Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Investigating the breakdown of the nerve agent simulant methyl paraoxon and chemical warfare agents GB and VX using nitrogen containing bases

Supporting Information

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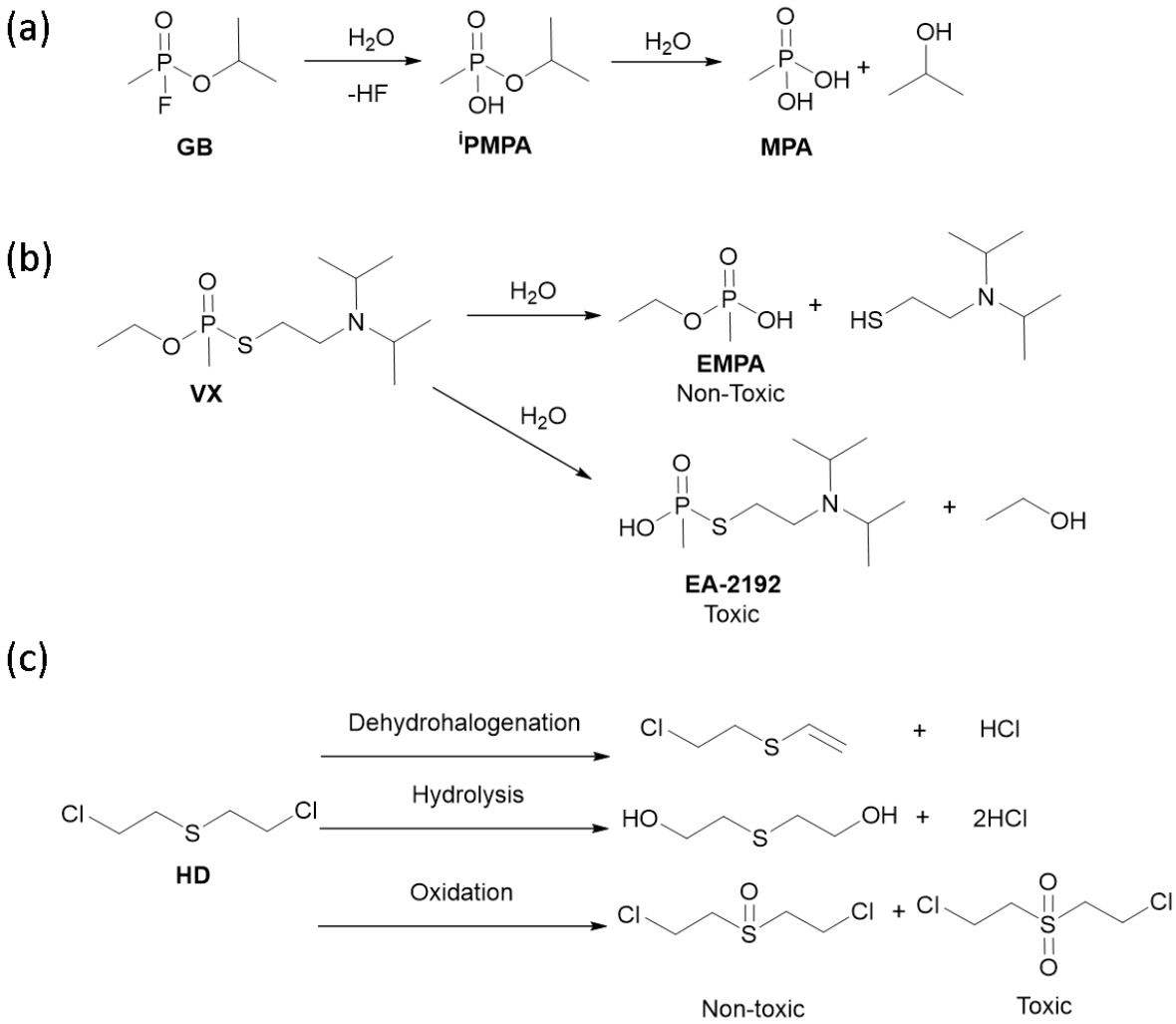
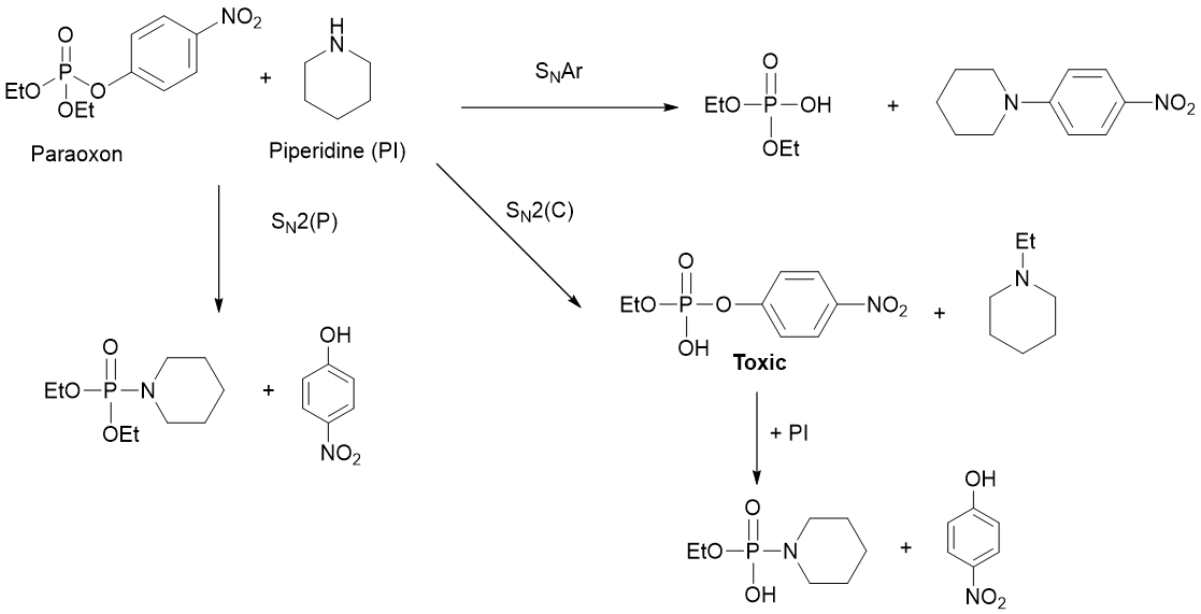


Scheme S1 The decontamination routes available for the breakdown of the nerve agents (a) GB and (b) VX, and the blister agent (c) HD.



Scheme S2 Breakdown pathways reported for the reaction of paraoxon with piperidine (PI). Figure redrawn from reference.[1]

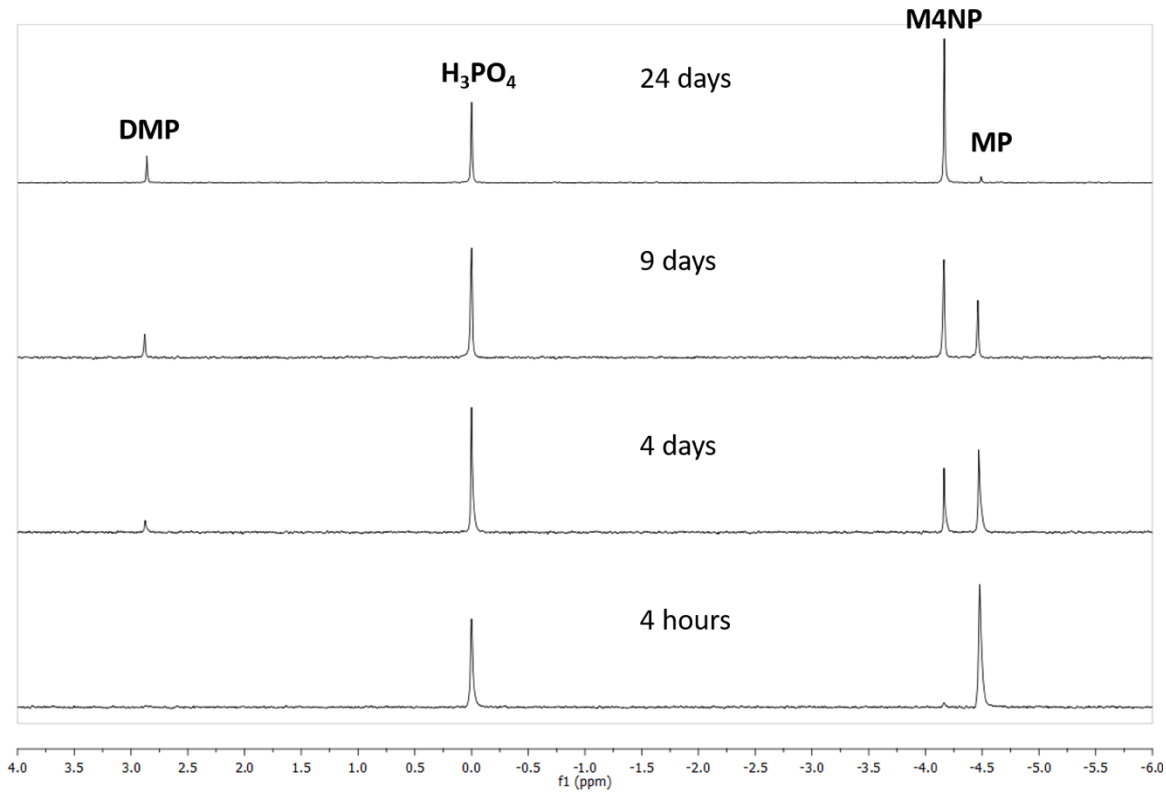


Fig. S1.1 $^{31}P[^{1}H]$ NMR spectra for breakdown of MP, using imidazole, showing the disappearance of the phosphorus peak corresponding to the **MP** (-4.5 ppm), and appearance of the two product peaks; methyl 4-nitrophenyl phosphate, **M4NP**, (-4.2 ppm), and dimethyl phosphate, **DMP**, (2.8 ppm). The peak at 0.0 ppm is from the phosphoric acid standard.

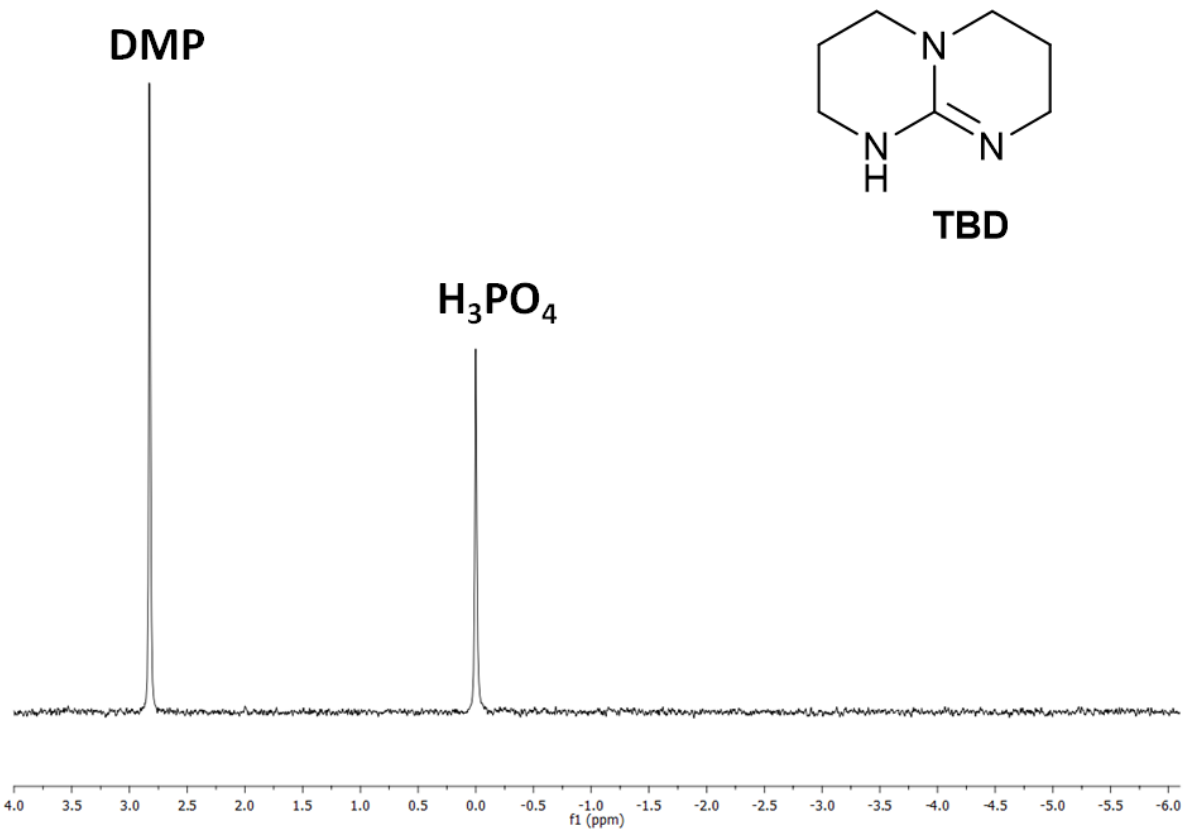


Fig. S1.2 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using TBD, after 1 hour.

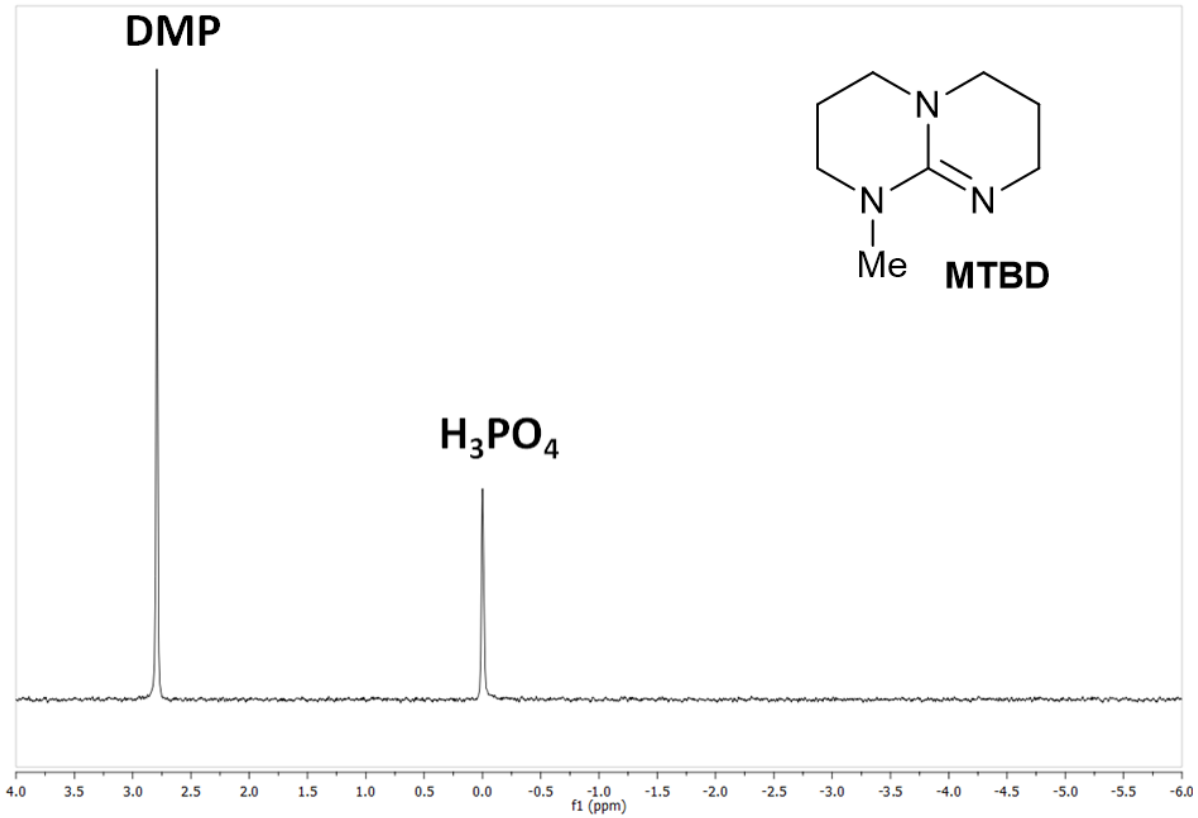


Fig. S1.3 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using MTBD, after 1 hour.

