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Supramolecular gels for the remediation of reactive organophosphorus compounds

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Supramolecular gels for the remediation of reactive organophosphorus compounds

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Pyridine-based gels formed with a cyclohexyl diamide gelator have been shown to undergo a gel-sol transition upon addition of the organophosphorus (OP) chemical warfare agent (CWA) simulant diethyl chlorophosphate (DCP). This is due to a reaction between the gelator and DCP resulting in the disruption
10 of the intermolecular hydrogen bonded gelator matrix and therefore the loss of gel stability. This selective phase change reliant on the presence of a reactive OP species provides a novel remediation and sensory method for this class of toxic compound.

Introduction

With recent reports of the use of organophosphorus (OP)
15 chemical warfare agents (CWAs) in areas of conflict combined with terrorist threats, the development of new sensory or remediation materials is of high importance.[1-4] The detection of highly toxic organophosphorus compounds by supramolecular systems has been of significant interest recently[5] as has the design
20 and synthesis of supramolecular gel systems.[6-8] There has been a concerted effort to use supramolecular gels as sensory materials because of their response to various stimuli.[6,9-12] Seminal examples include work by Escuder, Miravet and co-authors who have used intermolecular hydrogen bond formation to produce a
25 gel that is sensitive to the presence of catechol, with the introduction of this guest species found to disrupt the formation of the intermolecular hydrogen bond network.[13] This was followed by work from Steed and co-authors that showing that gel structures could be disrupted by the presence of anionic
30 species. These anion switchable gels were used as crystal growth media producing polymorphs of pharmaceutical interest.[14]

In previous work we have synthesised hydrogen bond donating receptors for selective phosphate binding.[15-18] This led us to investigate whether these systems could be utilised for CWA
35 sequestration[19] and catalytic breakdown[20,21]. The use of supramolecular gels as potential CWA sensors was first demonstrated in 2010 by Lee and co-workers who used 2-(2'-hydroxyphenyl)benzoxazole to detect diethyl chlorophosphonate (DCP) through a colour change within the gel as the DCP was
40 absorbed.[22] Recently we have shown that the formation of intermolecular hydrogen bonded supramolecular gels can be perturbed by the presence of the CWA soman (GD).[5]

Three known cyclohexyl di-amide gelators (**1**[23], **3**[24, 25] and **4**[26]), were synthesised in addition to a new gelator **2**. Gelator **2** was
45 prepared by reaction of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane and undecanoic acid using carbonyldiimidazole as the amide coupling agent. The product was obtained as a white powder in 57 % yield.

Cyclohexyl diamide gelators have attracted attention because of the helical structures formed by the gel fibres in a wide variety
50 of organic solvents, through the establishment of intermolecular hydrogen bonds between the amide groups.[27-30] In this paper we have explored the possibility that the polar/basic conditions within the gels could be used for remediation of organophosphorus compounds.

1 n = 8
2 n = 9
3 n = 10
4 n = 11

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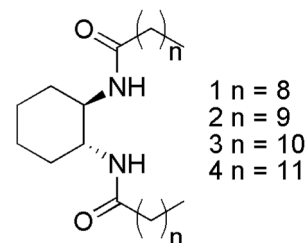
Gel formation studies

Gels were formed by heating gelators **1-4** with the appropriate solvent in a sealed vial at 100°C until all the solid had dissolved. The solutions were then allowed to cool to room temperature
60 (approximately 20°C). An inversion test was then used to check for gel formation.[31] The lower gelation limits for gelators **1-4** observed under these conditions are shown in Table 1. As well as common organic solvents the compounds were also found to gelate the CWA simulant dimethyl methylphosphonate (DMMP)
65 but not DCP. A general trend linking longer aliphatic chain length with lower minimum amounts of gelator required for gel formation was identified. There was little difference observed between the minimum amount of gelators **1-4** needed to form a gel in either triethylamine (TEA) or DMMP, however
70 significantly higher quantities of gelators **3** and **4** were needed to form a gel in pyridine. A gel failed to form under these conditions with gelators **1** and **2**.

Table 1 Minimum amount of gelator needed for full gel formation (mg/mL).

Solvent	Gelator (mg/mL)			
	1	**2**	**3**	**4**
Pyridine	a	a	13	7
TEA	4	5	3	4
DMMP	5	3	3	3
DCP	a	a	a	a

a) No gel formation noted with gelator present in quantities ≥ 25 mg/mL.

