Disruption of a binary organogel by the chemical warfare agent soman (GD) and common organophosphorus simulants.

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The chemical warfare agent (CWA) soman (GD) acts as a molecular stimulus for the disruption of an anthracene-based binary organogel prepared in cyclohexane. The CWA simulants dimethyl methylphosphonate (DMMP) and diethyl chlorophosphate (DCP) were also found to disrupt the binary organogel through changes in solvent polarity and reactions with the gelator.

There has been significant recent interest in the development of responsive supramolecular gels.1-3 The application of physical or chemical stimuli can result in changes in physicochemical properties of a gel that can be exploited in a range of applications including drug delivery and sensing4-11.

Supramolecular approaches that seek to mitigate the hazards posed by chemical warfare agents (CWAs) remain relatively unexplored12, although recent examples include work by Anzenbacher13 *et al.* onfluorescent sensors that display a turn-on fluorescence response to phosphonate and phosphate species and Estour14 *et al.* who have functionalized cyclodextrins with a nucleophilic group to degrade OP CWA guests. Kubik *et al* have also used cyclodextrin functionalised with hydroxamic acid as a scavenger for the OP CWA tabun (GA).15 Our research interests focus on the synthesis of low molecular weight, neutral, hydrogen bond donating molecules with selective guest recognition properties.16-20 In previous work we have shown that complexation of the organophosphorus (OP) CWA soman (GD) can be mediated by hydrogen bonding.21 These compounds were optimised and adapted which resulted in a group of hydrogen bond donating molecules that enhanced the rate of simulant22 and agent23 hydrolysis. Subsequently, we demonstrated the disruption of a series of hydrogen bonded supramolecular gels by the presence of GD through the formation of preferential GD:gelator complexes.24 Lee and co-workers have also reported a supramolecular gel system that exhibits a response to the presence of the CWA simulant diethyl chlorophosphate (DCP) through the formation of gelator:DCP hydrogen bonds.25

agant.tif

Herein, we report the disruption of an binary organogel by GD and through the use of simulants infer a mechanism of disruption based on changes to the polarity of the solvent environment, the formation of GD/simulant:gelator hydrogen bonds, and the presence of gelator-analyte reactions. Organogels composed of the low molecular weight binary gelator decylammonium anthracene-9-carboxylate (**1**) were first reported by Shinkai and co-workers and were demonstrated to be responsive to both light and heat stimuli.26 It was postulated by the authors that the carboxylate and ammonium groups of the gelator are strongly associated through the presence of both hydrogen bond and electrostatic interactions. The presence of these interactions suggests two mechanisms by which the organogel structure may be perturbed, and we show here that these materials are responsive to the presence of GD and the simulants DCP and DMMP.

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Organogels were prepared by heating compound **1** (1, 2.5 or 5.0 mg/mL) in cyclohexane (1 mL) until all the solid had dissolved before cooling to 15 ºC, allowing organogel formation to occur. The organogels were prepared with two different surface areas 0.95 cm2 for the addition of CWA or simulant liquid and 3.80 cm2 for studies involving the addition of simulant vapours. The samples were then allowed to warm to room temperature (19-20 ºC) and gelation confirmed by performing an inversion test prior to the addition of either GD or simulant. This simple optical method gives qualitative proof for the lack of flow in a sample, characterizing gel formation. 27 All organogels were found to be stable for periods of time greater than 30 minutes under ambient conditions.

Organogels of gelator concentration 2.5 mg/mL and total solvent volume of 1 mL were prepared and exposed to 0.01 and 0.05 mL volumes of GD. The sol formed as a result of organogel breakdown was present on the surface of the organogel and was readily removed by pipette without disruption to the remaining, underlying structure. Samples were removed from each gel/GD sample at times 2, 5 and 10 mins post-exposure (each gel-GD-time combination was a separate sample) and the resulting sol weighed on a balance and the extent of organogel breakdown calculated by weight %.The extent of organogel breakdown was found to be greater for the larger volumes of GD added and with increasing exposure time at time periods greater than 2 mins (Figure 1). A solution of compound **1** (1 mg/mL) and GD (2 mg/mL) in cyclohexane-*d*12 (1 mL) was prepared and allowed to stand for approximately 20 mins. Analysis of the solution by 31P and 1H NMR indicated that both compound **1** and GD remained intact and no reaction between the two species had occurred (ESI).

fig 1.TIF

**Fig. 1** Effects of the addition of GD to the surface of cyclohexane organogel (1 mL) containing compound **1** (2.5 mg/mL). (293 K)

