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Detection of nerve agent *via* perturbation of supramolecular gel formation†

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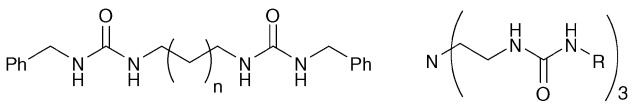
The formation of tren-based tris-urea supramolecular gels in organic solvents is perturbed by the presence of the nerve agent soman providing a new method of sensing the presence of organophosphorus warfare agents.

There has been significant interest and research effort devoted to the design and synthesis of supramolecular gel systems.[1] Stimuli responsive supramolecular gels are of particular interest for their potential role as sensors.[2] For example, hydrogen-bonded gels containing urea groups have been shown by Escuder, Miravet and co-workers to be sensitive to the presence of neutral phenolic guests with catechol disrupting the gel's hydrogen bonding network.[3] In seminal work, Steed and co-workers have shown that anions can disrupt the structures of gels[4] and have used this approach to dissolve crystal growth media and recover new polymorphs of pharmaceutical interest.[5]

Our work on developing new motifs for oxo-anion complexation[6] and particularly for phosphates[7] led us to explore whether similar motifs could be used for organophosphorus (OP) based nerve agent (NA) sequestration[8] and catalysis.[9] In a similar fashion we wished to explore whether we could employ the formation of hydrogen bonded NA complexes to disrupt a gel network and perturb a sol–gel transition which could be used to sense OPs. Our group and others have explored the use of the tripodal tren scaffold in anion complexation[10] and transport.[11] Tris-(2-aminoethyl)amine (tren) based tris-ureas have been shown to gelate organic solvents[12] and to have a high affinity for phosphates in non-aqueous media.[10] We therefore decided to examine whether the structure of tren-based organogels and related systems would be disrupted by the presence of a neutral OP-based nerve agent simulant so providing a new paradigm for nerve agent detection.

We prepared a series of bis- and tris-urea compounds of known gelators **1–3**[12a,13] and compound **4**. Bis-ureas **1** and **3** have previously been shown to gelate toluene, xylene, tetralin and octanol in quantities of less than 10 mg mL^{-1}.[13] Compound **2** has been shown to gelate xylene, toluene, tetralin and also benzene, dichloromethane and dichloroethane in quantities less than or equal to 10 mg mL^{-1}.[12a] We studied the gel formation properties of compound **4** by dissolving quantities of gelator into 1 mL of solvent by heating the sample and then allowing the sample to cool to room temperature. An inversion test[14] was then conducted to ascertain if a gel had formed. If no solution remained then the formation of a gel was deemed successful. Gelation was observed with tetralin (5 mg mL^{-1}), toluene (5 mg mL^{-1}), cyclohexanone (15 mg mL^{-1}), and ethyl acetate (15 mg mL^{-1}) however no gelation was observed with 2-octanol, hexane, ethanol or water.

A scanning electron microscopy (SEM) image of the xerogel formed in toluene by compound **4** is shown in Fig. 1. This shows that the toluene xerogel forms a branching fibrillar network structure.



1 n = 4
3 n = 7

2 R = benzyl
4 R = hexyl

We studied the effect of the nerve agent simulant, dimethyl methylphosphonate (DMMP), on gels formed by compounds **1–4**. We found that in some cases the simulant would disrupt the structure of the gel resulting in a gel–sol transition. However we found a high degree of variability in the time required for this transition to occur. Therefore as an alternative, and more quantifiable approach to study the response of these systems to DMMP, the formation of gels from precursor amines and isocyanates in the absence or presence of varying amounts of DMMP was studied at room temperature (20–21 °C).

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† Electronic supplementary information (ESI) available: Synthesis and characterisation information for compound **4** and further details on gel formation studies. See DOI: 10.1039/c3cc44841j

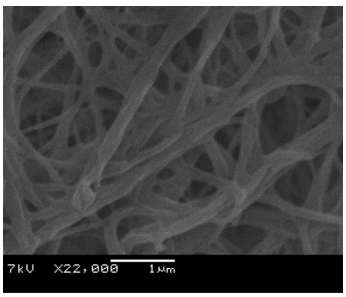
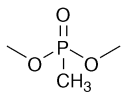
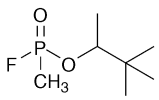


Fig. 1 SEM image of the xerogel formed by compound **4** and toluene after drying from a sample prepared from 15 mg mL^{-1} of gelator.

The urea based gelators (**1–4**) were formed *in situ*, in a similar fashion to systems explored by Hanabusa and others.[15] Solutions of the appropriate amine and either benzyl or hexyl-isocyanate were mixed in 0.5 mL aliquots at appropriate concentrations to produce 1 mL of 20, 15, 10 and 5 mg mL^{-1} gels containing compounds **1–4**. The samples were sealed, allowed to stand and inverted at 30 second intervals until a gel had formed. A gel was deemed to have fully formed when, upon inversion no solution remained. In most cases the gel formed within thirty seconds or not at all. The starting point ($t = 0$) for the experiment was taken at the point when the two solutions were mixed together and all experiments were halted after 10 minutes (see ESI†).



DMMP



soman (GD)

To test the effects of the presence of nerve agent simulant on the time taken for gel formation to occur DMMP was added to either the amine or isocyanate solution in 0.1, 0.05, 0.025 or 0.01 mL quantities (it was found that the systems behaved identically whichever precursor the simulant was added to). The amounts of gelator formed and phosphonate added are given in Table 1 – by taking the ratio of these values the equivalents of phosphonate:gelator may be calculated for the experiments presented here. An equal volume of the second precursor solution was then added to the mixture containing the simulant and the first precursor. The vial was then sealed and inverted at various times and the time taken for a full gel or partial gel to form was then noted. A partial gel is a mixture that contains both gel and solution. The experiments with gels which did show perturbation of formation time in the presence of DMMP were repeated, and the time taken to form the gel in these cases was shown to be reproducible. NMR experiments showed that no reaction occurred between either the amine (tren) or hexyl-isocyanate and the simulant. Additionally, there was no observable change in the rate of urea formation upon addition of DMMP (see ESI†).

