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Predicting the hydrolytic breakdown rates of organophosphorus chemical warfare agent simulants using association constants derived from hydrogen bonded complex formation events[†]

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Predicting the hydrolytic breakdown rates of organophosphorus chemical warfare agent simulants using association constants derived from hydrogen bonded complex formation events[†]

Organophosphorus (OP) chemical warfare agents (CWAs) represent an ongoing global threat, through either purposeful environmental release or the need to dispose of historic stockpiles. This presents a need for the development of novel decontamination technologies. Due to the toxic nature and legal limitations placed on OP CWAs, the use of appropriate OP simulants that mimic the reactivity but not the toxicity of the agents themselves is vital to decontamination studies. Herein, we show that association constants derived from non-specific hydrogen bonded complexation events may be used as parameters within models to predict simulant reactivity. We also discuss the limitations that should be placed on such data.

Keywords: hydrogen bond; simulant; chemical warfare agent; predictive models

Introduction

For almost a century organophosphorus (OP) compounds have been used globally as pesticides and chemical warfare agents (CWAs).¹ However, due to the inherent toxicity of these compounds combined with limited effective treatments,^{2,3} the accidental or purposeful release of these agents represents a continued global risk, as demonstrated by recent events in Germany (2020),⁴ UK (2018)⁵ and Malaysia (2017),⁶ as well as events in Syria (2013)⁷ and Japan (1995).⁸ The ongoing development of novel decontamination and remediation technologies to limit the harmful effects of these OP compounds if released therefore remains imperative.^{2,9}

In general, OP simulants represent the only viable option when developing novel approaches both to combat OP CWA release and for subsequent remediation due to the highly toxic nature of, and legal restrictions placed upon, the live agents themselves.^{10,11} However, it is not feasible for any single simulant to simultaneously mimic all the

chemical properties of an OP CWA without also inheriting undesirable molecular traits. Careful consideration of the appropriate properties of any simulant chosen to aid in the development of novel OP CWA detection, decontamination, or remediation methodologies^{12–15} is therefore required.

Within the field of supramolecular chemistry, the use of CWA simulants to develop such technologies is well documented.^{16,17} For example, Cragg and co-workers have highlighted the importance of simulant choice through their work comparing the coordination of OP CWAs and simulants binding within a cyclodextrin cavity.^{13–15} These findings are further supported through the work of Barlaz and co-workers.¹² In addition, work by Gale and co-workers¹⁸ have shown that simple tripodal compounds containing amino acids can not only bind to OP CWA agents, but also enhance the rate of their hydrolysis. In further work, this research group also demonstrated the use of responsive supramolecular organogels for not only sensing the presence of OP CWAs, but also CWA encapsulation and decontamination.^{19–21} Furthermore, Ward and co-workers have demonstrated that supramolecular cages can be used for catalysing the hydrolysis of organophosphates upon binding within the cage cavity and on the cages exterior surface.^{22,23} Similarly, Dennison and co-workers²⁴ have utilised a trivalent Europium complex to successfully bind a variety of OP structural analogues, to determine whether these could lead to the identification of next-generation VX simulants for supramolecular and spectroscopic purposes. Finally, work by Borguet, Rosi, Johnson and co-workers²⁵ has shown that DFT modelling can be used to predict ligand design for the uptake into metal-organic frameworks (MOFs), of the OP CWA simulant dimethyl methylphosphonate (DMMP).

Predictive models which utilise the derivation of potential simulant structure-desired physical property relationships (more generally referred to as structure activity

relationships – SARs) can be used by researchers to aid the effective identification of appropriate OP CWA simulants. Specifically, they permit the screening of any potential target molecules without first requiring their synthesis, accelerating the development process,^{11,26,27} to identify the most appropriate simulant for the work to be undertaken. This approach, used by Snurr and Mendonca,²⁸ drew upon density functional theory (DFT) studies on OP hydrolysis to develop a quantitative structure activity relationship (QSAR) model that supports the identification of appropriate OP CWA simulants for decontamination purposes.