The collection of data using actual nerve agents is limited, due primarily to their extreme toxicity. Therefore, to further probe the gel-to-sol breakdown processes the OP simulants DMMP and DCP were used to extend and expand on the results collected with GD. These represent two of the most commonly reported agent simulants, and as such present opportunities not only for further probing mechanistic behaviour of the organogel but to also furnish valuable information on simulant vs. agent behaviour. Briefly, the simulant DMMP contains a P-methyl bond, common to all G-series agents, but is relatively unreactive. Conversely, there is an absence of a P-methyl bond in DCP but the phosphorus centre is highly reactive. Simulant selection remains challenging, with any single simulant unlikely to emulate a large number of agent properties. Other methyl phosphonates are available that contain longer alkyl side-chains (e.g. diethyl methylphosphonate, diisopropyl methylphosphonate), as well as other phosphates such as diisopropyl methylphosphonate (DFP). The latter, in particular, is not used in this study as actual agent data was available, and the matrix of experiments that could be conducted with DFP versus DCP/DMMP would be much smaller given DFP’s high toxicity. In particular, the use of simulants such as DCP and DMMP allows for much greater quantities of material to be used in comparison to the agent experiments. Three gelator concentrations and four simulant volumes were used to create an expanded data set, with the results of these experiments shown in Figures 2 and 3.

Figure 5.TIF

**Fig. 2** Effects of DMMP addition to the surface of cyclohexane organogel (1 mL) containing compound **1**. (292-294 K)

Figure 2.TIF

**Fig. 3** Effects of DCP addition to the surface of cyclohexane organogel (1 mL) containing compound **1**. (292-294 K)

As expected the extent of organogel breakdown was found to increase as larger volumes of simulant were added and contact time between the organogel and simulant was increased. Both trends are highlighted in Figure 4. These factors effect comparative simulant concentration throughout the organogel. The rate of organogel breakdown was also perturbed by increasing the amount of compound **1** in the organogel, as larger aliquots of simulant were required to affect the gel-to-sol transition (Figure 5). As the amount of gelator present is increased the number of intermolecular interactions vital for organogel stability is also increased, meaning more interactions must be disrupted before the organogel loses stability and collapses. Information comparing the relative amounts of simulant and gelator can be found in Table S1.

fig 4.TIF

**Fig. 4** Effects of DCP addition to the surface of a cyclohexane organogel containing compound **1** (2.5 mg/mL). (292-294 K)

fig 3.TIF

**Fig. 5** Effects of DCP (0.001 mL) addition to the surface of a cyclohexane organogel containing compound **1**. (292-294 K)

The addition of DMMP to the surface of a cyclohexane organogel containing compound **1** did result in a gel-to-sol transition (Figure 2) and as with GD there was no reaction between the two species (see ESI). It is postulated that the breakdown of the organogel by DMMP is driven by changing solvent polarity and the formation of GD/simulant:gelator hydrogen bonds in a similar way to GD (cyclohexane εr = 2.028, DMMP εr = 22.329). Dilution factors were ruled out as a possible mechanism of organogel disruption by preparing DMMP/cyclohexane mixtures at the same volume proportions as that shown to break down the organogel. Compound **1** (5 mg, 2.5 mg and 1 mg) was dissolved in a solution of 0.91 mL cyclohexane and 0.05 mL DMMP, by heating, cooled to 15 ºC for 10 minutes and allowed to warm to room temperature. The same sets of experiments were conducted with 0.95 mL cyclohexane and 0.05 mL DMMP, in all cases the gel did not form, supporting the argument that the organogel collapse is not due to a dilution factor.

The addition of DCP to the surface of a cyclohexane organogel containing compound **1** also results in a gel-to-sol transition (Figure 3). DCP is more susceptible towards nucleophilic attack then GD or DMMP due to the presence of the chloride leaving group. Figure 6 shows comparative 31P NMR spectra of solutions produced by the addition of DCP (0.1 mL) to cyclohexane (1.0 mL) in the presence of compound **1** (20.0 mg). These spectra show that DCP was still present after the gel-to-sol transition and over time the hydrolysis product of DCP, diethyl hydrogen phosphate (DHP) was also identified. Resonances occurring at ~ -13 and -25 ppm were attributed to polymerised phosphorus species, identified by a 31P COSY NMR experiment. The remaining differences were found to result from species produced by the reaction of compound **1** with DCP. In the case of DCP, organogel breakdown is driven by changes in the polarity of the solvent environment, formation of GD/simulant:gelator hydrogen bonds and reaction processes that accelerate gel-to-sol transition. This suggests that for this system DMMP is a better simulant for modelling the effects of OP CWA introduction to this material.

Fig 6.tif

**Fig. 6** 31P NMR stack plot in cyclohexane (1 mL) locked to external D2O; (a) solution produced upon the breakdown of a organogel containing compound **1** (20 mg/mL) with the addition of DCP (0.1 mL); (b) same sample showing further breakdown of the DCP to DHP over a 24 h period. (292-294 K)

Further analysis of analogous CDCl3 mixtures by 1H, 13C and 31P NMR spectroscopy and high resolution mass spectrometry also indicated a reaction between compound **1** and DCP. The general mechanism shown in Scheme 1 is proposed for the reaction of compound **1** with DCP in both the cyclohexane organogel and CDCl3 solution. The formation of compounds **2** and **4** would result in the production of HCl which would in turn lead to carboxylate protonation (compound **3**). The formation of compounds **2**-**4** would reduce the number of ionic interactions vital for organogel formation and can also undergo hydrolysis to give DHP.

ionic break down.tif

**Scheme 1** Proposed reaction of DCP with anthracene carboxylate. Compounds **2** and **4** were identified by high resolution mass spectrometry from the dilution of a reaction mixture containing gelator **1** (10 mg/mL) and DCP (0.1 mL) in cyclohexane (1 mL) with acetonitrile. Experimental data can be found in the ESI.