Table 1 Amount of gelator (mmol) and added phosphonate (mmol)

	Amount of gelator in 1 mL of gel (mmol)			
Gelator	20 mg	15 mg	10 mg	5 mg
1	0.052	0.039	0.026	0.013
2	0.037	0.027	0.018	0.009
3	0.047	0.035	0.024	0.012
4	0.038	0.028	0.019	0.009
	Amount of phosphonate added (mmol)			
Phosphonate	0.100 mL	0.050 mL	0.025 mL	0.010 mL
DMMP	0.923	0.461	0.231	0.092
GD	—	—	0.140	0.056

Several different relationships between gelator (structure and concentration), solvent and DMMP concentration were observed to affect the time required for gel formation. The lower the concentration of the gelator the longer it takes for the gel network to form in the presence of DMMP. The addition of DMMP in the gel precursor solution in most cases extends the time required for the gel to form, with higher concentrations of DMMP leading to increasingly delayed gel formation. This is presumed to be a result of the hydrogen bond accepting DMMP interacting with the hydrogen bond donating groups of the urea functionality thus perturbing the formation of the hydrogen bond network in the gel matrix, along with increased solvent polarity. A combination of low gelator concentration and high concentrations of simulant leads to the longest gelation times. The full results can be found in the ESI.†

The results obtained with compounds **1** and **3** were similar and showed that the addition of simulant to the gelator solutions did not perturb the formation of the gel significantly under any conditions tested (see ESI†). Immediate gel formation in the presence of simulant appears to be a function of the bis-urea structure as the gel formation of the tris-urea analogue **2** was perturbed to a much greater extent by the addition of DMMP with gel formation at 10 mg mL^{-1} being delayed by over 3 minutes in toluene in the presence of 0.1 mL DMMP.

Gel formation by tris-urea compound **4** was perturbed to a greater extent by the presence of DMMP than compound **2**. The most successful set of conditions for perturbing gel formation by the systems studied was found to be the formation of a gel from the precursors to compound **4** (5 mg mL^{-1}) in toluene. In this case full gel formation was delayed by four minutes upon the addition of 0.01 mL of DMMP to 1 mL of the gel precursor solutions. Upon addition of 0.1 mL DMMP under the same conditions gel formation did not occur at all. Thus at this concentration of simulant (approximately 100 equivalents of simulant to gelator) there is a clear ON-OFF response in the absence *vs.* presence of DMMP. Gel formation in toluene proved to be perturbed more readily that that in tetralin (see ESI†).

The results that we observe may be due to two competing effects. The first is a solvent effect; with the addition of the larger amounts of phosphonate the polarity of the solution will be altered substantially resulting in inhibition of gel formation. However at lower concentrations of phosphonate, a complexation mechanism may occur in which guest species bind to the urea groups so inhibiting gel formation.

These experiments were used to find the optimum system for testing with nerve agent. Consequently the formation of gels from the precursors to compound **4** and toluene were tested in the presence of the nerve agent pinacolyl methylphosphonofluoridate

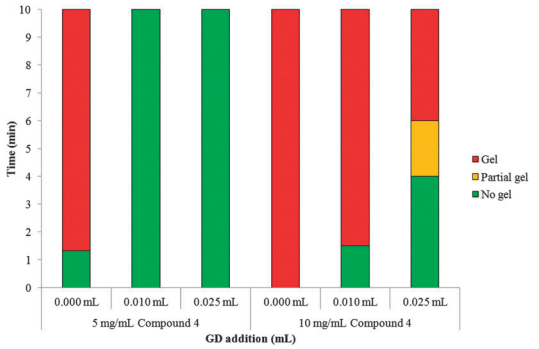


Fig. 2 The time required for complete/partial gel formation (1 mL) by compound **4** in toluene in the presence of GD (0.010 mL/0.025 mL). Gelation experiments were first observed after 0.5 min.

(soman, GD). GD was found to behave similarly to the DMMP simulant and result in longer times required for gel formation (Fig. 2). Interestingly lower concentrations of GD were required to stop gel formation completely. This may be due to the higher degree of polarity of GD *vs.* DMMP resulting in stronger hydrogen bonding interactions. Additionally, the fluorine group itself presents a hydrogen bond acceptor site for interaction with the gelator, although such interactions are likely to be significantly weaker than the N–H···O=P hydrogen bonds. Small quantities of fluoride generated from partial hydrolysis of the GD may also perturb the hydrogen-bonding network. Finally, the bulky alkyl side chain of GD may provide steric hindrance to gel formation once the molecule is associated with the gelator species. NMR experiments showed no reaction between either the amine (tren) or hexylisocyanate with GD (see ESI†).

The formation of hydrogen-bonded gels containing urea groups has been shown to be responsive to the presence of both the nerve agent simulant DMMP, and the nerve agent soman (GD), with the response to the latter being more sensitive. The guest-stimulated response is proposed to be due to a combination of solvent polarity and the perturbation of hydrogen bonding interactions between the gelator molecules by the competitive binding of the nerve agent or simulant with additions of phosphonate (0.01 mL). Thus this method represents a new procedure for sensing nerve agents that functions *via* the suppression of a sol–gel phase change. We are continuing to study the interaction of gelators with organophosphorus nerve agents at room temperature and exploring how this phenomenon can be used in detection technology. The results of these studies will be reported in due course.

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