Within our own work, we have demonstrated how simple, low-level computational modelling may be used to predict hydrogen bond mediated aggregation events,^{29,30} the resultant antimicrobial activity,³¹ and most recently to identify appropriate OP CWA simulants for the development of supramolecular detection technologies, through the calculation of association constants which maybe predicted using computationally derived parameters.¹¹ Herein, we build on this prior work, exploring the use of low-level computational modelling and supramolecular host:guest association constants to predict the reactivity of potential OP simulants towards the presence of NaOH, a base typically used within standard decontamination solutions,^{32,33} using a data set produced from the library of OP simulants **1-22**, Figure 1. It is hoped that our preliminary work in this area will aid other researchers towards the identification of appropriate OP simulants for the development of novel decontamination technologies.

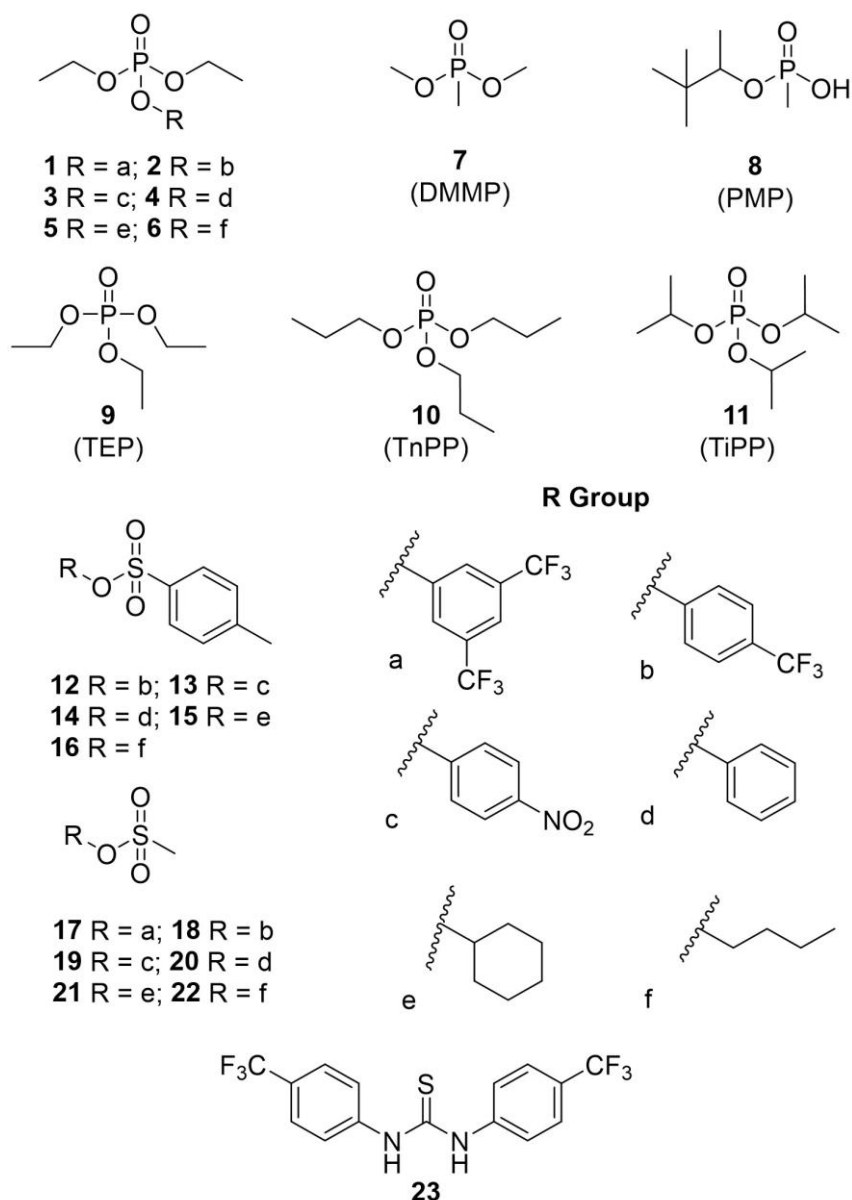


Figure 1 Chemical structures of compounds **1-23**.