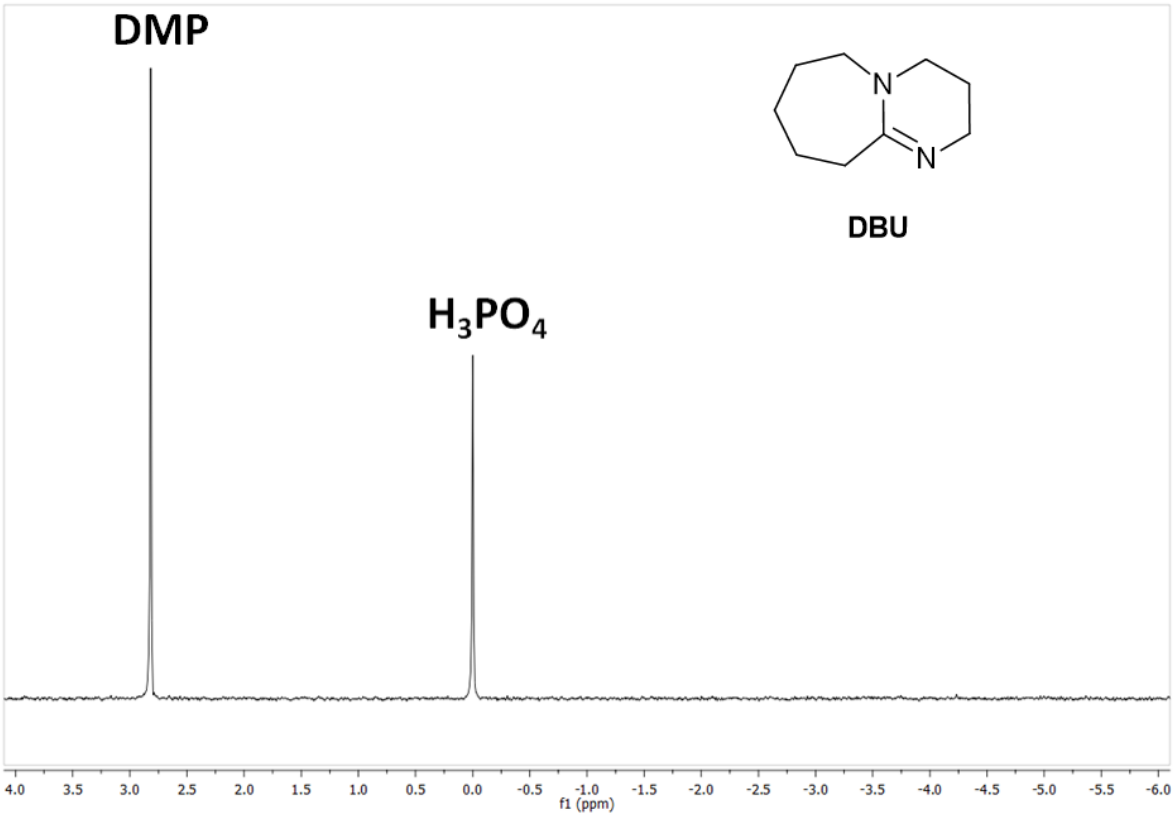


Fig. S1.4 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using DBU, after 1 hour.

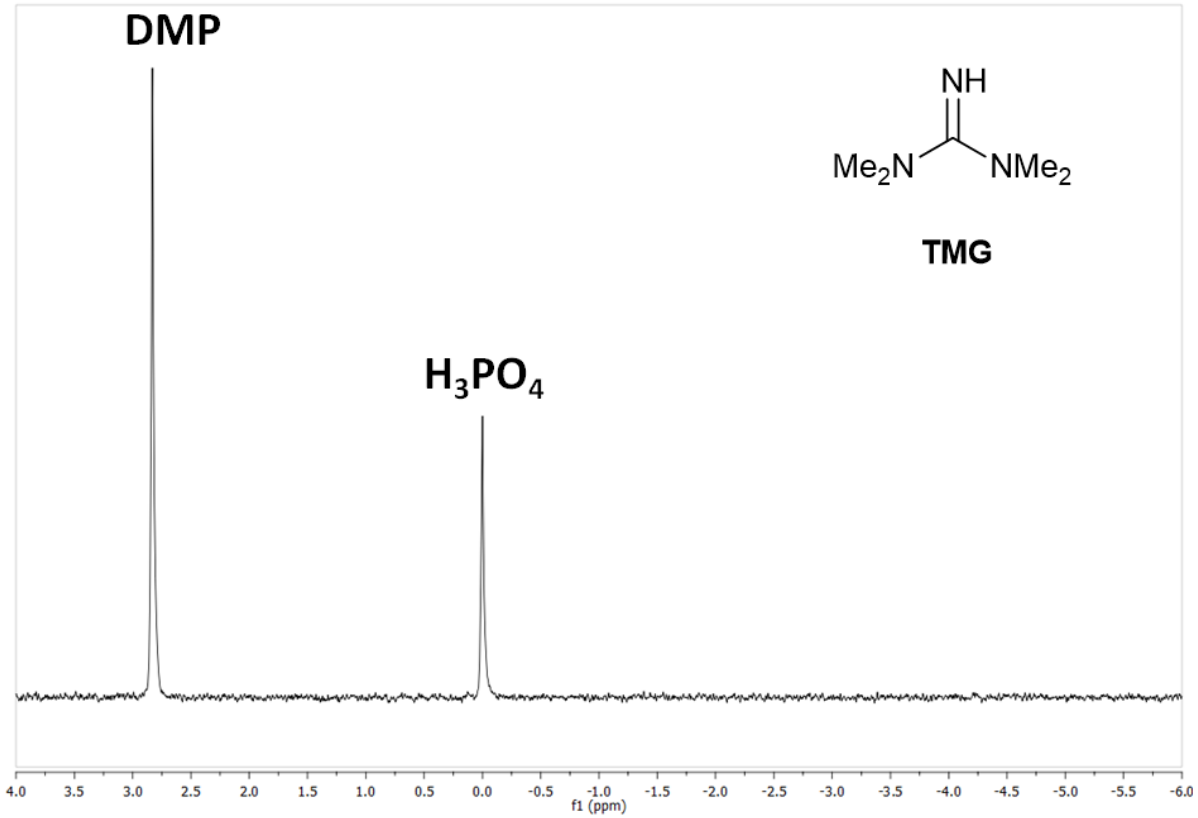


Fig. S1.5 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using TMG, after 2.5 hours.

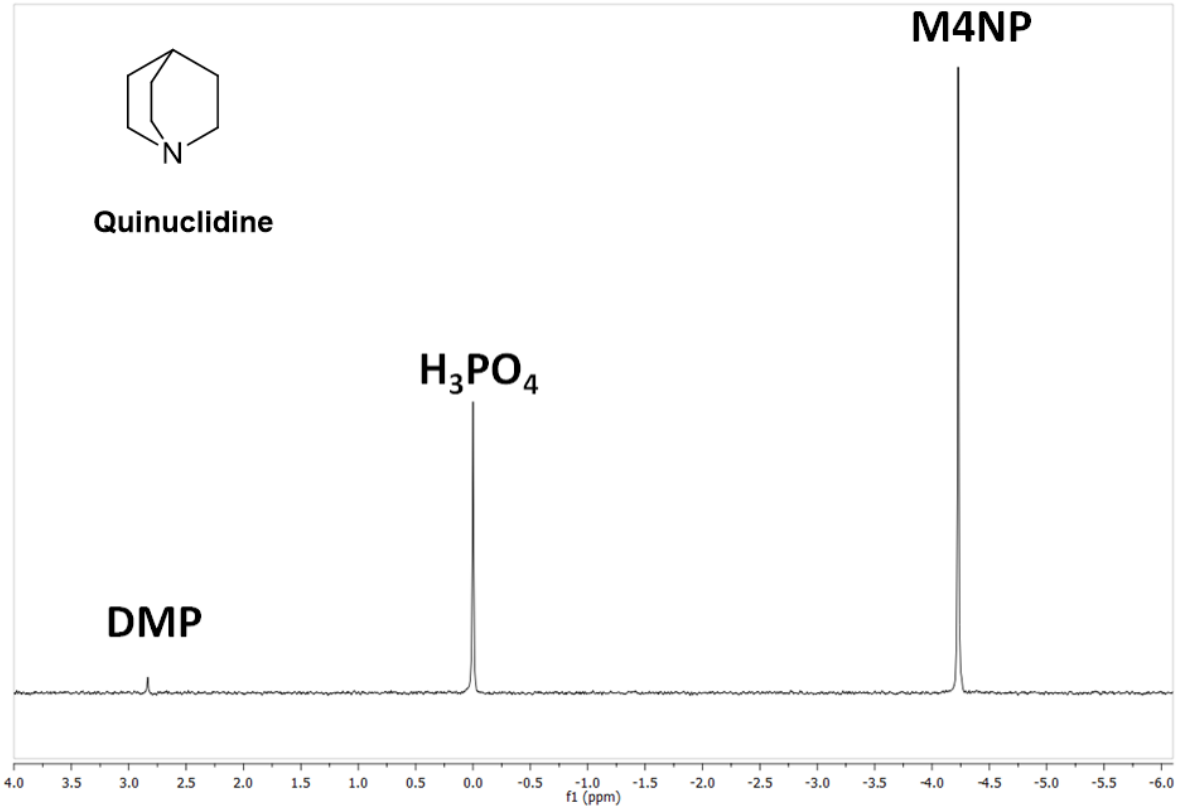


Fig. S1.6 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using quinuclidine, after 1 hour.

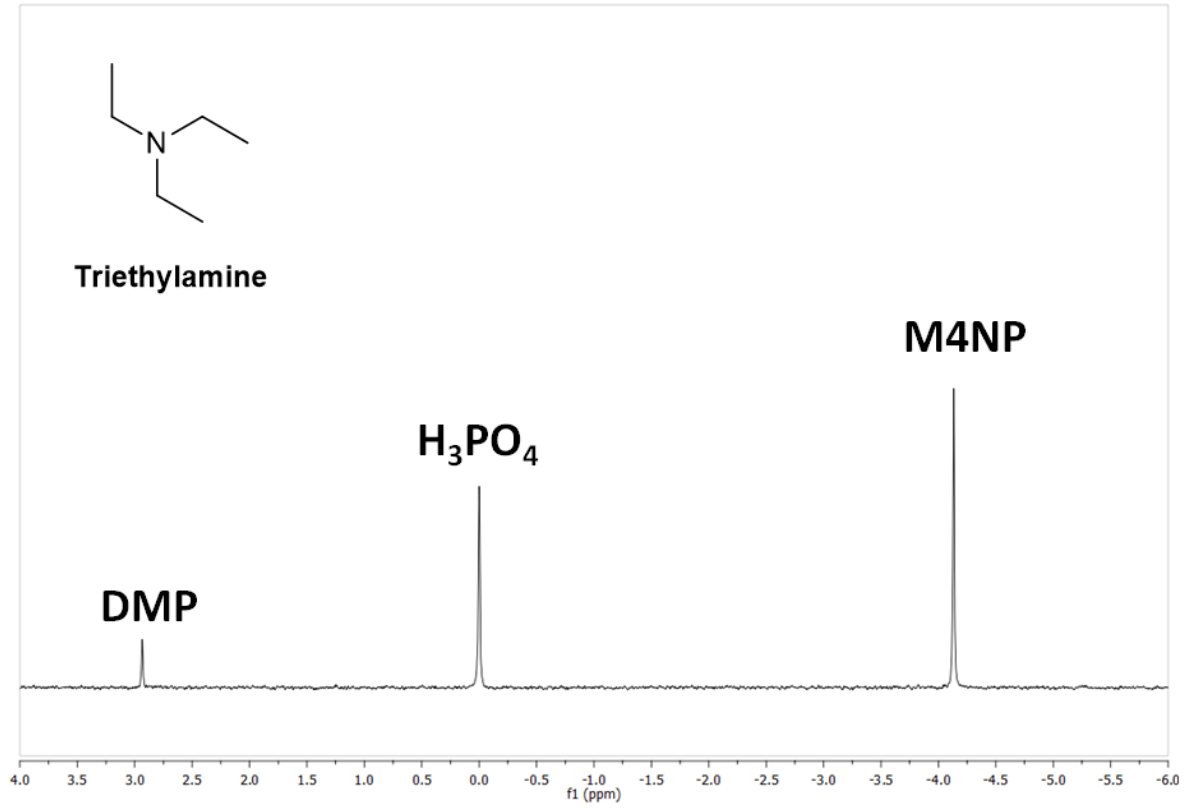


Fig. S1.7 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using triethylamine, after 4 days.

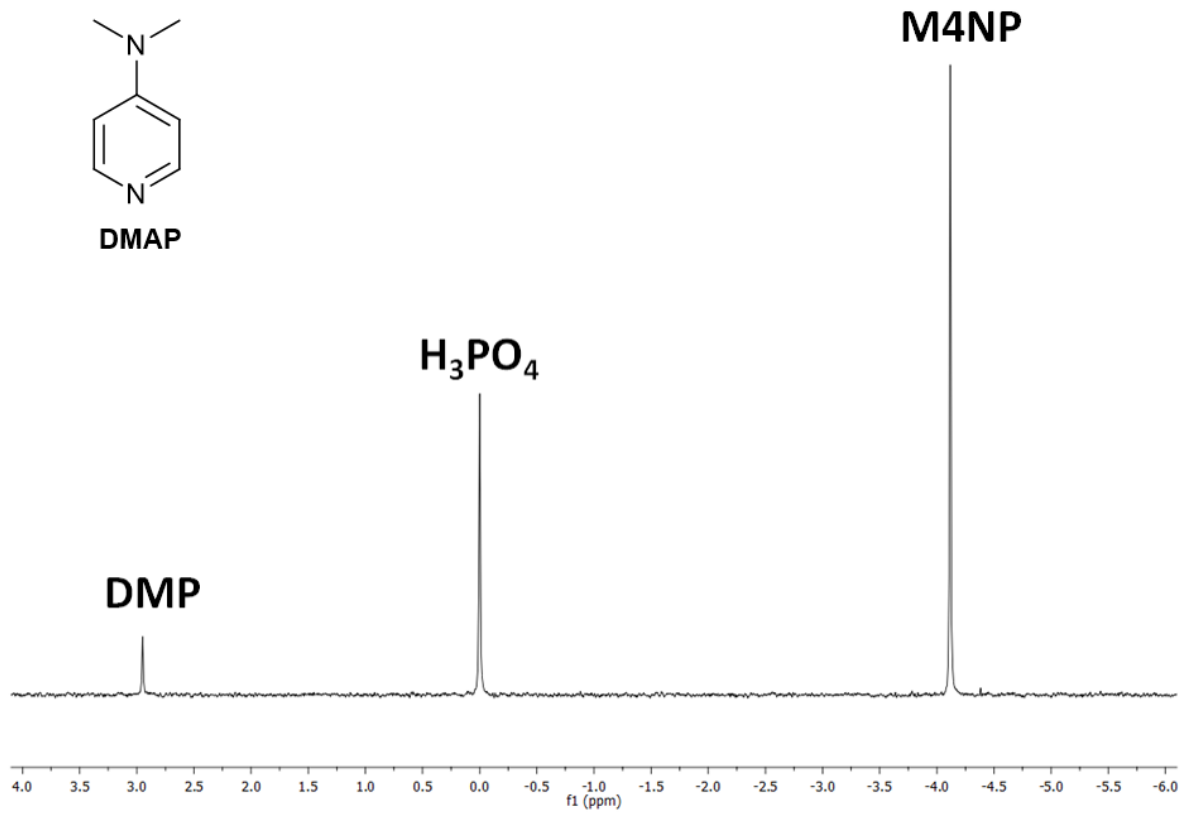


Fig. S1.8 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using DMAP, after 4 days.

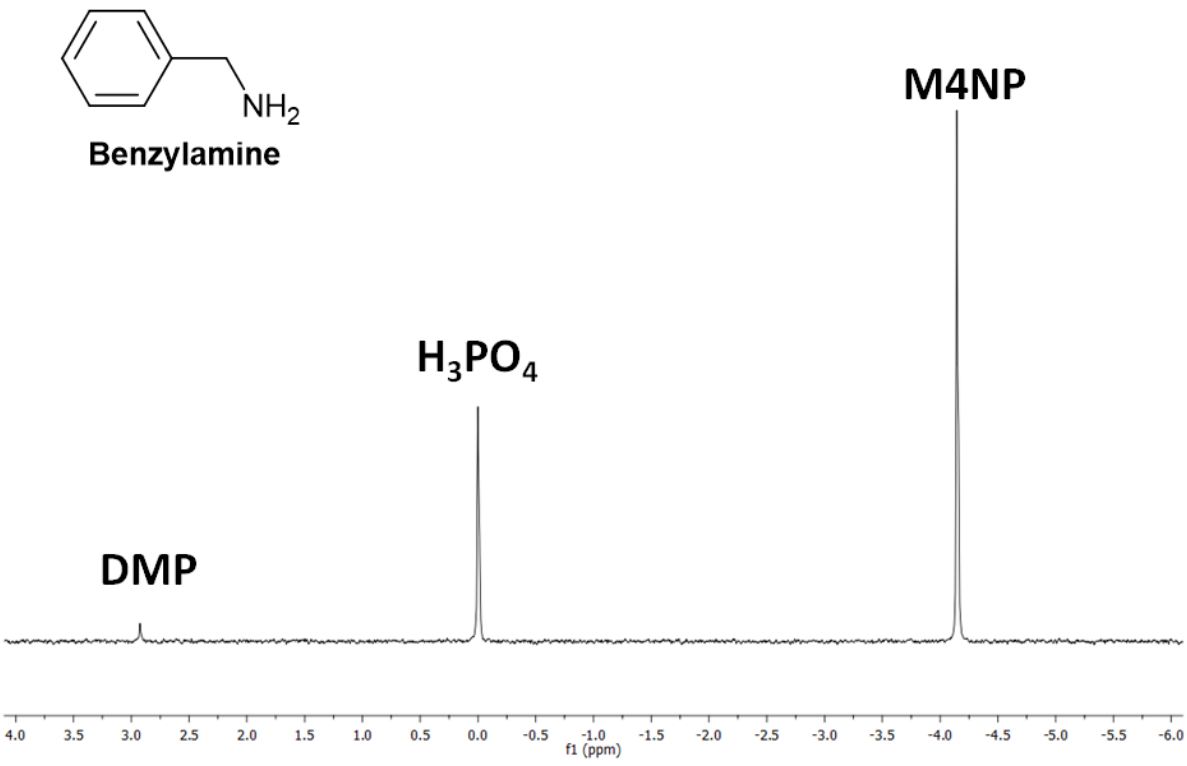


Fig. S1.9 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using benzylamine, after 4 days.

