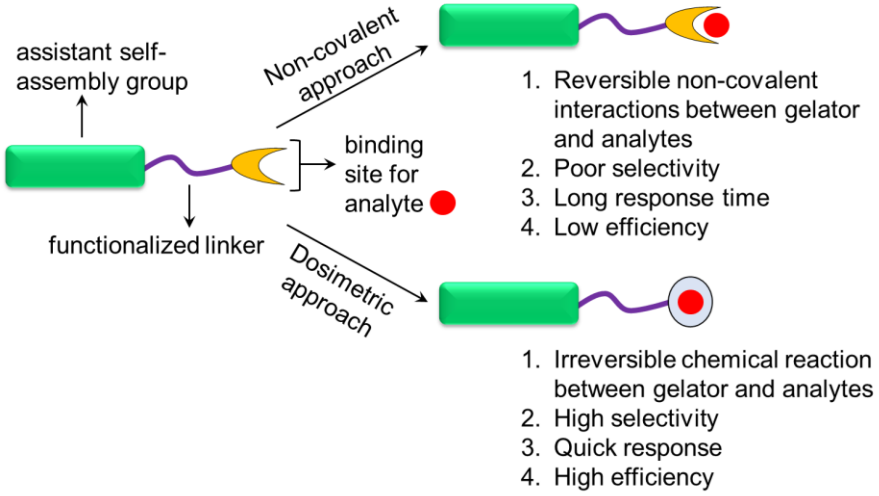
Graphical Abstract

Supramolecular gels formed by the self-assembly of organic molecules are useful in many areas from materials to medicine. Of the different applications, exploitation of gels for visual detection of analytes is a fairly recent trend in gel chemistry. Most of the gel-based sensors rely on non-covalent interactions between the gelator molecules and the added chemical analytes and therefore, often suffer from less selectivity and long response time. In this context, dosimetric gelator probes are superior to other gel-based sensors with high selectivity and fast response time. Unlike non-covalent binding site, dosimetric gelators typically contain a reaction centre and undergo a specific chemical reaction selective to an analyte resulting in either formation or rupturing of covalent bonds. In this review, we provide an up-to-date report of various reaction-based gel systems applied for sensing of analytes. We elaborately discus the concept, design principles, self-assembly properties, and reaction mechanisms of such gelators. We also highlight the limitations, challenges and the necessity of further exploration of dosimetric gels in this domain.



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Dosimetric gelator probes and their application as sensors

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ABSTRACT

Supramolecular gels formed by the self-assembly of organic molecules are useful in many areas from materials to medicine. Of the different applications, exploitation of gels for the visual detection of analytes is a fairly recent trend in gel chemistry. Most of the gel-based sensors rely on non-covalent interactions between the gelator molecules and the added chemical analytes and therefore, often suffer from less selectivity and long response time. In this context, dosimetric gelator probes are superior to other gel-based sensors with high selectivity and fast response time. Unlike non-covalent binding sites, dosimetric gelators typically contain a reaction centre and undergo a specific chemical reaction selective to an analyte resulting in either formation or rupturing of covalent bonds. In this review, we provide an up-to-date report of various reaction-based gel systems applied for the sensing of analytes. We elaborately discuss the concept, design principles, self-assembly properties, and reaction mechanisms of such gelators. We also highlight the limitations, challenges, and the necessity of further exploration of dosimetric gels in this domain.

1. Introduction

Supramolecular non-covalent interactions such as electrostatic interaction, hydrogen bonding, hydrophobic interaction, aromatic stacking are the heart of bio-organic chemistry.[1] Incorporation of such interactions into synthetic materials is a promising way to harvest life-like systems with tunable and adaptive properties.[2-4] In the last few decades, a vast area of materials research has been focusing on the development of self-assembled functional materials utilizing non-covalent interactions.[5-10] Among various functional materials, supramolecular gels represent a class of soft materials that have many applications in various fields including tissue engineering, catalysis, water purification etc.[11-15] Typically, supramolecular gels are formed when small organic molecules (called gelators) self-assembled to a fibrous network that immobilizes the solvent. As a result, despite containing a huge amount of liquid (~99 wt %), these materials potentially behave as a viscoelastic solid. Interestingly, the self-assembled structure of gels is maintained by non-covalent interactions which makes supramolecular gels dynamic and responsive to various external stimuli like light, pH, ultrasound, chemical analytes etc., allowing a change in the physio-chemical properties of the materials.[16-20] Such stimuli-responsive behavior expands the functions and applications of supramolecular gels in the fields of drug delivery, sensing, actuators, and optoelectronics.[14, 17, 21-29]

Of the different applications, exploitation of supramolecular gels for visual detection of chemical analytes is a fairly recent trend in gel chemistry.[27, 28, 30] Sensing of chemical analytes draws attention due to their environmental and physiological significance. Chemical analytes such as cations, anions, and neutral biomolecules like amino acids, carbohydrates etc. are associated with varieties of physiological processes in organisms.[31-35] However, metal ions and anions also cause environmental pollutions.[34, 36-38] Exposure of such analytes is extremely toxic to the human body and can have adverse effects on health, such as kidney failure, breakdown of the nervous system, brain damage, and various cognitive and motion disorders. Metal ions (such as Cu^{2+}, Cd^{2+}, Pb^{2+}, Hg^{2+} etc.) and anions (such as F^-, CN^- etc.) are extensively used in many industries and are directly discharged into the environment as industrial waste. Their accumulation into water and soil is a real threat to the aquatic ecosystem as well as for humans. In reality, with the rapid growth of industry and economy, environmental pollution has become a serious issue all over the world. Hence, detection and separation of such hazardous chemicals are of contemporary interest.[39, 40]

Various methods such as atomic absorption spectrometry, chromatography, electrochemical techniques, fluorescence, plasma mass spectrometry etc. have been developed to detect chemical analytes.[41-48] These methods include the use of expensive and sophisticated instruments, and well-trained personnel to operate them. However, each kind of sensor has its specificity, advantages, and limitations in certain aspects. In this context, supramolecular gels provide a means of detecting chemical analytes without use of any instrument.[27, 49, 50] Typically, a gel-based detection technique involves interaction between the externally added chemical analyte and the gelator molecules which can produce three different responses from the system (Figure 1).[49, 51, 52] An initially formed gel can

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undergoes sol formation due to destruction of the intermolecular forces on perturbation and thereby exhibits gel-to-sol transition. Alternatively, in presence of chemical analytes, the intermolecular interactions can be reinforced and so a sol-to-gel transition may also happen. Another possibility is a gel-to-gel transition associating with a change in color, macroscopic volume of the gel after treatment with the chemical analytes. Hence, gel-based sensors are simple, cost-effective, instrument-free, and the sensing event can be accomplished visually either by a phase transformation or by a naked eye detectable color change of the gel. Furthermore, compared to other methods like fluorometric and colorimetric sensing in the solution phase, the gel-based detection technique demands a relatively high concentration of gelator ($\geq 10^{-3}$ M). For a given gelator, gel phase interactions often show better selectivity for analytes than in the solution state.[53-55]

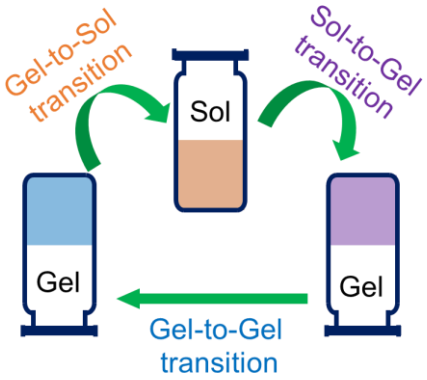

Figure 1. Schematic representation of phase transformations of LMWGs in presence of analytes.

In this context, several reviews have been published focusing on the sensing properties of gels. [30, 56-58] Liu *et al.* summarized various techniques of exploring hydrogels for molecular detection and biosensing.[50] Recently, the Li group reviewed the developments and prospects of anion responsive supramolecular gels.[28] Cao *et al.* presented fluorescent supramolecular gels as an effective sensing medium for various chemical analytes.[27] Scrutiny of the literature reveals that most of the gel-based sensors rely on non-covalent interactions between gelator molecules and the added chemical analytes and therefore, they often suffer from less selectivity and long response time. On contrary, dosimetric gelator probes (or reaction-based gelator probes) contain a reaction centre and interact covalently with the chemical analytes.[59] Depending on the reaction centre present in the backbone, gelator molecules undergo a specific chemical reaction selective to an analyte resulting in either formation or rupturing of chemical bonds. Such a chemical transformation during the recognition process alters the hydrophobic/hydrophilic balance of the compound (gelator) and so the gelation behaviour. Hence, with appropriate structural designs, such reaction-based probes always exhibit better selectivity compared to other gel-based sensors.[60] Despite such advantages, very little work has been carried out in this domain. This is probably due to poor understanding of gelling behavior of a chemical compound with proper structural parameters.[61-63] Although various computational techniques, crystal engineering approach, supramolecular synthon approach etc. are developed to predict gelation propensities of compounds, designing of molecules that would form gel is still a difficult task.[64-68] Additional burden relates to the incorporation of a specific reaction centre into the gelator skeleton as a subtle change in gelator structure significantly imparts the gelling behaviour.[60, 63, 69-71] Apparently, the discovery of new dosimetric gelators is mostly serendipitous even today, however, the discussion on functionalized properties of dosimetric gelators are hardly incorporated in reviews. Hence, a review systematically summarizing the design principles, self-assembly properties, reaction mechanisms, advantages and limitations of dosimetric gelator probes is a long overdue.