Synthesis

The synthesis of **1-23** (Figure 1) has been previously reported.^{11,34-42} However, ¹H NMR spectra for these compounds have been provided within the supplementary information as evidence of sample purity.

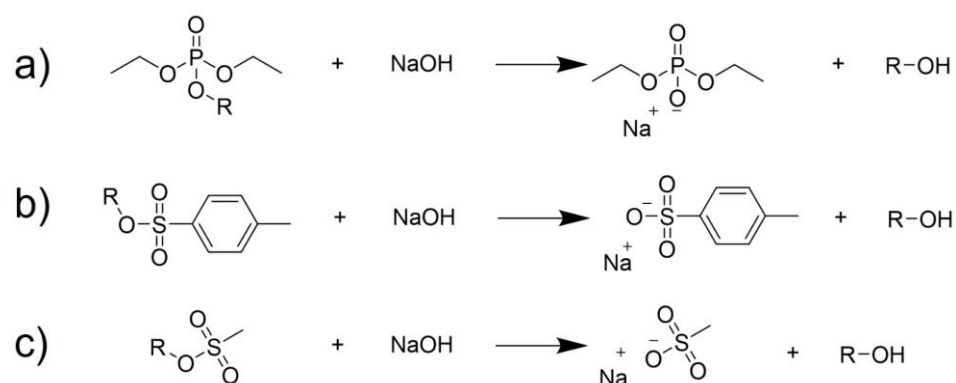
Results and discussion

Assessing simulant reactivity

Several OP CWA decontamination solutions/systems are commercially available, these include the US army developed skin decontamination M258 kit,⁴³ a two phase system which contains two packets to be used sequentially. Packet 1 contains a towelette impregnated with phenol (10 wt %), ethanol (72 wt %), NaOH (5 wt %), ammonia (\approx 1 wt %), and water (12 wt %), whilst Packet 2 contains a towelette impregnated with chloramine-B and a sealed glass ampoule filled with zinc chloride.^{32,43} DS2, a second decontamination solution, consists of diethylenetriamine (70 wt %), ethylene glycol monomethyl ether (28 wt %), and NaOH (2 wt %).^{32,33} Super tropical bleach (calcium hypochlorite (93 wt %) and NaOH (7 wt %)), when supplied as a solid or slurry with water is also considered useful for OP CWA decontamination.^{33,44} With the partial exception of super tropical bleach, all of these decontamination systems/solutions have in common the presence of an alcohol, NaOH, and H₂O. Here the hydroxyl ion acts as a nucleophile which attacks the electrophilic phosphorus centre, common to all members of this class of OP CWAs, neutralising/reducing the toxic effects of these agents.^{45–47} When considering the library of potential simulants **1–22**, the electrophilic centre analogous to that of the OP CWA is either the analogous P=O phosphorus or O=S=O sulfur atom.

The reactivity of potential OP CWA simulants **1–22** was evaluated by reaction of these compounds (see Scheme 1) in the presence of five equivalents of NaOH, with respect to the simulant, at 291 K in a methanol-*d*₄:D₂O 70:30 solution. These experimental conditions were a result of multiple optimisation studies in which ¹H NMR spectroscopy was used to monitor the relative proportions of reactant and simulant present

with respect to time; the results of these studies have been summarised in Table 1. Due to the range of reaction rates observed for compounds **1-22** under these conditions, it was not possible to calculate experimental hydrolysis rate constants for all the simulants tested. Thus, the % simulant breakdown after 6 hours has been used as a comparative simulant reactivity value to create this dataset. This approach enabled us to include values generated from these studies for all the potential simulants. In addition, where an experimental rate constant could be calculated (**1-4**, **7**, **12-16**, **18**, **21-22**) all reactions were found to follow first order kinetics apart from that of compound **18** which was found to obey second order kinetics with respect to the simulant, at present the reason for this has not been determined. The specific reasons preventing rate order assignment are detailed within Table 1, and further supported by data supplied within the supplementary materials.[†]



Scheme 1 Reaction of OP simulants a) **1-11**, b) **12-16**, c) **17-22** with NaOH.

