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^{1}H and ^{31}P Benchtop NMR of liquids and solids used in and/or produced during the manufacture of methamphetamine by the HI reduction of pseudoephedrine/ephedrine

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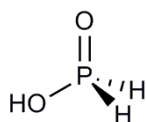
Abstract

In this study, the use of benchtop NMR spectroscopy in the analysis of solids and liquids used and/or produced during the HI reduction of pseudoephedrine was evaluated. The study focused on identifying organic precursors and phosphorus containing compounds used in and/or produced during the manufacturing process. Samples taken from clandestine laboratories, where this synthesis process was suspected of occurring, were analysed and evaluated. Benchtop NMR was able to distinguish between ephedrine, pseudoephedrine and methamphetamine as the free base and hydrochloride salt. This technique was also effective at identifying and distinguishing between phosphorus containing compounds used and/or produced during the manufacture of methamphetamine. Benchtop NMR was also determined to be effective at analysing samples from suspected clandestine laboratories.

Keywords: benchtop NMR, nuclear magnetic resonance, methamphetamine, clandestine laboratory, phosphorus, methamphetamine manufacture
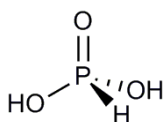
1.   Introduction

The synthesis of methamphetamine from pseudoephedrine/ephedrine using hydriodic acid (HI) either directly or *in situ* is well documented. [1-4] The manufacture of methamphetamine in New Zealand is almost exclusively carried out via this method, where HI is produced *in situ*, using iodine and either hypophosphorous acid, phosphorous acid or red phosphorus and water.
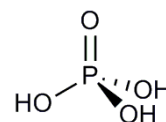
During the manufacture of methamphetamine by this method, the phosphorus containing species (red phosphorus, hypophosphorous acid and phosphorous acid) undergo oxidation by iodine, forming HI and the corresponding higher oxidation state phosphorous oxyacid. If oxidation continues, phosphoric acid will ultimately form which is stable and cannot act as a reducing agent.[5] The chemical structures of hypophosphorous acid, phosphorous acid and phosphoric acid are presented in Figure 1.

Figure 1: The chemical structure of the phosphorous oxyacids- hypophosphorous acid, phosphorous acid and phosphoric acid.

Nuclear Magnetic Resonance (NMR) is a powerful spectroscopic technique for characterising and quantifying molecules. The NMR spectrum produces a specific fingerprint for each compound, including isomers, and is inherently quantitative. However, the expense and maintenance of high field NMR instruments which use super conducting magnets have limited their widespread use outside of academia. Recent advances in the design of small, powerful permanent magnet arrays and electronics have permitted the development of compact benchtop NMR systems that are relatively inexpensive and simple to maintain. These benchtop systems overcome the limitations of high field NMR, making it possible to introduce NMR into the standard workflow of forensic laboratories.[6-8]

NMR spectroscopy can differentiate isomers, often with no sample manipulation or derivatisation, [9] which can be difficult using other techniques commonly used to analyse samples from suspected clandestine laboratories e.g. GCMS, HPLC and FTIR. The identification of isomers and other precursors can assist in identifying potential synthetic routes, which can assist greatly in the investigation of suspected clandestine laboratories.

Some benchtop NMR models do not require a deuterated solvent as a deuterium lock, and therefore samples from suspected clandestine laboratories can be measured directly to provide information about organic compounds and those that contain phosphorus or other NMR active nuclei.

This research discusses the use of ^{1}H and ^{31}P benchtop NMR in the analysis of solids and liquids used in/or produced during the manufacture of methamphetamine. Included in this research was the analysis of suspected clandestine laboratory casework samples. To the best of our knowledge this is the first report utilising a benchtop NMR to analyse these types of samples, including suspected clandestine laboratory samples.

2. Experimental
2.1 Chemicals (source, grade, purity (where applicable))

Pseudoephedrine hydrochloride (Emmellen Biotech Pharmaceuticals Limited, ca. 100% purity), hypophosphorous acid (Acros Organics, 50% in water), phosphorous acid (Sigma Aldrich, 99%), red phosphorus (BDH, ≥ 97%), phosphoric acid (Univar Analytical, 85%), sodium hydroxide (Merck KGaA, Emsure), toluene (Merck KGaA, Emsure), hydrochloric acid (Merck KGaA, Emsure, 37%), deuterium oxide (Appolo Scientific Limited, >99.9%D), chloroform-D1 (Merck KGaA, 99.8%). The methamphetamine hydrochloride and ephedrine hydrochloride were seized samples and have been shown to be pure through previous GCMS analysis. Pseudoephedrine (free base) was produced by basifying pseudoephedrine hydrochloride (Emmellen Biotech Pharmaceuticals Limited, ca. 100% purity) using sodium hydroxide solution and extracting into chloroform.