Gel-sol phase transition

5 The results from the gel formation experiments led us to investigate the effect of DCP addition to the surface of TEA or pyridine based gels formed with compounds **1-4**. A different response was observed with each of the different solvent systems. TEA based gels were found to absorb DCP into the solid where a 10 crystalline solid as shown in Figure 1, proved to be TEA·HCl by single crystal X-ray diffraction methods was formed.

Fig 1 SEM images of various xerogels. Left: gelator **3** from TEA, right: gelator **3** from TEA and DCP. Samples of gelator **3**/TEA before and after 15 the addition of DCP were dried under reduced pressure. Single crystal X-ray diffraction analysis showed this to be TEA.HCl formed upon the breakdown of DCP within the gel. The parameters of the unit cell (a = 8.240 Å, b = 8.240 Å, c = 6.984 Å, α = 90 º, β = 90 º, γ = 120 º)[32-34] were found to match literature values for TEA.HCl and the structure was 20 verified further by solving it with an isotropic refinement.
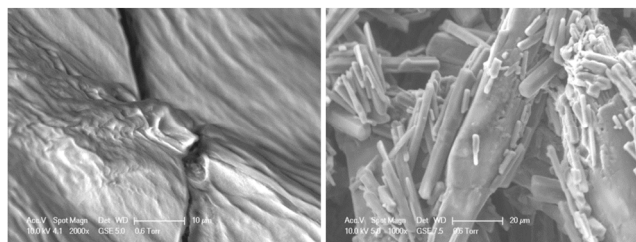
Pyridine based gels were found to undergo a gel-sol phase transition upon addition of DCP. The incorporation of HCl or diethylhydrogenphosphate (EP), the products of DCP hydrolysis, into pyridine gels formed from compounds **3** and **4** did not 25 promote a gel-sol transition. These gels were found to remain unchanged over periods of time >12 hrs. It was concluded that the gel-sol transition must be due to the combination of pyridine, DCP and gelator.

The gel-sol transition exhibited for a pyridine (1 mL) gel 30 formed by compound **3** (25 mg) upon the addition of DCP (0.1 mL) was studied using a combination of NMR spectroscopy and high resolution mass spectrometry (HRMS) techniques. The ^{1}H NMR spectrum showed that the amide NH resonance disappeared upon addition of DCP to a sample of the gel, suggesting a 35 reaction with the amide group (Figure 2), while HRMS provided evidence for the presence of compounds **5-9**. We propose the general mechanism shown in Scheme 1 for the reaction of gelators **3** and **4** within a pyridine gel upon the addition of DCP. These reactions decrease the number of available amide hydrogen 40 bond donor and acceptor groups available for the formation of intermolecular hydrogen bonds resulting in destabilisation and a gel-sol transition.
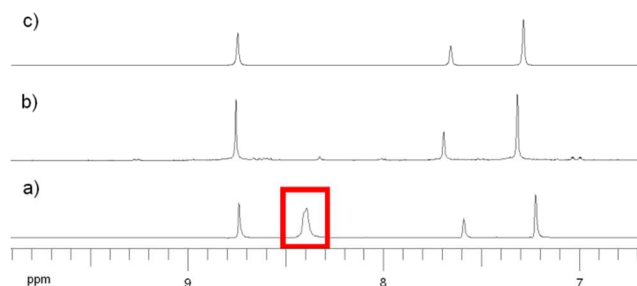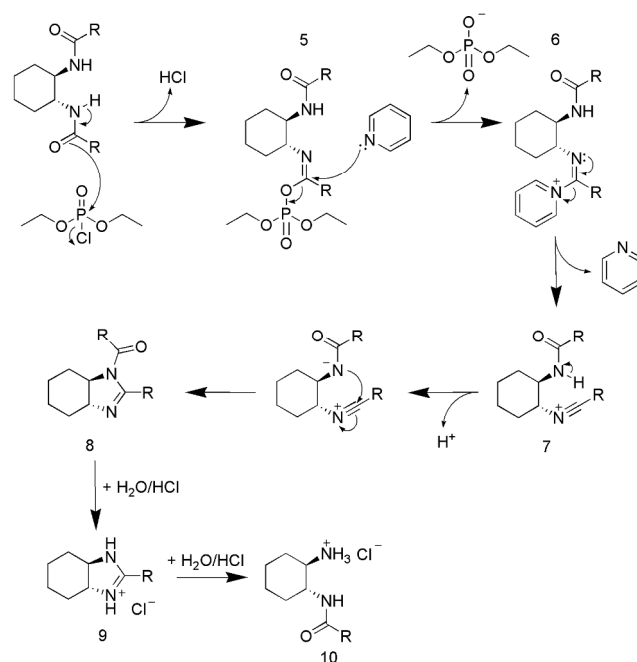