Table 1 Summary of average data (n=3) obtained from the reaction of the appropriate OP CWA simulant **1 – 22** (10 mM) with 5 equivalence of NaOH (50 mM) in a methanol-*d*₄:D₂O 70:30 solution at 291 K. Error = standard error of the mean.

OP CWA simulant	Simulant breakdown after 6 hours (%)	Rate order	Experimental rate constant (s ⁻¹)

1	92.8 (± 2.19)	1 st	0.42
2	47.9 (± 3.06)	1 st	0.22
3	100 ($\pm \leq 0.01$)	1 st	0.46
4	17.6 (± 0.01)	1 st	0.08
5	5.3 (± 0.23)	<i>a</i>	n/a
6	52.5 (± 0.01)	<i>a</i>	n/a
7	10.4 (± 0.01)	1 st	0.05
8	0 ($\pm \leq 0.01$)	-	-
9	0 ($\pm \leq 0.01$)	-	-
10	0 ($\pm \leq 0.01$)	-	-
11	0 ($\pm \leq 0.01$)	-	-
12	55.7 (± 2.24)	1 st	0.26
13	57.4 (± 0.06)	1 st	0.27
14	1.5 (± 0.05)	1 st	0.01
15	5.0 (± 0.36)	1 st	0.02
16	8.2 (± 0.52)	1 st	0.04
17	100 ($\pm \leq 0.01$)	<i>b</i>	-
18	80.9 (± 0.16)	2 nd	0.37 ^c
19	100 ($\pm \leq 0.01$)	<i>b</i>	-
20	2.1 (± 0.16)	<i>a</i>	n/a
21	66.5 (± 1.00)	1 st	0.31
22	94.1 (± 1.28)	1 st	0.44

a – Rate order could not be definitively assigned when fitting reaction data to either 1st order or 2nd order curves.

b – Rate of reaction could not be obtained due to speed of reaction being too fast to track using the NMR method.

c – Reaction rate units = M⁻¹.s⁻¹.

Predicting simulant reactivity

A series of 1:1 host:guest association constants, determined by ^1H NMR in a CD_3CN solution at 298 K, have previously been reported for compounds **1-22** with **23**, a low molecular weight, non-specific, hydrogen bond donating receptor; these binding events have also been evaluated in terms of the series of computationally derived parameters listed in Table 2.¹¹ We have previously reported the ability to use exhaustive parameter searches to rapidly identify predictive models for both the development of novel antimicrobials³¹ and organophosphorus simulant binding.¹¹ Here we used R data analysis software⁴⁸ to determine both direct and inverse predictive models for the percentage breakdown of potential chemical warfare agent simulants, building upon our previous work.

Table 2 List of parameters (P) used to produce potential simulant predictive models. P_1 – P_{20} are previously published data sets.¹¹ The experimental methods used to calculate P_0 – P_{20} are detailed within the supplementary information.[†]

Parameter number	Parameter	Parameter description
P_0	Breakdown after 6 hours (%)	Percentage breakdown after 6 hours determined via ^1H NMR experiments.
P_1	Association constant (M^{-1})	Association constant derived using a 1:1 binding isotherm.
P_2	E_{min} ($\text{kJ}\cdot\text{mol}^{-1}$)	Electrostatic surface energy minimum.
P_3	E_{max} ($\text{kJ}\cdot\text{mol}^{-1}$)	Electrostatic surface energy maximum.
P_4	Molecular Volume (\AA^3)	Total volume the molecule occupies.
P_5	Molecular Area (\AA^2)	Total molecular surface area.
P_6	Solvent accessible area (\AA^2)	Molecular surface area accessible with a 1.4 \AA radius probe.
P_7	Polar surface area (\AA^2)	Molecular surface area of any nitrogen and oxygen and any attached hydrogens.