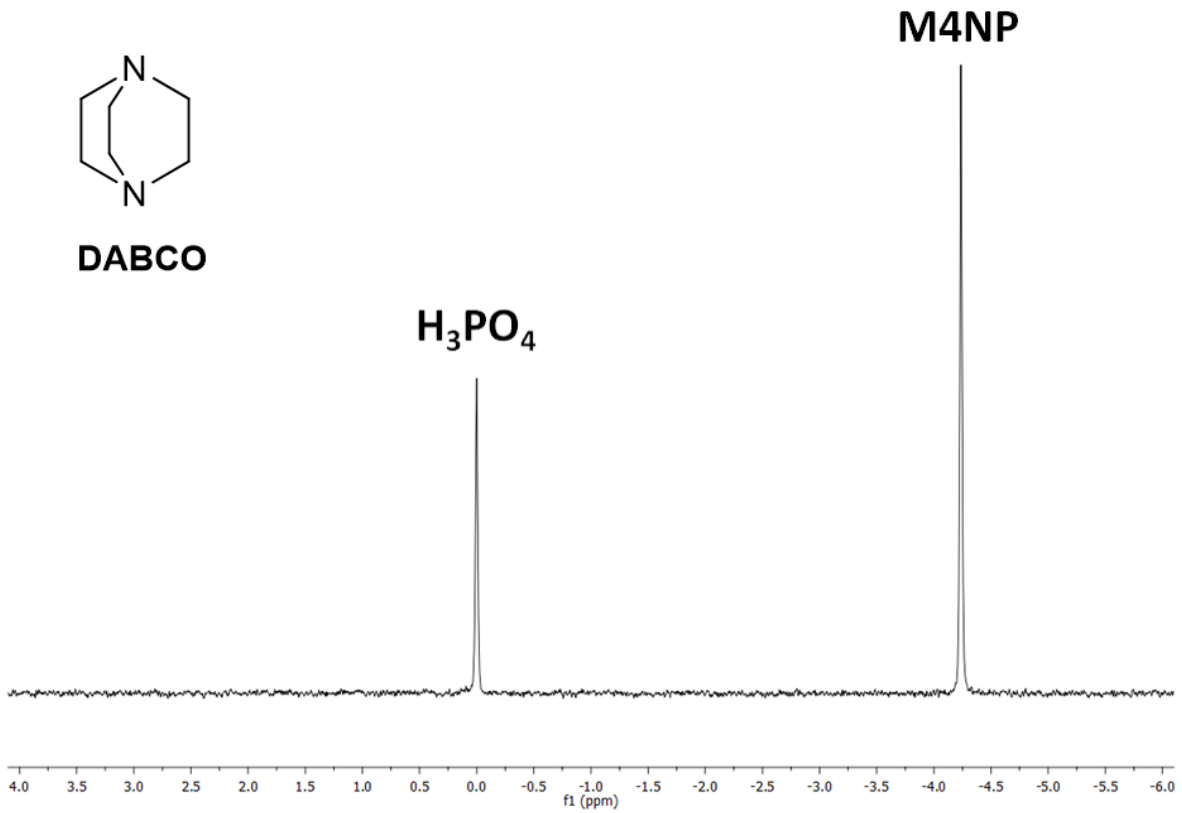


Fig. S1.10 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using DABCO, after 1 hour.

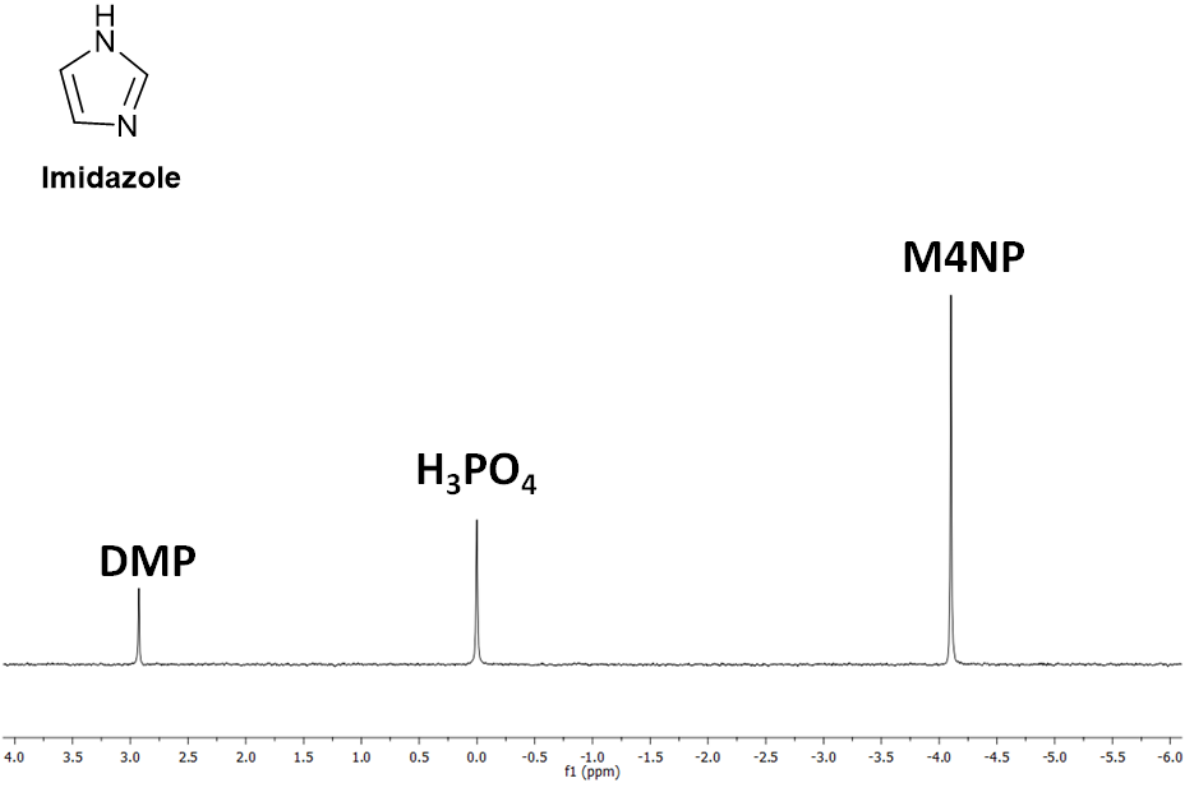


Fig. S1.11 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using imidazole, after 28 days.

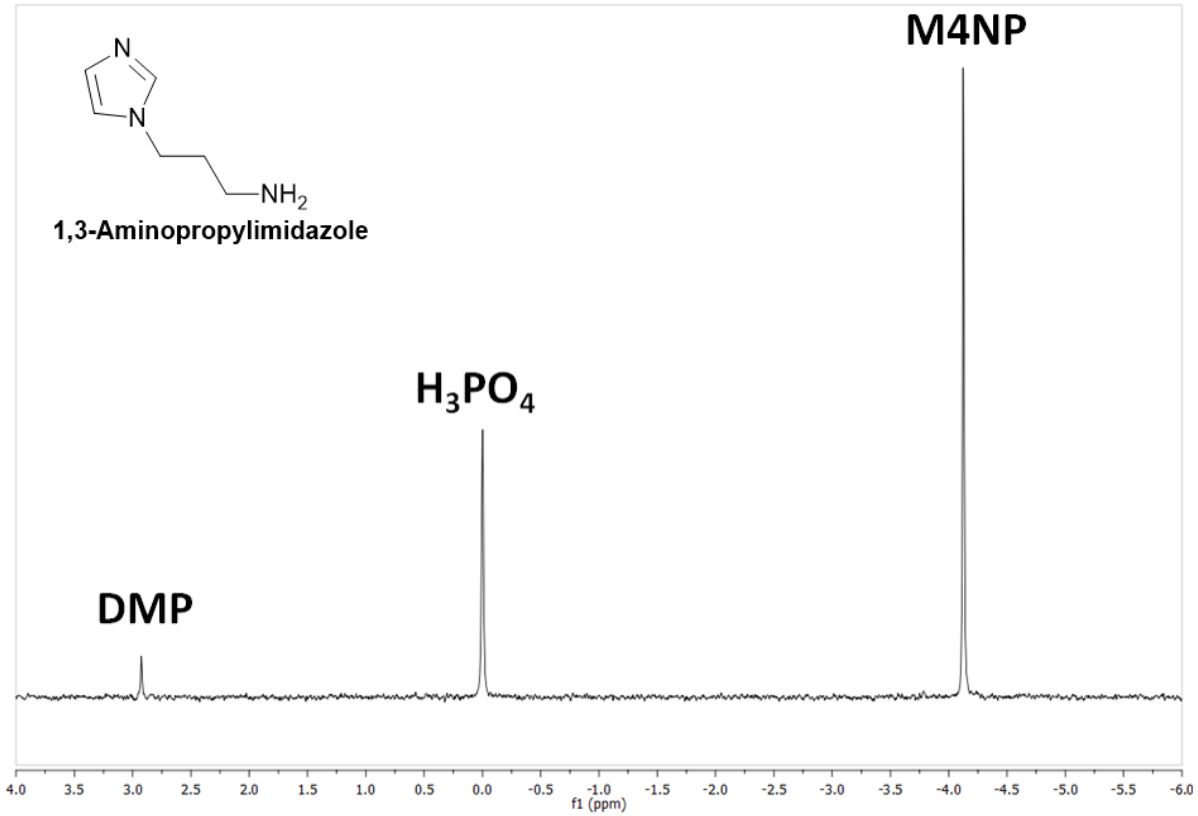


Fig. S1.12 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using 1,3-aminopropylimidazole, after 4 days.

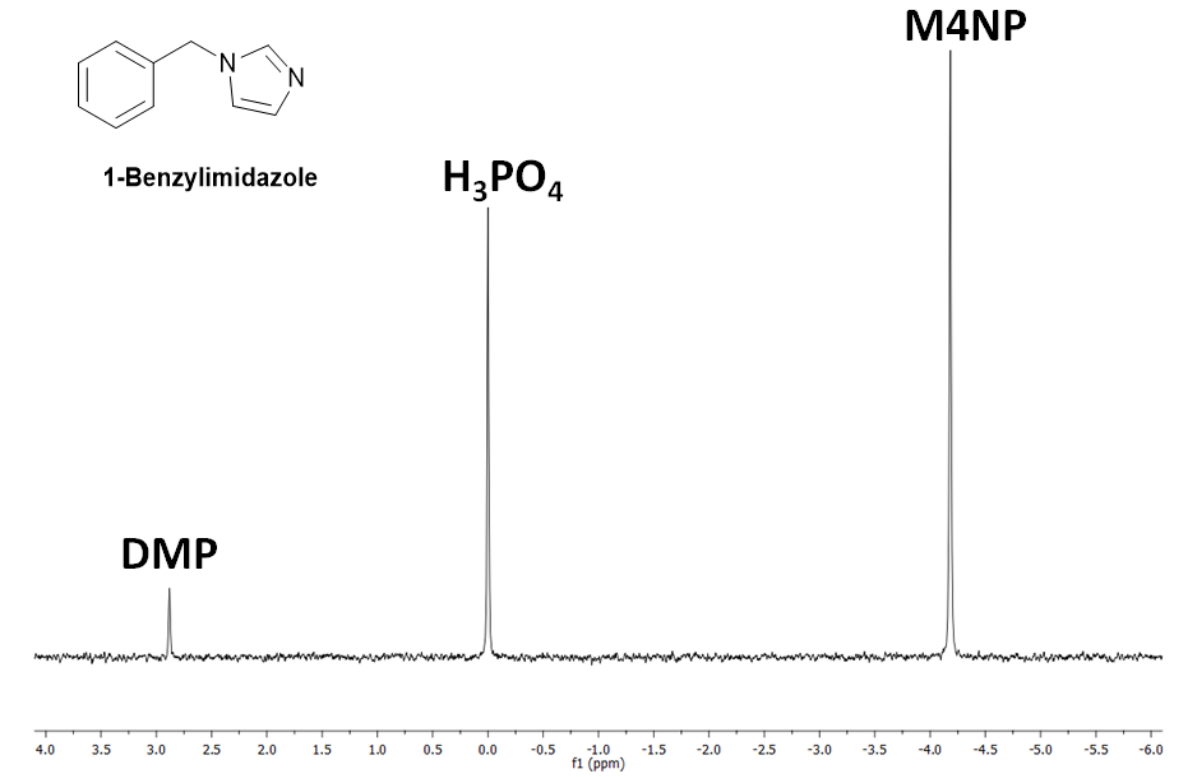


Fig. S1.13 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using 1-benzylimidazole, after 68 days.

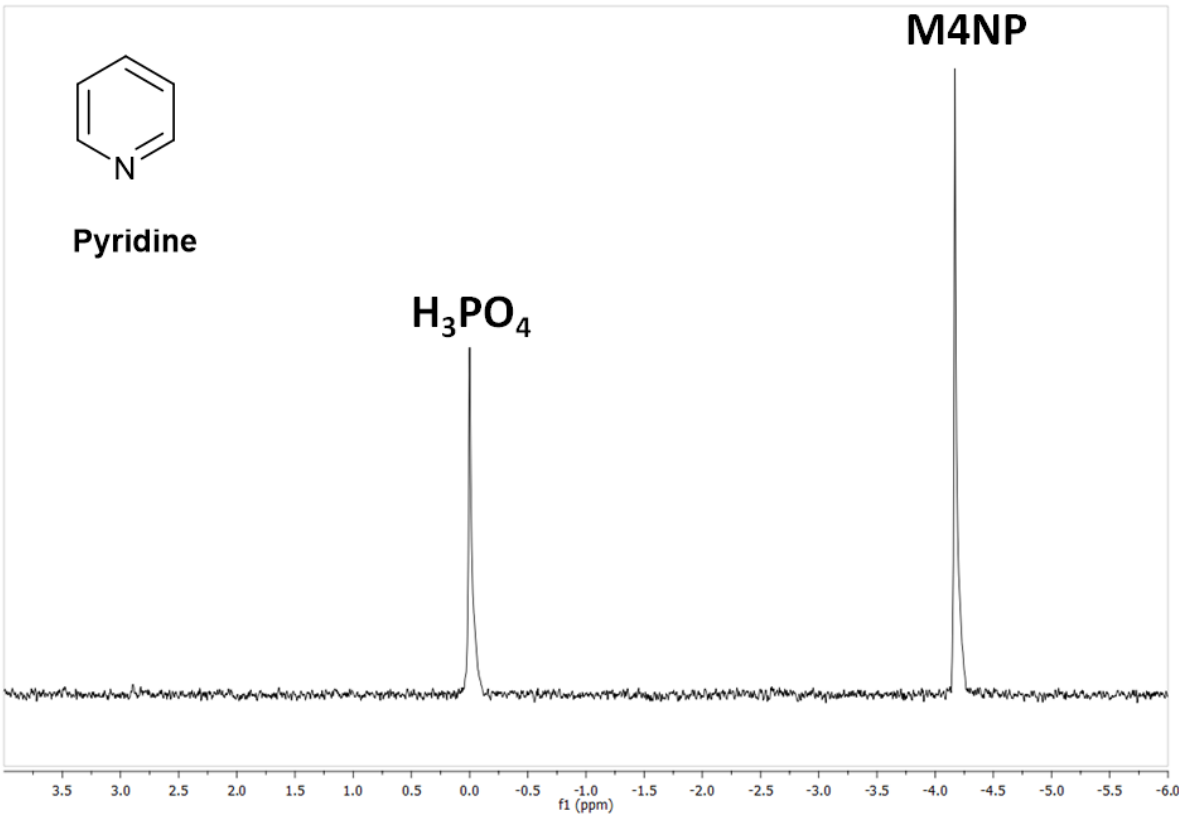


Fig. S1.14 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using pyridine, after 34 days.