Fig 2 ^{1}H NMR spectra in pyridine-d_5 (1 mL) a) with gelator **3** (25 45 mg/mL). The amide NH signal has been highlighted, b) sample a) with the addition of DCP (0.1 mL), c) with DCP only (0.1 mL). The signals shown at approximately 7.2, 7.6 and 8.7 ppm are residual solvent peaks from the NMR solvent.

50 **Scheme 1** A generalised reaction mechanism proposed for gelators **3** and **4** upon the addition of DCP to a pyridine based gel, resulting in gel breakdown. For gelator **3** R = (CH$_2$)$_{10}$CH$_3$.

The reaction of gelator **3** with DCP to give compound **5** and subsequent substitution of the phosphorus substituent with 55 pyridine to give compound **6** is analogous to the well-known reaction of amides with POCl$_3$.[35] The proposed formation of compounds **7** and **8** through elimination and intramolecular cyclisation has previously been suggested by Loughlin and co-workers.[36] The incorporation of DCP into the reaction mechanism 60 shows this system has potential to act as a novel selective remediation method for reactive organophosphonate compounds including CWAs and pesticides.

Single crystals were also obtained by slow evaporation of the sol produced by addition of DCP (0.1 mL) to a gel containing 65 gelator **3** (20 mg/mL) in pyridine (1 mL). One confirms the presence of compound **9** as shown in Figure 3. A second crystal structure shows the presence of compound **10** (Figure 4), produced by the hydrolysis of compound **9** known in litrature[36]. However compound **10** was not observed by HRMS.
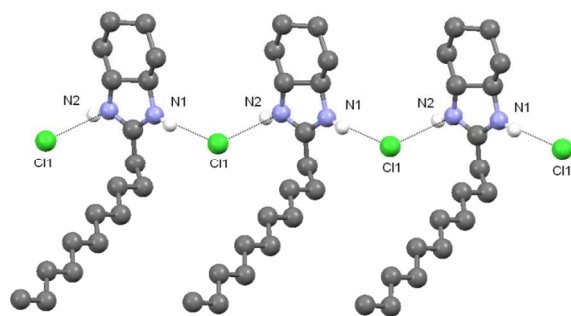
Fig 3 X-ray crystal structure of compound **9** which were found to form hydrogen bonded tapes with each chloride anion bound by two hydrogen bonds, one from each cyclic molecule (N1¨Cl1 3.130(2) Å, N2¨Cl1
5 3.077(2) Å. The hydrogen atoms attached to the alkyl units and second analogous tape have been omitted for clarity. Nitrogen atoms blue, hydrogen atoms white, carbon atoms grey, oxygen atoms red and chloride ion green.
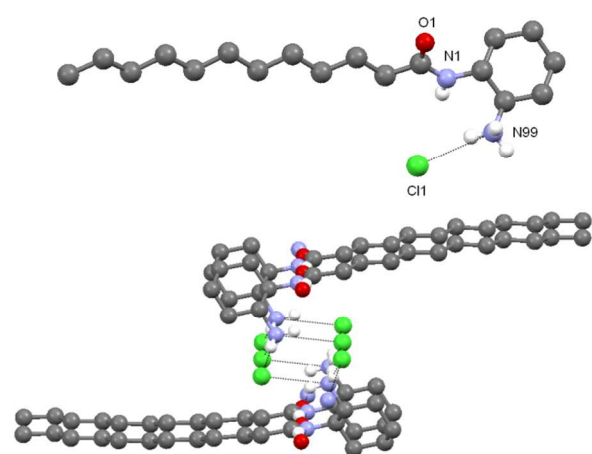

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Fig 4 Two views of the X-ray crystal structure of compound **10** which were found to form tapes through the formation of intermolecular hydrogen bonds between the amide hydrogen bond acceptor/donor groups (N1¨O1 2.992 (4) Å). Each ammonium group was found to form
15 hydrogen bonds to three chloride anions (N99¨Cl1 3.140(3) Å, 3.193(3) Å, 3.243(2) Å). The hydrogen atoms attached to the alkyl units have been omitted for clarity. Nitrogen atoms blue, hydrogen atoms white, carbon atoms grey, oxygen atoms red and chloride ion green.