P_8	% Polar surface area (\AA^2)	Percentage polar surface area.
P_9	Polarizability	How easily an electron cloud is distorted by an electric field.
P_{10}	Steric weighting factor (SWF) (\AA^2)	Molecular surface area within $1/8^{\text{th}}$ of the E_{min} .
P_{11}	Steric accessibility factor (SAF) (\AA^2)	Molecular surface area within $1/8^{\text{th}}$ of the E_{max} .
P_{12}	HOMO (eV)	Energy of the highest occupied molecular orbital.
P_{13}	LUMO (eV)	Energy of the lowest unoccupied molecular orbital.
P_{14}	Energy (kJ)	Total energy.
P_{15}	Electrostatic charge	The electrostatic charge of the HBA oxygen atom of the simulant.
P_{16}	Additive N \cdots O hydrogen bond length (\AA)	The sum of the N \cdots O hydrogen bond lengths calculated for a hydrogen bonded 1:1 complex of an appropriate simulant and non-specific hydrogen bond donating receptor 23 .
P_{17}	Log P	Calculated octanol water partition coefficient.
P_{18}	Dipole moment (D)	Separation of charge across the molecule.
P_{19}	Additive N-H \cdots O hydrogen bond length	The sum of the N-H \cdots O hydrogen bond lengths calculated for a hydrogen bonded 1:1 complex of an appropriate simulant and non-specific hydrogen bond donating receptor 23 .
P_{20}	Additive hydrogen bond angle difference from 180°	Sum of the N-H \cdots O angles difference from 180° , calculated for a hydrogen bonded 1:1 complex of an appropriate simulant and non-specific hydrogen bond donating receptor 23 .

Organocatalysis by (thio)ureas is generally considered to arise from enhanced reactivity/electrophilicity of the substrate induced by hydrogen bonding with the catalyst,

and catalyst efficacy is typically correlated with hydrogen bonding complexation strength of the substrate with the (thio)urea moiety.^{49–53} We therefore hypothesised that 1:1 association constants, derived using a non-specific hydrogen bond donating receptor (**23**), could be used as a predictor of reaction centre electrophilicity when the principle hydrogen bond accepting group is directly joined to the reactive centre. Thus, we further hypothesise these association constants could be used in the prediction of reaction rates.

To test this hypothesis, we performed exhaustive parameter searches including association constants to determine the role of this parameter in predicting the reactivity of potential simulants towards NaOH, under the experimental conditions described.[†] All predictive models were determined using Equations 1 and 2, to allow for the determination of both two and three parameter combinations with a direct and inverse linear relationship. Five datasets were produced taking into account the limitations of the experiments conducted: (1) all data generated for all parameters and potential simulants listed in Figure 1 and Table 2; (2) exclusion of association constant (P_1) from the complete data set (1); (3) exclusion of simulant data for those compounds which exhibit association constant values less than 10 M^{-1} from the P_1 data set, as these values are known to fall outside of experimental limitations; (4) exclusion of percentage breakdown data from P_0 , where potential simulant breakdown was found to be $< 10 \%$ over 6 hours, as these values were thought to fall outside of experimental limitations due to inherent integration errors; (5) and the exclusion of both association constant (P_1) $< 10 \text{ M}^{-1}$ and percentage breakdown values (P_0) $< 10 \%$.

$$\begin{aligned} P_0 &= P_x^a \times P_y^b \\ |a| + |b| &= 2 \end{aligned} \quad (1)$$

$$\begin{aligned} P_0 &= P_x^a \times P_y^b \times P_z^c \\ |a| + |b| + |c| &= 3 \end{aligned} \quad (2)$$

This approach allowed us to ascertain the importance of an experimental association constant, generated from a non-specific host:guest binding study, in the prediction of simulant reactivity. The models produced using these exhaustive search methods for datasets 1-5 were then ranked according to how well they fit the data in terms of their R^2 values. From this ranking, we then selected the ten best fitting models to Equation 1 and Equation 2. This resulted in the production of 20 models of best fit for each dataset 1-5, giving 100 models in total. From this list, we then extracted the parameters that feature in these models and took those as being the most relevant ones for the prediction of the simulant properties. A summary of these data is shown in Figure 2.

