specifically, 1 pM miR-21 can be detected within 40 min at 37 °C, and 10 pM (about 300 molecules in 50 μL) miR-21 could be discriminated in 7 days at 4 °C. This outstanding specificity of the assay based on TPE-DNA conjugates was demonstrated with 21 urine samples. Apart from the sensitivity and specificity, the reported assay benefits from a one-pot microRNA detection procedure and enables cycle amplification for ultrasensitive detection.

Pyrophosphate (PPi) is a biological anion involved in many biochemical reactions, including hydrolysis of ATP, DNA polymerization, as well as other metabolic processes.[52,53] Therefore, the development of biosensing probes for selective detection of PPi has attracted immense interest. Although many

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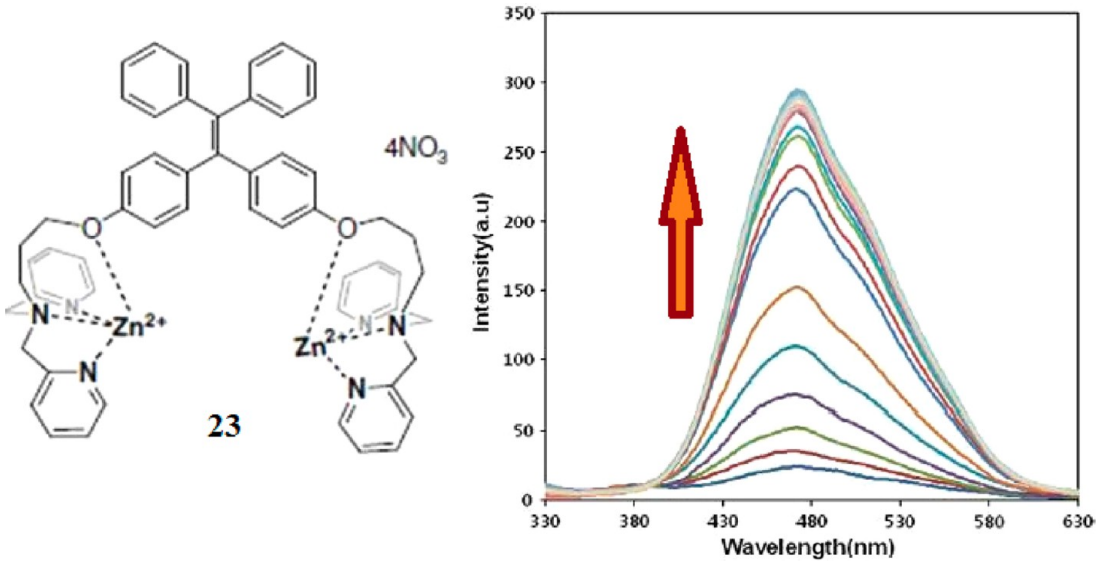

Figure 9. Changes in the fluorescence emission spectra of **23** by 1−2Zn (100 μM, λ_{ex} = 320 nm) upon the addition of PPi (sodium salt) in H_2O/DMSO (10:1, v/v) at 25 °C. Adapted with permission from ref 60. Copyright 2010 Elsevier.

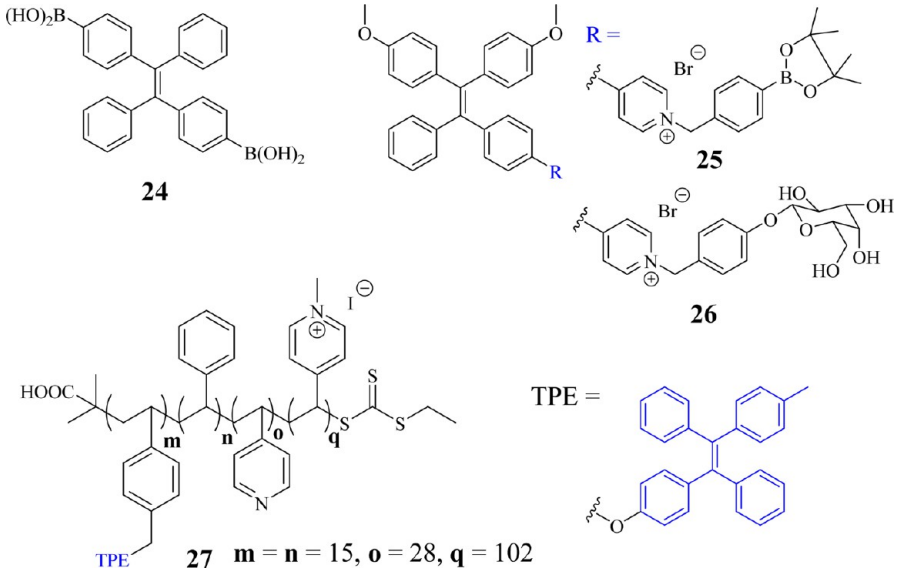

Figure 10. TPE-based AIE-active fluorescent probes for the detection of biologically active molecules.

techniques have been employed to recognize PPi such as the use of ion-selective electrodes, there is a need to find alternative methods with improved selectivity and sensitivity analysis.[54−59] Park and Hong developed a new TPE-based fluorescent sensor to detect PPi called 1−2Zn (**23**).[60] Compound **23** was synthesized by the S_N2 reaction of a TPE derivative with 2,2′-dipicolylamine in the presence of K_2CO_3 and KI in acetonitrile at reflux. The fluorescence enhancement of compound **23** upon addition of PPi was attributed to binding of PPi to 1−2Zn, which restricted the intramolecular rotation of the phenyl rings in **23**. Figure 9 shows the "turn-on" fluorescence emission of this TPE-based chemosensor as a function of concentration of PPi. It also exhibited good selectivity toward PPi over AMP and ATP.

It is well known that glucose is an important biomolecule for living organisms as well as a universal fuel for many biological processes. Therefore, the probe which can selectively detect glucose has been a major focus of research for many years.[60] Although there are several methods employed to detect glucose such as a chemical approach,[61−64] or fluorometric detection,[65,66] these glucose sensors tend to have relatively low selectivity. To meet this challenge, Tang's group developed a "light-up" biosensor for glucose in aqueous media.[67] This glucose probe was synthesized by functionalization of TPE with two boronic acid units to obtain TPE-diboronic acid (**15**; Figure 10). The emission from **24** was greatly increased upon addition of glucose because of RIR of the phenyl rotors of TPE by formation of the oligomer. High selectivity of **24** toward glucose over fructose, galactose, or mannose was observed, as these analytes are unable to oligomerize with **24**. In another study, Hu et al. reported a new fluorescence "turn-on" sensor for selective detection of glucose by incorporation of TPE with an *N*-4-(benzyl boronic pinacol ester) pyridinium bromide unit to obtain **25**.[68] By taking advantage of cascade enzymatic and chemical reactions between compound **25** with D-glucose, **25** was employed as a fluorescence probe for detection of glucose with a concentration as low as 3 μM. As expected, this sensor also showed good selectivity toward

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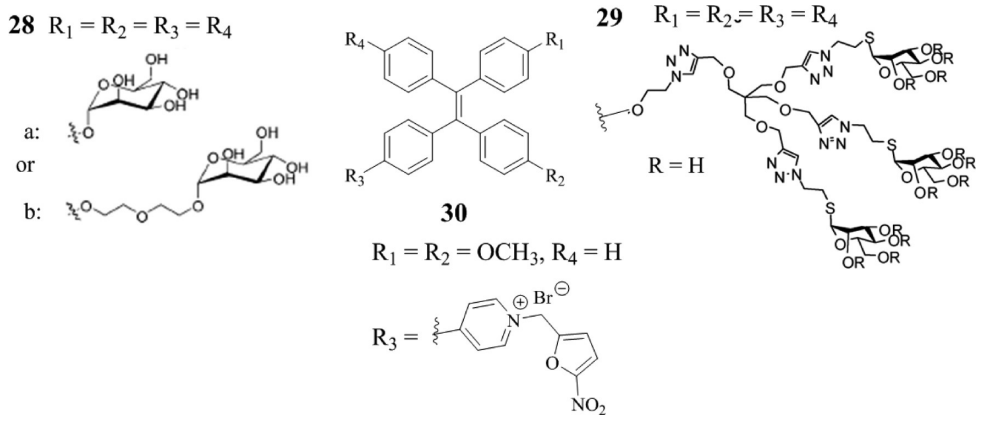

Figure 11. TPE-based compounds for proteins and lectin sensing.

glucose over fructose, galactose, and mannose. In a similar report, Tang and co-workers described the use of TPE bearing a positively charged pyridinium pendant in conjugation with a substrate of β-galactosidase (Gal) **26** to give the fluorophore some solubility in water to detect Hg^{2+} in both aqueous solution and living cells.[69] Typically, TPE-Gal was cleaved in the presence of β-galactosidase, and the β-galactopyranoside resulted in a phenolate intermediate, leading to spontaneous removal of *p*-quinone-methide to generate pyridine-substituted TPE. This obtained derivative is insoluble in aqueous solution, leading to aggregation and turn-on of the fluorescence. TPE-Gal has unique advantages over traditional fluorophores, including the ACQ effect in aggregation, high specificity toward β-galactosidase, high cell permeability, and low cytotoxicity. Furthermore, TPE-Gal can be used in living cells, making it very promising for cancer diagnosis.

TPE can be also incorporated into a polymeric matrix and used as fluorescence probe to recognize glucose in aqueous solution. The block amphiphilic copolymer **27** was obtained from a series of copolymeric reactions between TPE moieties, *S*-1-ethyl-*S*′-(α,α′-dimethyl-α′′-acetic acid) trithiocarbonate (EDMAT), and 2,2-azoisobutyronitrile (AIBN).[70] The copolymer **27** was then converted into polymeric micelles exhibiting comparatively strong fluorescence emission, and by heating and cooling the properties could be tuned. The fluorescent micelles of copolymer **27** were successfully employed for the detection of glucose in water by combination with two consecutive reactions, the first being cascaded enzymatic oxidation of glucose with GOx, followed by chemical oxidation of I^- by H_2O_2.

Protein−carbohydrate interactions facilitate a variety of biological process, such as trafficking, cell adhesion, cell−cell recognition, differentiation, signaling between cells, cellular metastasis, and viral or bacterial infections.[71] Therefore, the development of sensitive and selective protein detection is important in the fields of biological, medical, and environmental science. Various methods have been reported for the detection of proteins such as carbohydrate-binding with proteins, lectins, bacteria, and viruses.[72−74] However, these methods are not sufficiently sensitive in many cases for the trace detection of these analytes. In order to overcome this issue, TPE-based fluorescence turn-on sensing was developed for the first time in 2001.[75] Sanji's group reported mannose-substituted TPEs **28** for the selective detection of lectins (Figure 11). Typically, a mixture of the mannose-TPE conjugates with lectins displays an intense blue emission upon aggregation within a few seconds in a buffer solution. The conjugates show highly selective sensing for concanavalin A (Con A) with a detection limit as low as 20 nM, but do not respond to a galactose-binding lectin and PNA. Importantly, even Con A recognition is not observed even in the presence of proteins in a mixture. The TPE unit can be also conjugated with glycoside clusters for turn-on fluorescence sensing of lectins. In another report, Wang et al. designed and synthesized four TPE-based glyco-conjugates (**29**) via Cu(I)-catalyzed "click reaction" ligation and utilized then for biosensing of carbohydrate−proteins (Figure 11).[76]

Figure 12 illustrates the sensing mechanism of **29** for lectin, with emission-enhanced aggregation resulting from precise

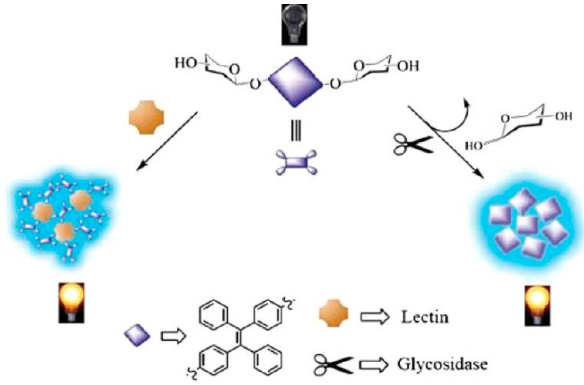

Figure 12. Mechanism of TPE-based artificial glyco-conjugates (**29**) as AIE fluorescent probes via carbohydrate−protein interactions. Adapted with permission from ref 76. Copyright 2011 Royal Society of Chemistry.

carbohydrate−lectin binding and selective glycosidase-induced hydrolysis.[76] The fluorescence emission enhancement of **29** is observed for Con A at a 1.0 μM concentration. However, no substantial change in photoluminescence was observed when derivative **29** was treated by BSA protein under the same conditions, enabling the selective fluorometric detection of Con A.

Recently, nitroreductase (NTR), a family of evolutionarily related proteins, was targeted by a TPE-based fluorescence probe.[77] The sensing mechanism of **30** toward NTR in aqueous solution is explained as follows: (i) the pyridinium moiety is expected to enhance the water solubility, and accordingly it is expected that **30** is weakly emissive in aqueous solution; (ii) upon the incubation of **30** with NTR, the nitro group is reduced to an amino group, followed by a 2,5-arrangement elimination and release of the pyridine-substituted TPE to form TPE-PY,

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which has low solubility in aqueous solution, leading to turn-on of emission due to aggregation.