Colorimetric properties

20 When DCP was added to a warmed pyridine/gelator solution containing compounds **3** and **4**, a colourless gel formed upon cooling. These gels broke down over time accompanied by a colour change from colourless to red. The same process was noted upon addition of DCP to the surface of a prepared gel as
25 shown in Figure 5. The addition of DCP, HCl and EP to pyridine failed produce colour changes observed with the presence of the gelator, suggesting that the colorimetric properties were due to complexes formed between the pyridine gelator and DCP.
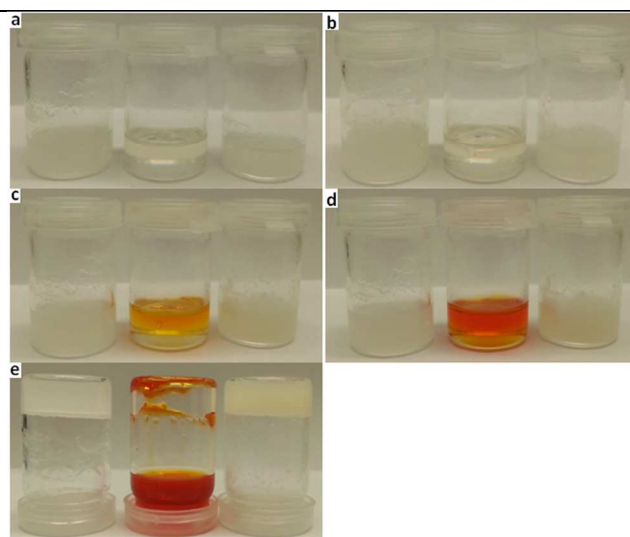

30 **Fig. 5** a) Gels containing Compound **4** (20 mg) and Left to Right DMSO (1 mL), pyridine (1 mL) and TEA (1 mL). b) The addition of DCP (0.1 mL) to the surface of gel samples. c) 1 hr 48 mins after DCP addition. d) 2 hrs 58 mins after DCP addition. e) 5 hrs 5 mins after DCP addition.

To further probe the colorimetric properties of the pyridine
35 based gels, four novel gels were synthesised with compound **4** (20 mg) and substituted pyridine solvents shown in Figure 6. DCP (0.1 mL) was then added to the surface of the gel and the effects monitored over time. Those samples containing deactivating electron withdrawing substituents (Figure 7)
40 remained stable over 95 hrs, absorbing the DCP into the gel structure. No obvious colour changes were observed with gels containing 3-acetylpyridine or 3-bromopyridine. A colour change was noted with the gel containing 4-acetylpyridine however the lack of a gel-sol transition suggests that the reactions shown in
45 Scheme 1 did not occur to any great extent as the gel matrix remains undisrupted.

The sample containing the activating electron donating methoxy-substituted pyridine (Figure 8) showed similar colour changes over time to the pyridine based gel and a partial gel-sol
50 phase transition was also observed. These studies suggest that the coloured compounds produced are dependent on the nucleophilic nature of the pyridine and are not dependent on the reactions shown in Scheme 1 that promote gel breakdown.

Numerous NMR, MS and chromatography methods were used
55 to attempt to characterise the compounds responsible for the colorimetric changes observed with the pyridyl based gels. The properties of the coloured systems were altered or disappeared during chromatography processes and the preparation of diluted samples and consequently we are unable to ascertain the nature of
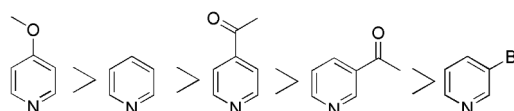60 the coloured compounds in these experiments.