2.2 Methamphetamine Synthesis

Methamphetamine was synthesised from pseudoephedrine hydrochloride using iodine and, hypophosphorous acid, phosphorous acid or red phosphorus and water. After the methamphetamine was synthesised, the reaction mixture was basified using a sodium hydroxide solution. The methamphetamine was then extracted from the basified reaction mixture by two different methods commonly observed in New Zealand, base toluene extraction and distillation using a household water distiller.

2.3 Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectra were obtained using a Magritek Spinsolve phosphorus benchtop NMR spectrometer operating at 43.1 MHz for ^{1}H and 17.5 MHz for ^{31}P. Reference samples for ^{1}H NMR were dissolved in the appropriate deuterated solvent and approximately 0.5 mL transferred into standard 5 mm NMR tubes. For the casework samples and phosphorus containing samples approximately 0.5 mL was transferred directly into the NMR tube. For spectra measured in deuterated solvents the ppm scale was calibrated to the residual solvent peak (4.78 ppm for D_2O and 7.26 ppm for $CDCl_3$). Where a deuterated solvent was not used, the ^{1}H NMR spectrum was referenced using a 10% H_2O in D_2O sample, setting the peak to 4.74 ppm. This calibration is then internally converted to reference the ^{31}P NMR spectrum.

3. Results and Discussion

At clandestine laboratories in New Zealand, ephedrine is predominantly found as the pure hydrochloride salt, while pseudoephedrine is predominately found as either the pure hydrochloride salt or as the free base. Pseudoephedrine, as the free base, is generally a product of a base/solvent extraction. The benchtop NMR was able to differentiate between these common starting materials. Pseudoephedrine and ephedrine hydrochloride, which are diastereoisomers, can be differentiated in the ^{1}H NMR spectrum by the different interactions of protons at positions 2 and 3 (Figure 2). In the ephedrine hydrochloride spectrum the *J*-coupling between 2 and 3 was 3.7 Hz. Thus, with a larger *J*-coupling between 3 and 4 of 6.7 Hz, the resonance for 3 appeared as a quartet of doublets (qd) and the chemical shift for 2 was at 5.17 ppm. For pseudoephedrine hydrochloride, the *J*-coupling between 2 and 3 was 9.1 Hz while the *J*-coupling between 3 and 4 was smaller at 6.6 Hz, therefore the resonance for 3 appeared as a doublet of quartets (dq) and the chemical shift for 2 was at 4.72 ppm.