Since biogenic amines play an important role in regulating cell growth and differentiation,[78] their identification and detection are important for food and healthcare. Although some methods with high sensitivity have been utilized for the detection of biogenic amines, these approaches are not suitable for routine use, as they often require a relatively long analysis time and sample pretreatment.[79] To overcome these issues, Nakamura et al. developed a fluorometric sensing method for screening and quantification of biogenic amines using AIE-active TPEs bearing carboxylic acid functional groups (**31**−**33**, Figure 13).[80] The

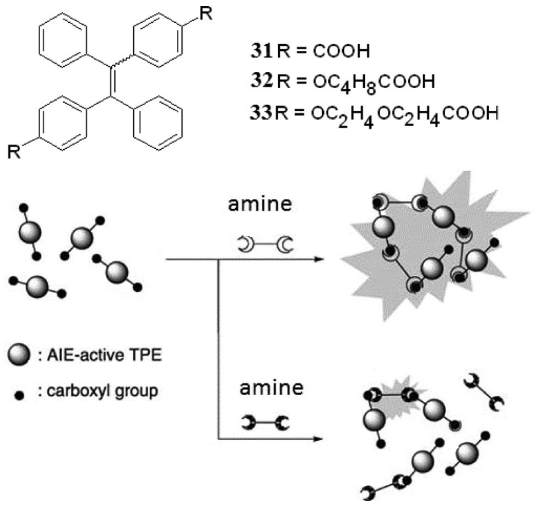

Figure 13. AIE-active TPEs with carboxylic acid moieties for biogenic amine sensing. Adapted with permission from ref 80. Copyright 2011 Wiley-VCH.

sensing mechanism is ascribed to the interaction between amines and carboxylic acids via either hydrogen bonding or electrostatic interactions. Thus, TPEs bearing carboxylic acid units show relatively high fluorescent emission upon addition of amines, including biogenic amines. The sensing array fabricated from compounds **31**−**33** allowed convenient naked-eye detection of biogenic amines at hazardous levels as low as 50 ppm, which is sufficient sensitivity for practical detection of biogenic amines.

On the other hand, the imbalance of biological thiol (for example, glutathione, GSH) levels has been shown to lead to various diseases such as cancer, aging, cardiovascular disease, neurodegenerative diseases, as well as other ailments.[81] Therefore, there is a need to develop protocols for selective detection of trace GSH is because of its significance in biological and clinical contexts.[82] A malononitrile-functionalized TPE derivative **34** was prepared in a single step by coupling of TPE-aldehye with malononitrile in refluxing ethanol, and utilized for selective detection of GSH (Figure 14a).[83] When the sensor is in contact with GSH, an addition reaction between the thiol group of GSH and the alkene bond of **34** occurs, which leads to fluorescence. Figure 14b shows that the malononitrile-functionalized TPE derivative **34** is selective for GSH over other biologically important amino acids which include cysteine (Cys) and homocysteine (Hcy) thiols. With excellent biocompatibility, **34** were also shown to be useful for mapping the distribution of intracellular free GSH. The malononitrile-functionalized TPE probe is novel, sensitive and selective for GSH detection, making it promising for biological and clinical applications.

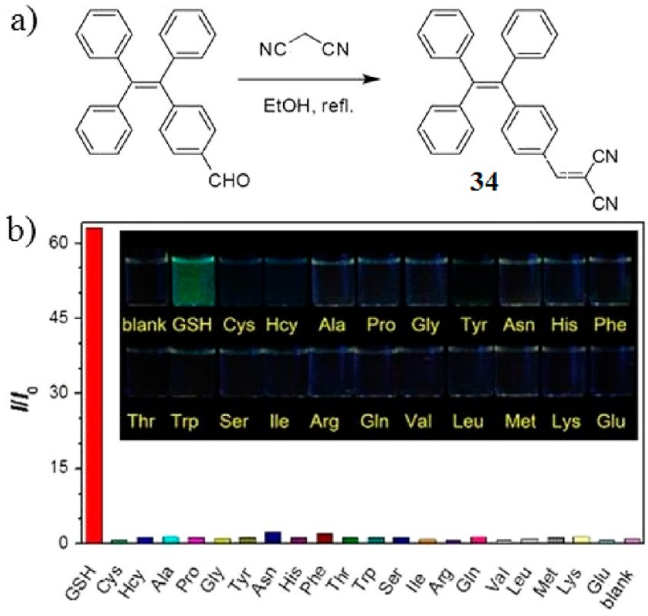

Figure 14. (a) Synthetic route toward the malononitrile-functionalized TPE derivative **34**. (b) Selectivity of **34** toward glutathione (GSH) over other amino acids. Adapted with permission from ref 83. Copyright 2014 Nature Publishing Group.

TPE-based AIE-active fluorogens have also been employed for selective sensing of acetylchlinesterase (AChE) activity, which is directly relevant to Alzheimer's disease, Parkinson's disease, and post stroke conditions.[84] Compound **35** was synthesized by functionalization of the TPE core with a maleimide group. The resultant sensor is weakly emissive due to the exciton annihilation process related with the n−π electronic conjugation of the carbonyl (C═O) with the olefinic (═C) functionality within the maleimide unit. However, upon addition of AChE, the maleimide ring of **35** is hydrolyzed by thiolcholine to produce AIE-active molecules, which exhibit significantly enhanced fluorescence emission (Figure 15). The fluorescence signal is readily detectable even by naked-eye with a low detection limit of 2.5 mU mL^{-1} for AChE. Furthermore, **35** has been effectively

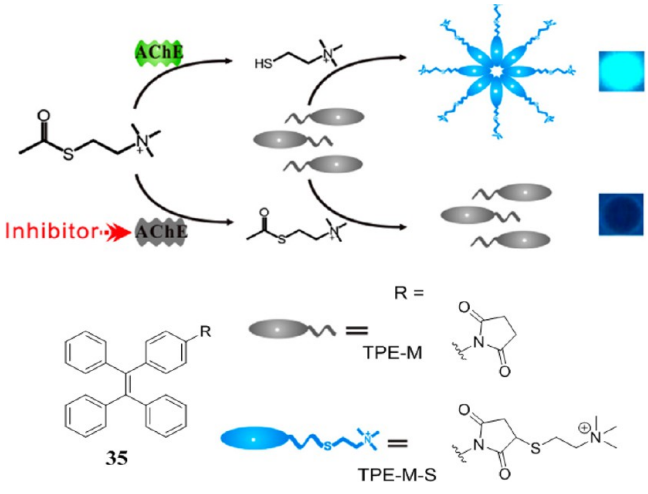

Figure 15. Graphical representation of the detection principle using **35** as a proposed fluorescent assay for AChE activity via cleavage by thiolcholine to produce AIE-active molecules. Adapted with permission from ref 84. Copyright 2016 Elsevier .

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used for detection of AChE from diluted human serum, showing its potential for use in practical real-world applications.

Lipase plays an important role in a range of biological fields including catalysis, drug discovery, and medical diagnosis. Shia et al. synthesized TPE-$COOC_6H_{13}$ (**36**), which hydrolyzes to produce TPE-COOH (**37**) in the presence of lipase (Figure 16),

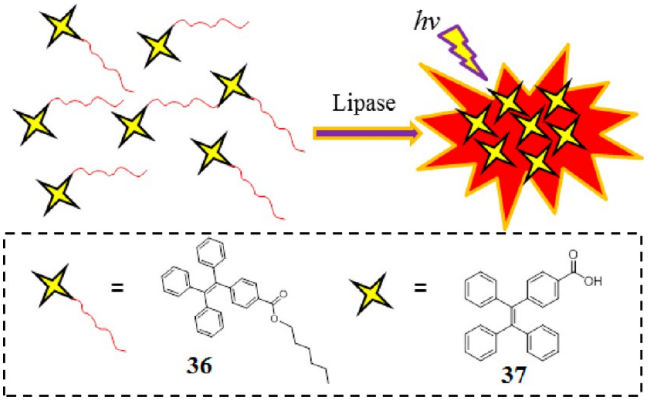

Figure 16. Lipase-induced hydrolyses of ester, which is of reduced solubility, leading to AIE activity. Adapted with permission from ref 85. Copyright 2017 Elsevier.

which due to its reduced solubility leads to AIE.[85] Dynamic light scattering (DLS) studies confirmed that aggregation occurred after hydrolysis. The study found that lipase with concentrations as low as 0.1 mg mL^{-1} can be detected and that the assay range of lipase was 0.1−1.3 mg mL^{-1}.

5. TPE-BASED FLUORESCENT SENSORS FOR IONS

Since the TPE core is a typical AIE fluorophore,[10] in order to detect ions, TPE derivatives should comprise an ion chelating or binding moiety to form a stable complex with the target ions in the detecting media. In general, in order to induce an alteration in detectable fluorescence, the binding between ion and the TPE derivative need to change the electronic and/or molecular features of the TPE-based fluorophore core. These changes can be achieved by electron transfer and/or photoexcited TPE luminogens, which can give a "turn-on" due to strong AIE fluorescence of the TPE derivatives.[1] Based on this mechanism, several AIE-active TPE derivatives have been synthesized and used as an alternative to chemosensors for detecting cations, such as Hg^{2+}, Zn^{2+}, Fe^{3+}, Cu^{2+}, and Ag^{+}, and anions, such as F^{-}, NO_3^{-}, CN^{-}, and pyrophosphate. This work is quite recent, with the first work of this kind reported by Sun and colleagues in 2011,[86] for TPE derivative **35** (Figure 17), which was employed as a fluorescence fluorophore to detect Zn^{2+}. In the absence of Zn^{2+}, the aqueous solution of compound **35** was shown to be nonemissive; however, upon addition of Zn^{2+}, blue fluorescence emitted strongly at a wavelength of 485 nm. This is because the intermolecular coordination between $-N(CH_2COO^{-})_2$ acted as binding moiety for Zn^{2+} to inhibit the intramolecular photo-induced electron transfer, as well as leading to strong AIE. This fluorescence turn-on sensor showed good selectivity for Zn^{2+} over a diverse range of transient and heavy metal ions. In 2015, Xu et al.[87] reported that TPE-C4-L2 (**38**) could detect Zn^{2+} in aqueous solution by Zn^{2+}-induced fluorescence enhancement due to aggregation. Interestingly, they also demonstrated that when **38** self-assembled on highly oriented pyrolytic graphite (HOPG) surface it could be used as a probe to determine the presence of Zn^{2+} in aqueous solution.

The coordination between **38** and Zn^{2+} on HOPG surface led to a fluorescence quenching phenomenon, which is the opposite to the fluorescence enhancement of **38** in aqueous solution.

By eliminating the polar moieties of the fluorogen (**40**) through interaction between Hg^{2+} and the polar tails of **40** (a deprotection reaction) to form the strongly emissive nonpolar aggregates of TPE-COH (**41**), Ozturk and Atilgan successfully demonstrated turn-on fluorescence sensing of Hg^{2+} (Figure 18).[88] The Hg^{2+} sensor showed good selectivity, with a detection limit of Hg^{2+} in water down to 0.1 μM. In a later example, Ruan et al.[89] described a new Hg^{2+} chemodosimeter using TPE-S (**42**) as a sensing material with a nitrobenzene group separated from TPE via two saturated carbon atoms. **42** was non emissive, however upon addition of Hg^{2+} a deprotection reaction proceeds, with the sensor becoming a fluorescent "turn-on" probe for Hg^{2+}. When encountering Hg^{2+} ions in solution, **42** was

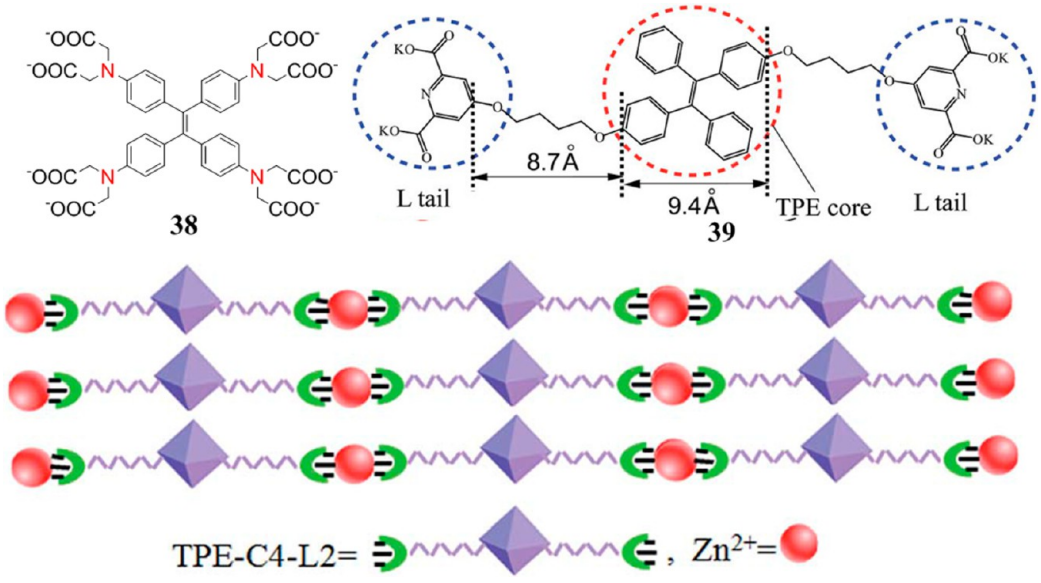

Figure 17. Sensing mechanism of **38** and **39** for Zn^{2+}. Adapted with permission from ref 87. Copyright 2015 Royal Society of Chemistry.