2. Designing of gel-based sensors: noncovalent *vs* dosimetric approach

The design of small molecule-based gelators capable of detecting analytes is an important aspect of supramolecular chemistry. Typically, an analyte responsive gelator contains three different segments: an assistant self-assembly group, a functionalized linker, and a binding site for the analyte (Figure 2).[28, 72] The assistant self-assembly segment is either a hydrophobic or hydrophilic group (e.g., long alkyl chains, steroid derivatives, aromatic π-surfaces, sugars) that assist self-assembly of the gelator molecules in solution.[73-77] Interestingly, aromatic π-surfaces like pyrene, naphthalene, anthracene, fluorenyl etc. typically act as a capping agent and encourage gelation through π-stacking, but they can also serve as a signaling unit to reflect the changes in the optical properties of the gelators upon interaction with the chemical analytes.[27, 75, 78-80] The linker segment usually contains amide or urea bonds that not only maintain structural rigidity and conformational flexibility of the gelator but also promote self-assembly through intermolecular hydrogen bonding.[81-86] The binding site represents the centre with which the chemical analyte interacts. Depending on the nature of the interactions, broadly two types of approaches are followed in designing the reaction centre. First, a noncovalent approach where the incoming guest/analyte interacts non-covalently with the gelators.[87-89] Such interactions are reversible and can be altered by applying a counter analyte (e.g., chelating agent). For different analytes, the binding site can be manipulated with various functionalities. For example, while pyridine, imine, benzimidazole, salicylimine, and acylhydrazone segments, etc. are utilized as metal ion binders,[89-91] hydrogen bonding functionalities such as hydroxyl, urea, salicylamide, amide, sulphonamide etc. are incorporated as anion binding functionality.[28, 58, 92, 93] In some cases, the binding site is manipulated with charged species like pyridinium, benzimidazolium, carboxylate etc. to allow better interaction with the oppositely charged guest/analyte.[56, 94, 95] Most of the gel-based sensors belong to this category. Although such systems are effective, however, there are several limitations of this approach. As the sensing event relies on non-covalent interactions, most of the gelators suffer from poor selectivity and often exhibit multiple responses for two or more analytes.[94, 96-99] As one example,

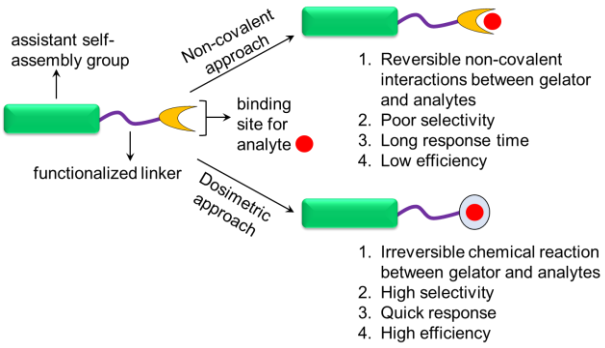

Figure 2. Cartoon representing designing of gel-based sensory probes.

Ghosh *et al.* introduced cholesterol-coupled sulfonyl hydrazone gelator **1** as a naked-eye sensor for anions.[100] Compound **1** formed a stable gel in DMSO-H_2O through intermolecular H-bonding and hydrophobic interactions involvingthe sulphonamide moiety and cholesteryl segment respectively (Figure 3). The gel exhibits interactions with basic anions and undergoes gel-to-sol transitions in presence of both F^- and CN^- due to deprotonation of the sulfonamide –NH. To discriminate the anions further, it demands different chelating agents which makes this approach complicated. For the given example, discrimination between F^- and CN^- was achieved by treating the anion-induced broken gels with Ca^{2+} which showed a strong affinity for F^- ions.[100] Consequently, scavenging of F^- ions by Ca^{2+} ions from the medium recovered gelation. Furthermore, for a given gel, the selectivity towards analytes also depends on the concentration of the analytes. For example, the DMSO:$CHCl_3$ (1:5, v/v) gel of the pyrrole functionalized tetra-amide **2** was destroyed into solution in the presence of 4 equiv. amounts of F^-, AcO^- and $H_2PO_4^-$ within 2.5 hours (Figure 3).[101] Cl^- ions also caused partial disintegration of the gel under identical conditions. Interestingly, when the concentration of the anions was reduced to 1 equiv., the gel showed phase transformation selective to F^- ions. At low concentration, other anions were unable to bring any changes in the gel structure even after 2.5 h. Hence, such systems are effective in selective anion sensing only at a low concentration of anions.[101, 102] Moreover, in many cases, the gelators take long response time (even several hours) to undergo phase transformation in presence of analytes. In short, poor selectivity, long response time and use of chelating agents for discrimination of analytes make this noncovalent approach complicated and less effective, which necessitated the development of reaction-based gelators to overcome such drawbacks.

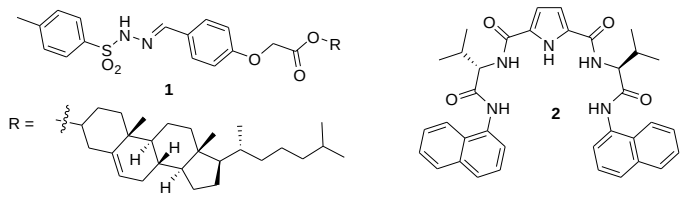

Figure 3. Chemical structures of compounds **1** and **2**.

The dosimetric gelator differs from other sensors only in the binding site where instead of reversible noncovalent interactions, a chemical reaction occurs in presence of the analyte which causes permanent structural changes of the compound either through formation or rupturing of a covalent bond (Figure 2).[49, 59] The rest of the gelator segments follow similar design strategies. The generation of such newly structure leads to a change in the gelling behavior of the system. The choice of the reaction centre entirely depends on the targeted analyte which makes these gelators superior over other gel-based sensors in terms of selectivity. Another advantage is their fast response time which can further be controlled by manipulating the analyte concentration.[60] This allows real-time monitoring of the sensing processes. Interestingly, the reaction centres are often either a part of a chromophoric unit or connected to a chromophore. As a result, there are always remarkable spectroscopic changes due to permanent chemical modifications which can be utilized to monitor the sensing process.[49] In the next section, we elaborately discuss the design strategies of different dosimetric gelator probes with an emphasis on self-assembly properties and the sensing mechanism of the compounds.

3. Designing of dosimetric gelator probes

The rational design of dosimetric gelator probes with targeted functionalities is a challenging task. To develop such gelators, the first step is to find out a chemical reaction that can be mediated by a particular analyte. This is important to avoid interference from other chemical analytes in the sensing process. The reaction centre is often chosen based on a particular property of an analyte (e.g., nucleophilicity, bond energy etc.). The next step is to synthesize a chemical compound incorporating the selected reaction centre. Here the design of the compound is vital. The compound must be synthesized following general strategies of designing supramolecular gelators (as discussed in Figure 2) so that the functionalized compound acts as a potential gelator. The third step involves solvents screening to identify an optimum condition such as concentration, temperature, solvent compositions, non-gelling additives etc. at which the functionalized compound results in a gel. Typically, to form a gel, a balance between hydrophobicity and hydrophilicity of the compound is required. When an analyte reacts with the gelator covalently, this hydrophobic/hydrophilic balance gets disturbed. Consequently, the gel collapse into solution and thereby executes its visual sensing. It is also possible that the functionalized compound does not form a gel in the tested conditions. In such cases, modification of chemical structure of the compound is carried out to enhance the self-assembly tendency in solution. This is usually achieved either by increasing the number of hydrogen bonding functionalities in the linker segment or by modifying the aromatic π-surface and increasing the surface area of the hydrophobic segment keeping the reaction centre intact.

3.1. Functionalized gelators with Michael acceptor groups

Dosimetric gelators with Michael acceptor functionalities are typically exploited to target analytes having high nucleophilicity involving an addition reaction. For example, higher nucleophilicity of CN^- compared to other basic anions such as F^- and AcO^- can be utilized to react irreversibly with dicyanovinyl moiety acting as a Michael acceptor.[103] Other anions remain silent to this reaction. Ghosh and co-workers provided a simple route to synthesize gelators with such functionalities. They took an aldehyde functionalized compound (compounds **3**) (Figure 4A). The aldehyde functionality can easily be modified with the desired Michael acceptor moiety involving a condensation reaction. They synthesized gelator **4** by Knoevenagel condensation reaction between the aldehydes **3** and malononitrile in water.[104] After solvent screening, it was noted that compound **4** gives an orange-yellow colored gel in CH_3CN. When the gel was treated separately with various anions, it was only CN^- that brought about a gel to sol transition within 10 mins associating with an intense deep red coloration. The gel state remained unaffected in presence of other anions such as halides (F^-, Cl^-, Br^- and I^-), AcO^-, $HP_2O_7^{3-}$, $H_2PO_4^-$, HSO_4^- and NO_3^-. These results thus demonstrated selectivity of the gelator **4** for CN^- ions in the sensing process over other anions. Such an unprecedented degree of selectivity was attributed to the higher nucleophilicity of CN^- than other tested anions that facilitates nucleophilic addition to the cyano-activated olefinic double bond. The cyanide adduct formation with the dicyanovinyl moiety was confirmed by recording the shifting of the vinylic proton (Ha) from 7.75 ppm to 4.41 ppm in presence of CN^- in proton NMR experiments (Figure 4B). Not only in the gel state but gelator **4** also showed interactions selective to CN^- ions in solution and recognized it by exhibiting ratiometric changes in absorption spectra.

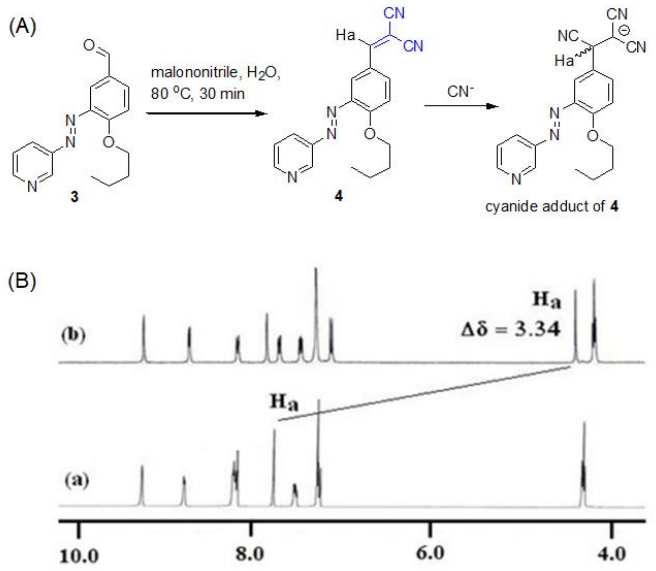

Figure 4. (A) Synthesis of **4** from the precursor aldehyde **3** and the change in chemical structure of **4** upon interaction with CN^-. (B) Partial ^{1}HNMR spectra of (a) **4** [c=1.18 x 10^{-2} M] and (b) **4** with 1 equiv. amount of CN^- after 15 mins in $CDCl_3$. Reproduced with permission from reference [104].