Comparing all five data sets, parameters P_2 , P_3 , P_4 , P_7 , P_8 , P_9 , P_{10} , P_{11} , P_{14} , P_{16} , P_{17} , P_{18} , P_{19} and P_{20} (see Table 2) occur ≤ 10 times within the 100 models. It is therefore unlikely that these parameters are significant for the construction of a predictive OP simulant breakdown model. These 100 models also indicate that P_{13} (LUMO Energy) should be considered a significant parameter with a total of 64 occurrences overall; this is not surprising as this orbital is directly involved in the reaction process. Gratifyingly, the parameter with the second highest number of occurrences is P_1 (the association constant), with a total of 35 occurrences over the 80 models, where this parameter was included within the initial datasets (Figure 2a, c, d, and e). Furthermore, the occurrences of this parameter were limited to models that were produced by data sets 3 (Figure 2c) and 5 (Figure 2e). Importantly, it is these two datasets that consider the experimental limitations of association constant determination – in effect, the good fit arises after excluding the noise. In addition, as highlighted in Figure 2d, where the experimental limitations are considered for the % simulant breakdown, but not for the association constant parameters, we see the occurrence of P_1 drop to zero, supporting the importance

of including such limitations in these datasets. After screening, the 20 models with the highest R^2 values used data set 5 (Figure 2e) which takes into account the experimental limitations placed on both the reactivity and association constant data. Within these models, the association constant parameter (P_1) occurs 21 times. We therefore believe that this result confirms that experimental association constants for hydrogen bonded complex formation can be utilised in the construction of predictive reactivity models for the identification of OP simulants.