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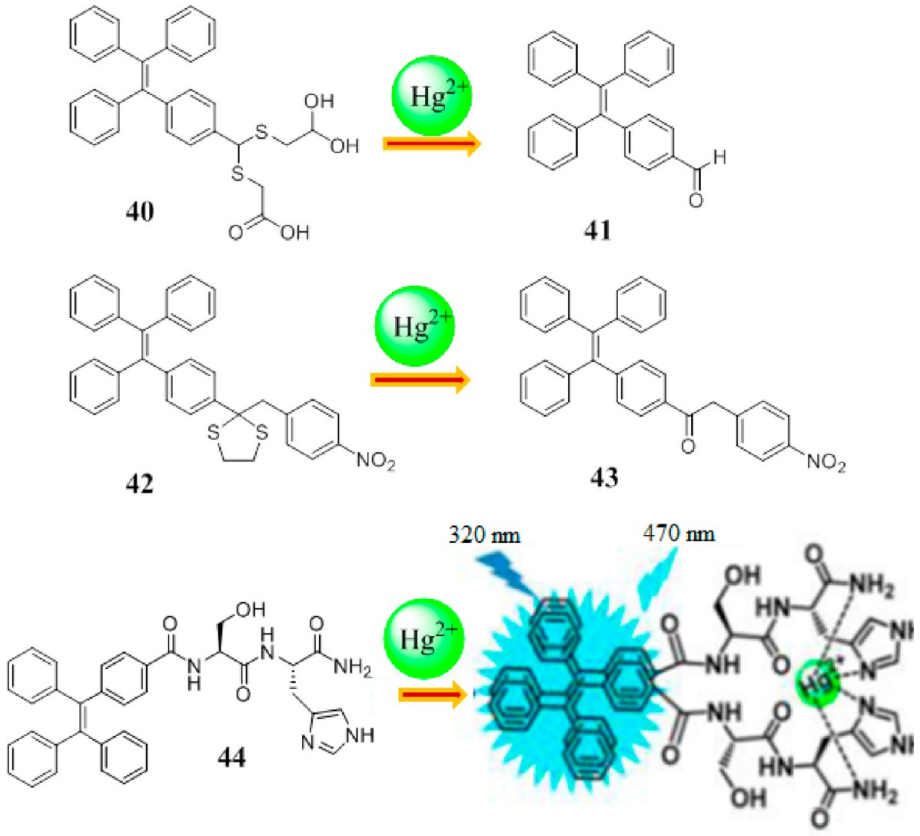

Figure 18. TPE-based AIE-active derivatives for Hg^{2+} detection. Adapted with permission from ref 90. Copyright 2016 American Chemical Society.

converted to the ketone TPE-O (**43**) due to the strong acceptor characteristics of nitro functional group, which leads to the formation of the enol with a D-π-D structure. This process could be monitored by a simple color change from pale yellow to deep purple. The TPE-S-based **42** exhibited excellent selectivity for Hg^{2+} over other cations. Furthermore, practical test strips that were fabricated from compound **42** showed an apparent color change from transparent to purple, which was able to observed by the naked-eye with a detection limit of 0.1 μM. In another report, Neupane et al. synthesized a peptidyl chemosensor (**44**) bearing a TPE fluorophore moiety for selective turn-on detection of Hg^{2+} in the presence of 16 other metal ions: Ca^{2+}, Cd^{2+}, Co^{2+}, Pb^{2+}, Cu^{2+}, Ag^{+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, Zn^{2+}, Cr^{3+}, Fe^{3+} as perchlorate anions and Na^{+}, Al^{3+}, K^{+}, Hg^{2+} as chloride anions by excitation at 320 nm in aqueous buffered solutions, as well as in penetrated live cells.[90] The turn-on emission of the **44** showed a highly sensitive response to 1.0 equiv of Hg^{2+} with a detection limit 5.3 nM, which is lower than the maximum acceptable limit of Hg^{2+} in drinking groundwater designated by the Environmental Protection Agency (EPA). Thus, the TPE fluorophore **44** using an AIE process is not only of academic interest but also demonstrates real-world applicability for the detection of Hg^{2+} in water solution as well as cells.

Wu and co-workers reported the construction of a new supramolecular system through self-assembly of a thymine-substituted copillar[5]arene and a TPE derivative **45** in the presence of Hg^{2+} through host–guest interactions between the pillararene cavity of copillar[5]arene and the nitrile moiety of TPE.[91] These supramolecular interactions generate criss-crossed networks composed of copillar[5]arene and TPE, which in the presence of Hg^{2+} produced spherical nanoparticles. Taking advantage of the AIE properties of TPE, the supramolecular aggregates exhibit strong fluorescence leading to convenient detection of the Hg^{2+}-comprising nanoparticles, and a subsequent removal procedure shown in Figure 19. This protocol thus demonstrated a practical strategy for both the sensing and removal of Hg^{2+} ions in water by the construction of supramolecular self-assembled aggregates.

Li and co-workers synthesized an isoreticular series of luminescent metal–organic frameworks (LMOFs) by incorporating a pyridyl-substituted TPE as an AIE-active fluorophore and functionally diverse co-linkers into Zn-based structures such as $[Zn_2(ofdc)_2(tppe)]\cdot S$ (LMOF-261, -262, and -263) as shown in Figure 20.[92] Their study demonstrated that LMOF-263 was selective for the detection of toxic heavy metals with detection limits of 3.3 ppb for Hg^{2+} and 19.7 ppb for Pb^{2+}. They also demonstrated high selectivity for Hg^{2+} over light metals such as Ca^{2+} and Mg^{2+}, with detection ratios of 167.4 and 209.5 ppb, respectively. These LMOFs exhibited remarkable water stability, high porosity and strong luminescence properties, making them exceptional candidates as a fluorescent chemical sensors and adsorbents for aqueous pollutants.

In 2012, Yan and co-workers described a selective and sensitive fluorescence "on–off" chemosensor based on TPE for recognition of Fe^{3+} in water.[93] The probe **46** was designed by attaching dithioacetals, which consisted of four carboxylic groups, to the TPE moiety as shown in Figure 21a. In compound **46**, four carboxylic groups act as iron chelators which can selectively bind Fe^{3+} and remain soluble in aqueous solution to induce a change in fluorescent intensity. In aqueous solution, **46** was strongly emissive in the green region with a quantum yield of 0.06993; however, upon addition of Fe^{3+}, an 8.71-fold decrease in fluorescent intensity was observed at 465 nm. This chemosensor had good sensitivity of 0.25 μM and was selective for Fe^{3+}.

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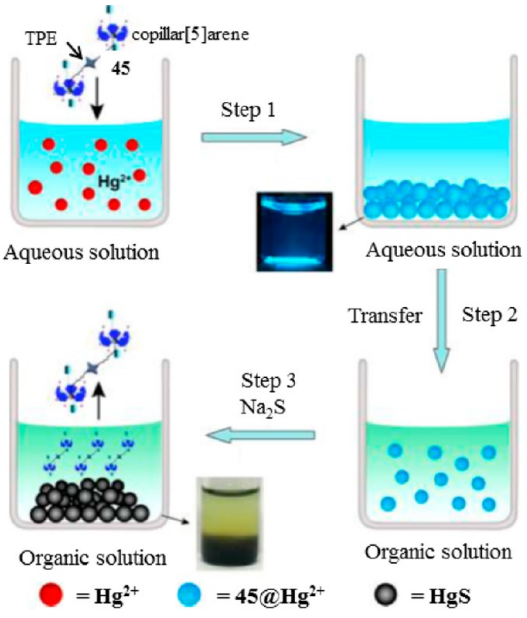

Figure 19. Graphical illustration of the application of **45** in removing Hg^{2+} in water. Adapted with permission from ref 91. Copyright 2017 American Chemical Society.

Another AIE fluorescent Fe^{3+} probe (**47**) was synthesized from TPE and 2-methylpyridyl-2-methylthiophenylamino through a click reaction.[94] The sensing mechanism of **47** was similar to that of **46**, which was based on the AIE quenching behavior of Fe^{3+} when forming a complex with the fluorogen. In this case in particular, Fe^{3+} coordinated with the pyridine and thiophene units as shown in Figure 21b, and the dramatic fluorescent quenching effect was only observed with Fe^{3+} upon addition of various metal ions in a THF/H_2O solution of **47**. The detection limit of this probe for Fe^{3+} was determined to be 0.7 μM. Along with Fe^{3+}, other trivalent metal cations such as Cr^{3+} and Al^{3+} could be also detected by using a simple supramolecular compound of pyridinyl-functionalized TPE fluorophore, **48**.[95] This chemosensor **48** was shown to be very sensitive and selective for recognition of trivalent metal ions over a wide range of mono- and divalent ions.

An Ag^+ fluorogen (compound **49** in Figure 22) was designed by anchoring bis(2-pyridin-2-ylmethyl) (BPA) to the TPE core, and linked with triazole moieties through a click reaction.[96] In THF/H_2O solution, compound **49** emitted weakly at a wavelength of 435 nm, however upon addition of Ag^+, the fluorescent intensity increased by a factor of 4. This increase in fluorescent intensity was attributed to the coordination of Ag^+ with the BPA moieties to form complexes of lower solubility, which may enhance the fluorescence of TPE through

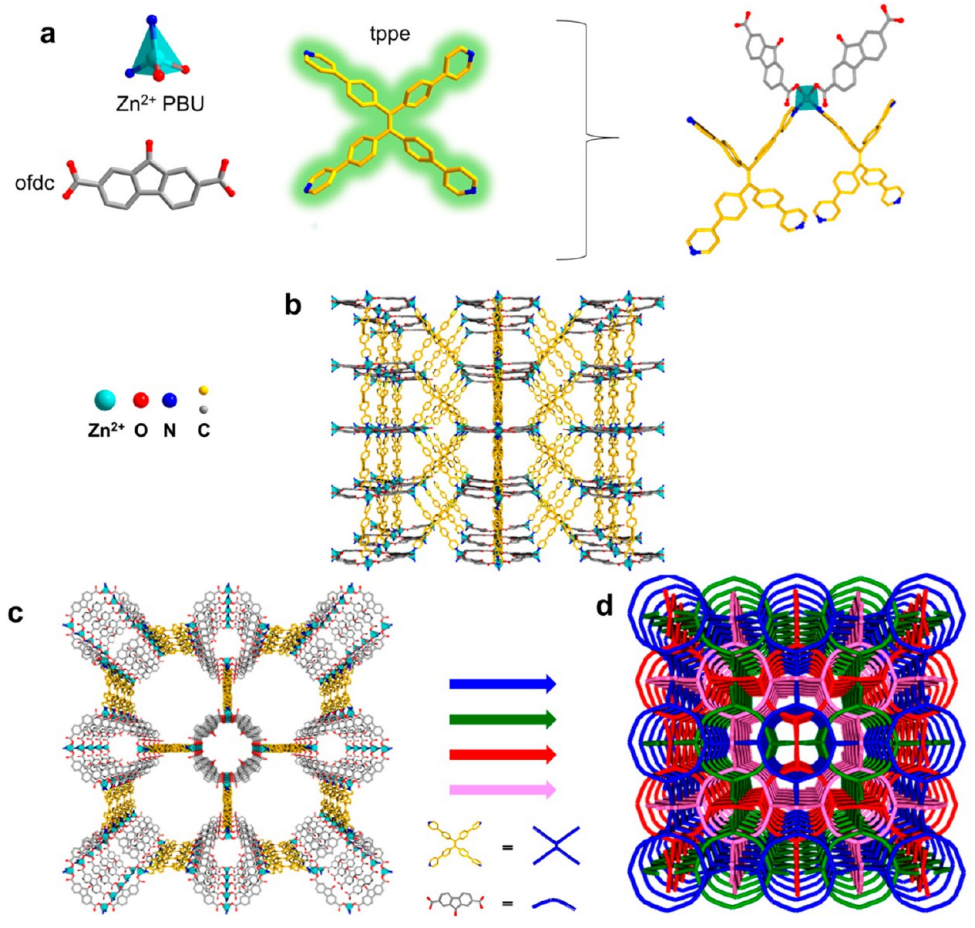

Figure 20. (a) PBU of LMOF-261 showing a pseudotetrahedrally coordinated Zn center bound to two fluorophoric tppe ligands and two ofdc linkers. (b) LMOF-261 individual framework viewed along the *b*-axis, showing edge sharing pentagonal and rhombohedral channels. (c) On *c*-axis showcasing edge sharing octahedral and cylindrical channels. (d) Simplified PBU of LMOF-261 depicting 4-fold interpenetration of 1,1,2,2-tetrakis(4-(pyridin-4-yl)phenyl)ethane ligands and two ofdc linkers. Adapted with permission from ref 92. Copyright 2016 American Chemical Society.

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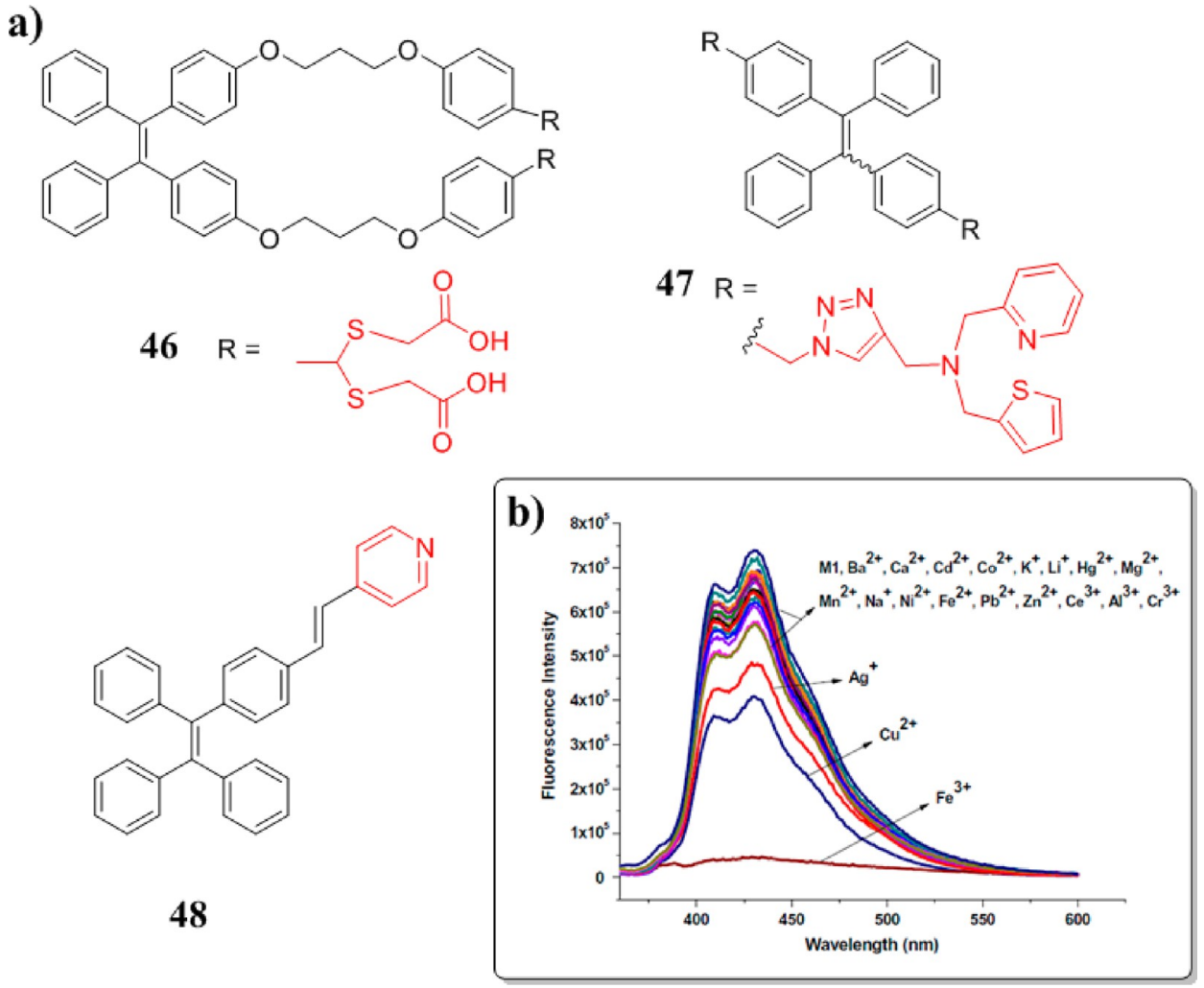