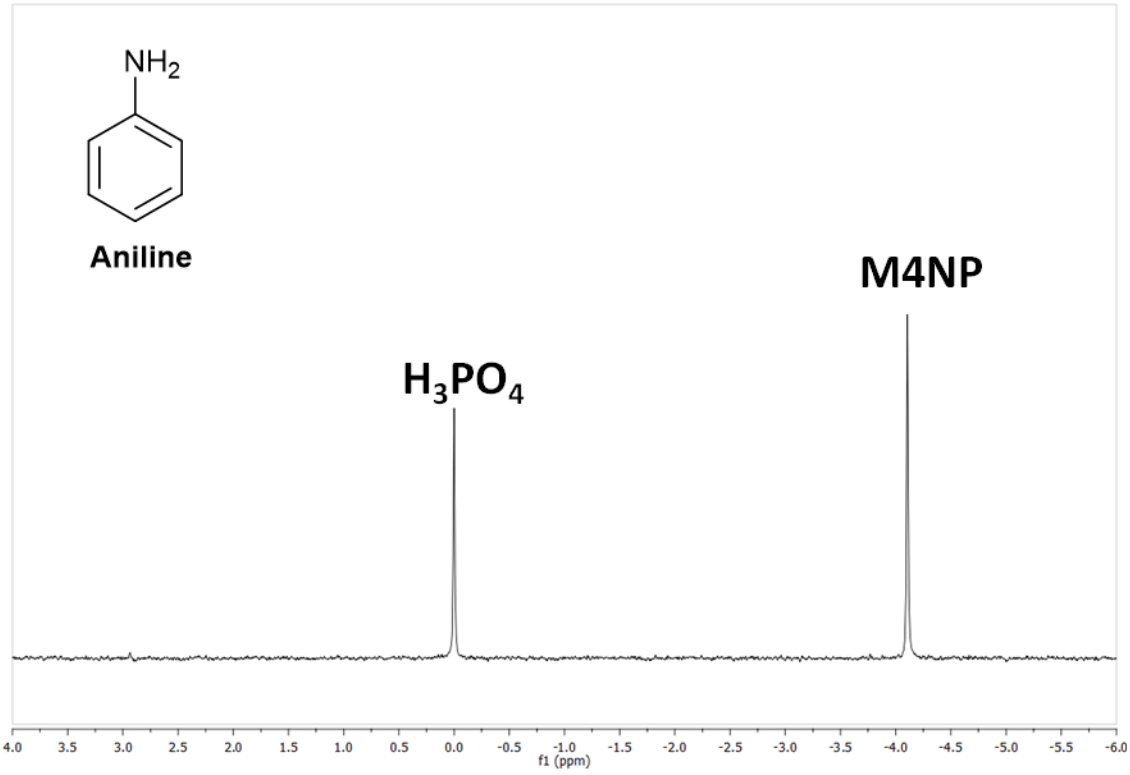


Fig. S1.15 $^{31}P[^{1}H]$ NMR spectrum for breakdown of MP, using aniline, after 68 days.

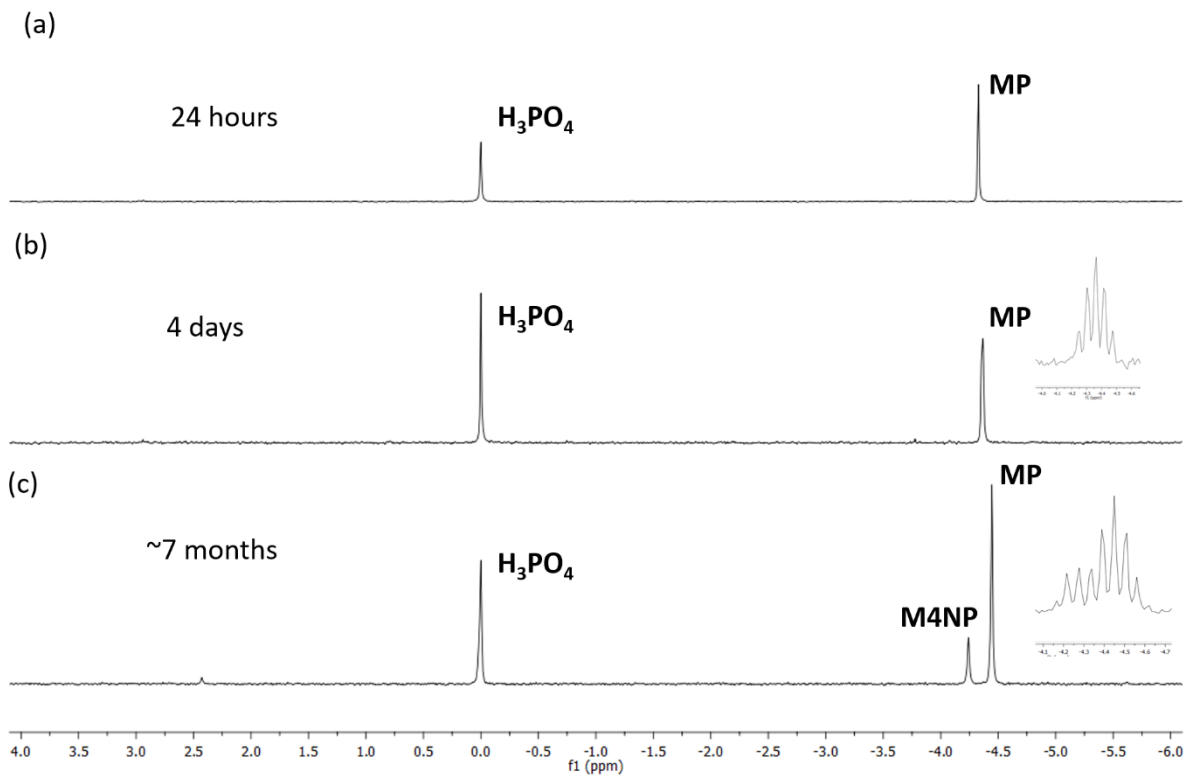


Fig. S1.16 $^{31}P[^{1}H]$ NMR spectra for reaction of MP in water and CD_3CN (1:1 v/v), conditions used for screen of bases (**Table. 1**) after (a) 24 hours, (b) 4 days and (c) approximately 7 months at room temperature. Inserts show the splitting of the peaks from the ^{31}P NMR. The peak at 0.0 ppm is from the phosphoric acid standard.

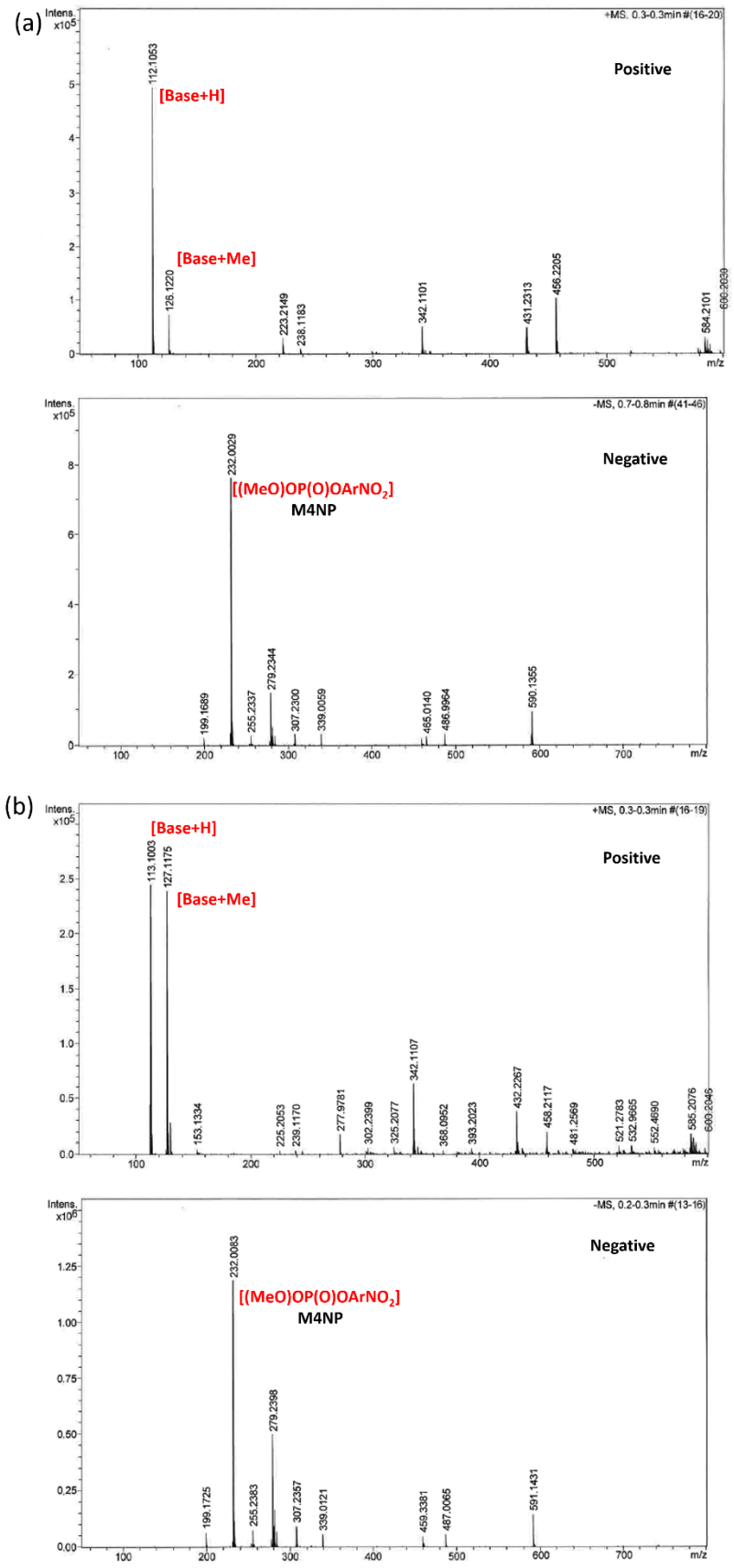


Fig. S2 Mass spectra, in positive and negative polarity, for reactions performed using (a) quinuclidine (MW=111.18 g mol^{-1}) and (b) DABCO (MW=112.17 g mol^{-1}), using 8.8 equivalents of base and 827 equivalents of water. Both reactions gave >98% the toxic breakdown product (**Fig. S1.6&10**).

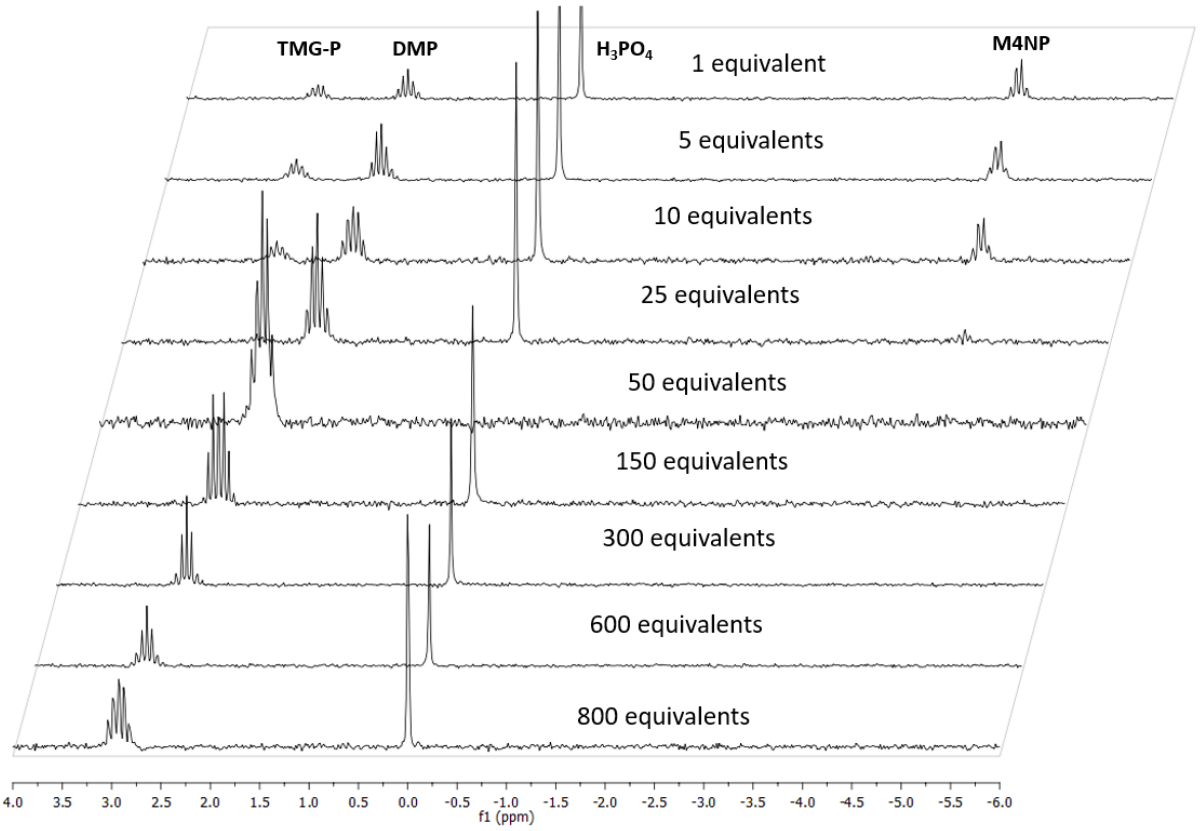


Fig. S3 ^{31}P NMR spectra for the breakdown of MP, after 24 hours at room temperature, with varying amounts of water (1–800 equivalents) and 5 equivalents of the TMG base. The peak at 0.0 ppm is from the phosphoric acid standard. NMR sample for 50 equivalents water ran without capillary hence the absence of the peak at 0.0 ppm, from H_3PO_4.

Table S1 Breakdown products (%) for MP hydrolysis with varying amounts of water (1–800 equivalents) using 5 equivalents of the TMG base, after 24 hours at room temperature. Dimethyl phosphate (DMP), methyl 4-nitrophenyl phosphate (M4NP), and dimethyl (bis(dimethylamino)methylene)phosphoramidate (TMG-P).

Water (equivalents)	**Percentage products (%)**		
	DMP	**M4NP**	**TMG-P**
1	35	41	24
5	41	35	24
10	56	23	21
25	87	6	7
50	97	1	2
150	100	0	0
300	100	0	0
600	100	0	0
800	100	0	0

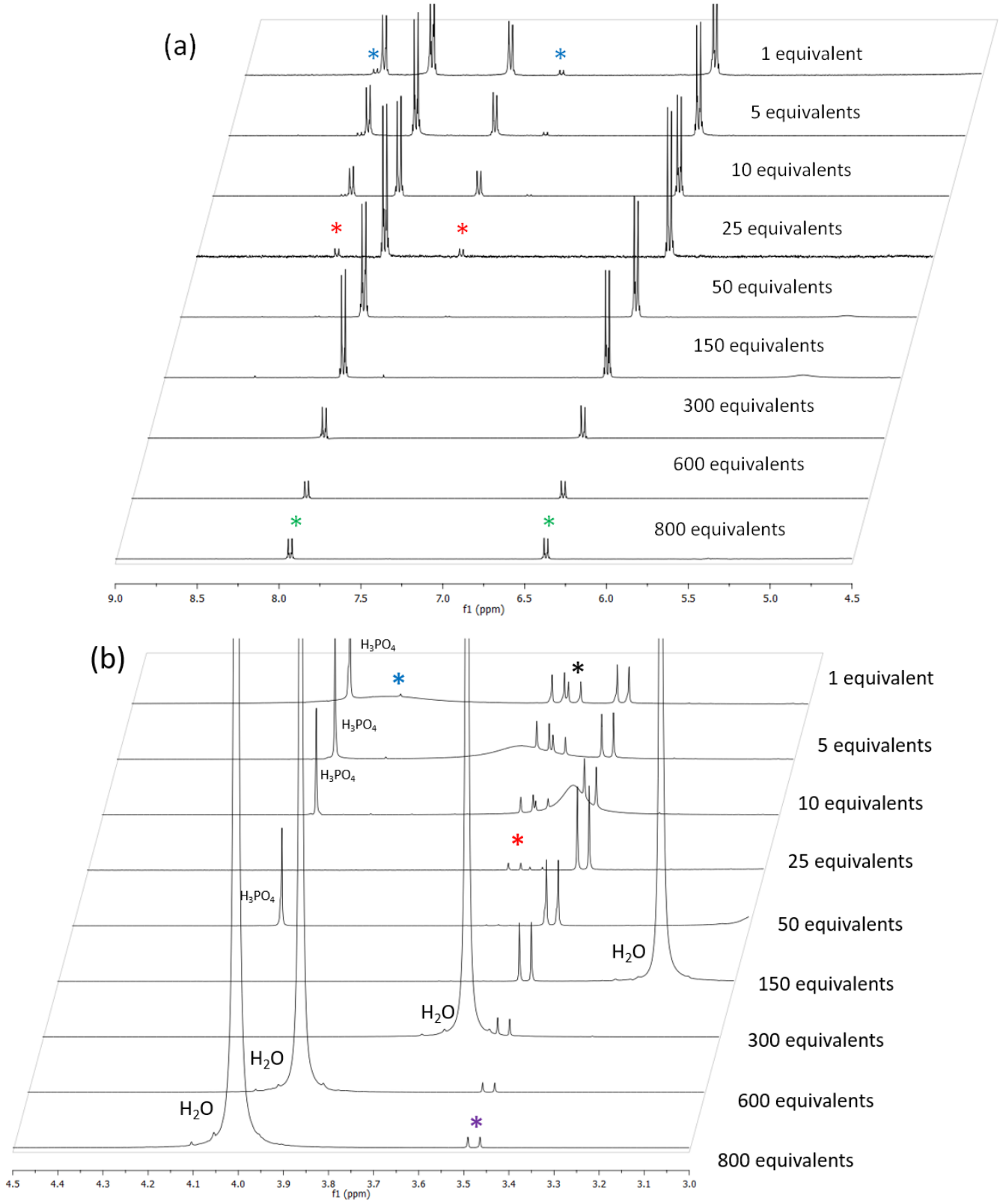


Fig. S4 ^{1}H NMR spectra for the breakdown of MP, after 24 hours at room temperature, using 5 equivalents of the TMG base with varying amounts of water (1–800 equivalents) in (a) the aromatic and (b) the aliphatic proton region. NMR sample for 25, 150, 300, 600, and 800 equivalents water ran without the H_3PO_4 containing capillary hence the absence of the peak at 4.0 ppm, from H_3PO_4. Peaks assigned as 4-nitroanisole (*), 4-nitrophenolate (*), DMP (*), TMG-P (*), and M4NP (*).