Using a similar strategy, the same research group synthesized gelator **6** by reacting aldehyde **5** with malononitrile in ethanol (Figure 5).[60] Compared to **4**, compound **6** exhibited better gelation ability and could gelate a number of solvents such as cyclohexane, DMSO-CH_3OH (1:1, v/v), DMF-CH_3OH (1:1, v/v), and toluene-CH_3OH (1:2, v/v). The gelation of **6** in various solvents was primarily driven by hydrophobic interactions exerted by the large cholesteryl segment. Like **4**, the toluene-CH_3OH (1:2, v/v) gel of **6** (conc. 8 mg/mL) also recognized CN^- ions selectively from a series of anions involving rapid disintegration to sol (within 15 mins in presence of 2 equiv. of CN^-). Again, the addition of CN^- to the dicyanovinyl core resulted in a change in the chemical structure of the compound leading to collapse of the organogel network. Importantly, at a particular gelator concentration, the rate of gel to sol transition was controlled by reducing the concentration of CN^- ions. It was found that, even 0.5 equiv. amounts of CN^- was sufficient to collapse the gel within 4h. In the sensing process, the detection limit for CN^- was calculated to be 2 x 10^{-3} M.

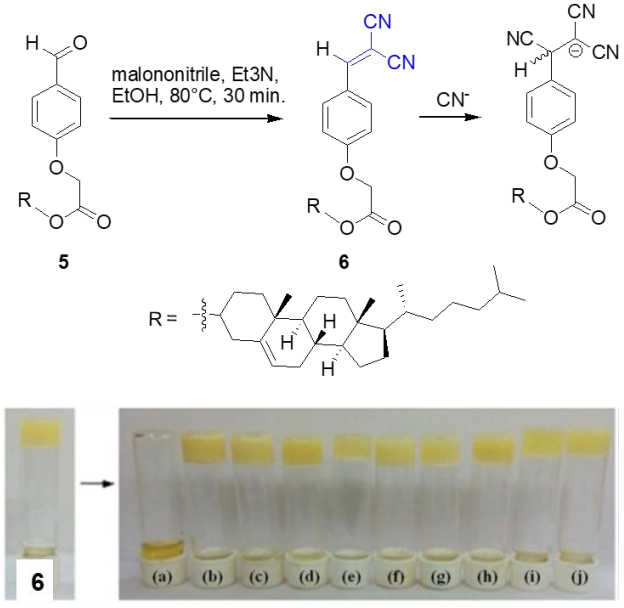

Figure 5. (Top) Synthesis of **6** from the precursor aldehyde **4** and the change in chemical structure of **6** upon interaction with CN^-. (Bottom) Phase transformation of the organogel of **6** in presence of various anions. |From left to right: (a) CN^-, (b) F^-, (c) AcO^-, (d) $H_2PO_4^-$, (e) Cl^-, (f) Br^-, (g) I^-, (h) HSO_4^-, (i) CLO_4^- and (j) NO_3^-. Reproduced with permission from reference [60].

Structural analysis of **4** and **6** reveals that both the compounds are devoid of any hydrogen bonding functionality to interacts with anions. This is perhaps crucial to achieving selective interaction with CN^-. In this context, it is obligatory to discuss the anion sensing behavior of compound **7** (Figure 6).[104] Compound **7** has similar Michael acceptor functionality to that of **4**, but instead of ether linkage, it contains a phenolic -OH group on the backbone. In solution, unlike **4**, compound **7** exhibited changes in absorption spectra for multiple anions like F^-, AcO-, AcO^-, $HP_2O_7^{3-}$ and $H_2PO_4^-$. The changes in the absorption spectra were due to deprotonation of the phenolic -OH group in the presence of anions. Interestingly, CN^- ions also brought about similar spectral changes in the solution. The authors established that, instead of Michael addition, CN^- ions undergo H-bonding with the phenolic -OH of **7** and caused deprotonation similar to other basic anions. Even if the Michael acceptor group contains hydrogen bond donor functionality, CN^- undergoes hydrogen bond formation instead of Michael addition.[105] For example, the monosubstituted diaminomaleonitrile core containing a free amine group is a well-known Michael acceptor (compound **8**) (Figure 7).[105] The Schiff base **8** can be achieved from the same aldehyde **5** after reaction with diaminomaleonitrile. Compound **8** exhibited gelation in 1,2-dichlorobenzene and DMF-H_2O (1:1, v/v). The 1,2-dichlorobenzene gel of **8** turned into solution in presence of both F^- and CN^- ions due to deprotonation of the free amine group as confirmed by various spectroscopic studies. These results highlight the necessity of proper design of gelator molecules to be effectively used as reaction-based sensors.

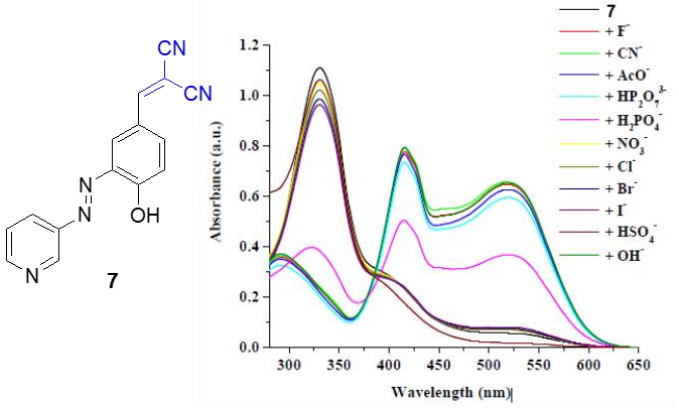

Figure 6. UV-vis spectral changes of **7** (c = 2.50 x 10^{-5} M) upon addition of 4 equiv. of various anions (c = 1.0 x 10^{-3} M) in CH_3CN containing 0.25% DMSO. Reproduced with permission from reference [104].

Although compound **8** acted as a H-bonding motif-based sensor for anions, the same gelator served as a dosimetric sensor for hydrazine, a base having greater nucleophilicity compared to other analogous amines, in DMF-H_2O (1:1, v/v) (Figure 7).[106] Nucleophilic attack of hydrazine at the malenonitrile segment resulted in collapse of the hydrogel network into the sol, and thereby executes its visual sensing. As a result of hydrazine adduct formation, the imine proton of **8** underwent a substantial upfield chemical shift in ^{1}H-NMR spectroscopy. Other amines such as NH_2OH, ethylenediamine, ethanolamine, triethylamine, n-

propylamine, ethylamine, n-butylamine, and aniline were unable to bring about any changes in the gel state due to poor nucleophilicity. The selectivity of **8** for hydrazine was also investigated by recording the changes in absorption spectra in the solution. While the addition of hydrazine decreased the absorbance at 323 nm and 280 nm, corresponding to n-π* and π-π* transitions, respectively, the rest of the tested amines were noninteractive.

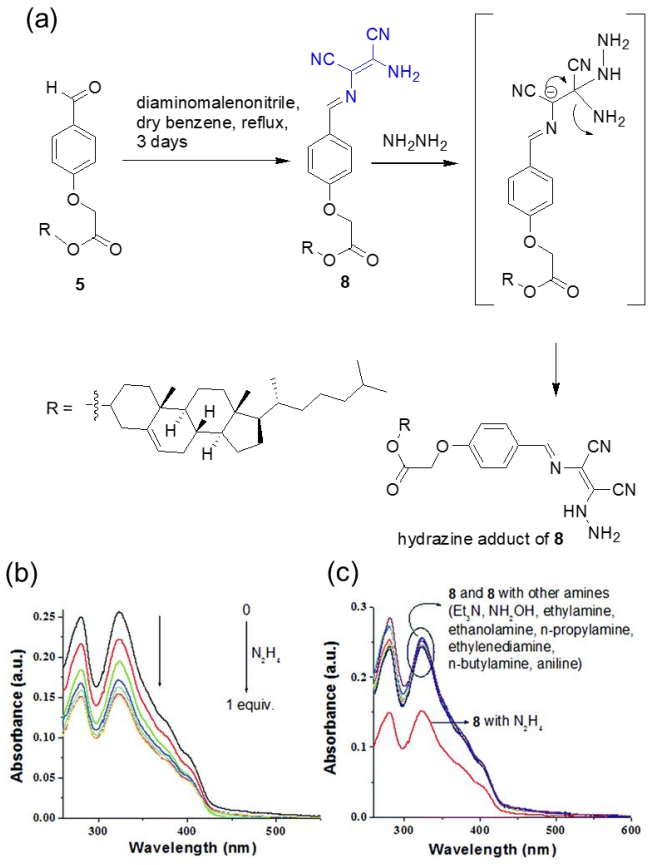

Figure 7. (a) Synthesis of **8** from the precursor aldehyde **5** and the change in the chemical structure of **8** upon interaction with hydrazine.[106] (b-c) Changes in the absorbance of **8** (c = 2.50 × 10^{-5} M) upon addition of 1 equiv. amount of (b) hydrazine and (c) different amines (c = 1.0 × 10^{-3} M) in DMF–H_2O (1 : 1, v/v). Reproduced with permission from reference [106].

In a recent study, Fang *et al.* successfully explored 2-(hexadecylthio)oxazolo[4,5-b] phenazine **9** as a cyanide sensor involving a gel-to-gel transition.[107] The phenazine derivative formed a stable gel in DMSO through Van der Waals interaction exerted by the long alkyl chain. Additionally, the organogel exhibited strong aggregation-induced yellow emission at 523 nm due to π-π stacking. When aqueous solutions of anions were added to the gel, a red-shifted emission with quenching in emission intensity of the gel was noticed selective to CN^- ion. During the sensing process, the gel state was maintained throughout, however, the color of the gel was changed from yellow to non-fluorescent under UV-light in the presence of CN^-. The changes in optical properties of the gel were ascribed to the destruction of π-π stacking due to cyanide adduct formation as shown in Figure 8. The gel state displayed negligible interaction with other anions. Interestingly, the gel showed a detection limit of 4.18 x 10^{-10} M for CN^- ions, which is significantly lower than most of the reported fluorescent gel-based sensors.

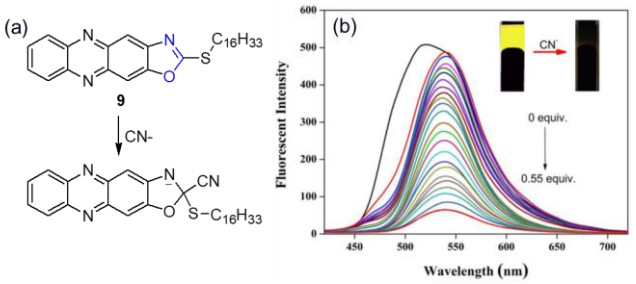

Figure 8. (a) Chemical reaction occurred between **9** and CN^-. (b) Change in emission spectra of the DMSO gel of **9** upon addition of different concentrations of CN^-. Inset represents the corresponding change in color of the gel. Reproduced with permission from reference [107].