Figure 21. (a) TPE derivatives **46**–**48** for Fe^{3+} sensing. (b) Changes of fluorescence emission with **47** as sensing probe upon addition of various ions. Adapted with permission from ref 95. Copyright 2013 Royal Society of Chemistry.

aggregation.[97] Depending on the concentration of Ag^+, coordination with BPA moieties occurred in different modes. At low concentration of Ag^+ ($\leq$1 equiv of **49**), two molecules of **49** bind with one Ag^+ ion in a head-to-tail type configuration, whereas at higher Ag^+ concentration, two BPA moieties of one molecule **49** coordinate with Ag^+ to form complexes. The lowest concentration of Ag^+ that could be detected by this chemosensor was 0.2 μM. Another Ag^+ chemosensor using a TPE-based fluorophore was reported by Li and colleagues (compound **50**).[98] This "turn-on" fluorescence sensor had a 0.874 μM detection limit with good selectivity toward most of the studied competing ions and was also shown to be reusable.

Recently, Wen et al.[99] synthesized the "turn-on" fluorescent TPE-PDA (**51**) sensor for Th^{4+} by functionalizing TPE with 2,6-pyridinedicarboxylic acid (PDA), where PDA acted as a chelating unit for Th^{4+}. This chemosensor displayed excellent sensitivity and selectivity toward Th^{4+} over lanthanides, transition metals, and alkali metals (Figure 23a). The Th^{4+} can be detected by both the naked eye through visual observation, and also with emission enhancement with a detection limit down to ppb levels. In the same year, these authors also reported a "turn-off" fluorescent TPE-based sensor (compound **52**) for uranyl detection (the most common and stable form of uranium).[100] Under UV light, derivative **52** differentiated uranyl from lanthanides, transition metals, and alkali metals, visible by the naked eye (Figure 23b). When Th^{4+} formed complexes with **52**, it would cause quenching, which dramatically decreases the emission intensity comparing to the other tested ions.

Detection of Cu(II) is important for diagnosis of disease, mapping biological systems and also for environmental monitoring. The Feng group designed and synthesized the TPE-based macrocycle (**53**) for selective detection of Cu^{2+} by a condensation reaction between the TPE dialdehyde and 1,2-benzenediamine (Figure 23c).[101] In the presence of Cu^{2+} ions, **53** self-assembled into nanofiber structures in aqueous solution, leading to a sensitive and selective response. When the macrocycle coordinated with Cu^{2+}, noticeable changes in the fluorescent intensity and could be visualized by naked eye under both UV light and visible light. In another report, Tang and co-workers synthesized a chitosan-based AIE-active TPE bioconjugate for selective detection of Cu(II) in aqueous solution.[102]

Wei et al. synthesized TPE-based an AIE-active fluorescent probe for the selective detection of Al^{3+}, where diethylenetriamine units were used as the binding site for Al^{3+} (Figure 24). A large enhancement of fluorescence emission from 2.0×10^{-6} to 1.1×10^{-5} M was observed when binding with Al^{3+} with a 1:1 stoichiometry, and a detection limit of 5×10^{-7} M was observed.[103]

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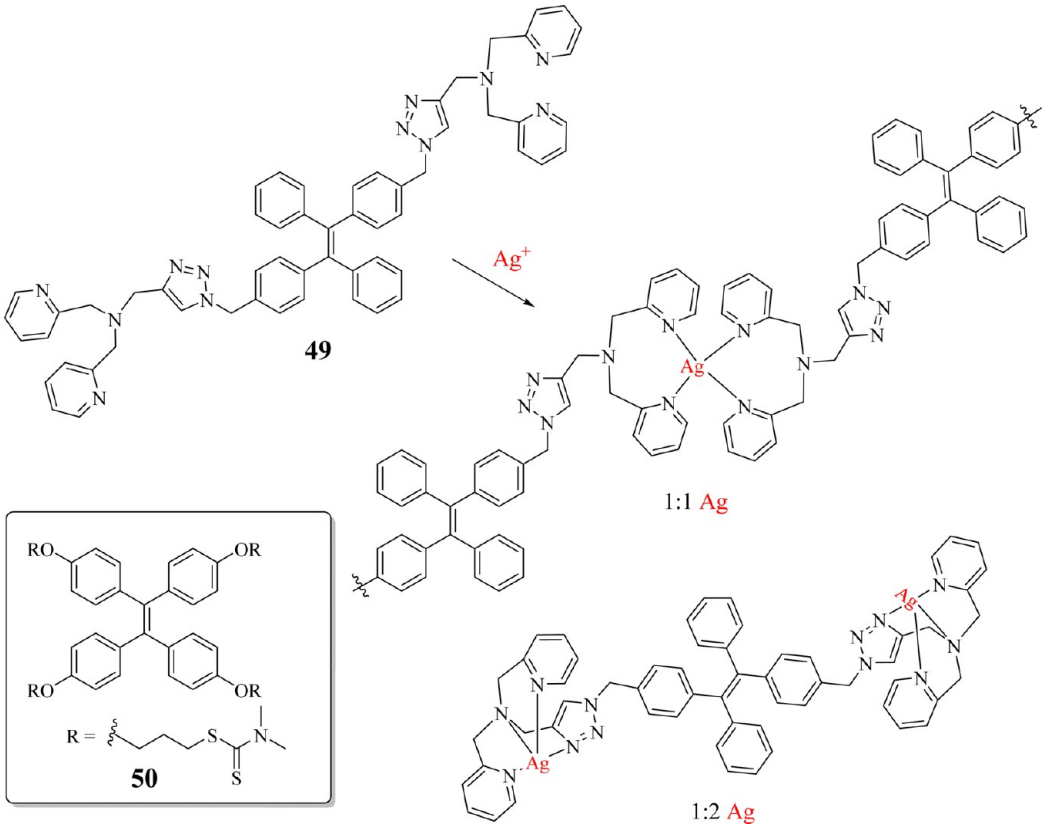

Figure 22. TPE derivatives **49** and **50** for sensing of Ag^+.

The versatility of TPE-based chemosensors is apparent when it is considered that they have not just been used for the detection of cations, but also for anions. In 2010, Hong and Park developed a TPE-based "turn-on" fluorescent chemosensor comprising a dipicolylamine(dpa)−Zn(II) complex that acted as a chelate, with TPE moieties for the detection of pyrophosphate (PPi) as shown in compound **54** in Figure 25.[60] The enhancement in fluorescence was attributed to binding of PPi to the dpa-Zn complex, which restricted the intramolecular rotation between phenyl rings in dpa-Zn. This sensor had high sensitivity with a detection limit of 9.9 μM and good selectivity for PPi ions compared to the other anions tested. Another Zn(II) complex, dicyclen-TPE zinc complex dDT·Zn (**55**), was also designed and used for PPi sensing.[104] The detection limit for PPi in aqueous solution achieved with this sensor was as low as 22.8 nM. PPi was also detected using a TPE-based imidazolium macrocycle as a fluorophore (**56**).[105] In aqueous solution, compound **56** was positive in charge, and no induced-aggregate fluorescence was observed upon addition of common ions including PPi. However, when Zn(II) ions were added, strong fluorescence was observed in the presence of PPi, with no response observed for the addition of other anions, confirming selectivity. PPi could also be detected by self-assembly into nanoparticles with the TPE-based fluorophore (**57**), as reported by Xu and co-workers.[106] Fluorogen **57** could selectively respond to PPi in aqueous solution over other organic phosphate anions with a 45-fold increase of fluorescent intensity. The lowest concentration of PPi that could be detected by this chemosensor was shown to be 133 nM.

A range of TPE-based fluorophores have been designed for use as probes to detect the fluoride anion (F^-). In 2014, Turan et al.[107] synthesized a silyloxy-functionalized TPE derivative (compound **58**, Figure 26) for sensing of F^- ion in aqueous solution. The mechanism for F^- sensing by **58** is due to the cleavage of the silyl groups to form four phenoxide ions, which are strongly conjugated with the TPE core. This leads to strong intramolecular charge transfer, which is responsible for fluorescent quenching, as well as a visual green color of **58** in solution. Additionally, **58**-impregnated cellulose strips were fabricated to visually detect the F^- in aqueous solution, with the change in the color of strips clearly from white to green without and with F^-, respectively. Using the same mechanism for F^- sensing, a new AIE-based TPE derivative (MOTIPS-TPE, **59**) with one silyl group and a pyridinium pendant was developed.[108] This turn-on fluorescent sensor selectively responded to the F^- over other common ions in aqueous solution without the addition of surfactants, with a detection limit of 90 nM. Chen and co-workers reported a TPE-based metal−organic framework $[Cu_4I(TIPE)_3].3I$ (**60**) (TIPE = tetra(3-imidazoylphenyl)-ethylene), which can detect F^- in aqueous solution.[109] With this chemosensor, F^- was detected through a fluorescent quenching mechanism with a calculated detection limit of 2.11 μM. Another fluorogen designed from a TPE moiety with four alkyl or aryl urea groups, **61**, which was used as F^- sensor, was reported by Kassl and colleagues.[110] Compound **61** responded to several monovalent anions; however, the largest fluorescent response was observed for fluoride ion.

In 2014, Zhang et al.[111] reported a cyanide (CN^-) chemosensor in aqueous solution with a TPE derivative containing dicyanovinyl groups (**62**). The sensor solution was prepared by mixing **62** in DMSO with CTAB surfactant in water and upon addition of CN^-, the color of solution changed from yellow to colorless. Furthermore, the emission changed from orange to blue under UV light as a result of shifts in both the

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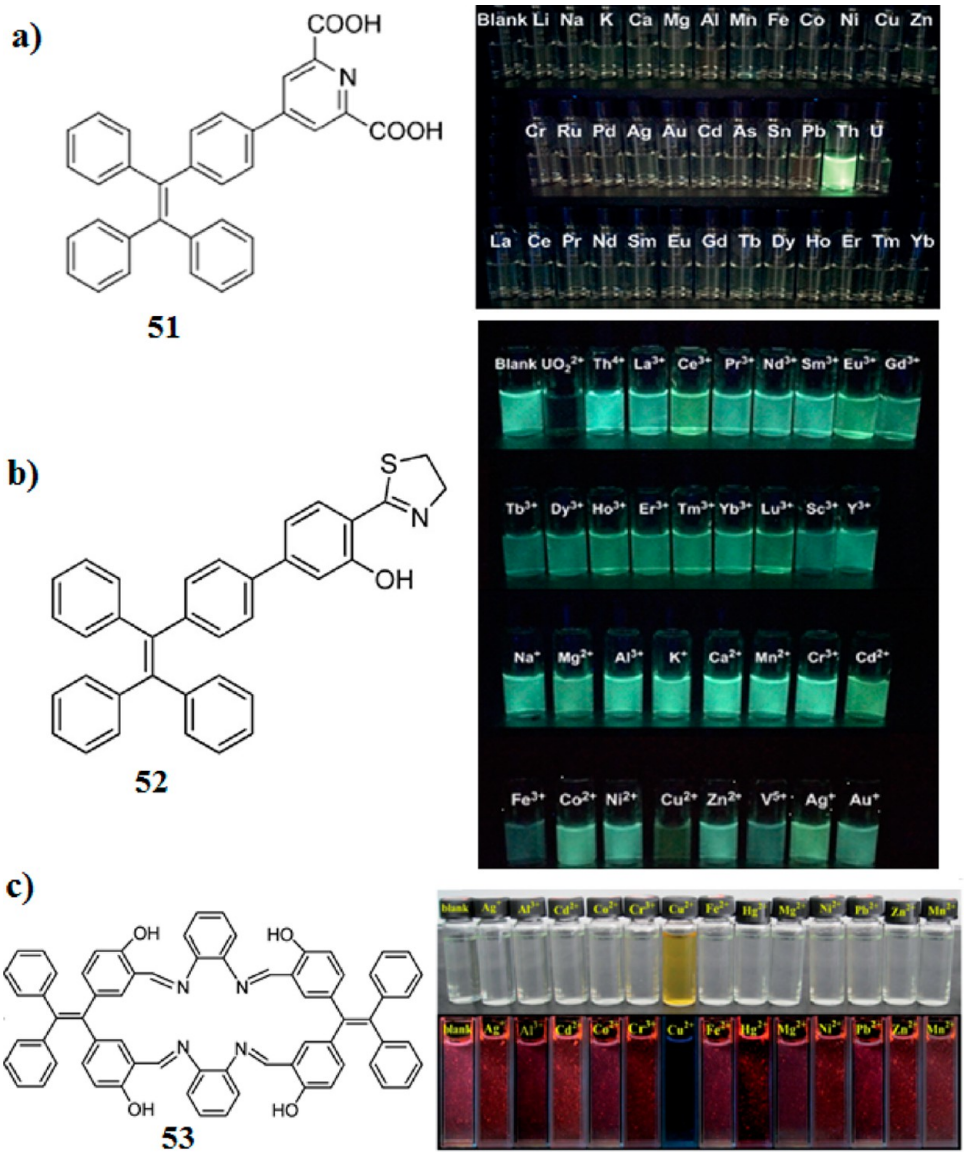

Figure 23. TPE derivatives for the detection of (a) Th^{4+}, (b) UO_2^{2+}, and (c) Cu^{2+} ions. (a) Adapted with permission from ref 99. Copyright 2016 Wiley-VCH. (b,c) Adapted with permission from refs 100 and 101. Copyright 2016 and 2014 Royal Society of Chemistry, respectively.

absorption and fluorescent spectra. Competition studies also revealed this sensor to be selective toward CN^- over other tested anions with a detection limit of 0.2 μM. The sensing mechanism of **62** toward CN^- was through the nucleophilic addition of CN^- to the dicyanovinyl group of **62**, leading to formation of a negatively charged compound (Figure 27). This led to the assembly of nanoparticles, which decreased the fluorescent intensity. Furthermore, the CN^- ion would deprotect the dicyanovinyl groups, which may further change the absorption band.