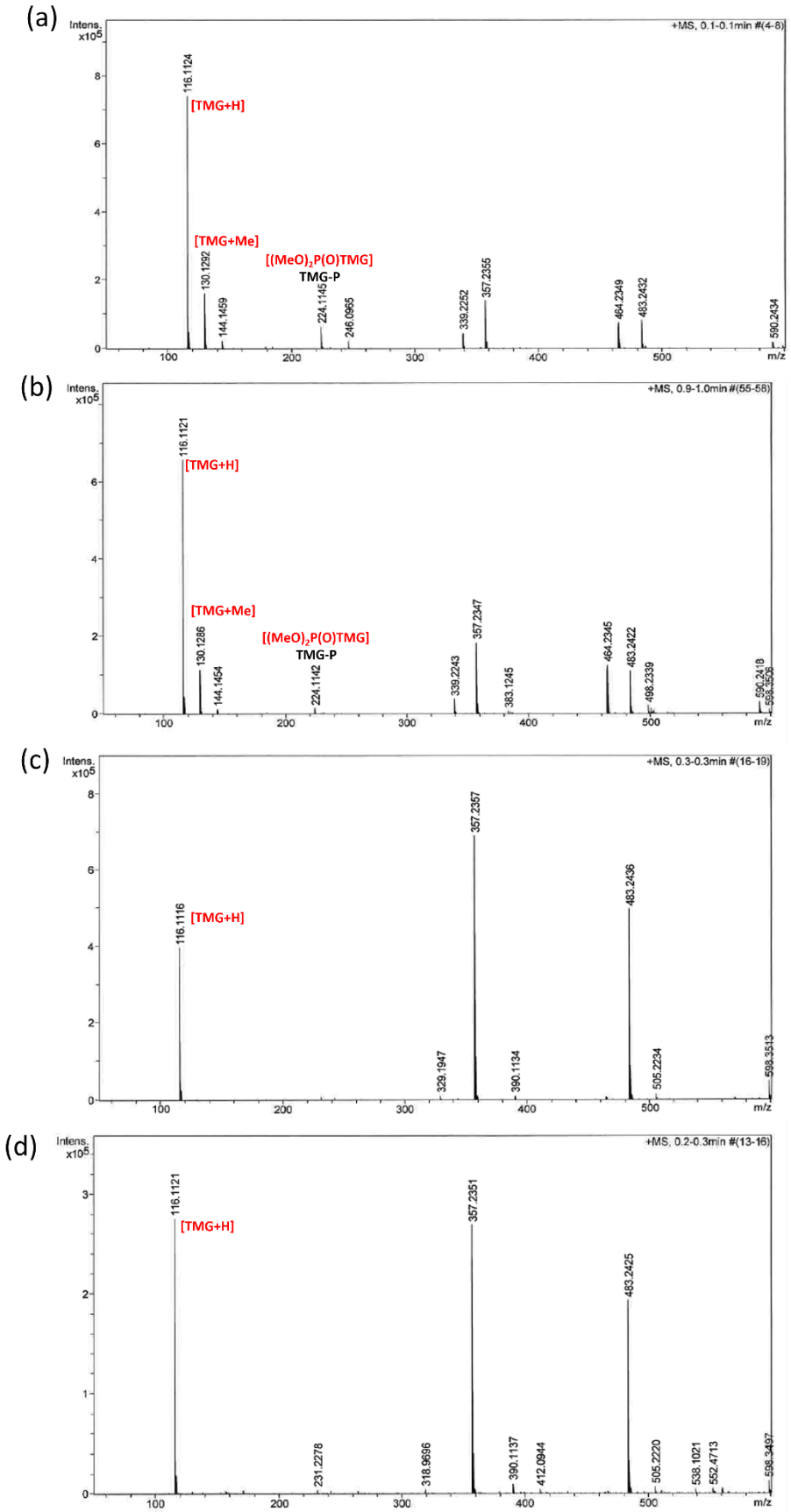


Fig. S5 Mass spectra, in positive polarity, for reaction of the TMG base (MW=115.18 g mol^{-1}), 5 equivalents, against MP using (a) 1.0, (b) 5.0, (c) 50, and (d) 800 equivalents of water.

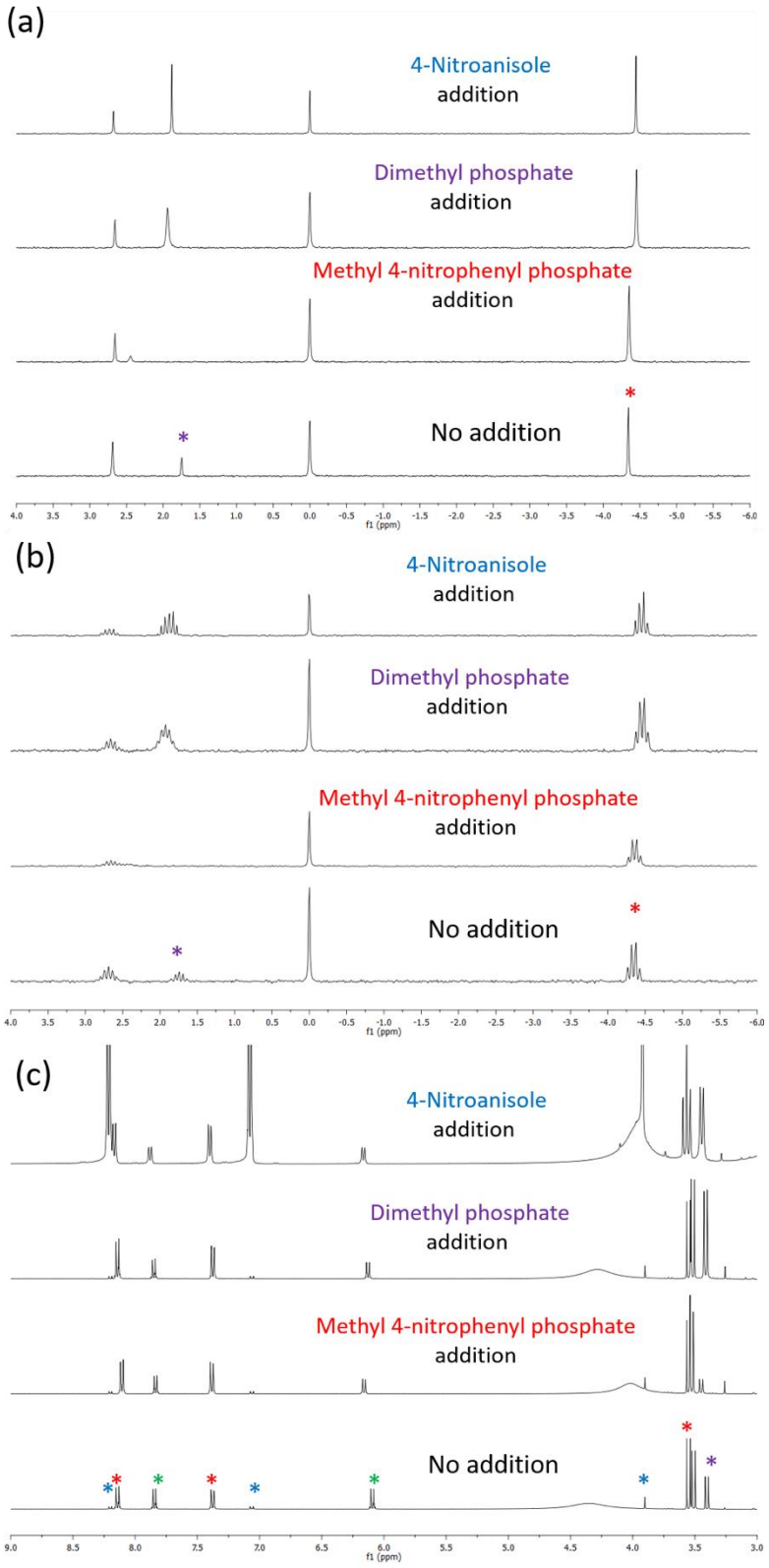


Fig. S6 (a) $^{31}P[^{1}H]$, (b) ^{31}P, and (c) ^{1}H NMR spectra for reaction of TMG (5 equivalents with respect to MP) against MP, using water (1 equivalent with respect to MP), before and after the addition of methyl 4-nitrophenyl phosphate (*), 4-nitroanisole (*), and dimethyl phosphate (*). Changes in peaks (*) highlighted for each addition product. ^{1}H NMR spectra obtained without capillary present.

^{31}P peak at 2.60 ppm (**TMG-P** product), *proton peaks from 4-nitrophenolate.

The peak at 0.0 ppm is from the phosphoric acid standard.

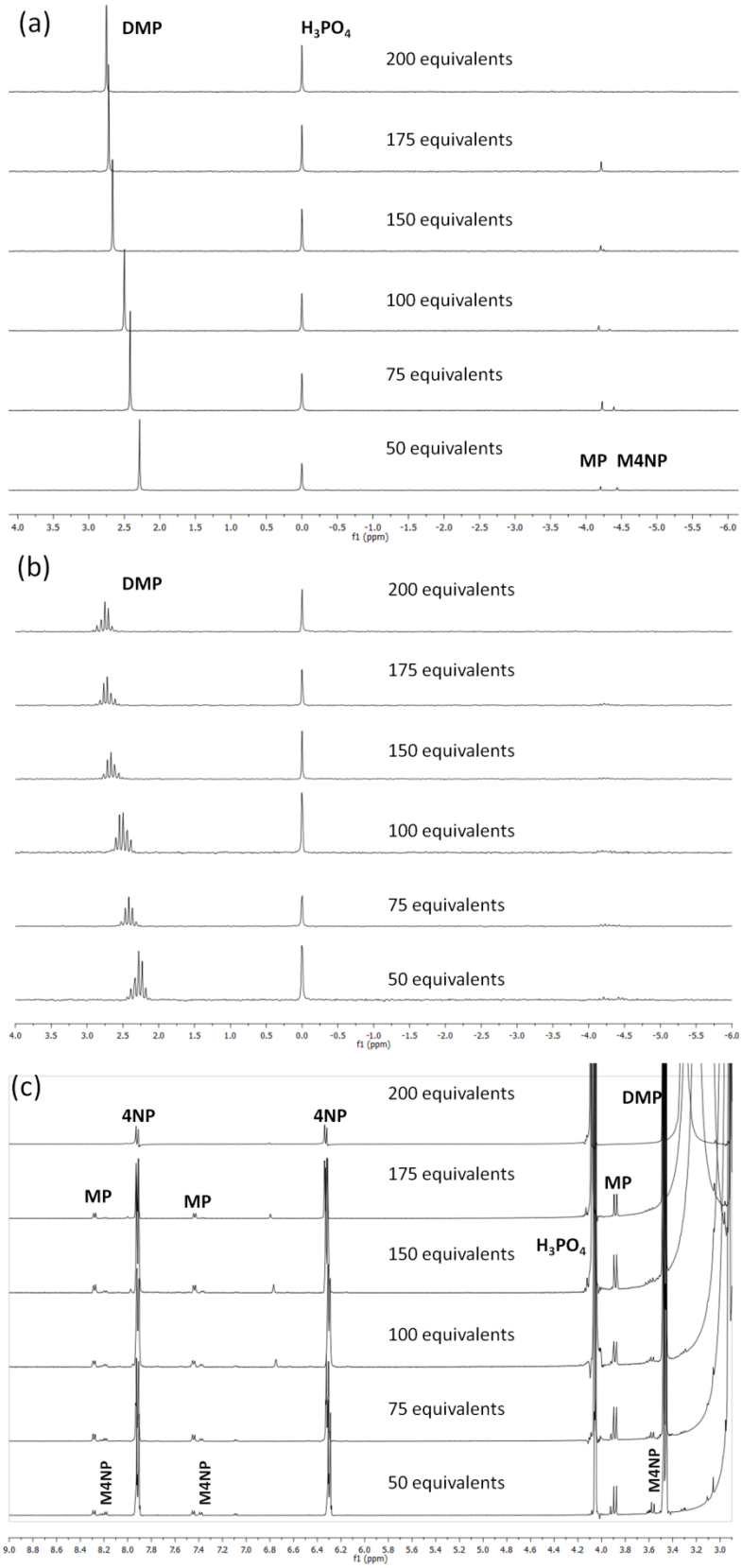


Fig. S7 (a) $^{31}P[^{1}H]$ NMR, (b) ^{31}P NMR, and (c) ^{1}H NMR for reactions of TMG (2 equivalents) against MP using 50, 75, 100, 150, 175, and 200 equivalents of water, after 24 hours at room temperature. The peak at 0.0 ppm in ^{31}P NMR and 4.0 ppm in ^{1}H NMR is from the phosphoric acid standard. Peaks assigned from products including; Dimethyl phosphate (DMP), methyl 4-nitrophenyl phosphate (M4NP), 4-nitrophenolate (4NP), and starting simulant methyl paraoxon (MP).

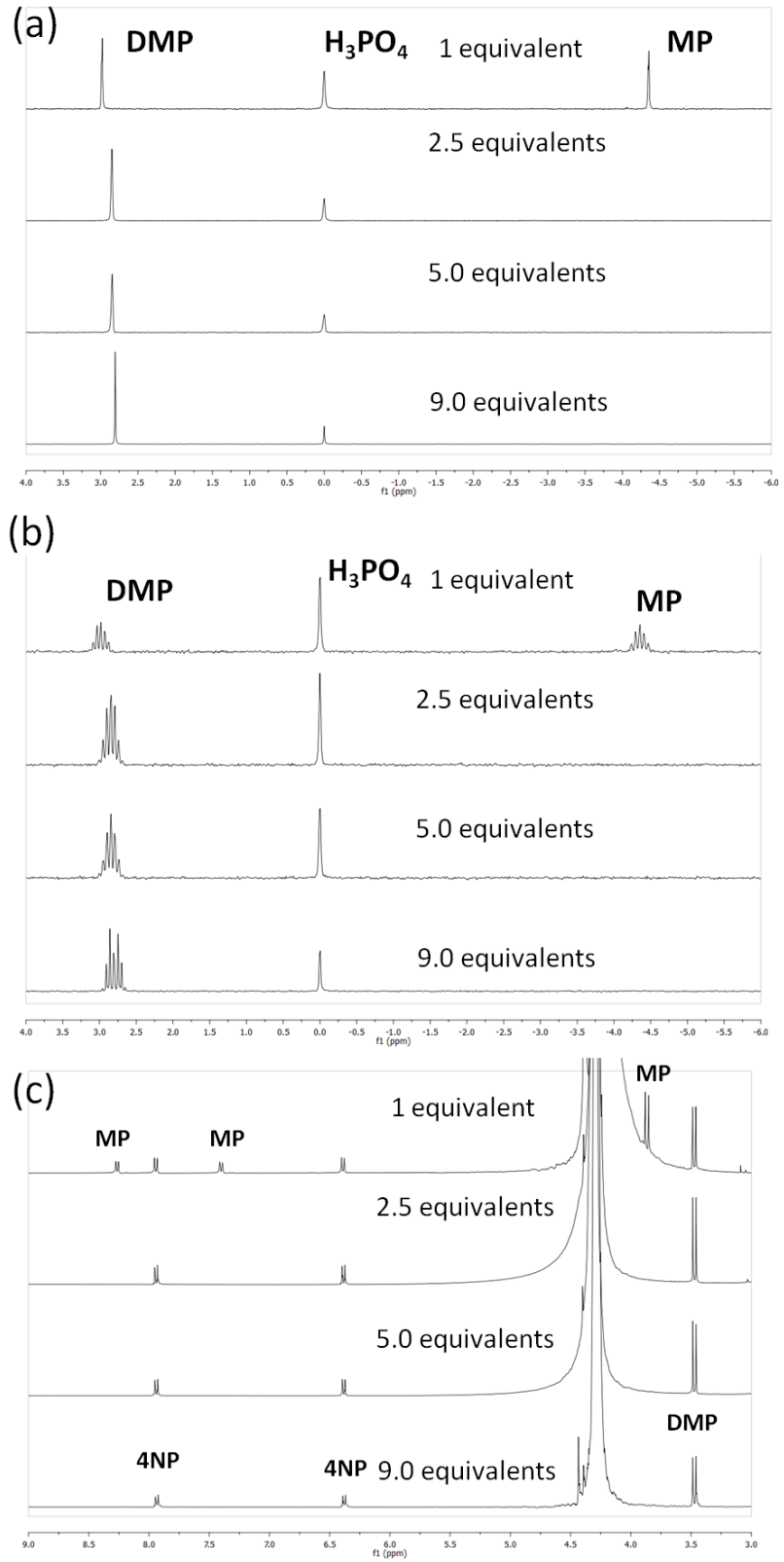


Fig. S8(a) $^{31}P[^{1}H]$ NMR, (b) ^{31}P NMR, and (c) ^{1}H NMR for reaction of TMG (1.0, 2.5, 5.0, and 9.0 equivalents) against MP using excess water (827 equivalents), after 24 hours at room temperature. ^{1}H NMR for 2.5 and 5.0 equivalents spectrum ran without capillary present. The peak at 0.0 ppm is from the phosphoric acid standard. Products including 4-nitrophenolate (4NP), dimethyl phosphate (DMP), and starting simulant methyl paraoxon (MP) assigned.