Pseudoephedrine hydrochloride can be differentiated from the free base in the ^{1}H NMR spectrum due to the ionisation of the nitrogen causing a downfield shift for positions 2, 3 and 5 in the hydrochloride salt (Figure 3). Methamphetamine hydrochloride had a similar spectra to pseudoephedrine and ephedrine hydrochloride and base (Figure 4). However, methamphetamine hydrochloride was easily distinguished by the proton at position 2. The ^{1}H NMR spectrum for methamphetamine, pseudoephedrine and ephedrine (hydrochloride and base) were compared with those reported on the SWGDRUG database using high field NMR. [10] Other than the peak resolution, which was significantly less using benchtop ^{1}H NMR, there were no significant differences between the spectrum of high field and benchtop NMR.
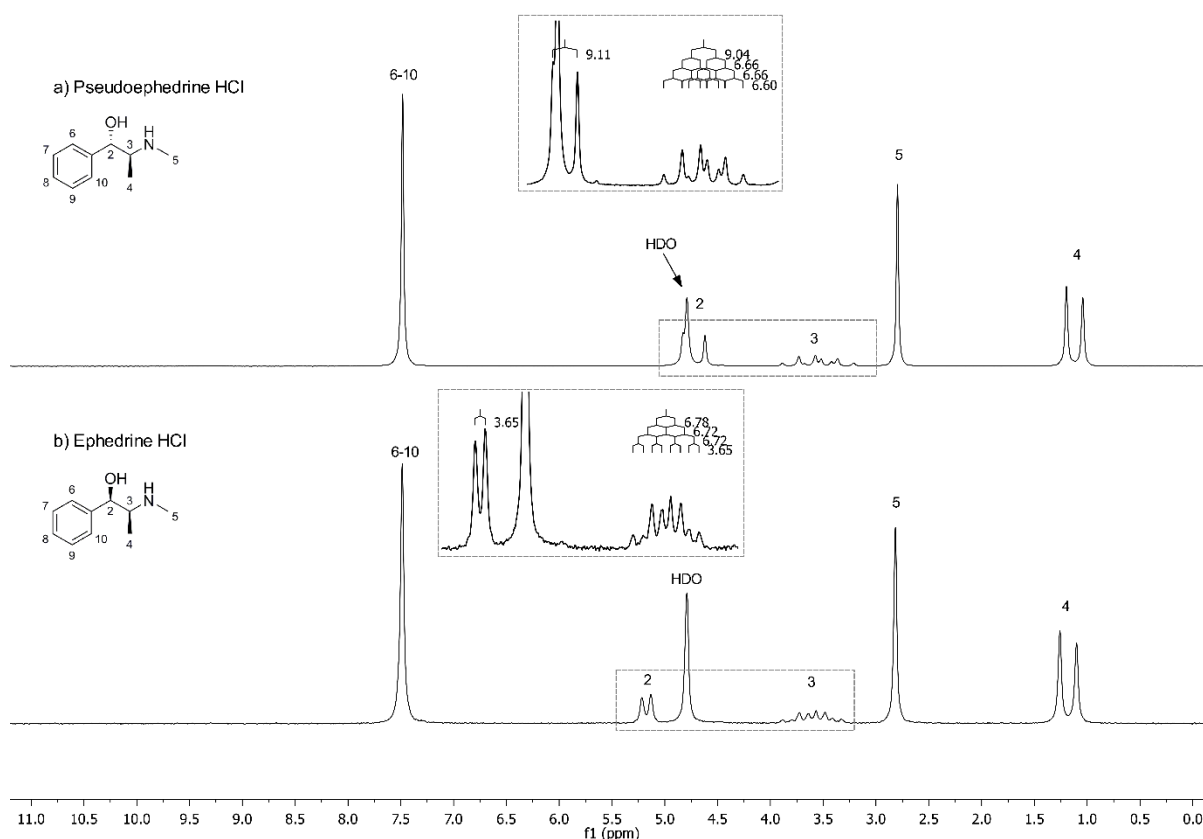
Figure 2: ^{1}H NMR spectra of a) pseudoephedrine hydrochloride and b) ephedrine hydrochloride (dissolved in D_2O).
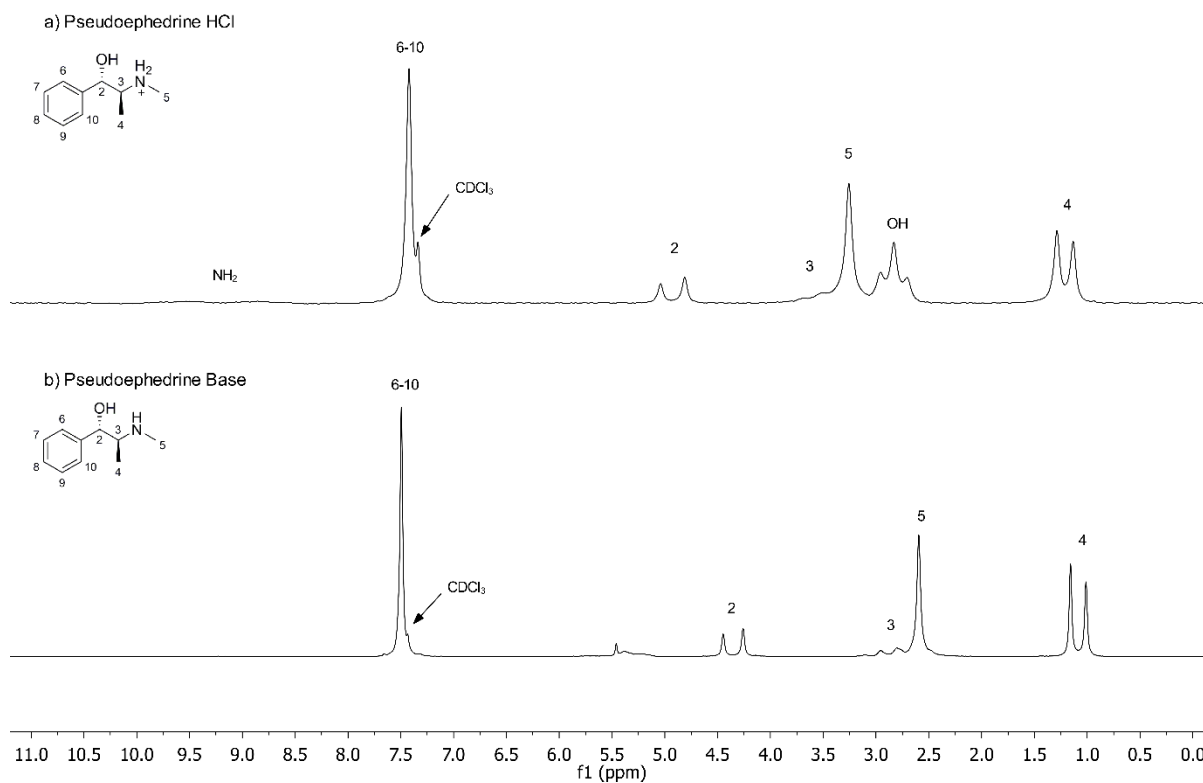