6. DETECTION OF EXPLOSIVES

The wide use and accessibility of nitroaromatics such as TNT, TNP, TNB, DNT, DNP, PNT, PNP NB, and phenol (Figure 28) represents serious threats for security as well as for the environment. Nitroaromatics, even at a low level, are a health hazard including possible eye injury, red skin, liver damage, and aplastic anemia. Therefore, the trace detection of explosives has become an increasingly urgent and important issue.

Many methods have been reported to selectively detect nitroaromatics explosives including, but not limited to, fluorescence, mass spectrometry, gas chromatography, X-ray imaging, and Raman spectroscopy.[112−116] Among these methods, fluorogens have become promising materials for detection of explosives because of good demonstrated selectivity and sensitivity toward nitro groups.[117,118] In a general mechanism, fluorescence compounds with electron-rich functional groups bind with the electron-deficient nitro groups of the explosive by ArH$-\pi$, $\pi-\pi$, and $CH_3-\pi$ interactions, to induce fluorescence quenching through a photo-induced electron transfer.[119] Recently, TPE derivatives with strong AIE have been extensively studied for sensing explosives.

Based on the $CH_3-\pi$ interaction between nitroaromatics with the cavity of TPE macrocycles, Feng et al. reported a series of TPE-based macrocycles **63**, **64**, and **65** (Figure 29) by conjugating 1,2-benzenedioxy, 1,3-benzenedioxy, and 1,4-benzenedioxy units, respectively, with two phenyl rings of the TPE moiety.[120] The as-prepared TPE macrocycles showed typical AIE effects, being nonemissive in diluted solution but

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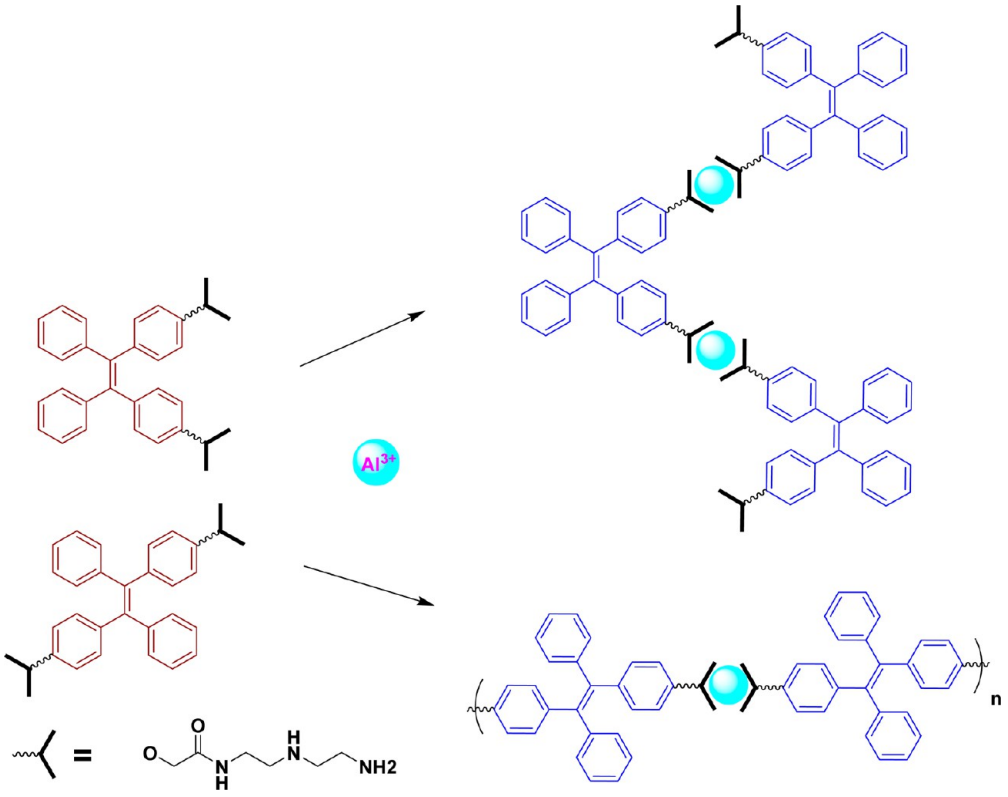

Figure 24. AIE-active TPE-based probe bearing diethylenetriamine receptor site for Al^{3+} detection through aggregation-induced emission.

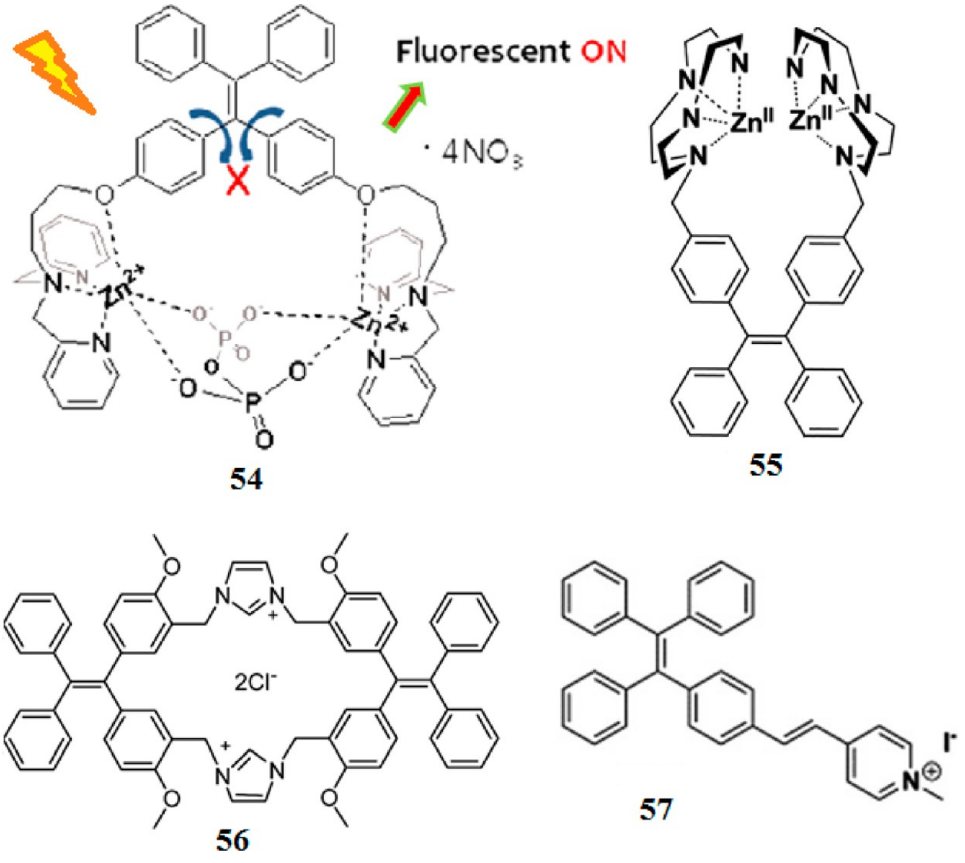

Figure 25. TPE-based derivatives for "turn-on" fluorescent chemosensor for ions.

emitting strongly in aggregated form. Interestingly, it was also demonstrated that the aggregate fluorescence of these TPE fluorophores could be quenched by TNT and DNT bearing a methyl group through $CH_3-\pi$ interaction. This quenching effect

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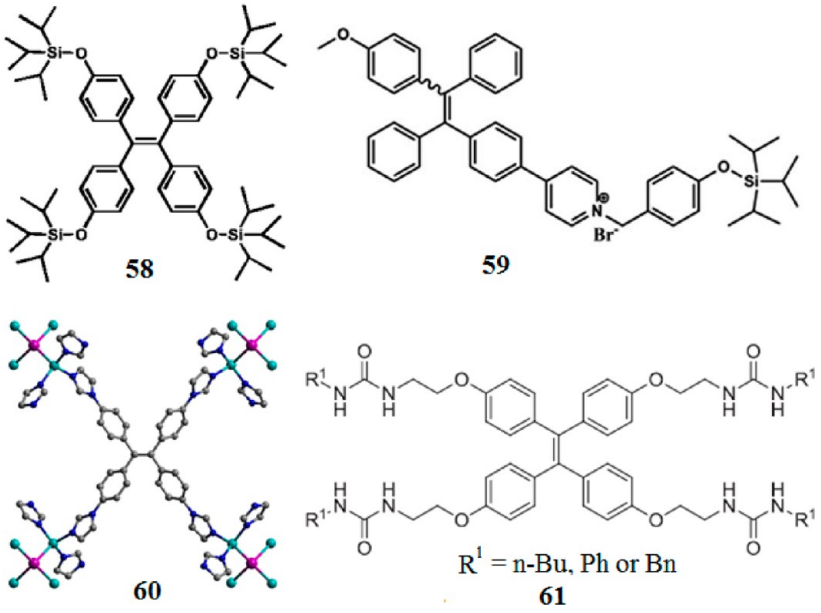

Figure 26. TPE derivatives (**58**–**61**) for the detection of F^- ion.

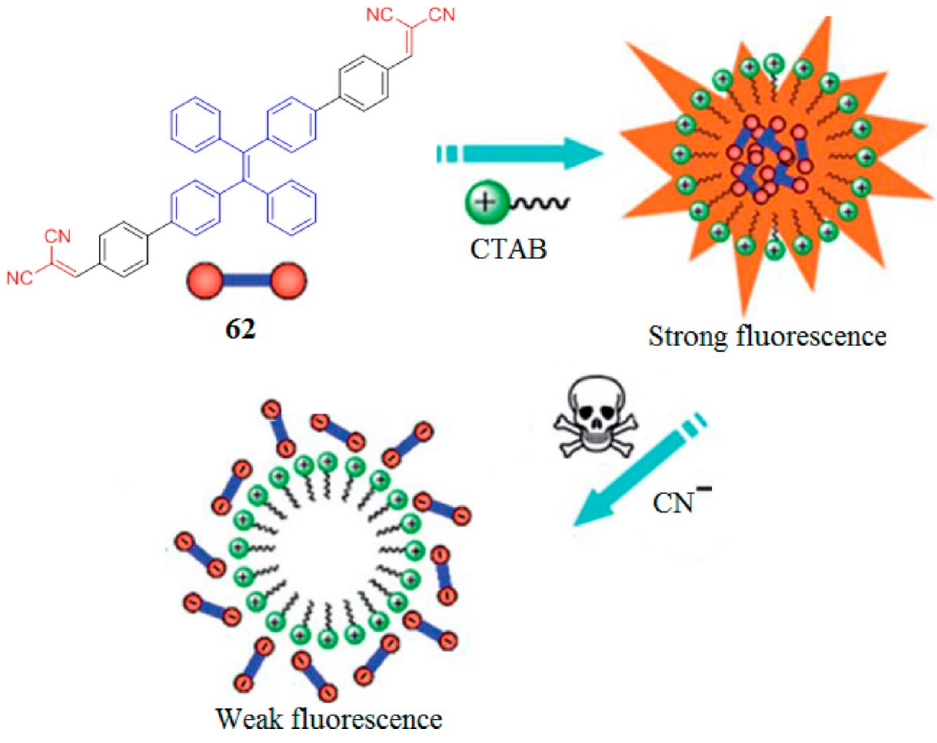

Figure 27. Detection mechanism of TPE containing dicyanovinyl groups (**62**) as probe for cyanide (CN^-). Adapted with permission from ref 111. Copyright 2014 Royal Society of Chemistry.

was employed to detect a number of explosive compounds in aqueous solution at a low level of 0.2−4 ppb. Furthermore, a test paper was fabricated from the fluorophore **63** to detect TNT at 1.0×10^{-13} M level with a detection limit of 0.45 pg cm^{-2}. Later, Feng and co-workers also successfully synthesized the TPE Schiff-based macrocycle **66** that demonstrated the AIE effect upon cntat with nitroaromatic explosives.[121] The macrocycle **66** could be used as a fluorescence sensor to selectively and sensitively recognize 2,4,6-trinitrophenol (TNP) and 2,4-dinitrophenol (DNP) among several nitroaromatic compounds at the nanomolar level. In addition, this sensor showed a strong diminishing of fluorescence with DNP compared to TNP, providing a practical means to discriminate between these explosives. More recently, Mahendran's group synthesized a TPE−2-pyrone conjugate (**67**) bearing both the donor−acceptor moieties.[122] Compound **67** is nonemissive in solution but is strongly fluorescent upon aggregation. Nanoaggregates of **67** were exploited as a fluorescent sensor to selectively detect picric acid (PA) over a number of nitroaromatic compounds. For practical application, fluorescent test strips were also fabricated on TLC plates. The **67**-coated TLC test strips could detect PA with a concentration as low as 22 nM.