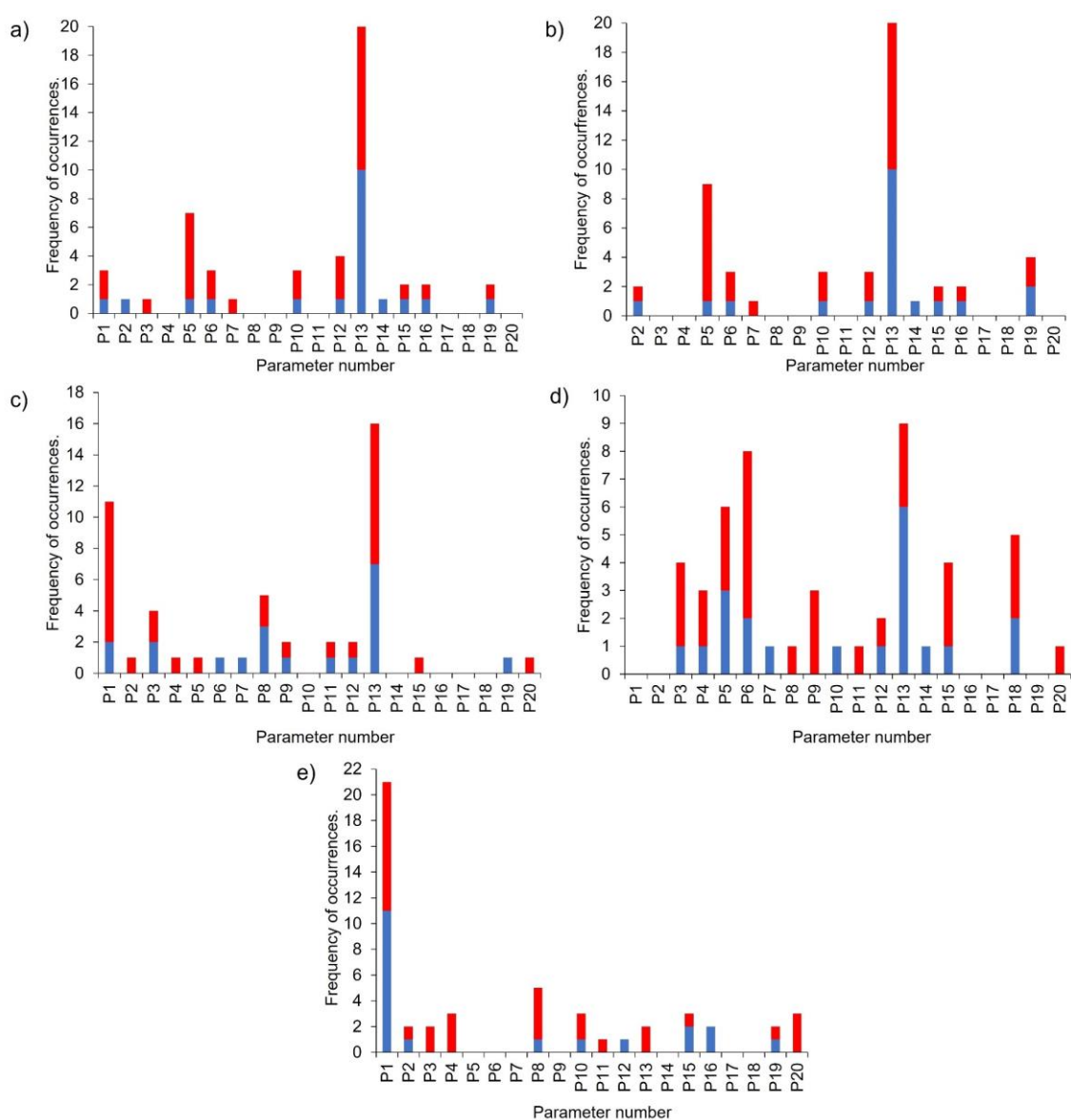


Figure 2 The frequency of occurrences in the top 10 models, produced by an exhaustive search of fits, ranked by R^2 analysis for each parameter to: i) Equation 1 (blue); and ii) Equation 2 (red), in a) dataset 1 (includes 440 data points in total), b) dataset 2 (includes 418 data points in total), c) dataset 3 (includes 240 data points in total), d) dataset 4 (includes 260 data points in total) and e) dataset 5 (includes 140 data points in total).

When comparing the top 20 models, defined by R^2 analysis, through the fitting of datasets 1-5 to Equations 1 and 2, the models produced from dataset 5 reported the highest R^2 values. Of these top 20 predictive models, those produced using Equation 2 reported higher R^2 values than from Equation 1. The models reporting the three highest R^2 values ($R^2 = 0.9596$, 0.9359 and 0.9204 respectively) have been identified as current lead predictive models and are shown in Figure 3. These models include: i) Figure 3a – P_1 (association constant), P_4 (molecular volume) and P_8 (% polar surface area); ii) Figure 3b – P_1 (association constant), P_4 (molecular volume) and P_{13} (LUMO); iii) Figure 3c – P_1 (association constant), P_{11} (SAF) and P_{13} (LUMO).