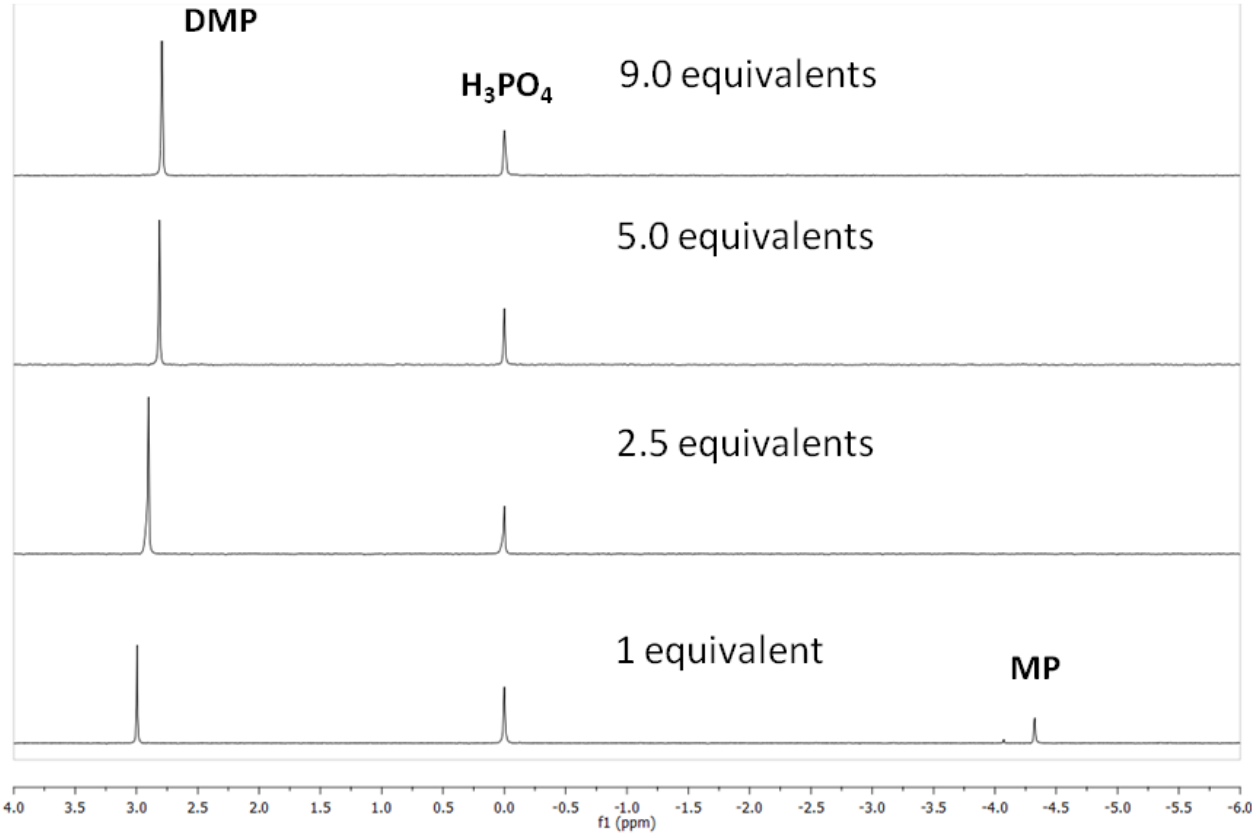


Fig. S9 $^{31}P[^{1}H]$ NMR for reaction of MTBD (1.0, 2.5, 5.0, and 9.0 equivalents) against MP using excess water (827 equivalents), after 24 hours at room temperature. The peak at 0.0 ppm is from the phosphoric acid standard. Product dimethyl phosphate (DMP) and starting simulant methyl paraoxon (MP) assigned.

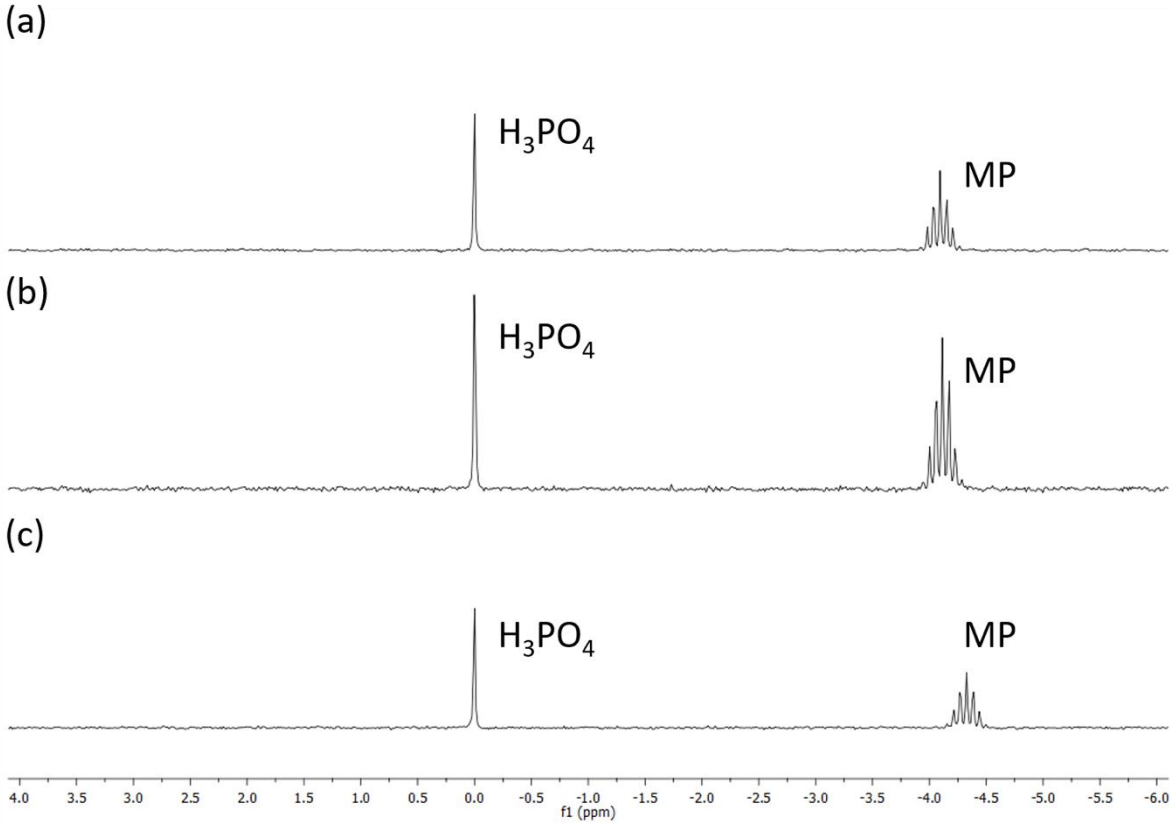


Fig. S10 ^{31}P NMR for reactions of MP using (a) 800, (b) 50, and (c) 1 equivalent of water without the presence of base, after 24 hours at room temperature. The peak at 0.0 ppm is from the phosphoric acid standard.

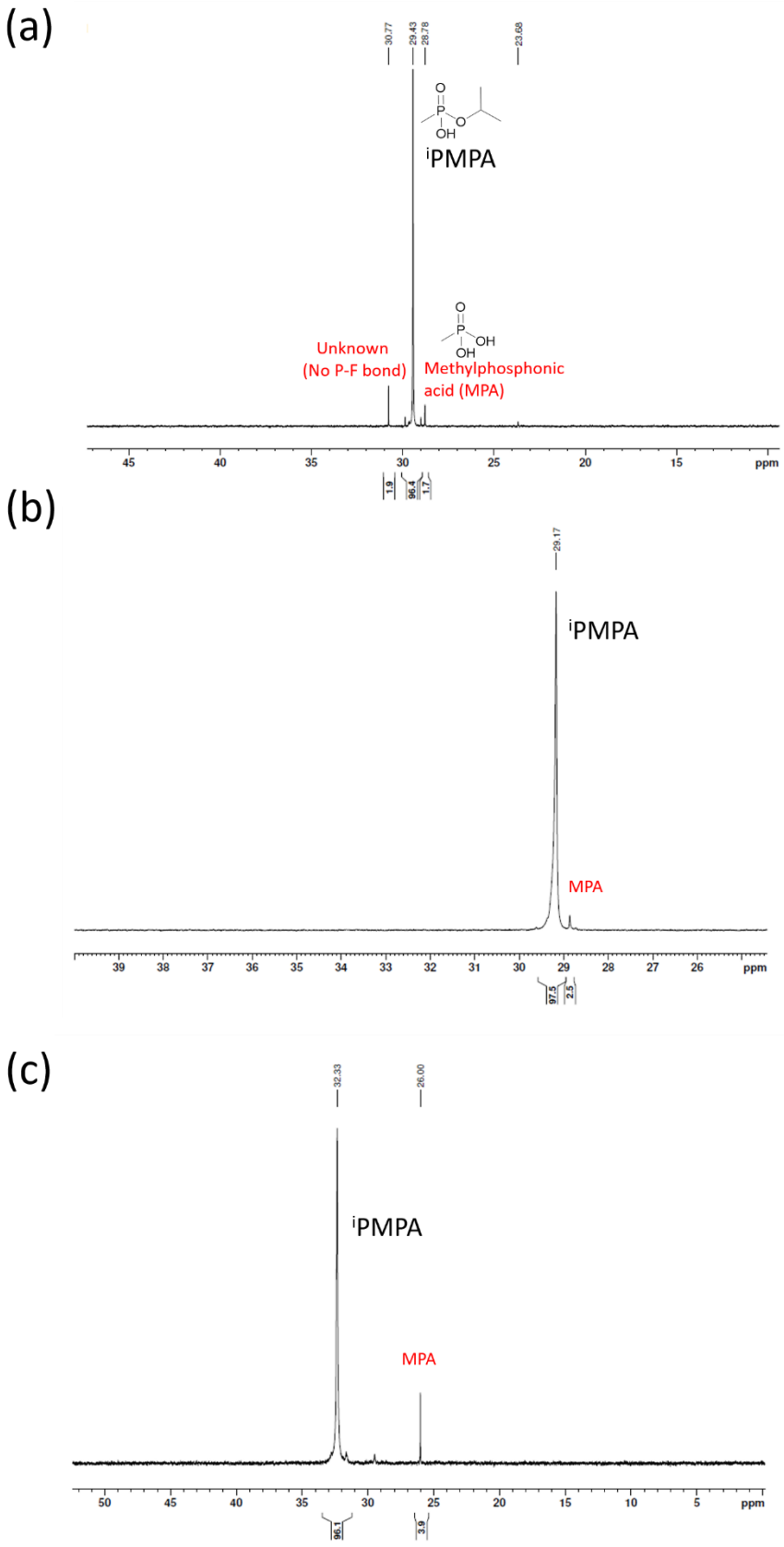


Fig. S11 ^{31}P NMR for reactions of GB using (a) 800, (b) 50, and (c) 1 equivalent of water without the presence of base, after 24 hours at room temperature. The desired breakdown product for GB hydrolysis, isopropyl methylphosphonic acid (^{i}PMPA), assigned.

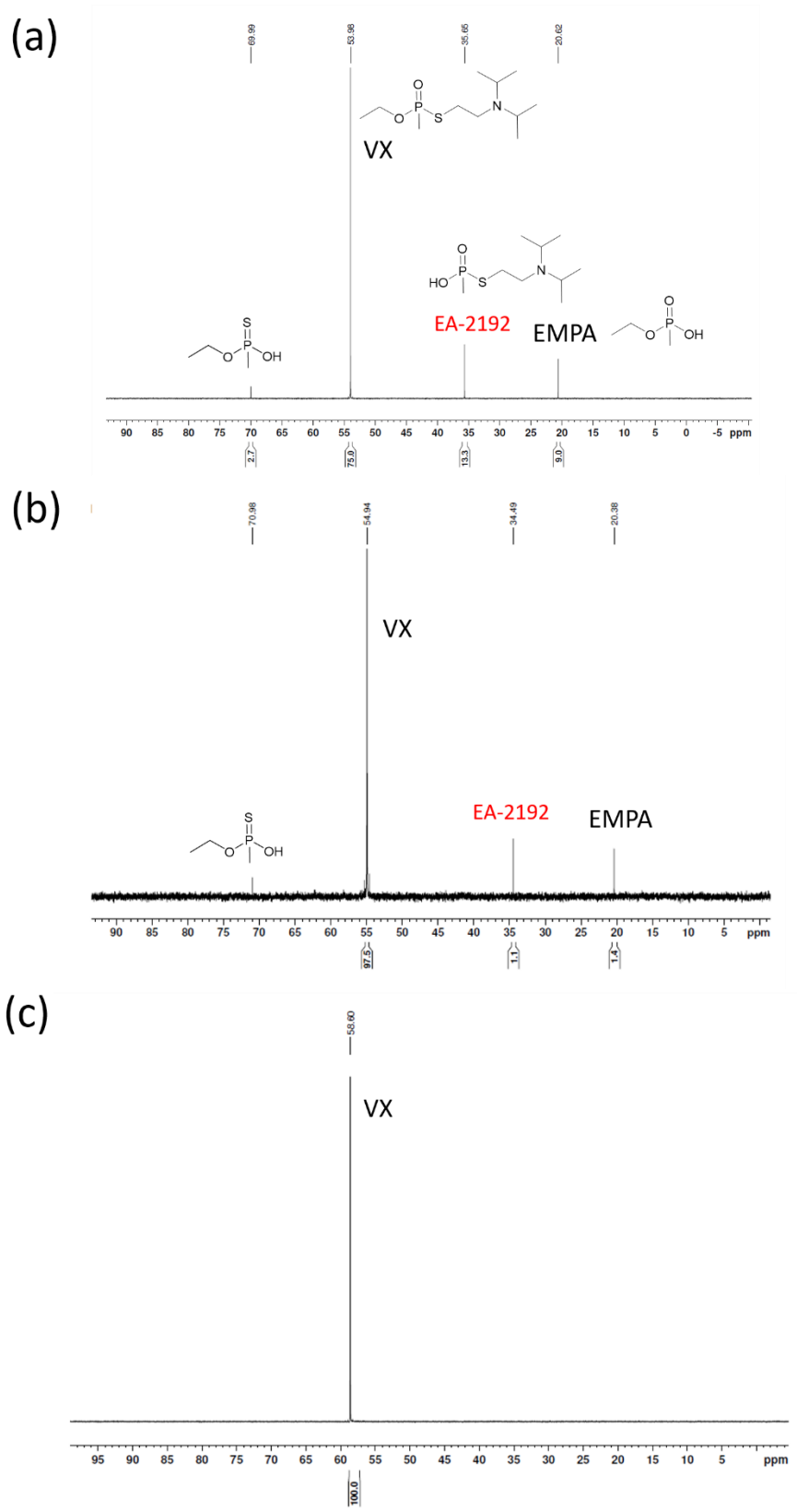


Fig. S12 ^{31}P NMR for reactions of VX using (a) 800, (b) 50, and (c) 1 equivalent of water without the presence of base, after 24 hours at room temperature. The desired breakdown product, ethyl methyl phosphonate (EMPA), thioic acid product, at 70 ppm, and toxic breakdown product (EA-2192) assigned.

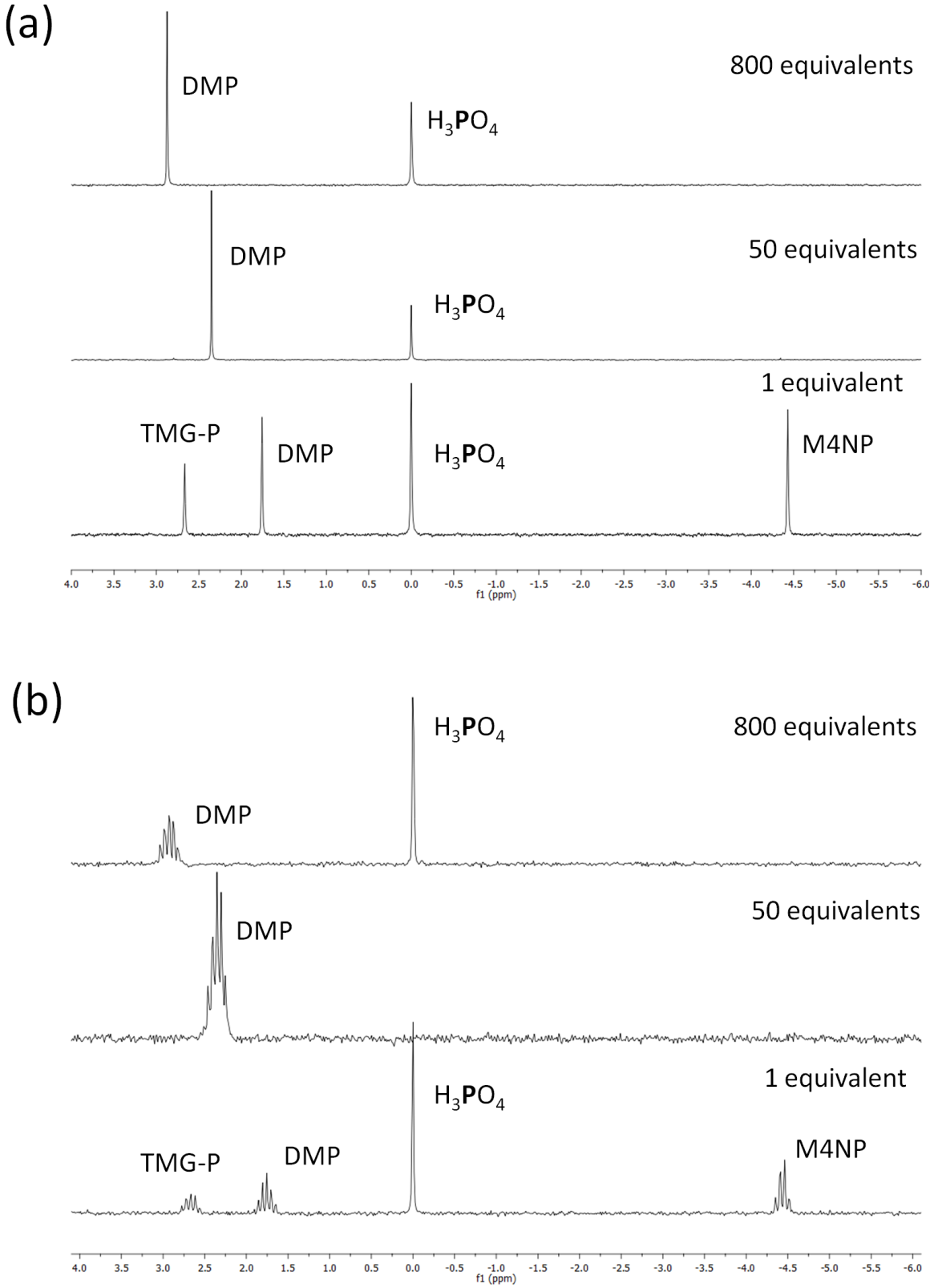


Fig. S13 (a) $^{31}P[^{1}H]$ NMR, and (b) ^{31}P NMR for reactions of MP using 800, 50, and 1 equivalent of water, with TMG as base (5 equivalents), after 24 hours at room temperature. The peak at 0.0 ppm is from the phosphoric acid standard, absent from the 50 equivalents ^{31}P NMR.