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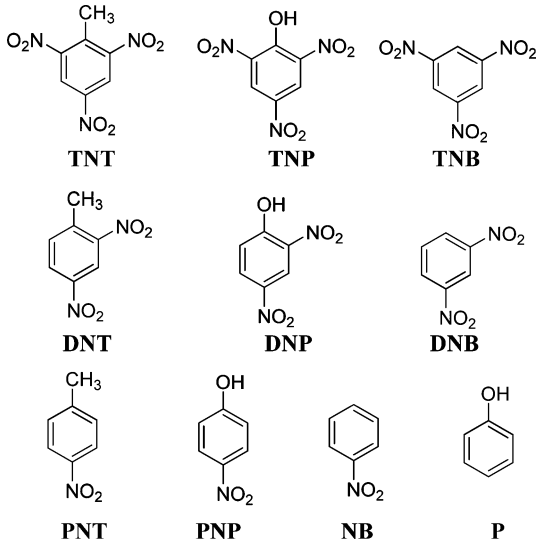

Figure 28. Structures of common nitroaromatic explosives.

In order to achieve sensitive and selective detection of explosive compounds, TPE units are usually incorporated into a polymer matrix (Figure 30). In 2012, Wu and colleagues successfully designed and synthesized a conjugated hyperbranched polymer **68**, with a hole-transporting and electroluminescent group by using a one-pot Suzuki polycondensation reaction between TPE moieties and carbazole units.[123] The resulting polymer showed strong electron-accepting capability and could be effectively used as a chemosensor for detection of explosives through a photoinduced electron transfer (PET) quenching process. In the same year, Wu's group also reported a new functional TPE-based polymer **69**, which was constructed from TPE units, carbazole and 1,3,4-oxadiazole moieties.[124] In solution, compound **69** is weakly emissive, however it emits strongly either in the solid state or in thin films. Nanoaggregates of **69** in a THF/water mixture were used as a probe to detect PA in water. The fluorescence intensity of **69** decreased rapidly upon addition of PA, even at PA concentrations as low as 1 ppm level. Test strips were also developed for sensing of PA by inserting filter paper into THF solutions of **69**. In another report, Li et al. synthesized TPE-based hyperbranched poly(aroxycarbonyltriazoles) **70** with controlled molecular weight and high regioregularities using metal-free "click" polymerization of tripropiolates and TPE-containing diazide.[125] The resulting polymers showed typical AIE behavior, and their aggregates could be exploited as fluorescent sensors for detecting PA with a low detection limit of 1 μg/mL through the superamplification quenching of fluorescence of **70**. In 2014, the TPE-based AIE-active fluorescent conjugated polymer **71** was designed and synthesized by Ghosh's group.[126] The polymer **71** was synthesized by using the Sonogashira cross-coupling reaction of pentiptycene diacetylene and 1,2-bis(4-bromophenyl)-1,2-diphenylene with 71% yield. Thanks to the inclusion of TPE units, the polymer **71** shows the unique feature of AIE and reveals a strong quenching effect upon addition of electron-deficient explosive compounds. The polymer **71** was tested for direct detection of explosives in both solution (aggregates form in THF/H_2O mixture) and in thin films. The results clearly demonstrated that **71** is a promising material when used as a chemosensor for the detection of nitroaromatic compounds at ppb levels, and the presence of TPE in the polymer also enhances the sensitivity and effectiveness of the fluorescent sensor in thick films. Recently, Dong and co-workers successfully fabricated two TPE-containing AIE-active polytriphenylamines, **72** and **73**, by employing a series of reactions such as Suzuki–Miyaura-type, Suzuki-type, and Yamamoto-type couplings.[127] The obtained polymers were fabricated into thin films to detect 1,3,5-trinitrobenzene (TNB) vapors through a donor–acceptor interaction of the electron-rich **72** and **73** with the TNB analyte, which causes fluorescence quenching in the films of both derivatives. The sensors showed high sensitivity and reversibility, with more than 90% of fluorescent intensity recovered after repeated cycling.

TPE moieties conjugated with metals to form AIE-active metal–organic materials for the direct detection of nitro explosives have also been studied (Figure 31). In 2013, Li's group reported a luminescent metal–organic material in gel by incorporating AIE motifs of tetrakis(4-carboxyphenyl)ethylene (**74**) with Al^{3+} ions.[128] The resultant gel was employed to detect PA in water through the fluorescent quenching effect. The results show that the **74**-based gel can detect PA at concentration as low

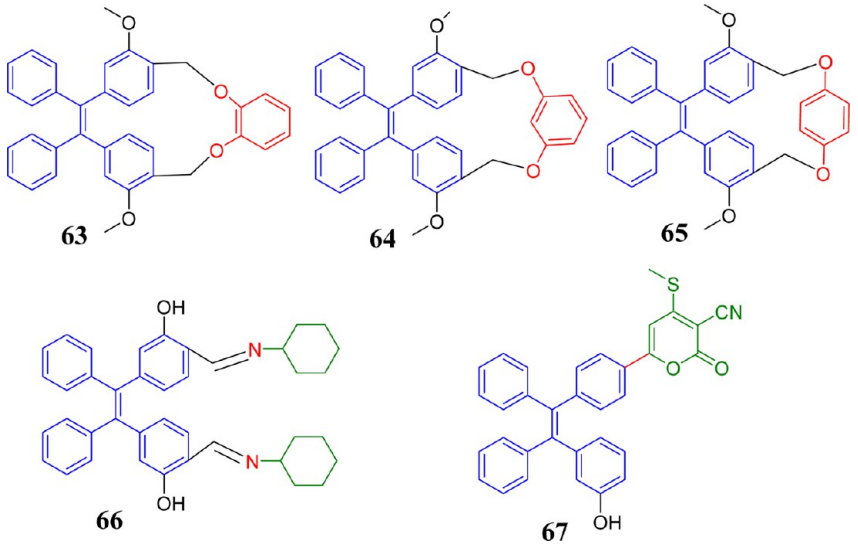

Figure 29. TPE derivatives **63**–**67** for sensing of nitroaromatic explosives.

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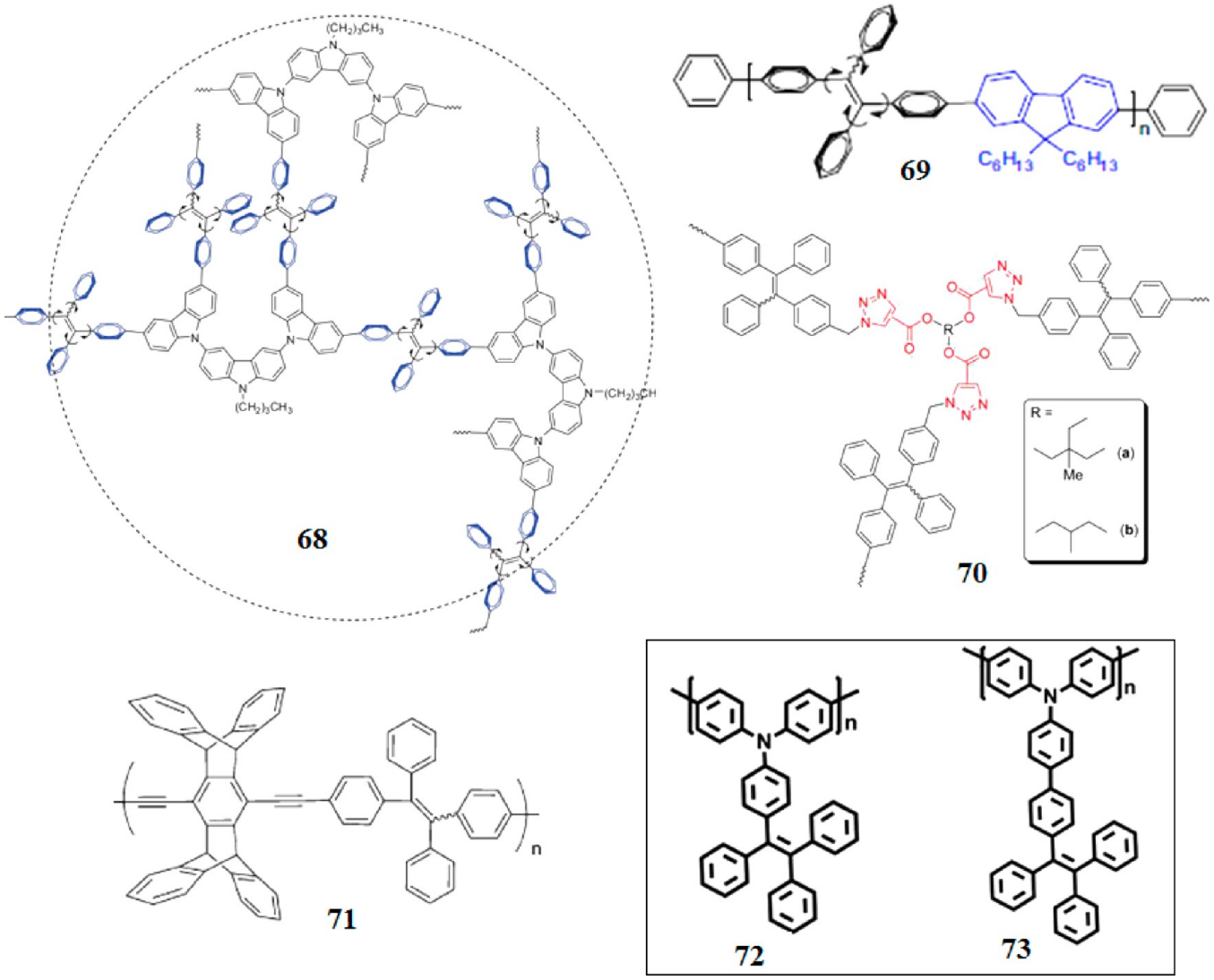

Figure 30. TPE-based polymers for nitroaromatic explosives sensing.

as 0.76 ppm and is highly selective over other nitro explosives in aqueous solutions. Yan and his colleagues also designed and fabricated a series of AIE-active metal−organic materials based on supramolecular coordination complex platforms (compounds **75**−**79**) between TPE-based dipyridyl ligand and di-Pt(II) acceptors through self-assembly as shown in Figure 27.[129] These metallacycles all reveal AIE behavior, being weakly emissive in dilute solution, with enhanced quantum yields upon aggregation. Thanks to a strong AIE effect in the condensed state and their ability to interact with electron-deficient compounds, these metal−organic materials were shown to be sensitive for nitro explosives. More recently, a TPE luminogen was used as an AIE-active motif to incorporate into a zirconium metal−organic framework (**80**) via the strategy of mixed dicarboxylate struts.[130] The functionalized MOF shows a strong blue-green emission in the solid state. When using the MOF **80** as a fluorescent sensor to detect nitro explosives, high sensitivity and selectivity toward nitrophenol-type explosives was observed. The sensing mechanism is based on photoluminescence quenching due to electrostatic and hydrogen-bonding interactions between electron-deficient explosives and the MOF.

7. TPE-BASED pH SENSORS

TPE-based fluorogens have been studied as fluorescence-based pH sensors to monitor pH changes in biological samples with excellent sensitivity and specificity (Figure 32). Chen et al. were first to use a TPE-based luminogen for pH sensing.[131] In this work, they functionalized TPE moieties with *N*-alkylated indolium to form a red-emissive zwitterionic hemicyanine dye (**81**) in reasonable yield. This resulting luminogen (**81**) showed different emission colors and intensities toward solution pH over a broad range. With pH < 5, strong red emission was observed, at pH 5−7 strong to modest red emission was observed, and a weak to no emission was observed at pH 7−10. Interestingly, no emission to strong blue emission was observed at pH 10−14, and strong blue emission at pH > 14. This pH sensing behavior is reversible, as it was repeated in number of cycles by exposing **81** to acidic and basic media. In 2014, we synthesized a pyridyl-functionalized TPE (**82**) via a Suzuki-type coupling reaction of tetrabromo-TPE with 4-pyridineboronic acid in the presence of $Pd(PPh_3)_4$.[19] Compound **82** showed noticeable changes in both optical, emission and calorimetric properties as a function of solution pH in organic solvents ($CHCl_3$, DMF and MeOH), and these changes could be monitored either by the naked eye or by photoluminescence. In another study, Luo's group reported a

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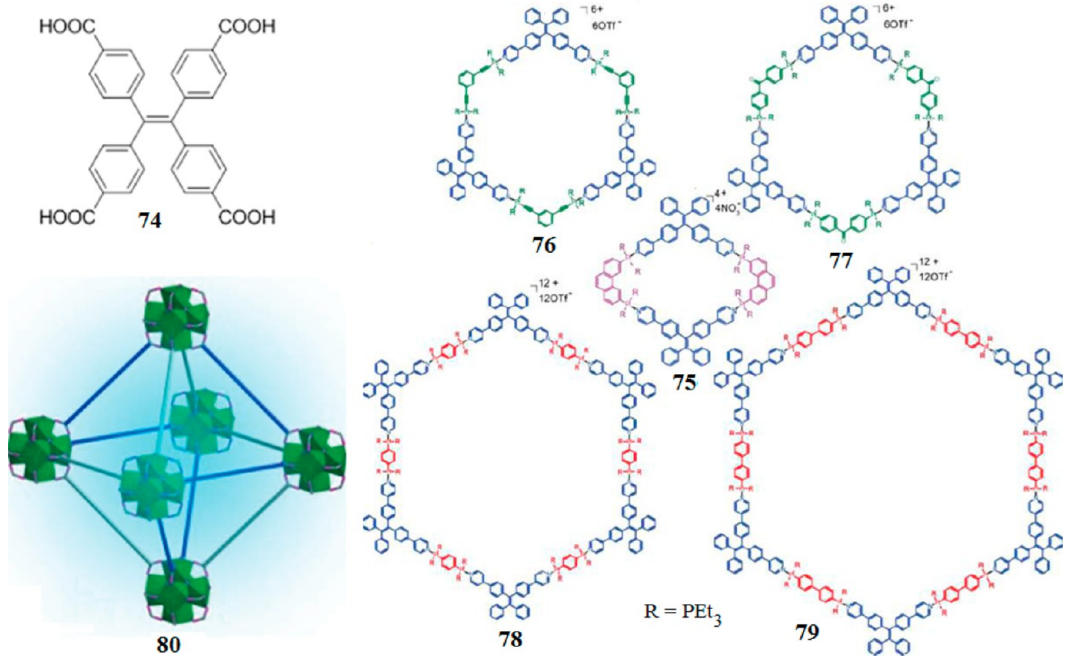

Figure 31. TPE-based metal−organic framework materials for the direct detection of nitro explosives.