In the same line, a supramolecular gelator **10** (Figure 9), with indolin-2-one and quinoline moieties has been reported to form an orange-colored gel in DMSO/H_2O (1:1).[108] Apart from the quinoline-indolin-2-one fluorochrome, the structure contains an *N*-alkyl functionality possessing a large hydrophobic area. The addition of water is suggested to enhance the solvophobic interactions, which acted as the driving force for self-assembly. When aqueous solutions of various anions were added to the DMSO solution of **10**, the color of the gel changed from orange to purple only in the presence of CN^- ion. It was concluded that **10** undergoes a pseudo-Michael attack by cyanide ion followed by a ring-closing reaction. Subsequent proton shift from the quinoline -OH and tautomerization reactions finally contributed to produce corresponding conjugate anion responsible for the dark purple coloration of the gel.

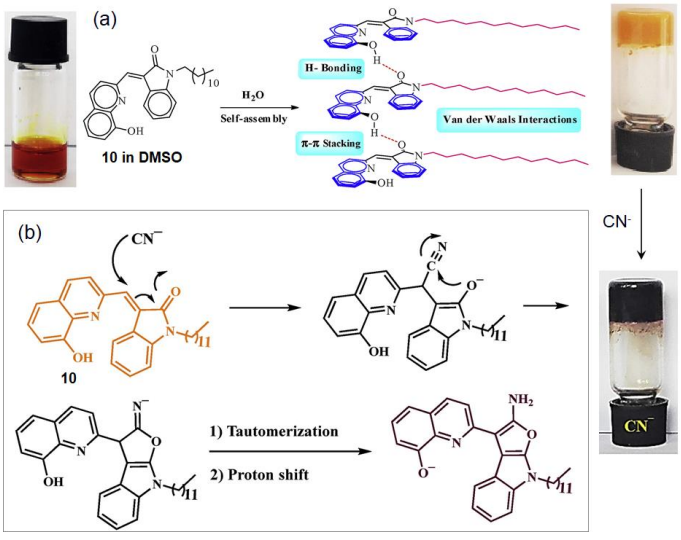

Figure 9. (a) Suggested modes of self-assembly of **10** during gel formation in DMSO/H_2O. (b) Proposed mechanism for the interaction of **10** with CN^- during gel to gel transition. Reproduced with permission from reference [108].

3.2. Diazotization reaction for detection of nitrite

A large family of functionalized gelators contains photoresponsive azo-functionality.[109, 110] The azo-based gelators are synthesized from a diazonium ion intermediate which is typically generated in situ by the reaction of an aromatic amine with nitrous acid.[111, 112] Subsequent treatment of the diazonium ion with another molecule of an electron-rich aromatic

compound leads to the formation of an orange-yellow azo dye. The nitrous acid is produced within the reaction medium by the treatment of a metal nitrite salt with an acid. McNeil group unutilized this concept to detect NO_2^- ions in water involving a retrosynthesis strategy.[113] First, they identified an azo-based hydrogelator (compound **11**) from the literature survey followed by synthesis of the same gelator following Griess reaction [114] as described in Figure 10. When a suspension of the 3,5-Dichloroaniline in aqueous H_2SO_4 was treated with an aqueous solution of $NaNO_2$, a corresponding diazonium ion was formed. Further addition of sodium-6-hydroxynaphthalene-2-sulfonate (in borax buffer) to the reaction mixture followed by heating allowed the components to get dissolve in water. On cooling the system to room temperature resulted in red/orange colored azo-sulfonate gel. This method was effective in sensing nitrite ions in tap, river, and pond water, as well as water taken from a muddy pond with a detection limit of 500 ppm. However, the success of gel formation after the heat-cool operation depends on the stability of the diazonium salts. It was noticed that aromatic amine with electron-withdrawing substituents led to the formation of stable diazonium salt and thereby were more effective to give a gel.

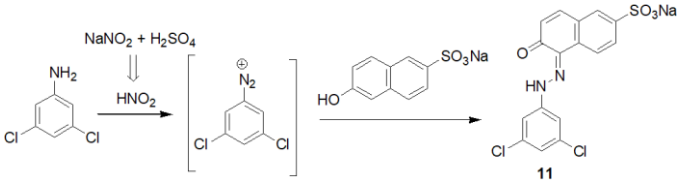

Figure 10. Synthesis of gelator **11** involving diazotization reaction.[113]

The Yi research group modified this strategy to detect NO_2^- over a series of other anions involving a multicomponent system.[115] They synthesized a naphthalimide functionalized compound (**12**) with a terminal carboxylic acid (Figure 11). Compound **12** was insoluble in acetonitrile, however, in presence of 1,2-diaminoanthraquinone (DAQ), a red-colored gel was obtained due to intermolecular hydrogen bonding between the components. In the two-component gel, while compound **12** is noninteracting, the DAQ moiety served as the colorimetric and fluorescence sensing unit for nitrite. On addition of either pure water or aqueous solutions of NaF, $NaHCO_3$, $NaSO_3$, $NaNO_2$, and Na_3PO_4 resulted in collapse of the gel network in all cases with the suspension of the chemical compound **12**. Interestingly, in presence of $NaNO_2$, the gel to sol transition was associated with a color change of the system from red to colorless. As suggested by the authors, **12** provides necessary protons for the conversion of $NaNO_2$ to nitrous acid. The subsequent reaction between the diaminoanthraquinone core with HNO_2 resulted in the formation of a colorless triazole derivative through a diazonium intermediate. In UV-vis, the strong absorbance of the multicomponent gel of **12** and DAQ at 500 nm disappeared in the sol obtained after treatment with $NaNO_2$. Furthermore, in fluorescence, the emission of the gel at 639 nm corresponding to the DAQ moiety became labeled off suggesting maximum conversion of diaminoanthraquinone into triazole in presence of $NaNO_2$. Such spectroscopic changes were not observed during gel to sol transition by other anions. These results indicated a high selectivity of the **12**+DAQ gel for NO_2^- compared to other anions. One potential advantage of the system is that after decomposition of the two-component gel, the organic compound **12** was precipitated out which could be recovered and reused as a circulating material.

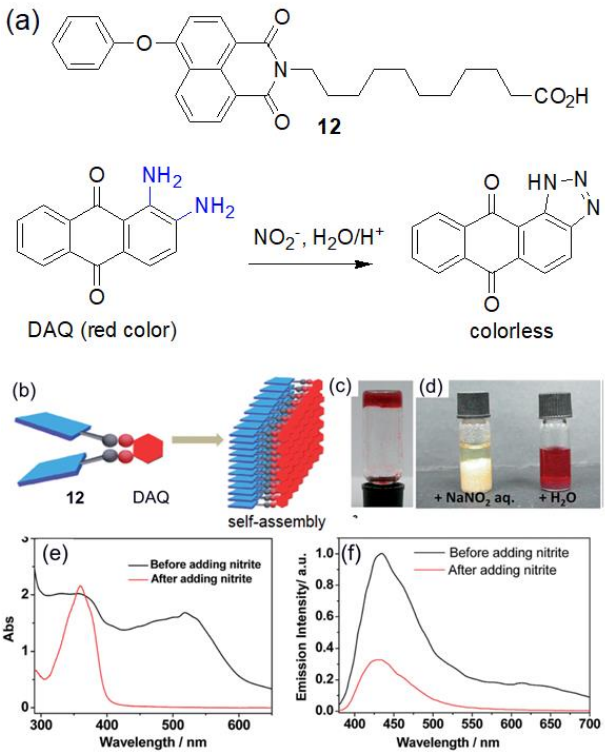

Figure 11. (a) Chemical structure of compound **12** and the chemical reaction between DAQ and nitrite. (b) Proposed interaction mode of **12** and DAQ in the multicomponent gel system. (c) Photographs of the multicomponent gel of (**12** + DAQ). (d) Photographs of the multicomponent gel of (**12** + DAQ) after treatment with aqueous $NaNO_2$ (left) and pure water (right). (e) Absorption and (f) emission spectra of gel **12**+DAQ before and after treatment with NO_2^-. Reproduced with permission from reference [115].

3.3. Metal ion triggered spirolactam ring-opening of rhodamine

Rhodamine is a dye that belongs to the Xanthene family.[116, 117] Owing to excellent photophysical properties, rhodamine derivatives are widely used as fluorometric and colorimetric sensors for metal ions.[118] The sensing event typically involves coordination of metal ions into the binding cleft of the receptor followed by chelation-induced opening of the spirolactam ring (Figure 12).[118] The closed-form of the spiroring is colorless and nonfluorescent, however, switching to the ring-opened structure generates pink color with significant enhancement in emission intensity because of an increase in the effective π-conjugation length.[118-120] Interestingly, scavenging of the metal ion by suitable chelating agent results in regeneration of the closed ring structure.[118, 121-123] Hence, incorporation of rhodamine moiety into the gelator enables devising of gel-based sensors for metal ions with excellent photophysical changes.

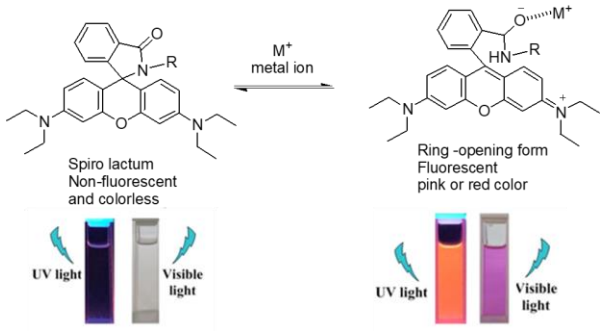

Figure 12. Metal ion-induced spirolactam ring-opening process of rhodamine derivative. Reproduced with permission from reference [124].

Panja *et al.* introduced the 2,6-aminopyridine-decorated rhodamine B **13** with a formamide functionality that undergoes gelation in toluene-hexane (1:1, v/v) (Figure 13).[125] Intermolecular hydrogen bonding involving the formamide moiety and the hydrophobic interactions exerted by the rhodamine segment was responsible for the self-assembly of the molecules in a less polar solvent. Scanning electron microscopy revealed the formation of non-twisted rod-like fibers in the aggregated state. When the gel was treated with different metal ions (2 equiv.), the gel remained unaffected except Ag^{+} which ruptured the gel into a violet-colored sol within 2h. The Ag^{+} induced gel to sol transition of **13** was associated with strong metal coordination including the amide ion (obtained after spiroring opening), pyridyl nitrogen atom, and formamide carbonyl that disturbed the intermolecular association of the molecules. The appearance of a new band at 575 nm in UV−vis of the disrupted gel established the spiroring opening (Figure 12).