The formation of compounds **3** and **4** due to the reaction of compound **1** with DCP also caused us to investigate the comparative fluorescence properties of compound **1** in cyclohexane *vs.* the sol produced upon organogel breakdown in the presence of DCP (Figure 7). Solutions containing compound **1** (spectrum b) or anthracene-9-carboxylic acid (spectrum e) in cyclohexane gave similar fluorescence spectra with maxima at 456 and 435 nm, however the fluorescence intensity of anthracene-9-carboxylic acid was attenuated in comparison to compound **1**. The sol created by the reaction of the cyclohexane organogel with the DCP (spectrum c) was found to give a different fluorescence spectrum with a single maximum at 468 nm.

flour.TIF

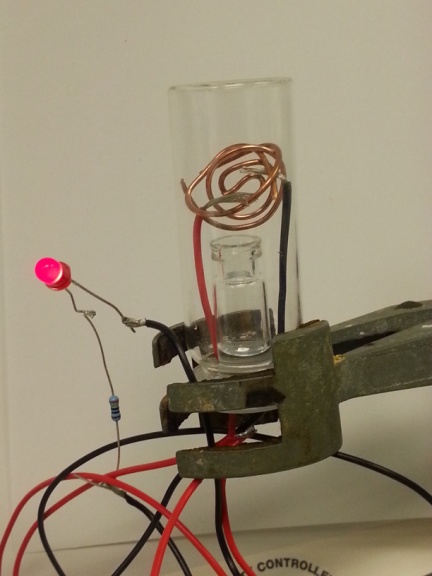
**Fig. 7** Fluorescence spectra of; (a) cyclohexane; (b) 0.027 mM solution of compound **1** in cyclohexane; (c) the sol produced from the gel-to-sol transition of a organogel containing compound **1** (9.8 mg/mL) in cyclohexane (1 mL) with the addition of DCP (0.1 mL) after a 4545 fold dilution with cyclohexane; (d) 0.695 mM solution of DCP; (e) 0.045 mM solution of anthracene-9-carboxylic acid. Excitation wavelength = 363 nm. (292-294 K).

Due to the sensitivity of this system towards DCP and DMMP, organogel samples containing compound **1** (1 mg/mL) and cyclohexane (1 mL) were explored for sensitivity towards simulant vapours (DCP and DMMP have vapour pressures of 0.130 and 1.631 mmHg respectively at 25 ºC). An illustration of an experimental set up is shown in Figure 8. The inverted organogel samples remained unchanged for periods of time >30 min in the absence of simulant and the presence of DMMP (0.1 mL). A gel-to-sol transition was not noted with the presence of DCP vapours with 0.10 mL, 0.05 mL and 0.01 mL aliquots added to the sealed system. The DCP was allowed to evaporate under ambient conditions and the complete organogel breakdown times recorded. These breakdown times were found to increase from 280 to 680 seconds upon addition of 0.10 mL and 0.01 mL DCP aliquots respectively. Each experiment was repeated three times and the results were reproducible (Figure S14).

figure 8.TIF

**Figure 8** Experimental setup used to observe organogel degradation in the presence of simulant vapours.

These principles were then adapted to produce the rudimentary detection system shown in Figure 9. The organogel was used to suspend a copper coil above both the DCP sample and positive/negative electrical terminals, similar to the set shown in Figure 8. As the organogel was dissolved by the presence of DCP vapours the copper coil was released and connected the positive and negative terminals resulting in the completion of an electrical circuit resulting in the switching on of a LED.



**Figure 9** Left: Copper coil suspended in organogel above the sample DCP and positive/negative contacts; Right: Organogel dissolved resulting in the release of copper coil, completion of the electrical circuit resulting in the LED switching on (292-294 K).

Conclusions

We have shown that a simple binary organogel is capable of acting as a responsive material towards the CWA GD and simulants DCP and DMMP through a gel-to-sol transition. Further investigation indicated that compound **1** was capable of reacting with DCP resulting in increased organogel breakdown rates when compared to samples doped with GD or DMMP. We have shown that a gel-to-sol transition can be triggered by DCP vapours, resulting in the production of a simple electrical sensing system. We have also highlighted that in cases such as this, although DCP is a commonly used OP CWA simulant, it may not give the most comparable results to OP CWAs such as GD, due to the enhanced reactivity of the chloride leaving group.

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Notes and references

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