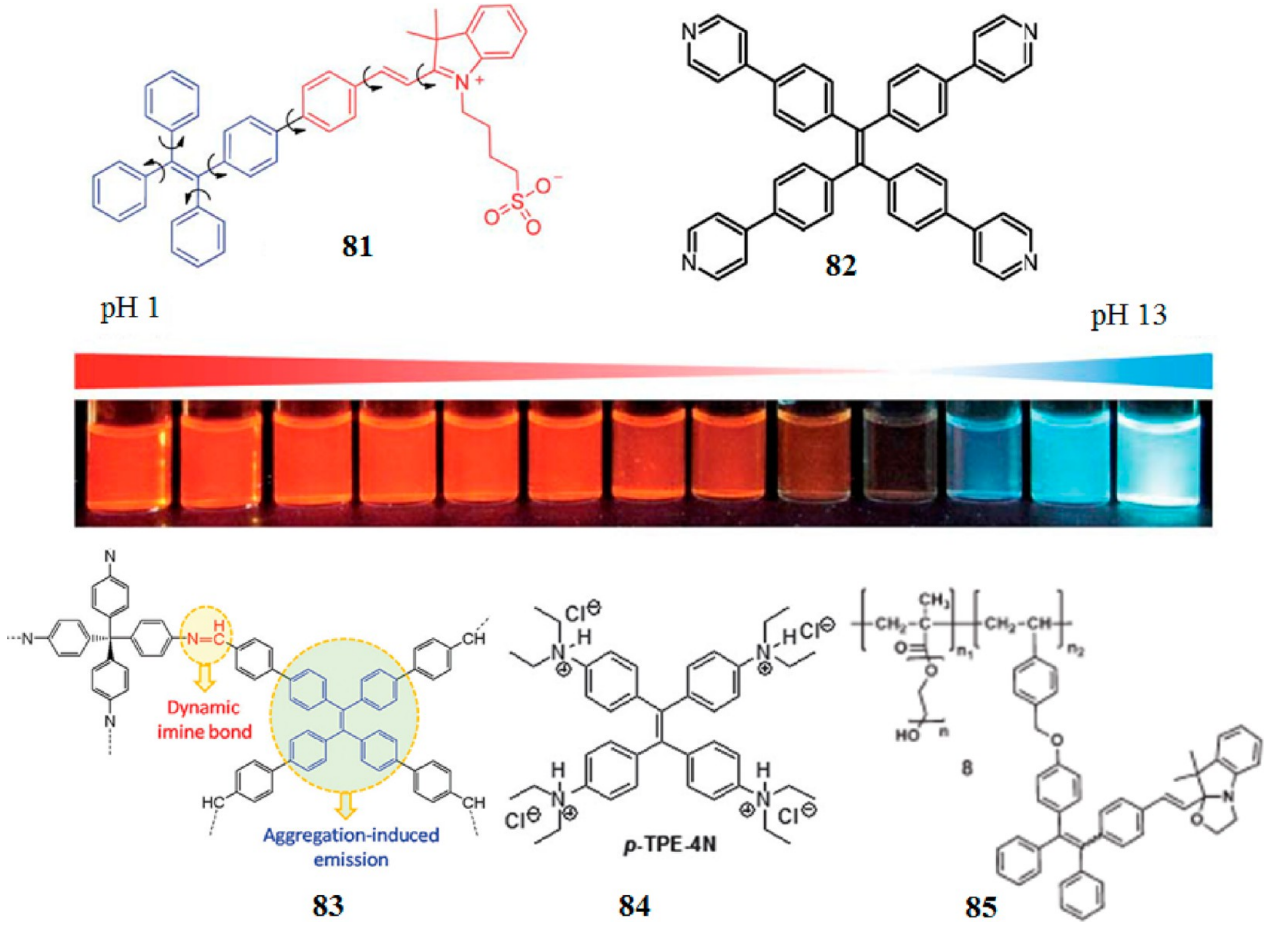

Figure 32. pH sensors based on TPE derivatives, **81**−**85**. Adapted with permission from ref 134. Copyright 2016 Royal Society of Chemistry.

highly porous (S_{BET} = 512 m^2 g^{-1}) AIE-active gel (**83**).[132] This dynamic covalent gel was prepared by the imine bond formation reaction of tetraamine building blocks with TPE moieties and the resultant gel **83** showed a response toward strong acids. In 2015, Wang and his colleagues designed and synthesized a new TPE derivative, i.e., tetra(4-(diethylamino)phenyl)ethene (**84**), by a

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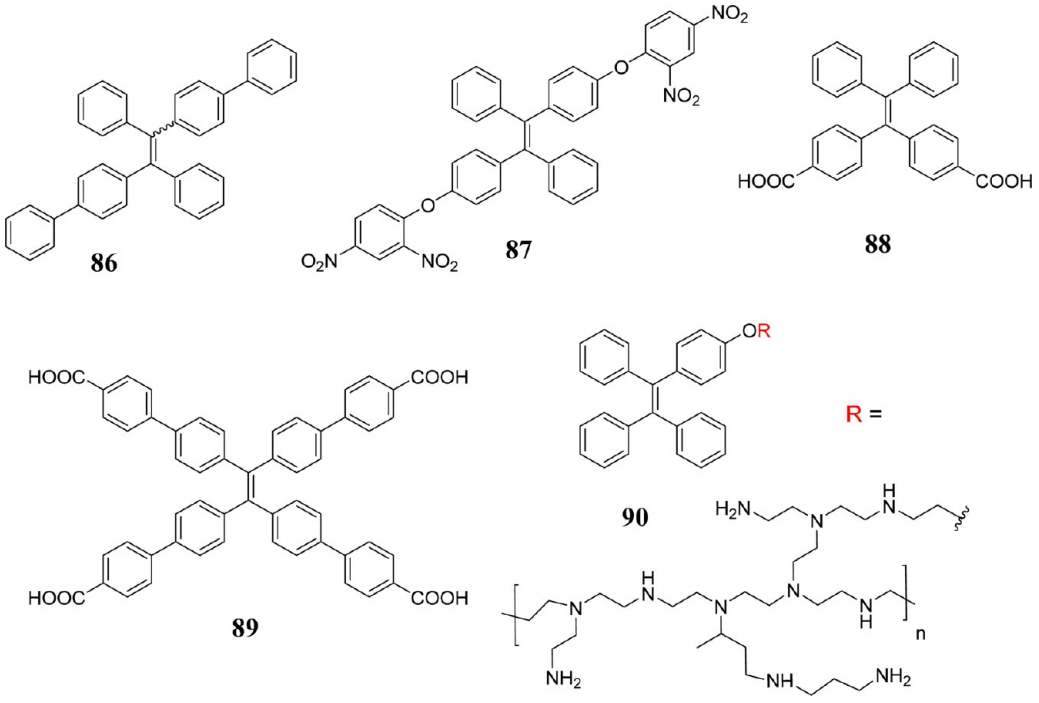

Figure 33. TPE derivatives, **86**–**90**, for the detection of gas and volatile organic compounds.

one-step reaction from bis(4-(diethylamino)phenyl)methanone in 85% yield.[133] **84** exhibited reversible fluorescence switching in acidic and basic solutions, which was due to the strong proton capture capability of **84**. The process was reversible and could be repeated many times without significant decrease in the intensities in the solid state by protonation and deprotonation of **84** in acid and base. A good linear relationship between the emission intensity with the pH (4.4–6.0) was confirmed.

More recently, a TPE-containing AIE-active copolymer (**85**) consisting of TPE-based units and poly(ethylene glycol) methyl ether methacrylate was synthesized by Qi's group.[134] Upon exposure of chemosensor **85** to a controlled pH in Tris-HCl buffer solution, a switch between cyan and red with a decrease of pH value was observed. This emission switching of **85** was due to not only the extended π-conjugation within the molecule, but also intramolecular charge transfer (ICT) through opening of the spiro ring of the oxazoline side chain.

8. GAS AND VOLATILE ORGANIC COMPOUND SENSORS

TPE-based fluorophores (**86**–**90**) have also been used as fluorescence sensors for the detection of gas and volatile organic compounds (VOCs) based on both "turn-on" fluorescence via AIE mechanism and "turn-off" fluorescence via fluorescence quenching mechanism, depending on the interaction between the sensing probes and the analytes (Figure 33).

In 2007, Dong's group prepared a simple diphenylated derivative of TPE (**86**) by utilizing the McMurry reaction.[135] This typical AIE-active molecule showed a response to vapors of chloroform, and emission was "turned-off" and "turned-on" for wetting and dewetting with solvent vapors, respectively. A dual signaling sensor (**87**) consisting of TPE and dinitrophenyl ether was designed and fabricated for the detection of hydrogen sulfide (H_2S) gas.[136] This TPE-based sensor can distinguish H_2S by both changes in fluorescence emission and color (Figure 34). In dilute solution, compound **87** is colorless, however upon

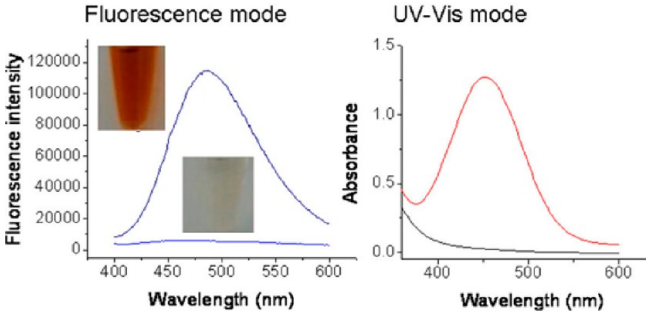

Figure 34. Fluorescence (left) and adsorption spectra (right) of H_2S gas using compound **87** as a probe. Adapted with permission from ref 136. Copyright 2015 American Chemical Society.

addition of H_2S, the solution color changes quickly to brown, allowing discrimination of various concentrations of H_2S by the naked-eye. Similarly, the fluorescence intensity of **87** in solution increased significantly when H_2S was added. **87** is very sensitive, with a detection limit down to the nanomolar level for H_2S, and was selective for H_2S over a wide range of analytes. Very recently, the Tang group synthesized a peptide-functionalized TPE-based fluorescent nanoprobe bearing 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(poly ethylene glycol)-2000] 1,2-dioleoyl-3-trimethylammoniumpropane (chloride salt) (DOTAP) and 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[maleimide(polyethylene glycol)-2000] (DSPE-PEG2000-Mal) for selective detection of H_2S over other interferents. This fluorescent nanoprobe also demonstrated good cell-membrane permeability and was shown to be useful for the visualization of exogenous and endogenous H_2S levels, as well as the detection of H_2S in zebrafish.[137]

Detection or separation of VOCs from aqueous solution is important for water treatment and analysis. Many conventional and reported methods in literature for VOC detection are time-consuming, tedious and expensive. Thus, there is continuing

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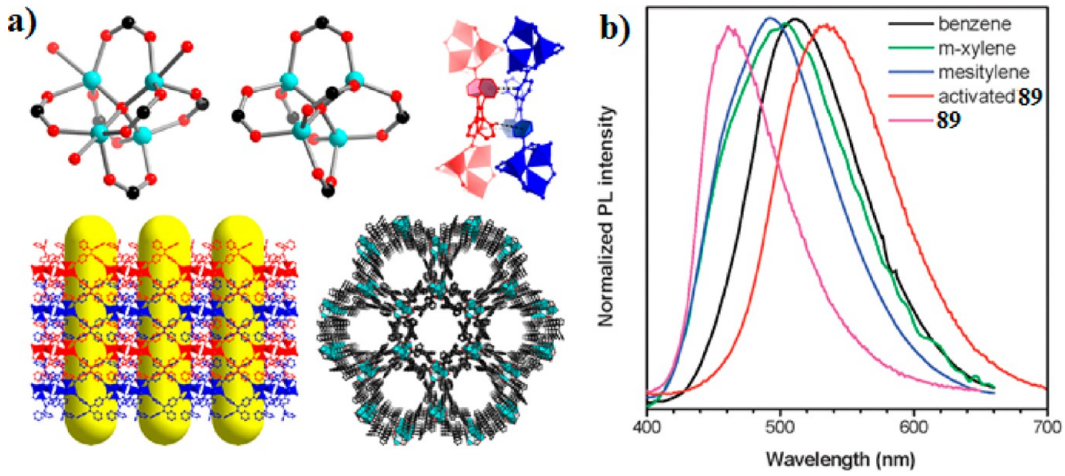

Figure 35. (a) Crystal structure of TPE-based metal−organic framework **87**. (b) Photoluminescence spectra of as-synthesized **89** and activated **89** with selected guest VOCs (λ_{ex} = 365 nm). (a) Adapted with permission from ref 138. Copyright 2014 American Chemical Society. (b) Adapted with permission from ref 139. Copyright 2015 Royal Society of Chemistry.

need to develop a simple protocol for detection of VOCs. TPE, with the unique feature of the AIE effect, has emerged as a popular building block to construct luminescent MOFs for the detection of VOCs.