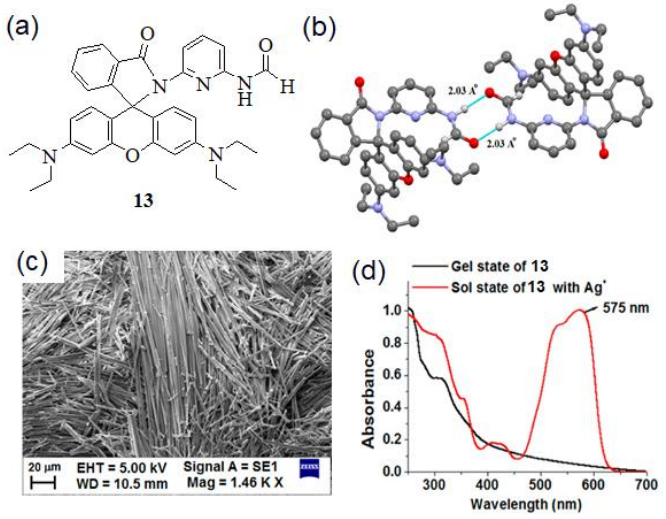

Figure 13. (a) Structure of the gelator **13**. (b) Hydrogen-bonded dimer of **13** from single crystal X-ray. (c) SEM images of the xerogel of **13** obtained from toluene-hexane (1:1, v/v). (d) UV-vis spectra of **13** in gel and sol states. Reproduced with permission from reference [125].

Das and co-workers synthesized an alginate coupled rhodamine compound **14** (Figure 14).[126] Compound **14** recognized Hg^{2+} and Cr^{3+} in solution with the emergence of a strong absorption band at 562 nm and an emission band at 582 nm corresponding to spiroring opening. Visually the color of the solution turned pink from colorless. Interestingly, alginates are polysaccharides that can gelate water in presence of various metal ions cations like Na^{+}, Ca^{2+} etc.[127] With this in mind, they prepared alginate gel beads by adding Ca^{2+} to the aqueous solution of **14**. In the gel beads, while alginate binding to Ca^{2+} involving the hydroxyl and carboxylic groups maintained the gel network, the free rhodamine moiety served as a signaling unit. The gel beads were capable of scavenging both Hg^{2+} and Cr^{3+} ions from water. Binding of the metal ions to the rhodamine fragment led to an intense pink color of the beads. Hence, such gels beads were not only effective for visual sensing of metal ions but are also capable to remove toxic metal ions from contaminated water. Following a similar technique, later on, Liu *et al.* reported a rhodamine-functionalized polyacrylamide hydrogel which was capable of detection and separation of trace amounts of Fe^{3+} ions (detection limit is 1.1 µM) from water.[128] Unlike other dosimetric gelators, rhodamine couped gelators have the unique advantage that they can be reused after separation of the metal ion from the gelator-metal complex by using chelating agents such as EDTA, KI etc. (depending on the metal ion). [127, 128]

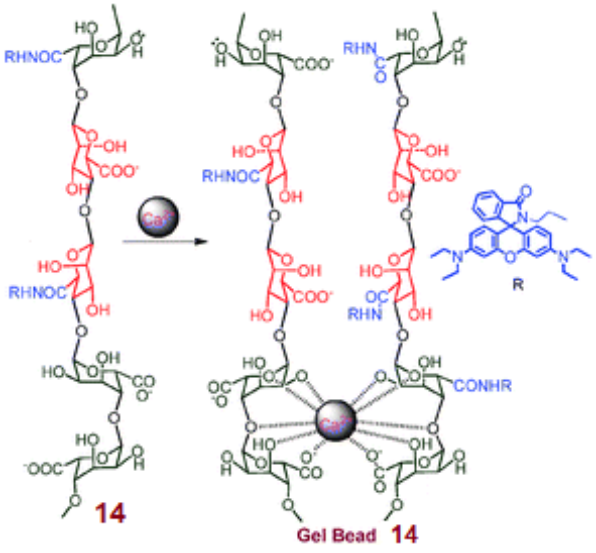

Figure 14. Synthesis of alginate gel bead from rhodamine-alginate compound **14**. Reproduced with permission from reference [126].

4. Designing of dosimetric gelators using protection-deprotection chemistry

Apart from the above mentioned detection strategies, the 'protection–deprotection' chemistry of functional groups can be used for this purpose. The basic concept is to find out a suitable gelator-nongelator pair in a particular solvent corresponding to a protected-deprotected state (or vice versa) of a functional group present in the gelator skeleton. Generally, a gelator is first converted into a nongelator after functionalization with a protecting group (Figure 15). Elimination of the protecting group by a chemical analyte leads to the regeneration of the gelator and thereby validates its visual sensing by exhibiting a sol to gel transition. Alternatively, protection followed by deprotection of a functionalized compound can causes gel to sol transition if the protected state has gelling tendency but the deprotected state loses gelation ability due to change in hydrophobic/hydrophilic balance of the compound in the same solvent. As the protection-deprotection chemistry is widely explored in the field of synthetic organic chemistry,[129] this approach is useful to design many gelators for sensing studies.

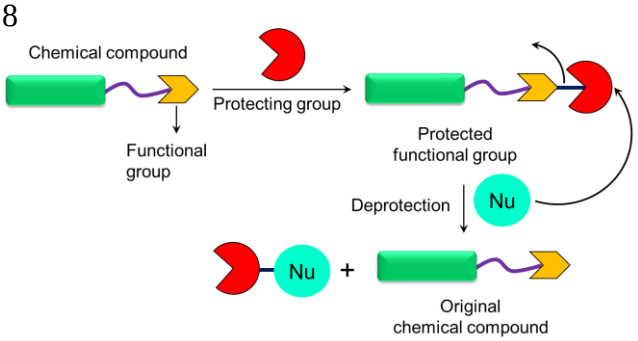

Figure 15. Demonstration of the general concept of protection deprotection chemistry exploited in sensing of chemical analytes (Nu).

4.1. Protection-deprotection chemistry of alcohols

Protection-deprotection chemistry of alcohols is the most adapted technique to identify a gelator-nongelator pair in the sensing study. Chemical compounds containing alcoholic functionalities (both aliphatic and aromatic alcohols) can be derivatized in several ways; for example, silylation, esterification etc. Removal of the protecting group can be triggered by various chemical analytes leading to regeneration of the original chemical compound at room temperature whilst the rate of deprotection can be controlled by varying the concentration of the analytes.

4.1.1. Silyl ethers in sensing of fluoride

Alcohols can easily be protected through silylation reaction.[130] The silyl ethers are extensively sensitive to fluoride ions and readily undergo desilylation reaction because of higher Si-F bond energy (141 kcal/ mol) than the Si-O bond (103 kcal/ mol).[131, 132] Other oxyanions and halides do not respond to this reaction. Although this strategy has been used for colorimetric and fluorimetric detection of fluoride over a long time, [131, 132] to the best of our knowledge, the first silyl-ether containing low molecular weight gelator (**15**) was introduced for fluoride sensing by Özçubukçu *et al.* in 2019 (Figure 16).[133] They found that while the L-Tyr-OH produced a clear solution in 2-ethylhexanol, the tert-butyldimethylsilyl (TBDMS) protected L-Tyr(TBDMS)-OH (**15**) yielded an organogel with a minimum concentration of 1 wt/v% in the same solvent. In the presence of aqueous NaF, cleavage of the Si-O bond resulted in the formation of the nongelator L-Tyr-OH. As a consequence, a gel-to-sol transition occurred over time. In this process, the organogelator **15** showed quite a low detection limit of 0.2 ppm for fluoride ions.

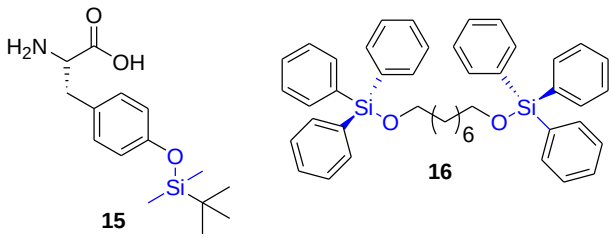

Figure 16. Structure of the gelators **15** and **16**.

In the same line, in 2020, Sing *et al.* presented compound **16**, a diphenylsilyl derivative of 1,8-octanediol as a potential organogelator (Figure 16).[134] Compound **16** formed stable gel in many organic solvents like DMSO, Propan-1-ol, Propan-2-ol etc. Aromatic stacking between the phenyl groups acted as the driving force for gelation of **16**. Interestingly, neither the original precursor 1,8-octanediol nor the monosilyl derivative of 1,8-octanediol undergoes gelation under similar conditions. When DMSO solutions of different halides (F^-, Cl^-, Br^- and I^-) were added on the top of a pre-formed gel of **16** (5 wt %, in DMSO), a gel to sol transition was noticed selectively for F^- ions. The degradation time was dependent on the concentration of fluoride and varied from ~6 to 24 h for 5 to 3 equiv. of fluoride at 20 ºC. The collapse of the gel was ascribed to the fluoride-induced partial or complete desilylation of **16** (depending on the concentration of fluoride) that generates the non-gelling compounds. Interestingly, at a particular fluoride concentration, the rate of desilylation could be increased by increasing the temperature that decreased the response time for the gel to sol transformation.

4.1.2. Protection of alcohols by esterification

The most common approach of protecting alcohol functionality is through the formation of ester. Strategic removal of the acid segment is further possible by suitable nucleophiles. Apparently, the sensing mechanism involves addition of a nucleophile to the electrophilic ester carbonyl followed by elimination of the acid segment bearing the nucleophile. In this approach, typically, compounds comprising of aromatic -OH are subjected to esterification because of the following reasons: (i) to utilize the stacking capability of the aromatic surface in gelation, (ii) to increase the reactivity of the ester carbonyl susceptible to the nucleophilic attack, and (iii) to achieve dramatic changes in UV-vis and fluorescence properties between the protected and deprotected states.