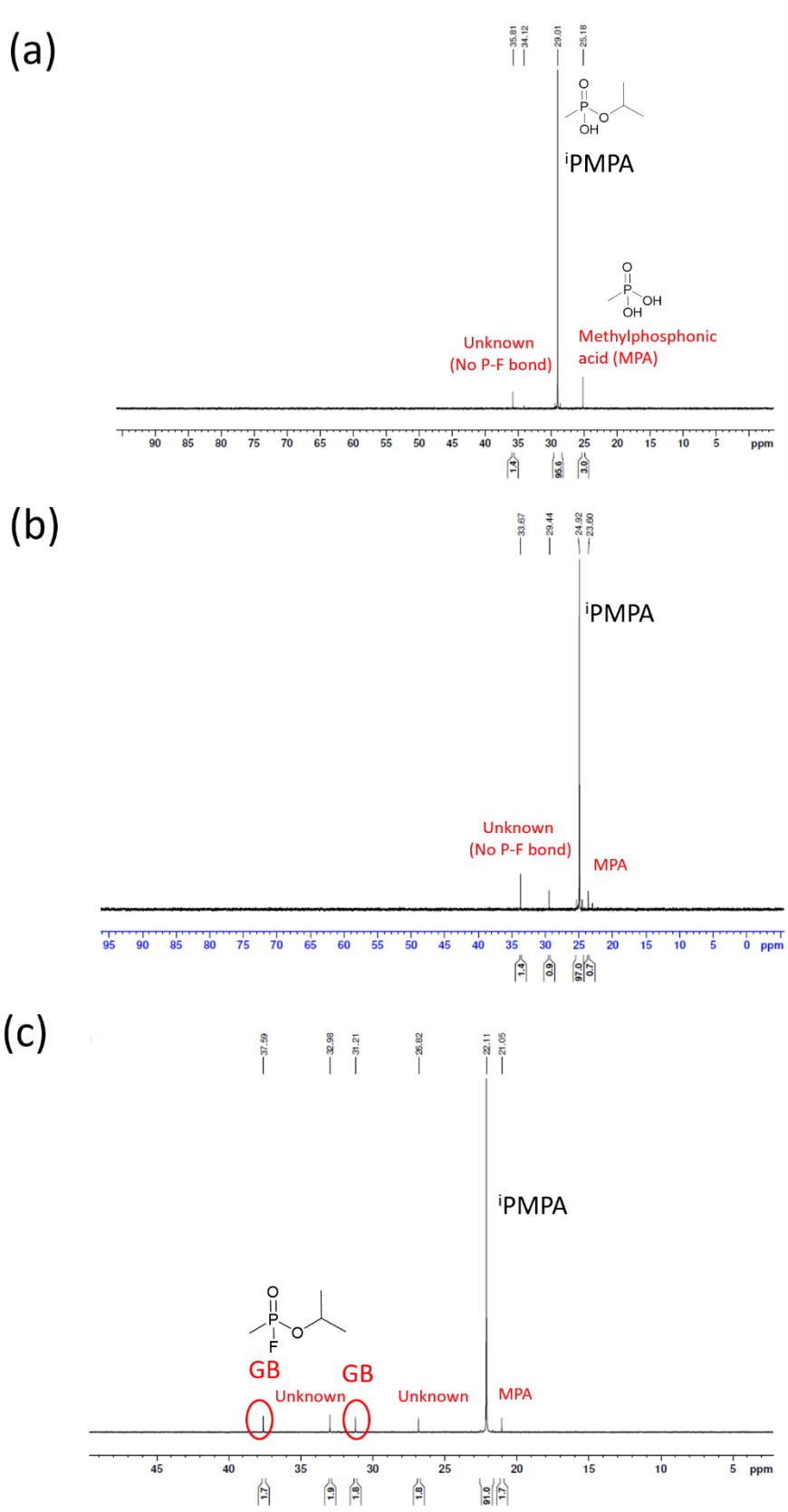


Fig. S14 ^{31}P NMR for reactions of GB using (a) 800, (b) 50, and (c) 1 equivalent of water, with TMG as base (5 equivalents), after 24 hours at room temperature. The desired breakdown product for GB hydrolysis, isopropyl methylphosphonic acid (^{i}PMPA), assigned. GB agent, present in spectrum (c) occurs as a doublet due to phosphorus-fluorine coupling.

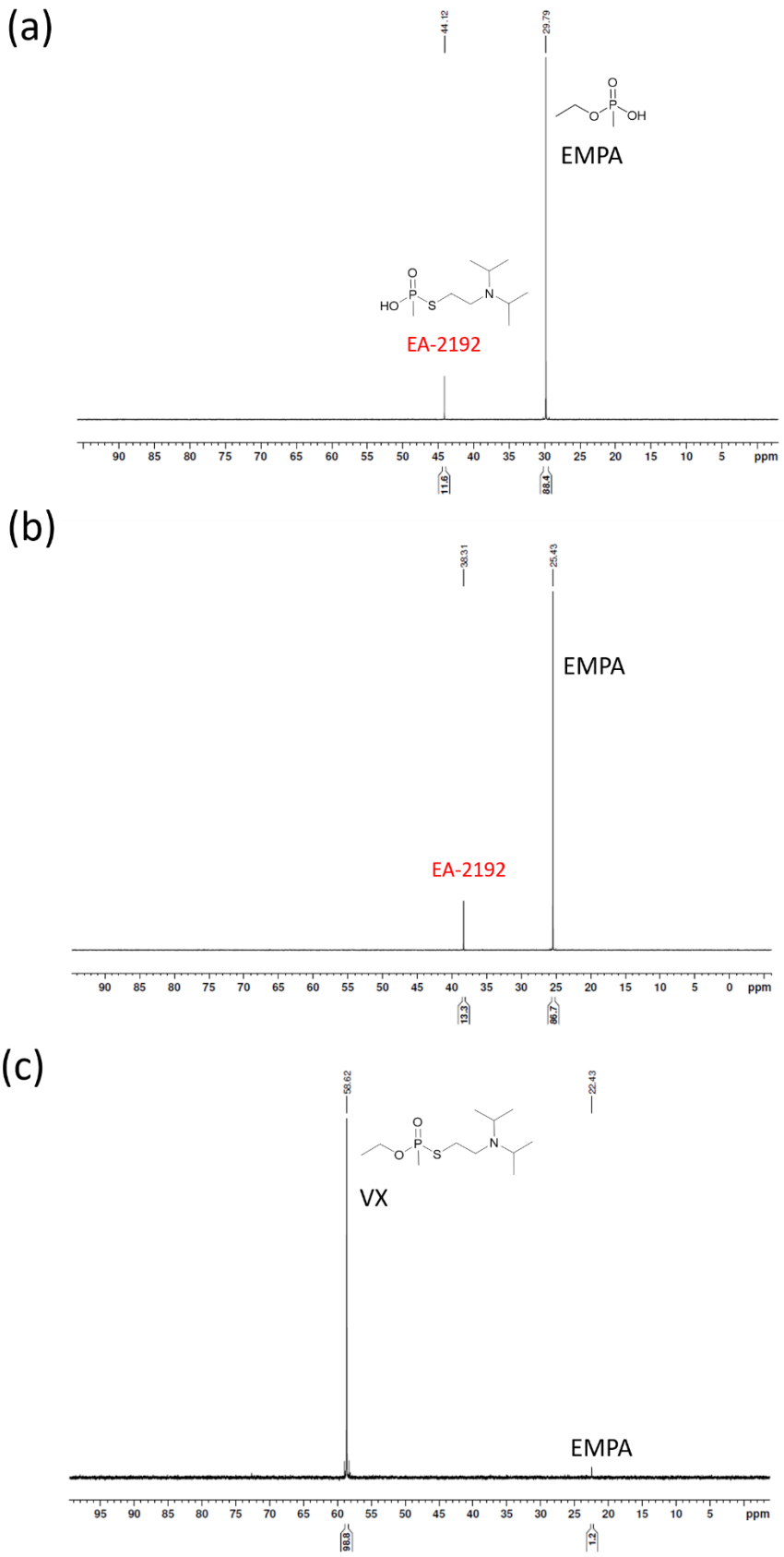


Fig. S15 ^{31}P NMR for reactions of VX using (a) 800, (b) 50, and (c) 1 equivalent of water, with TMG as base (5 equivalents), after 24 hours at room temperature. The desired breakdown product, ethyl methyl phosphonate (EMPA) and toxic breakdown product (EA-2192) assigned.

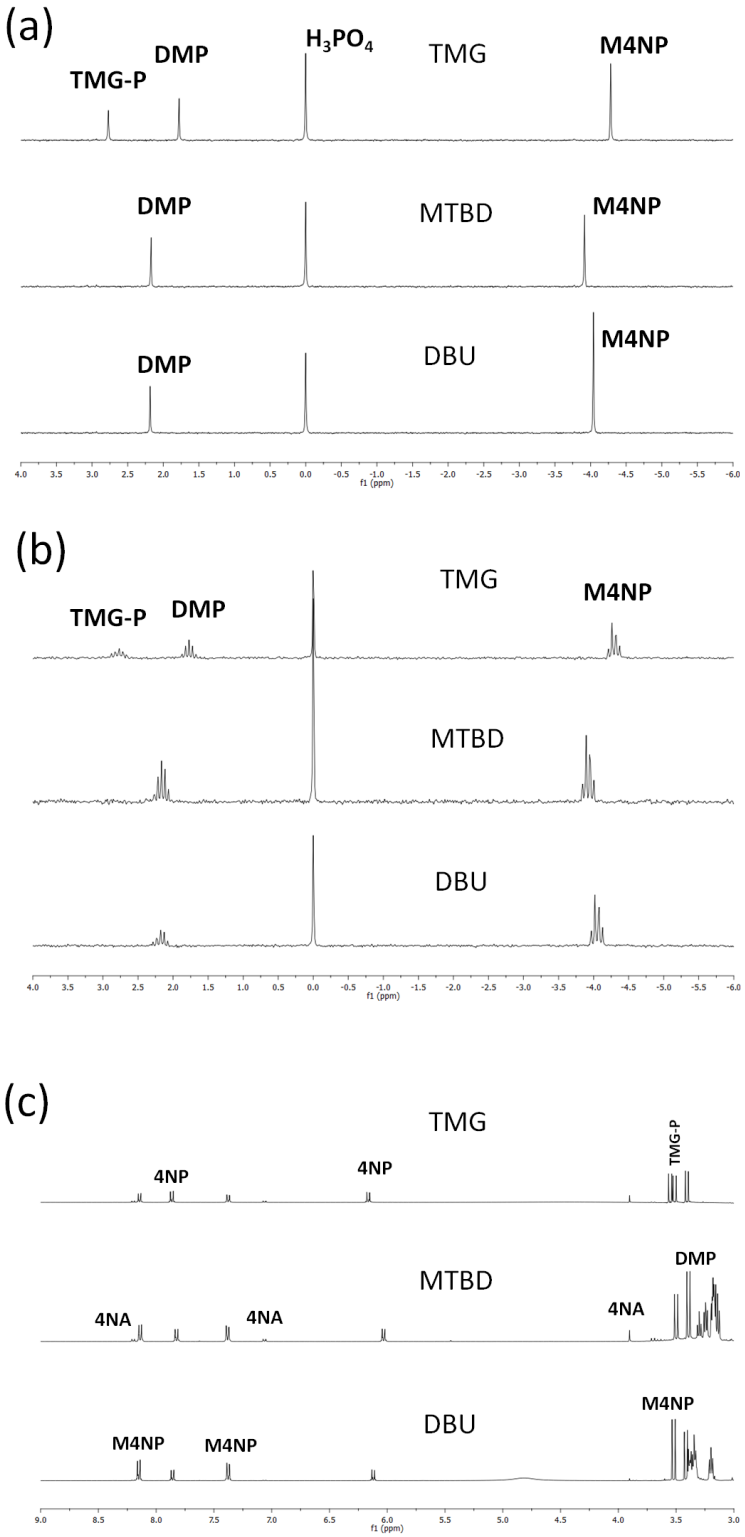


Fig. S16 (a) $^{31}P[^{1}H]$ NMR, (b) ^{31}P NMR, and (c) ^{1}H NMR for reaction of TMG, MTBD, and DBU (2 equivalents) against MP without addition of water, after 24 hours at room temperature. The peak at 0.0 ppm is from the phosphoric acid standard. Products including 4-nitrophenolate (4NP), dimethyl phosphate (DMP), methyl 4-nitrophenyl phosphate (M4NP), 4-nitroanisole (4NA), and dimethyl (bis(dimethylamino)methylene)phosphoramidate (TMG-P) assigned.

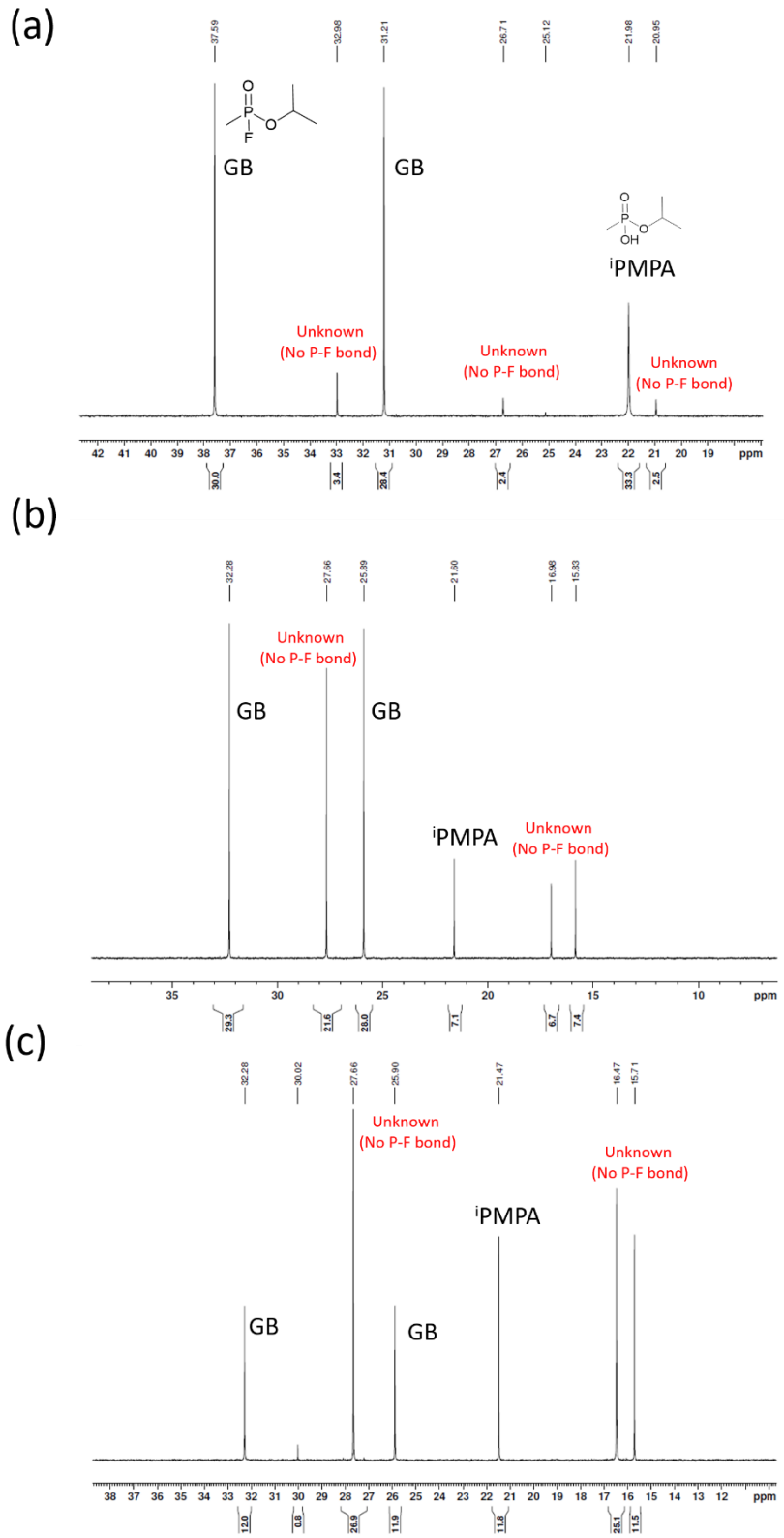


Fig. S17 (a) ^{31}P NMR for reactions of (a) TMG, (b) DBU, and (c) MTBD (2 equivalents) against GB without addition of water, after 24 hours at room temperature. The desired breakdown product for GB hydrolysis, isopropyl methylphosphonic acid (^{i}PMPA), assigned.