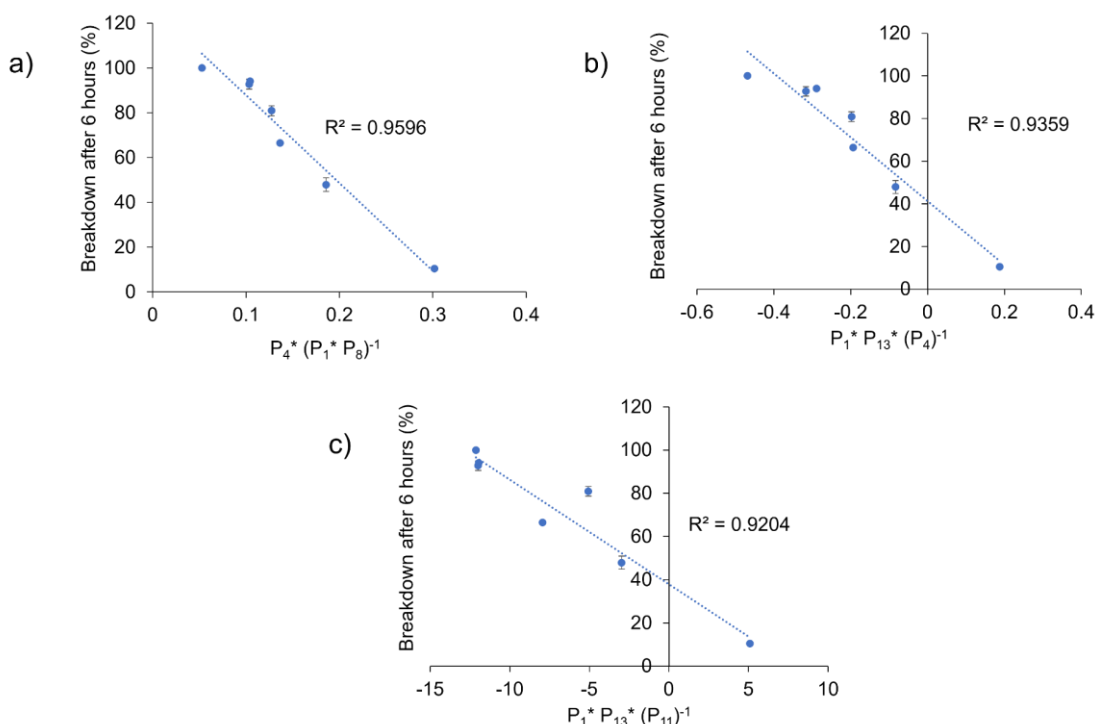


Figure 3 Top three predictive simulant breakdown models defined through the ranking of R^2 values (from highest to lowest), obtained from fitting datasets 1-5 to Equations 1 and 2. The models shown in a-c were generated from dataset 5.

Physical property considerations

In addition to breakdown rate, there may be other physical properties required of a simulant to make its use practical in exercises such as live testing scenarios. The choice of simulant is therefore often a compromise between competing demands, for example the simulant might have to be readily available in advance of live experiment and thus require medium/long term storage. Considering possible practical requirements, we explored several physical parameters for the simulants detailed herein: storage stability, viscosity, hydrolytic stability, density, and surface tension. The key values are summarised in Table 3; the remainder can be found within the ESI.[†]

Table 3 Further physicochemical parameters calculated for **1-22**. For experimental details see ESI.[†] Storage stability was monitored over a one month period, samples were stored in sealed containers at room temperature, and the % breakdown then recorded. The hydrolytic stability of these potential simulants was ascertained in a DMSO:H₂O (70:30) solution, over 14 hrs at 291 K, values reported represent % compound breakdown over this time frame. For liquid samples, the density, surface tension, and viscosity values were calculated at 298 K.

No.	Stability		Density (g.cm ⁻³)	Surface tension (mN.m ⁻¹)	Viscosity (mPa)
	Storage breakdown (%)	Hydrolytic breakdown (%)			
1	0	0	1.39	18.0	4.8

2	0	0	1.17	23.2	6.2
3	0	0	1.83	26.1	15.5
4	0	0	1.30	25.9	4.1
5	0	0	1.06	27.2	5.5
6	0	0	1.19	24.4	0.8
12	0	0	<i>a</i>	<i>a</i>	<i>a</i>
13	0	0	<i>a</i>	<i>a</i>	<i>a</i>
14	0	0	<i>a</i>	<i>a</i>	<i>a</i>
15	2	0	<i>a</i>	<i>a</i>	<i>a</i>
16	0	0	1.31	28.6	6.8
17	0	0	<i>a</i>	<i>a</i>	<i>a</i>
18	0	0	<i>a</i>	<i>a</i>	<i>a</i>
19	0	0	<i>a</i>	<i>a</i>	<i>a</i>
20	0	0	<i>a</i>	<i>a</i>	<i>a</i>
21	0	0	1.45	32.0	2.8
22	0	0	1.12	22.7	12.2

a = not a liquid under experimental conditions.

Conclusion

We have identified three predictive models for potential OP CWA simulant breakdown in the presence of five equivalents of NaOH, in a methanol-*d*₄:D₂O 70:30 solution at 291 K. It is envisioned that the development of such predictive methodologies will enable the production of next-generation OP CWA decontamination technologies that rely on nucleophilic breakdown reaction mechanisms specifically. Additionally, we have shown the importance of considering experimental limitations on both association

constant and reactivity datasets. The breakdown data are supported by a variety of physicochemical characterisation data which are of use selecting an appropriate OP CWA simulant. It is hoped that the use of structure activity relationships, achieved using similar, predictive methodologies to those detailed here, will enable the increasingly effective identification of appropriate simulants to aid in combatting the threat of OP CWAs.

Acknowledgements

R. Ellaby, D. Chu, A. Pépés, E. R. Clark and J. Hiscock would like to thank the University of Kent for funding. Additionally, J. Hiscock would also like to thank UKRI for the funding of her Future Leaders Fellowship (MR/T020415/1).

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