Ghosh and co-workers utilized this concept to synthesize gel-based sensors for hydrazine, perborate, and sulfide. Initially, they synthesized the naphthalene couped azo-dye **17** (Figure 17). Compound **17** behaved as a potential gelator in semi-aqueous solvents like CH_3CN-H_2O (1:1, v/v), DMSO-water (1:1, v/v) etc.[135] As suggested, π-π stacking between the naphthalene rings and water linking through pyridyl nitrogen acted together to yield the gels. Acetylation of the phenolic -OH in **17** gave the compound **18** which formed a stable gel in DMSO-H_2O (1:1, v/v) but produced a clear solution in CH_3CN-H_2O (1:1, v/v). Thus, compounds **17** and **18** exhibited different phase behaviors in CH_3CN-H_2O (1:1, v/v). On treatment of the solution of **18** in CH_3CN-H_2O (1:1, v/v) with a series of chemical analytes such as CN^-, F^-, $H_2PO_4^-$, AcO^-, N_3^-, HSO_4^-, BO_3^-, hydrazine, NH_2OH, *n*-butylamine, ethylamine, ethylenediamine and ethanolamine, a sol to gel transition occurred only in the presence of hydrazine and perborate. Other analytes were noninteractive with **18** and so there were no phase transformations. Using ^1H NMR and mass spectroscopy, they confirmed that both hydrazine and perborate facilitate the deacetylation of **18** resulting in the generation of the compound **17** responsible for gelation. However, the rate of deacetylation and so appearance of the gel was faster in the case of hydrazine (took ~1 h) because of greater nucleophilicity compared to perborate (took ~12 h). A number of controlled experiments were performed either by manipulating the concentrations of these two analytes or by varying the concentration of **18** that confirmed strong propensity for hydrazine over perborate to generate the gelator **17** inside the reaction medium. The gels obtained from **18** after treatment with hydrazine and perborate displayed flake-like morphology, similar to the original gel of **17** in CH_3CN-H_2O (1:1, v/v). According to the authors, this was the first report of sensing hydrazine and perborate using the sol-gel methodology.

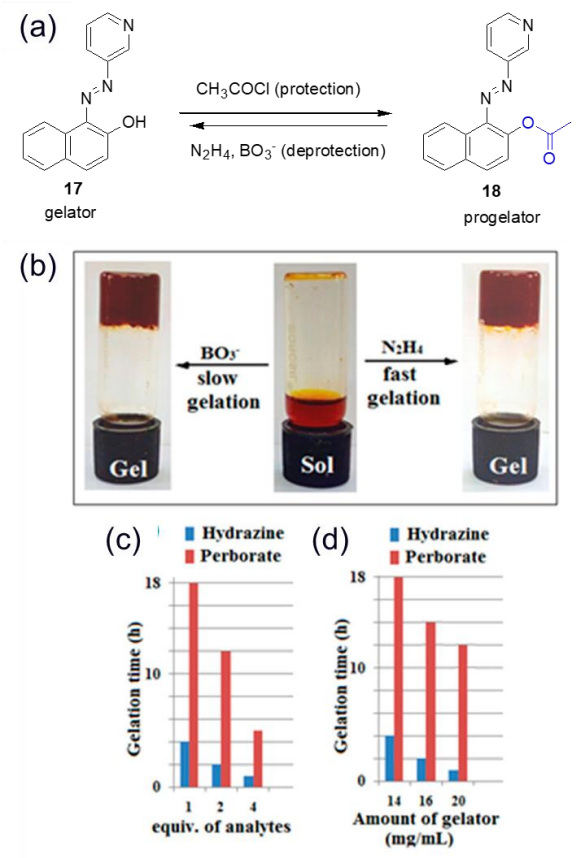

Figure 17. (a) Structure of the compounds **17** and **18**. (b) Photograph representing the sol to gel transitions of **18** in presence of hydrazine and perborate. (c-d) Comparative graphs showing the variation of gelation time with (b) the addition of different equiv. amounts of analytes to the fixed amount of **18** (14 mg/mL) and (c) the different concentrations of **18** in presence of 1 equiv. of different analytes. Reproduced with permission from reference [135].

Using a similar concept, they further synthesized compound **19** through sulfonylation of the phenolic -OH in **17** (Figure 18).[59] Compared to the acetyl segment in **18**, the dinitrobenzenesulfonyl (DNBS) group in **19** has a better leaving tendency which makes **19** more prone towards addition-elimination reaction in presence of nucleophiles. Compound **19** did not show gelation in any of the tested solvents. When equivalent amounts of different anions (S^{2-}, F^-, Cl^-, Br^-, I^-, AcO^-, SH^-, $H_2PO_4^-$, HPO_4^{2-}, BO_3^-, $S_2O_3^{2-}$, HSO_4^-, NO_3^-, HSO_3^-) and amino acids (L-glycine, L-cysteine, L-valine, L-alanine) were added to the solution of **19** in DMSO-H_2O (1:1, v/v), it was only S^{2-} where a stable gel was obtained just after 5 min. Other analytes including week nucleophiles such as BO_3^-, HS^-, and L-cysteine remained inert to such changes even after 1h and thereby showed a weaker interaction with **19** under similar conditions. The sol to gel transition in presence of S^{2-} was established due to the rapid removal of the DNBS group leading to an in situ conversion of the progelator **19** to the azo-naphthol gelator **17**. Proton NMR of the compound isolated after reaction of **19** with S^{2-} merged with the signals of **17** and thereby confirmed the removal of the DNBS group. Such a chemical transformation caused 70 nm red shifts in UV-vis during sol to gel transition.

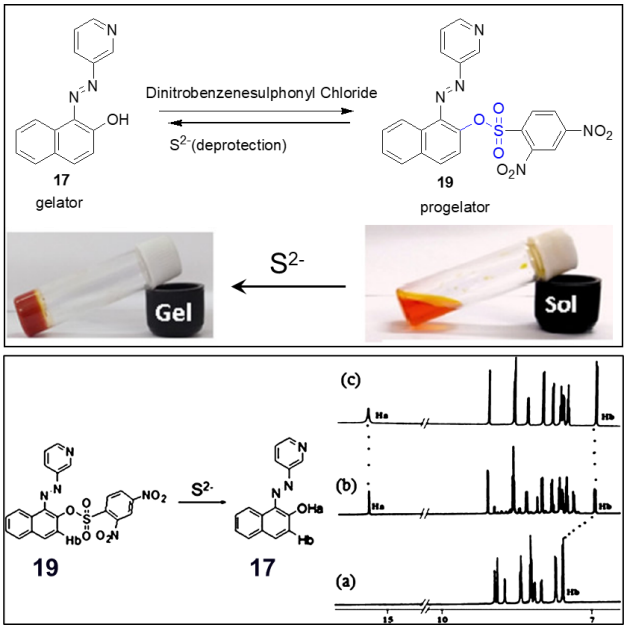

Figure 18. (Top) Structure of the compounds **17** and **19**. The photographs of sol and gel states represent the phase transformation of **19** in presence of S^{2-} in DMSO-H_2O (1:1, v/v). (bottom) Partial ^1H NMR spectra of **19** (a) in the absence and (b) presence of 1 equiv. amount of sulfide and (c) compound 17 in d_6-DMSO containing 4% D_2O. Reproduced with permission from reference [59].

4.2. Protection-deprotection chemistry of aldehydes

Like alcohols, the aldehyde functionality of a gelator can also be protected in several ways, e.g., dynamic imine bond formation, thioacetal protection etc. In gel chemistry, the protection-deprotection chemistry of aldehydes is mainly exploited for the sensing of cations.

4.2.1. Thioacetal protection-deprotection technique for selective sensing of Hg^{2+}

The reaction of aldehydes with thiols in presence of $BF_3.OEt_2$ at low temperature affords the thioacetals.[136] Such thioacetals are prone towards hydrolysis in presence of Hg^{2+} resulting in regeneration of the aldehyde. Strong affinity of sulfur for Hg^{2+} over other cations makes this reaction highly selective. Typically, a progelator to gelator conversion pathway is followed during execution of the sensing event. For example, treatment of the aldehyde **5** with 1-dodecanethiol gives the dithioacetal **20** (Figure 19).[136] While compound **5** formed gel in DMF-H_2O (1:1, v/v), **20** behaved as a non-gelator in the same solvent. When different metal ions were added into the solution of **20** in DMF-H_2O (1:1, v/v), an instant sol to gel transition occurred for Hg^{2+}. On contrary, gelation was found to be unsuccessful in all other cases. Presence of Hg^{2+} results in appearance of the aldehyde -CH proton near 10 ppm in ^1H NMR which indicates Hg^{2+} ions gradually hydrolyzed the thioacetal group of **20** and enriched the medium with the original gelator **5** causing appearance of the gel.

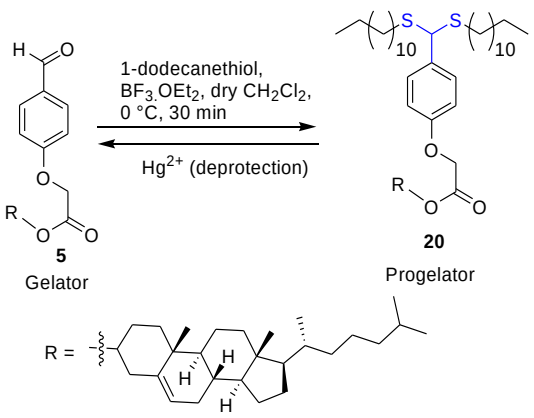

Figure 19. The design concept of dosimetric gelator **20** for selective sensing of Hg^{2+} involving thioacetal protection/deprotection chemistry. [136]

A similar methodology was undertaken by Raza *et al.* to synthesize compound **21** from the precursor aldehyde **3** (Figure 20).[137] Compound **21** served as a dual sensor for metal ions and recognized both Hg^{2+} and Ag^{+} ions via sol to gel conversion in DMSO-H_2O (1:1, v/v). Interestingly, while dethioacetalization of **21** followed by in-situ generation of the precursor aldehyde **3** was responsible for gelation for Hg^{2+}, Ag^{+} ion-induced gelation of **21** involved dithiane-Ag^{+} interaction in contrast to the deprotection to aldehyde functionality (Figure 20b-c). Similarly, the tripodal compound **22** validates selective sensing of Hg^{2+} through a sol to gel transition caused by the dethioacetalization of **22** (Figure 20).[138]