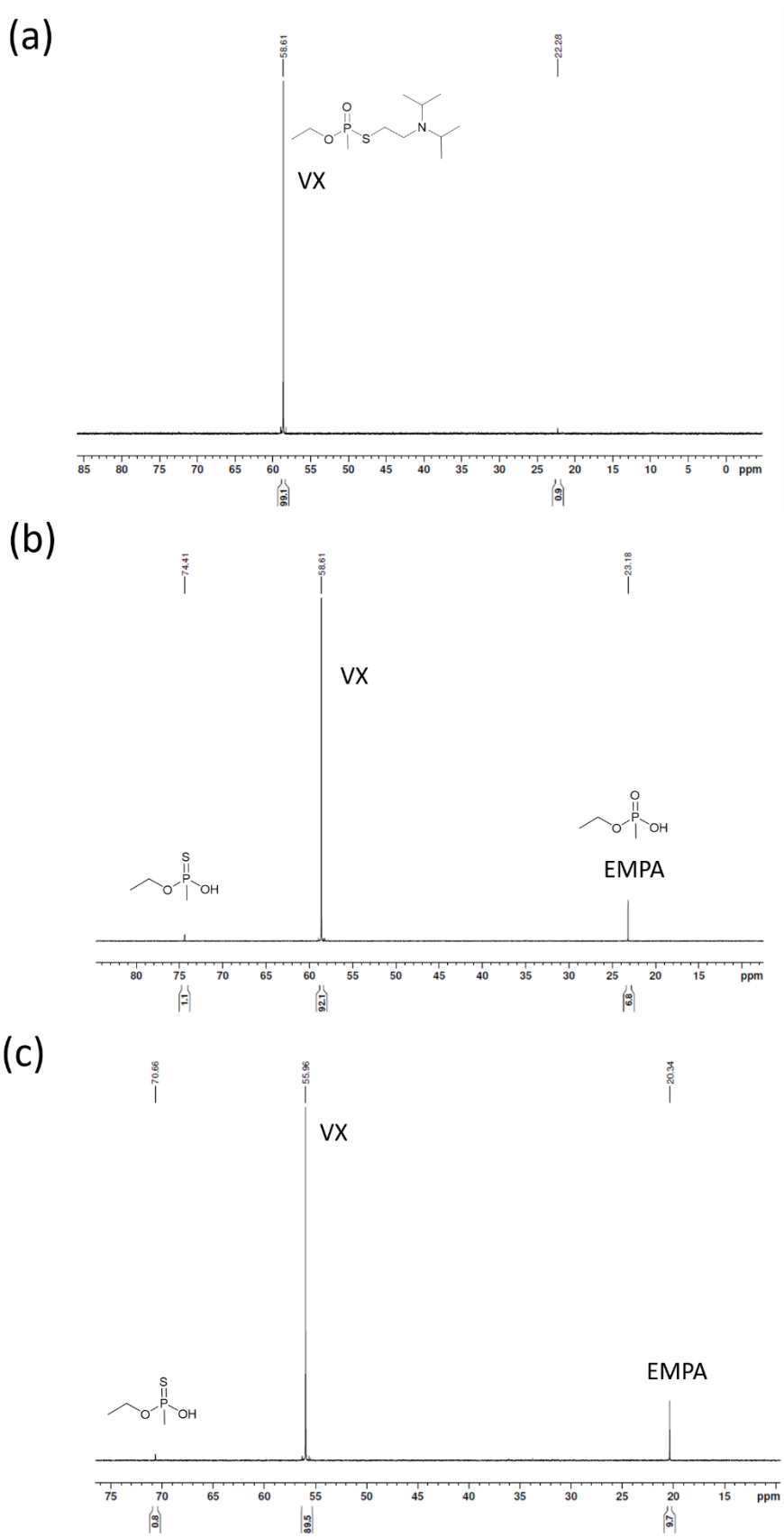


Fig. S18 (a) ^{31}P NMR for reactions of (a) TMG, (b) DBU, and (c) MTBD (2 equivalents) against VX without addition of water, after 24 hours at room temperature. The desired breakdown product, ethyl methyl phosphonate (EMPA), and thioic acid product, at 70–75 ppm assigned.

Table S2 Breakdown products (%) for hydrolysis of MP, GB, and VX with varying amounts of water (1,50, and 800 equivalents) in the absence and presence of 5 equivalents TMG base, after 24 hours at room temperature. Dimethyl phosphate (DMP), methyl 4-nitrophenyl phosphate (M4NP), dimethyl (bis(dimethylamino)methylene)phosphoramidate (TMG-P), isopropyl methylphosphonic acid (^{i}PMPA), and ethyl methyl phosphonate (EMPA).

CWA/simulant	Water (equivalents)	TMG (equivalents)	Percentage products (%)						
			DMP	M4NP	TMG-P	iPMPA	GB other	EMPA	VX other
MP	1	0	0	0	0				
	50	0	0	0	0				
	800	0	0	0	0				
GB	1	0				97	2		
	50	0				96	3		
	800	0				96	3		
VX	1	0						0	0
	50	0						1	2
	800	0						9	16
MP	1	5	35	41	24				
	50	5	97	1	2				
	800	5	100	0	0				
GB	1	5				91	6		
	50	5				97	2		
	800	5				95	4		
VX	1	5						1	1
	50	5						86	13
	800	5						88	11

Table S3 Breakdown products (%) for breakdown of MP, GB, and VX against bases TMG, DBU, and MTBD, without addition of water, after 24 hours at room temperature. Dimethyl phosphate (DMP), methyl 4-nitrophenyl phosphate (M4NP), dimethyl (bis(dimethylamino)methylene)phosphoramidate (TMG-P), isopropyl methylphosphonic acid (^{i}PMPA), and ethyl methyl phosphonate (EMPA).

CWA/simulant	Base	Percentage products (%)						
		DMP	M4NP	TMG-P	^{i}PMPA	GB other	EMPA	VX other
MP	TMG	28	48	24				
	DBU	40	60	0				
	MTBD	29	71	0				
GB	TMG				33	9		
	DBU				7	35		
	MTBD				11	65		
VX	TMG						0	0
	DBU						6	1
	MTBD						9	1

Synthesis

All chemicals were purchased from commercial suppliers and used as received. Anhydrous toluene, triethylamine, and methanol were used in the synthesis of MP. Anhydrous acetone was used in the synthesis of lithium methyl 4-nitrophenyl phosphate.

Synthesis of methyl paraoxon (MP), dimethyl 4-nitrophenyl phosphate

MP was synthesised according to a modified literature procedure,[2] and used throughout for the breakdown experiments.

Triethylamine (2.0 mL, 14 mmol) was dissolved in toluene (10 mL) in a two-neck round bottomed flask, equipped with a stirrer bar under a nitrogen atmosphere. To this was added a solution of 4-nitrophenyl phosphorodichloridate (1.9 g, 7.4 mmol) in toluene (20 mL) whilst maintaining the flask at 0 °C. Finally, methanol (0.6 mL, 15 mmol) was added drop wise and the resulting solution stirred at room temperature for 18 hours. After such time, the reaction solution was filtered and the solvent evaporated under vacuum. The crude product was purified by silica gel chromatography eluting with 20% ethyl acetate/hexane to afford MP as a yellow-clear oil (1.14 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.24 (d, 2H, ^{3}J=9.2 Hz), 7.38 (d, 2H, ^{3}J=9.2 Hz), 3.92 (d, 6H, ^{3}J(H,P)=11.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 155.5, 145.1, 126.0, 120.6, 55.5 ppm; ^{31}P NMR (400 MHz, CD_3CN): δ (ppm) -4.3 ppm (referenced against H_3PO_4 standard).

Synthesis of lithium methyl 4-nitrophenyl phosphate

The lithium salt of methyl 4-nitrophenyl phosphate was synthesised from MP, according to a modified literature procedure.[3] This compound was used for addition experiments in order to confirm the presence of M4NP in the breakdown experiments (Fig. S6).

Methyl paraoxon (0.25 mL, 1.4 mmol) and lithium bromide (0.12 g, 1.4 mmol) were dissolved in dry acetone (20 mL) and the resulting mixture refluxed for 5 hours. The solution was cooled and left at room temperature overnight. The resulting precipitate was collected and washed several times with diethyl ether. Lithium methyl 4-nitrophenyl phosphate was obtained as a white solid (0.15 g, 45%). ^{1}H NMR (400 MHz, CD_3CN/DMSO) : δ (ppm) 8.11 (d, 2H, ^{3}J=9.2 Hz), 7.40 (d, 2H, ^{3}J=9.1 Hz), 3.52 (d, 3H, ^{3}J(H,P)=11.1 Hz). ^{13}C NMR (400 MHz, CD_3CN/DMSO): 160.5, 143.2, 126.0, 121.0, 53.3; ^{31}P NMR (400 MHz, CD_3CN/DMSO): δ (ppm) -4.4 ppm (referenced against H_3PO_4 standard).

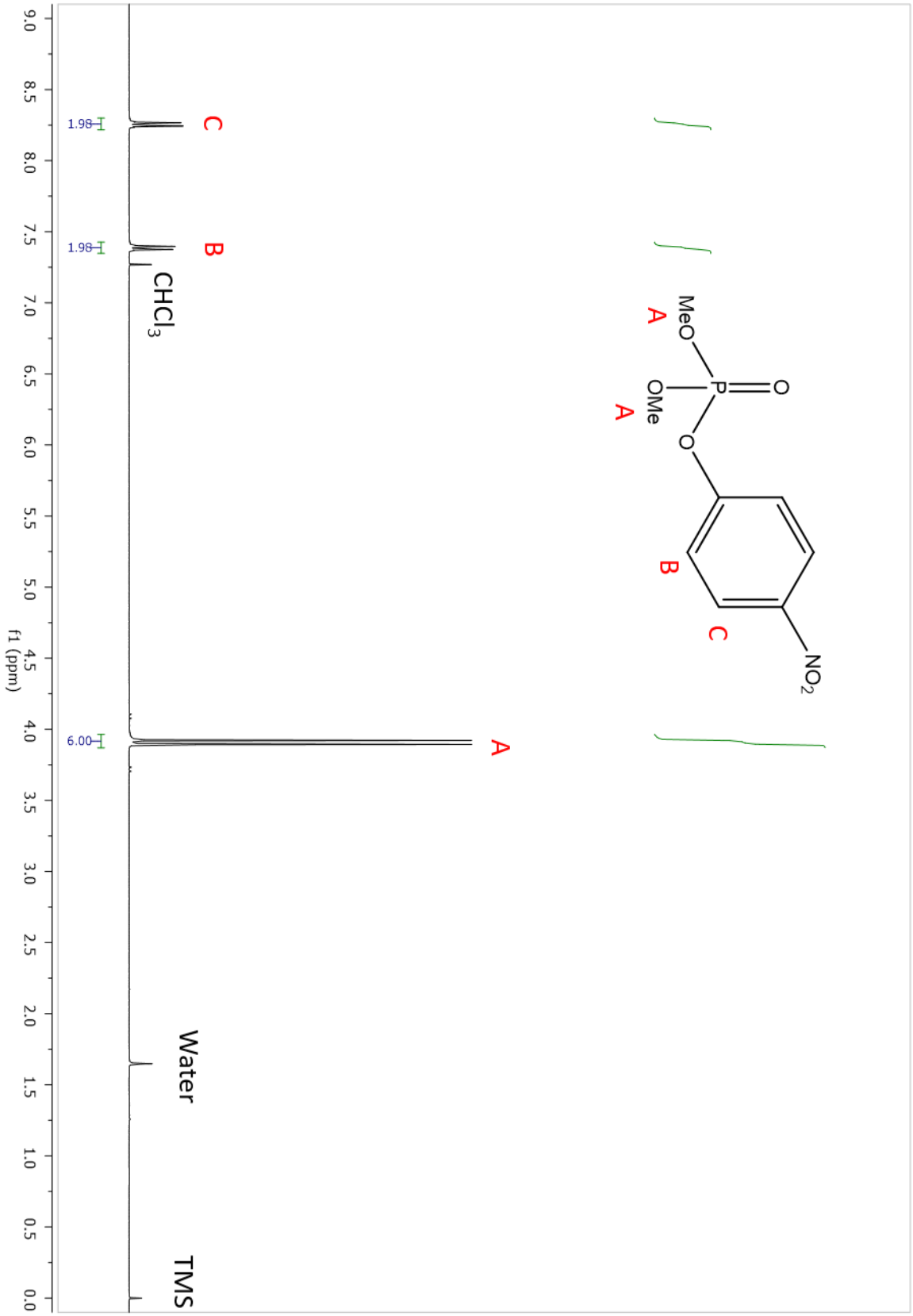


Fig. S19 ^{1}H NMR spectrum for dimethyl 4-nitrophenyl phosphate, methyl paraoxon (MP) in $CDCl_3$.

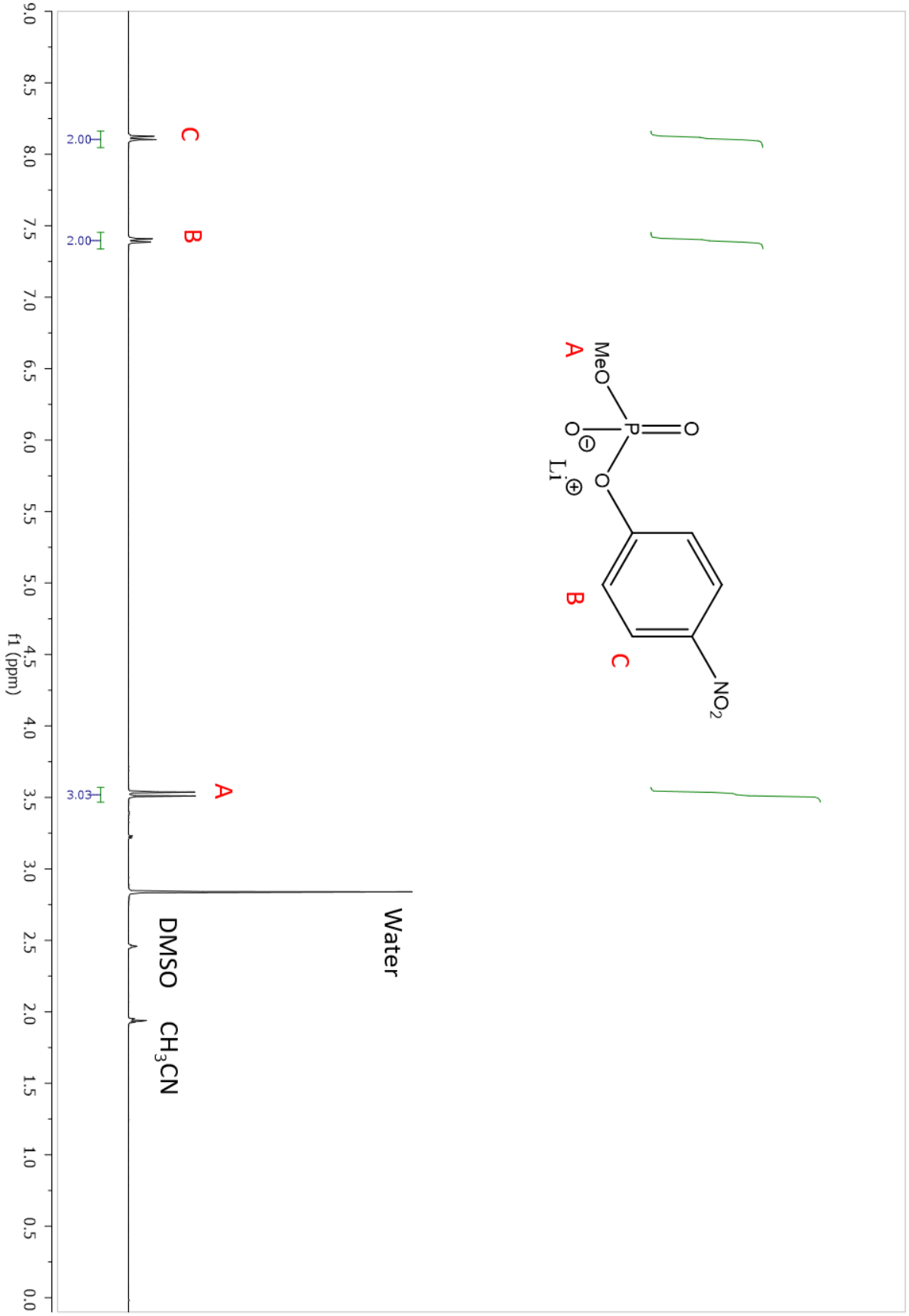


Fig. S20 ^{1}H NMR spectrum for lithium methyl 4-nitrophenyl phosphate, in CD_3CN/DMSO.

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