Fig. 6 Substituted pyridine based compounds arranged in descending basicity.[37]
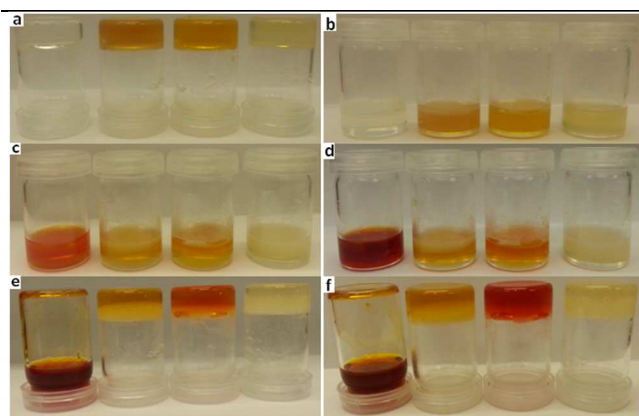
Fig. 7 a) Gels containing Compound **4** (20 mg) and left to right pyridine (1 mL), 3-acetylpyridine (1 mL), 4-acetylpyridine and 3-bromopyridine (1 mL). b) The addition of DCP (0.1 mL) to the surface of gel samples. c) 6 hrs after DCP addition. d) 21 hrs after DCP addition. e) 24 hrs after DCP addition. f) 95 hrs after DCP addition.
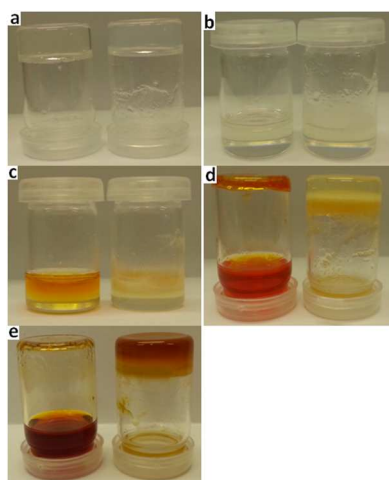

Fig. 8 a) Gels containing Compound **4** (20 mg) and pyridine (1 mL) (left) and 4-methoxypyridine (1 mL) (right). b) The addition of DCP (0.1 mL) to the surface of gel samples. c) 4 hrs after DCP addition. d) 6 hrs after DCP addition. e) 91 hrs after DCP addition.

Conclusions

We have shown that bis-amide based organogelators (**1**–**4**) have the potential to act as selective sensors and remediation agents for toxic reactive organophosphorus compounds such as CWAs and pesticides through a selective gel-sol phase transition accompanied by a colorimetric change. The phase transition was shown to be due to a reaction between the gelator, DCP and pyridine whereas the colorimetric change is suggested to be independent of this process but dependent on the nucleophilic nature of the pyridine. The compounds responsible for this colour change could not be identified due to stability issues. TEA-based gels were shown to absorb DCP into the solid state, breaking it down *in situ,* resulting in the crystallisation of TEA.HCl with the solid nature of this gel maintained.

Acknowledgements

Notes and references

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† Electronic Supplementary Information (ESI) available: CCDC 986072, 986073. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/.

‡X-ray data were collected on a Rigaku AFC 12 diffractometer mounted on Rigaku FR-E+ Super Bright Ultra High Flux rotating anode CCD diffractometer equipped with VariMax very high flux (VHF) optics and Saturn 724+ CCD detector.[38]

Crystal data for compound **9**. CCDC 986072 M = 314.93, Monoclinic, a = 16.137(5), b = 7.876(2), c = 16.214(5) Å, α = 90.00°, β = 108.606(4)°, γ = 90.00°, V = 1953(10) Å^3, T = 100(2) K, space group P21, Z = 4, 8458 reflections measured, 7852 unique reflections (Rint = 0.0273). The final R1 values were 0.0532 (I > 2σ(I)). The final wR(F2) values were 0.1150 (I > 2σ(I)). The final R1 values were 0.0532 (all data). The final wR(F2) values were 0.1182 (all data). The goodness of fit on F2 was 1.096.

Crystal data for compound **10**. CCDC 986073 M = 332.95, Monoclinic, a = 10.722(4), b = 5.224(16), c = 18.916(7) Å, α = 90.00°, β = 103.55(6)°, γ = 90.00°, V = 1030.0(6) Å^3, T = 100(2) K, space group P21, Z = 2, 4418 reflections measured, 3963 unique reflections (Rint = 0.0269). The final R1 values were 0.0697 (I > 2σ(I)). The final wR(F2) values were 0.1110 (I > 2σ(I)). The final R1 values were 0.0697 (all data). The final wR(F2) values were 0.1192 (all data). The goodness of fit on F2 was 1.118.

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