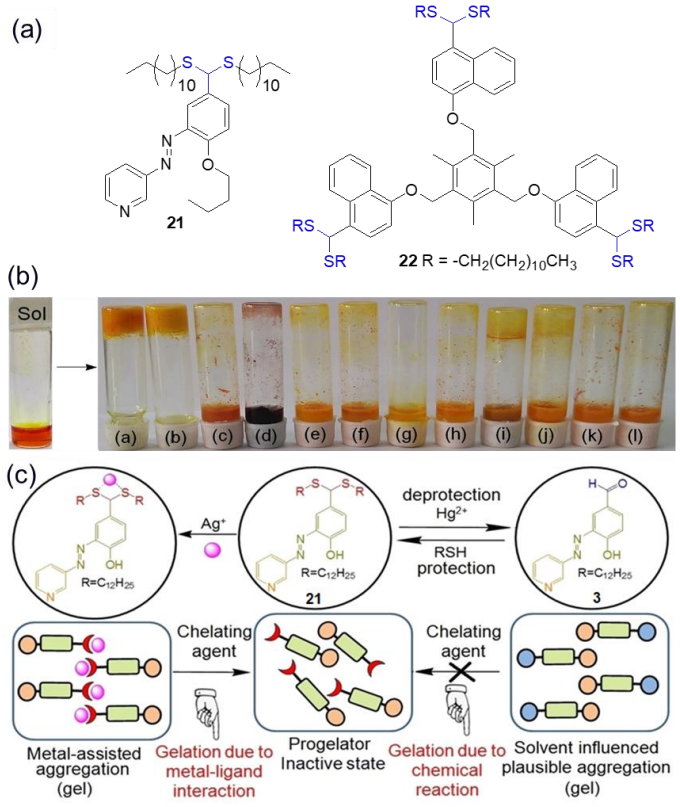

Figure 20. (a) Structure of the compounds **21** and **22**. (b) Photograph showing the phase transformations of **21** (*c* = 30 mg/ mL) in presence of 3 equiv. amount of different metal ions after 1 h in DMSO-H2O (1:1, v/v) [from left to right: Hg^{2+}, Ag^{+}, Cd^{2+}, $Cu^{2+,}$ Fe^{2+}, Fe^{3+}, Co^{2+}, Zn^{2+}, Pb2+, Ni^{2+}, Ca^{2+} and Al^{3+}]. Figure (c) shows different mechanism of gel formation by **21** with Hg^{2+} and Ag^{+} ions. Reproduced with permission from reference [137].

4.2.2. Dynamic covalent bond formation/rupturing

Imine bond formation from the reaction between a primary amine and an aldehyde or ketone has emerged as a powerful tool to construct various functional gelators.[139, 140] However, the imine bonds can easily be broken under mild conditions: *e.g.*, the presence of Lewis acids (such as H^{+}, metal ions) hydrolyses the imine into the precursor carbonyl and amine.[141, 142] Such reversible and dynamic behavior of imine bonds offers the opportunity to device gel-based sensors for metal ions.

Panja and Ghosh synthesized the imine functionalized gelator **23** from the aldehyde scaffold **5** (Figure 21).[143] The cation sensing behavior of **23** was examined in DMF/H_2O (1: 1, v/v). Of the different metal ions, only Hg^{2+} brought about a quick sol to gel transition. Gelation was unsuccessful in the presence of the other metal ions such as Ag^{+}, Cu^{2+}, Pb^{2+}, Zn^{2+}, Cd^{2+}, Fe^{2+}, Fe^{3+}, Ca^{2+}, Ni^{2+}, Co^{2+}, and Mg^{2+}. ^{1}H NMR and HRMS studies confirmed hydrolysis of the imine bond of **23** and subsequent generation of the aldehyde **5** which acted as the actual gelator and caused gelation in DMF/H_2O (1: 1, v/v). However, the only drawback of this method is that in some cases the metal-induced hydrolysis of imine may not be selective. As an example, the cholesterol-coupled naphthalene imine **24**, a derivative of the same aldehyde **5**, was able to form a self-supported gel in $CHCl_3$/MeOH (1: 2, v/v) (Figure 21).[143] It is to mention that, in $CHCl_3$/MeOH, the aldehyde **5** was highly soluble and no gel formation was noted. When the organogel of **24** was treated with the same metal ions, gel to sol transition occurred in presence of Cu^{2+}, $Fe^{3+,}$ and Hg^{2+} ions. From proton NMR and mass spectroscopy, the authors suggested that cleavage of the imine bond to **5** took place in all cases. Hence the detection process suffered from poor selectivity. These results emphasize that, apart from the choice of the gelator/non-gelator pair, care should also be taken after the selection of the solvent system as the reactivity of analytes depends on solvation.

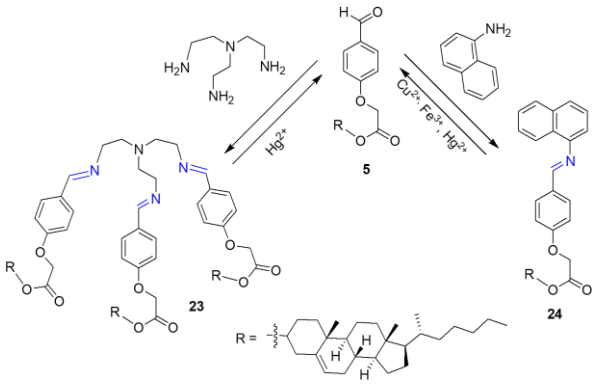

Figure 21. Synthesis of the imine-functionalized gelators **23** and **24** from precursor aldehyde **5**.[143]

In a recent study, sensing behavior of the 1, 8-naphthalimide functionalized cholesteryl amide **25** (Figure 22) has been demonstrated by Sun *et al.*[144] Compound **25** formed a red-colored gel in 1, 4-dioxane. During gelation, the amide groups served as the hydrogen bonding units and the cholesteryl moiety promoted self-assembly via van der Waals interaction. In addition, π-π stacking interactions between naphthalenes also participated in the gel formation. The hydrazine group acted as the reaction centre and underwent covalent bond formation with formaldehyde (FA). The -C=N bond formation between **25** and FA resulted in a rapid color change of the gel from red to yellow. Interestingly, in DMSO, compound **25** exhibited a sol to gel transition in presence of both aqueous as well as gaseous FA with

remarkable enhancement in emission intensity. The sol to gel transition time was evaluated by recording time-variable emission spectra of **25** in presence of FA that showed a gradual increase in emission followed by reaching the plateau after 120 mins.

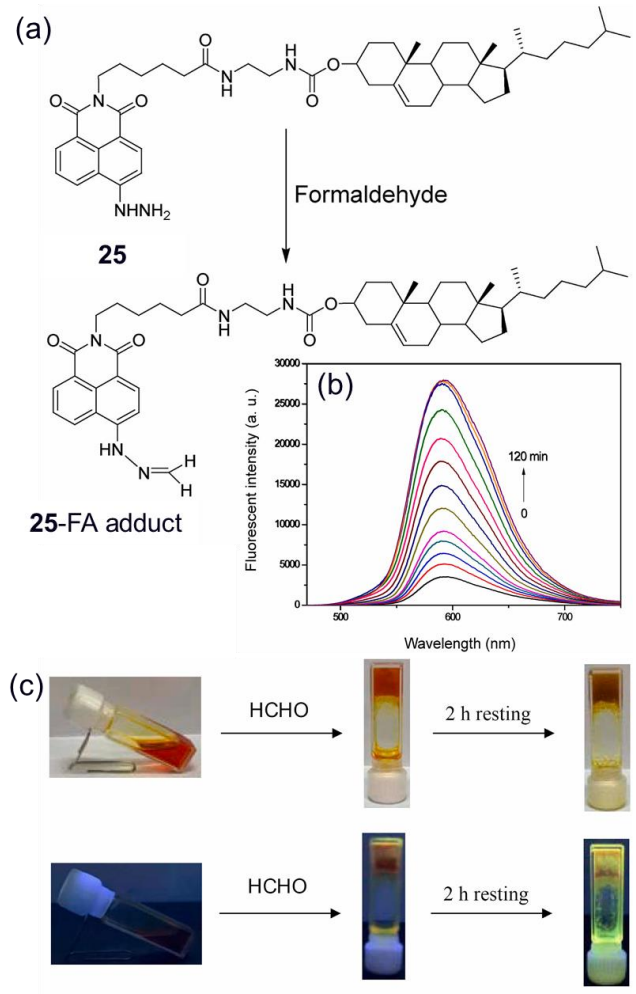

Figure 22. (a) Proposed sensing mechanism of formaldehyde by **25**. (b) Time variable fluorescence spectral changes of **25** in presence of FA (220 mM) (λex = 420 nm). (c) Photographs of phase changes of **25** (30 mg in 1 mL of DMSO) in the presence of FA (220 mM) under daylight, and under 365 nm UV irradiation. Reproduced with permission from reference [144].

5. Redox-based dosimetric gelators

Redox-based dosimetric gelators contain a redox reaction centre that produces responses upon oxidation or reduction in presence of the analytes. This type of gelator is mainly used as sensors for biomolecules such as glutathione (GSH), reactive oxygen species like H_2O_2, as well as other disease-related species like H_2S, nitric oxide (NO) etc. Depending on the targeted analytes different redox-sensitive groups such as boronic acid, nitro, azo, disulfide etc. are incorporated into the gelator skeleton. Apart from the redox responsive unit, the rest of the gelator structure follows a general principle irrespective of the analytes (Figure 23). Amino acid functionalized dipeptides and tripeptides are preferably chosen as the self-assembling segment while the *N*-terminus of the peptide chain is further coupled to a benzyl-substituted self-immolative aromatic group by a carbamate linkage. The self-immolative aromatic group bears the redox-responsive centre so that the redox-induced chemical transformation could further instigate a tandem elimination reaction which eventually leads to the cleavage of the carbamate group and thereby generate the peptide. As a consequence, in presence of biomolecules, the gel usually returns to the solution state.