The first TPE-bearing MOF with responsive "turn-on" fluorescence for sensing of VOCs was reported by Zhang and co-workers in 2014 (Figure 35a).[138] This "turn-on" fluorescence MOF was constructed from the TPE-based ligand 4,4′-(2,2-diphenylethene-1,1-diyl)dibenzoic acid (compound **88**) and $Zn(NO_3)_2{\cdot}6H_2O$ in *N*,*N*-diethylformamide. The resultant MOF exhibits strong responses toward VOCs such as benzene, toluene, xylene, and mesitylene via peak shifts in the fluorescent emission spectra. These fluorescence shifts were ascribed to the interaction between VOCs and the phenyl rings in MOF, with restriction in the rotation/vibration of these phenyl rings able to block nonradiative decay and trigger peak shifts. Another TPE-based MOF used for VOC sensing was constructed from tetrakis[4-(4-carboxyphenyl)phenyl]ethene (**89**) as a building block with Zn^{2+}, and was designed and synthesized by Liu's group.[139] To prepare for VOC sensing, the MOF was activated by a solvent exchange process with dichloromethane, followed by drying under vacuum at 50 °C. The wavelengths of fluorescence emission of the activated MOFs are greatly shifted when exposed to various VOCs (Figure 35b). For example, when MOF **89** was exposed to mesitylene, the activated MOF showed a strong blue shift of 42 nm compared to the pristine activated MOF. Recently, we reported a highly fluorescent MOF bearing a TPE functionality for sensing VOCs, in which tetrapyridine-tetraphenylethene (**82**) and zinc chloride were used.[140] The resultant MOF has an infinite 1D ribbon structure with large channels (13.4 × 17.5 Å), and exhibits AIE behavior in the solid state, which further enhanced when sensing VOCs. Our studies clearly demonstrate that the 1D MOF can be used as a fluorescence sensor for the detection of methyl-substituted VOCs.

Compounds containing the TPE moiety have also been conjugated into a polymer matrix to obtain luminescent materials, for the direct detection of gas as well as VOCs. Ghosh and co-workers linked pentiptycene TPE with acetylene with the Sonogashira cross-coupling reaction to prepare polymer **71** (for structure see Figure 30).[141] This polymer sensitively responds to aromatic and aliphatic isocyanates in air with a detection limit at the ppt level, which is much lower than the permitted exposure limit of 5 ppb. The response time of polymer **71** toward isocyanates is very fast, within a period of 10−60 s. In 2016, Lu and co-workers constructed a new TPE-based sensory polymer (**90**) for CO_2 detection by a facile two-step reaction between branched polyethylenimine and a TPE unit.[142] The pristine polymer **90** solution emits very weakly. However, upon addition of CO_2, fluorescence intensity at 475 nm is increased up to 19-fold. The sensing mechanism is attributed to the reaction of CO_2 with alkylamines to induce a phase transition from solution-to-precipitation, which induces the AIE behavior of **90**. This new polymer also exhibits excellent selectivity toward CO_2 in ethanol over CO, SO_2, H_2S, and common VOCs. Recently, Zhao and co-workers reported a series of porous organic framework (POFs) molecular rotors with responsive fluorescent behavior bearing AIE-active TPE moieties.[143] These fluorescent POFs recognize various VOCs of different size by specific fluorescence emissions due to the AIE mechanism. These POFs, when exposed to different VOCs, restrict the degrees of motion of the flexible phenyl ring of the TPE rotors, leading to the restricted freezing of rotors in fluorescent conformations. Importantly, the gas-phase detection of arene vapors using POFs was shown to be sensitive, selective, and recyclable. Thus, POFs based on AIE-active TPE have demonstrated the great potential of these materials for chemical sensors for VOC detection.

In another recent report the Tang group reported the construction of fluorescent nanosheets via self-assembly of TPE with cyclodextrins (CDs) in which the hydrophobic TPE luminophores are inserted between two hydrophilic CD layers based on the grasp-report strategy, which detect VOCs rapidly and selectively.[144] The mechanism of detection of VOCs follow a simple strategy, the hydrophobic cavity of the outer CD layers collected VOCs and subsequently transport them to the TPE layers where quenching of the emission of TPE occurs as illustrated in Figure 36. These self-assembled nanosheets allowed rapid detection of xylene within 1 s at a concentration of 5 μg/L.

The Chen group reported the synthesis of a three-dimensional TPE-based MOF in which 4′,4‴,4⁗,4⁗′,4⁗″-(ethene-1,1,2,2-tetrayl)tetrakis(1,1′-biphenyl-4-carboxylic acid (old number **89**) assembly with $Cd(NO_3)_2{\cdot}4H_2O$, produced the new porous MOF $[Cd_3(ettc){\cdot}1.5(H_2O)_2(dmf)]_n{\cdot}(dmf)_{12n}$ (UTSA-86). They also found that this multifunctional MOF exhibited good

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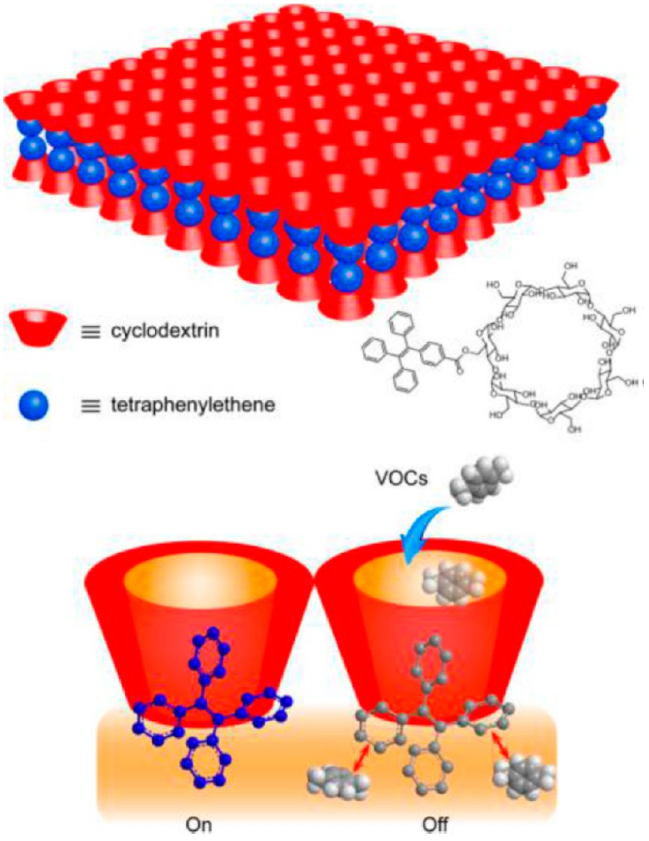

Figure 36. Graphical illustration of self-assembled nanosheets of CDs and TPE for sensing of VOCs. Adapted with permission from ref 144. Copyright 2016 American Chemical Society.

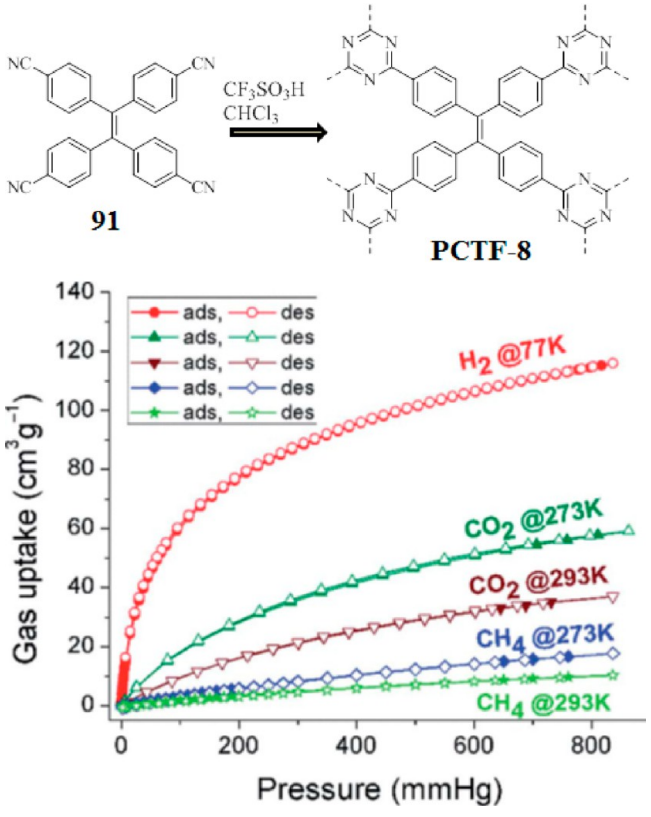

Figure 37. Synthesis of PCTF-8 from tetra(4-cyanophenyl)ethylene **91** by using TFA as a catalyst at room temperature for use in sensing of H_2, CO_2, and CH_4. Adapted with permission from ref 146. Copyright 2016 Royal Society of Chemistry.

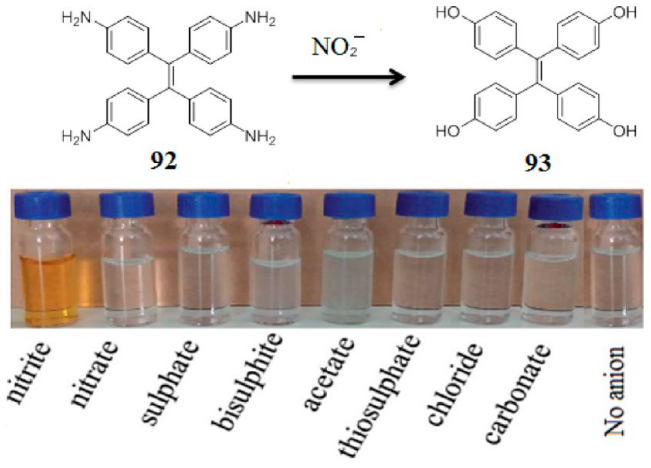

Figure 38. Colorimetric response of TA-TPE **92** toward NO_2^- and selectivity over other anions. Adapted with permission from ref 18. Copyright 2016 Royal Society of Chemistry.

stability, high porosity, and moderately high selectivity for CO_2/CH_4 and CO_2/N_2 gas separation at room temperature. This luminescence MOF was also used for selective sensing of Cu^{2+} and Zn^{2+} metal ions.[145]

Bhunia and co-workers synthesized the porous covalent triazine-based framework (PCTF-8) from tetra(4-cyanophenyl)-ethylene units which directly connected to strong electron-accepting triazine rings **91** in $CHCl_3$ in the presence of a catalytic amount of trifluoromethanesulfonic acid (TFA) as shown in Figure 37.[146] The PCTF-8 framework shows good thermal stability (>400 °C) due to presence of triazine groups and was shown to be a very good candidates for practical applications in postcombustion CO_2 (56 cm^3 g^{-1}) and CH_4 (17 cm^3 g^{-1}) capture. The PL properties of the PCTF-8 framework were used for detection of nitroaromatics, where the fluorescence emission intensity was quenched (ca. 71%) in the presence of 2,4,6-trinitrophenol (TNP). Interestingly, the authors also used the PL properties of the PCTF-8 framework for H_2 evolution from water in the presence of an electron donor and a co-catalyst for organic photocatalysis (Figure 35).

TPE derivatives can also be used to sense small ions and molecules. We recently reported the design and synthesis of tetraamino-substituted tetraphenylethene (TA-TPE) **92** (Figure 38), which was used for sensing of nitrite ions (NO_2^-) through a visible color change in water via a reductive pathway.[18] TA-TPE **77** is colorless in water, but in the presence of NO_2^- ions it changes to dark yellow tetrahydroxyl-TPE **93**. The detection limit of NO_2^- ions was as low as 17.7 ppb.

9. CONCLUSION AND PERSPECTIVE

In this Review we have discussed various sensors based on the AIE-active luminophore TPE. The versatility of these types of sensors has been demonstrated through the broad range of analytes, including ions, pH, biological molecules, and glucose, among others. Since 2001, several research groups have used the TPE core as a building block for the creation of various functional architectures with a range of applications including self-assembly, mechanoluminscent materials, and OLEDs. This Review has also covered synthetic strategies that allow researchers to function-

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alize TPE derivatives, allowing tuning of photophysical and chemical behavior via modification at the periphery and conjugation to biological moieties such as peptides, amino acids, receptors for binding sites for various analytes. We have also shed some light on approaches to utilize TPE the molecular structure and properties to design TPE-based functional architectures to fulfill needs in the areas of sensing, in particular biosensing. Furthermore, we have shown that such modifications lead to TPE derivatives that adopt preferred conformations in supramolecular systems with a wide variety of soft matter with applications in biomedical and sensing research areas. A high level overview of the diverse types of biosensors was also provided along with working principles, advantages, and applications of various biosensors. We have also illustrated various difficulties for selective sensing for which some solutions exist, such as the AIE phenomenon; however, still more research efforts are required in order to find better alternatives in conjunction with AIE-active molecules. An important point will be the immobilization of biomolecules; i.e., biomolecules are attached to the transducer as strongly as possible, but the problem with this is that the reaction of enzymes in free solutions is better understood than in the solid state and aggregated states. The second point is selectivity, and research should be focused on the development of cheaper biosensors that are both selective and sensitive in the presence of common interferences.

Nevertheless, we believe that AIE-active molecules in conjugation with selective receptor sites for specific analytes to develop faster, consistent, precise, transportable and low-cost biosensors and can be achieved in near future. The development of new TPE-based AIE luminogens in conjugation with optically active dyes (naphthalenediimide, perylenediimide, porphyrin, etc.)[147−150] that are able to show red light or near-infrared light emission, and their utilization in applications such as supramolecular assemblies,[151−153] MOFs,[154] and solar cells[155] would also be key points for further research in this area. We have demonstrated that TPE luminophores in conjugation with other functionalities, combined with AIE properties of TPE derivatives, offers researchers an open field to investigate new materials with a broad range of applications

In conclusion, we have established that TPE itself is an ideal building block to construct diverse functional materials in the future. The TPE-based AIEgens are easy to synthesize and modify, and it is this AIE activity in the solid state that makes them unique. Although the advantage of AIE in TPE derivatives has been employed in some applications as described in this Review, we believe there are still many possible applications that have not yet been exploited, and that the research in this Review will continue to be expanded upon by a large community of researchers.

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