The Hamachi group reported hydrogelation of pboronophenylmethoxycarbonyl (BPmoc) and p-nitrophenylmethoxycarbonyl (NPmoc) conjugated Phe-Phe dipeptides **26** and **27** at neutral pH, respectively.[145] They also observed that incorporation of another Phe-residue in **26** makes the tripeptide **28** more effective in forming hydrogel at a relatively low concentration.[146] The oxidation of boronic acid (for **26** and **28**) or the reduction of the nitro group (for **27**) by H_2O_2 and $Na_2S_2O_4$ respectively, led to the decarboxylation of the modified peptide, thereby yielding the Phe-Phe (or Phe-Phe-Phe) quasi-liquid state (Figure 23). Moreover, instead of direct exposure of the gels to the biomolecules, enzymes were immobilized into the hydrogels to utilize these systems as biocatalysts through in situ generation of H_2O_2 or reducing agents and consequently degradation of the hydrogels over time.[146, 147] For example, glucose oxidase (GOx) and glucose were integrated into the hydrogels of **26** and **28**. The GOx-catalyzed oxidation of glucose resulted in gluconic acid and H_2O_2 inside the gel matrix. H_2O_2 instigates the oxidative decarboxylation of the phenylboronic acid segment yielding a gel to sol transformation over time. Other oxidase enzymes such as sarcosine oxidase (SOx), choline oxidase (COx), and urate oxidase (UOx) similarly transformed the peptide gels into solution by generating H_2O_2 selectively in presence of sarcosine, choline, and uric acid respectively. Similarly, lactate dehydrogenase (LDH) and nitroreductase (NR) were immobilized into the hydrogel of **28**. In presence of NAD^+ and lactic acid a biocatalytic cascade was activated, where the LDH reduction of NAD^+ to NADH by lactate occurred. The generated NADH in presence of NR caused reduction of the nitro group of **28** to yield the corresponding aminophenylmethoxycarbonylPhe-Phe dipeptide. Then oxidative decarboxylation of the modified amino-dipeptide led to the deprotected Phe-Phe residue associating with gel to a solution.

Following a similar concept, Sun and co-workers introduced azidobenzyl functionalized tripeptide **29** for sensing of H_2S (Figure 23).[148] The hydrogel of **29** turned into a solution in presence of equivalent amounts of H_2S with a change in aggregated structures from nanofibres to amorphous morphology. H_2S initially reduced the azo group to amine which further initiates a cascade elimination reaction yielding the tripeptide segment as the major product in HPLC. Interestingly, the gel remained unaffected while treated with other sulfur containing reducing biomolecules like Glutathione (GSH) indicating a good selectivity in the sensing event. In a recent study, Yang group demonstrated a simple route to synthesize biomolecule responsive gelators by modifying the self-immolative aromatic groups keeping the peptide segment intact.[149] The tripeptides **30**-**32** only differ in the redox responsive centre, however, all of them formed gel at neutral pH (PH 7 -7.4). The hydrogels of **30**-**32** turned into solution in presence of glutathione, NO, and H_2S respectively due to removal of the aromatic segments as shown in Figure 24. They also established that the biomolecules induced gel to sol transition can also be used in controllable delivery of encapsulated drugs. Moreover, biocompatibility of the hydrogels to LO2 cells endorsed potentiality of the hydrogels for biomedical applications.

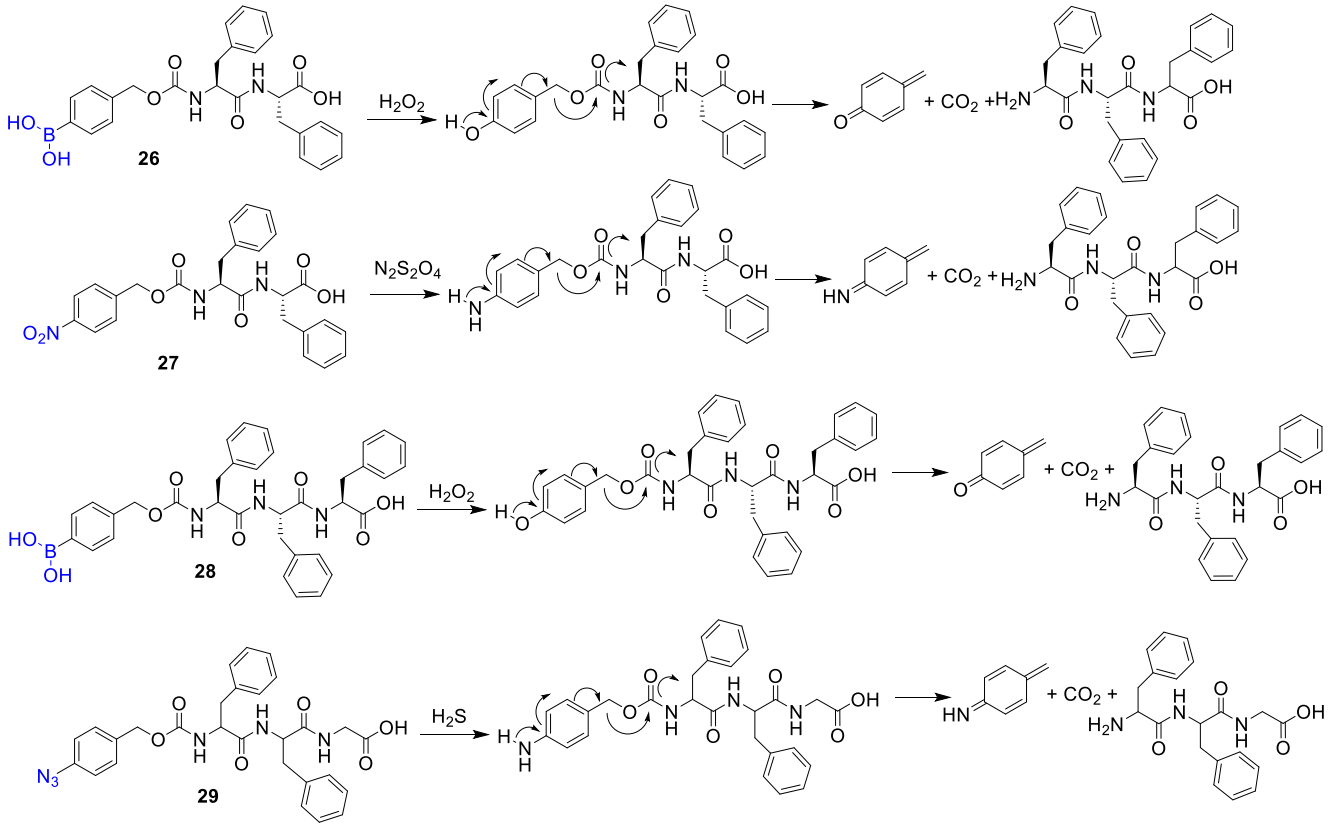

Figure 23. Sensing mechanisms of H_2O_2, $S_2O_4^{2-}$ and H_2S by redox responsive gelators **26**-**29**.

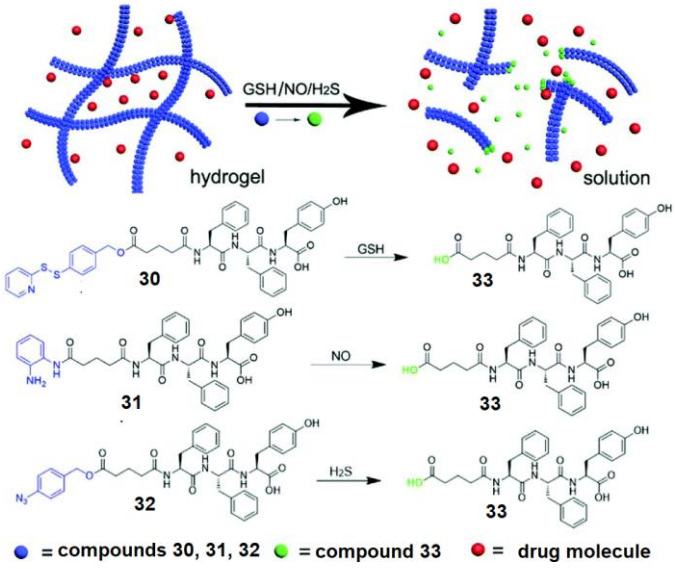

Figure 24. Structures of the gelators **30**-**22** and possible reaction mechanisms for the gel to sol transitions in presence of different biomolecules. Reproduced with permission from reference [149].

6. Conclusions

Gel-based sensors have huge potential in materials and medicinal chemistry.[11-15, 21-29] Supramolecular gels have offered various ways to detect analytes (e.g., hydrogen bonding, displacement approach etc.). This review focuses on a particular type of gel-based sensor which interacts with the analytes involving a chemical reaction. Apart from an up-to-date summary of various dosimetric gelators, attention has been given to the approaches, methodologies, syntheses, and also sensing mechanisms. Dosimetric sensors are unique in their design principles but very useful, particularly in terms of selectivity towards analytes. A series of dosimetric gelators can be synthesized simply by modifying the reaction centre from a known gelator scaffold. However, very little work has been carried out in this direction. The examples taken in the discussion should inspire people to design new gel-based advanced materials with selective responsive properties.

The study so far carried out in this domain have several limitations. The major disadvantage of this approach is that the chemical reaction causes permanent changes of the gelators and thereby imposes limitations on reusing them. So far, rhodamine-based gelators are the only available scaffold that could be reused after treatment with chelating agents (section 3.3). Hence, the synthesis of more rhodamine or xanthene-based gelators for different chemical analytes is highly desirable. Additionally, apart from rhodamine, attention should be given to find out different reaction-based scaffolds that could be recyclable. Another issue is that the sensing event is mostly executed either by a sol-gel phase transformation or by a visually detectable color change of the gel. Properties like shrinking-swelling of gels in response to an analyte are unexplored for dosimetric gelators. It would be interesting to devise actuators involving such systems with reversible reaction centres (section 3.3).

Another drawback is lower detection limit of the gels. Although some of the reported gelators display a low detection limit than the recommended limit of the WHO, their sensitivities for analytes are not very good in the majority of cases. This can be overcome by the synthesis of super-gelators capable of forming gels at extremely low concentrations. In this context, the study of structure-property relationship of gelators is highly desirable for improving the sensitivity of detection. Furthermore, most of the chemical analytes come from industrial waste. Hence, apart from the sensing of the analytes, emphasis should also be given to the absorption and separation of analytes from contaminated water. An effective way to counter all these issues is to construct supramolecular polymer gels with dosimetric

characteristics. Alginate, chitosan, cellulose etc. are biopolymers and could be easily functionalized with desirable reaction centres.[126] These modified polymers could be effective gelators capable of forming gels at extremely low concentrations.[126] With appropriate design, it would be possible to detect and separate the water soluble toxic analytes by such materials with a very low detection limit. [127, 128] Such supramolecular polymers would also be effective in devising chemical reaction-based gel actuators.

Lastly, unlike other design-based sensors (fluorometric and colorimetric etc.) dosimetric gelators are rarely investigated for in vivo detection of analytes.[50, 149] In this context biomolecules responsive gelators (section 5) have huge potential in controlled drug delivery, synthesis of biomarkers etc. Hence, the design of fluorophore-embedded dosimetric gelators is highly desirable for constructing bioimaging sensing probes.[12] We envisage that the insights provided in this review would be effective in constructing new dosimetric gelators where all these limitations can be encountered.

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Conflict of interest

None.

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