Figure 3: ^{1}H NMR spectra of a) pseudoephedrine hydrochloride and b) pseudoephedrine (free base) (dissolved in $CDCl_3$).
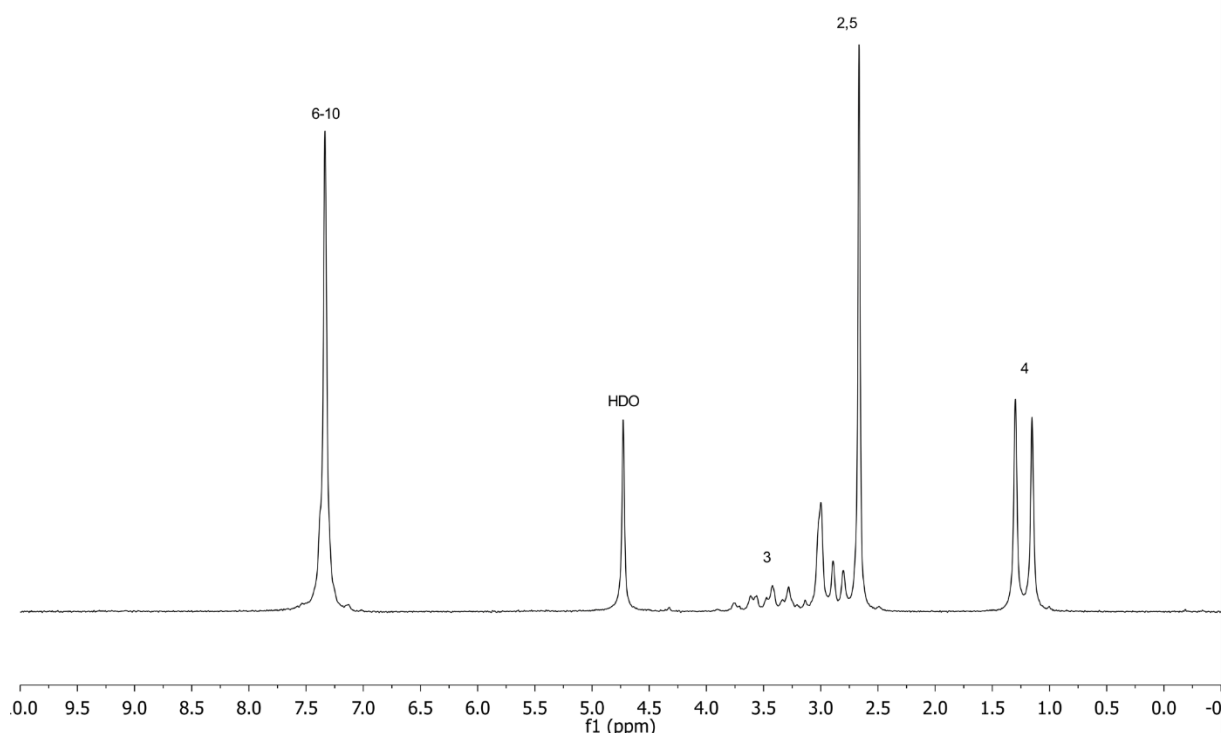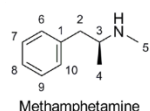
Figure 4: ^{1}H NMR spectra of methamphetamine hydrochloride (dissolved in D_2O).

Red phosphorus, hypophosphorous acid and phosphorous acid are used to reduce iodine, producing hydriodic acid *in situ* and ultimately resulting in the production of phosphoric acid. The benchtop NMR was able to differentiate between phosphorous acid, hypophosphorous acid and phosphoric acid in both the acid and basic anion form (Figure 5 and 6). The chemical shifts for phosphorous acid, hypophosphorous acid and phosphoric acid, as the acid, were 4.8, 11.7 and -0.4 ppm, respectively. These values were in agreement with those reported in the literature using high field NMR spectroscopy (phosphorous acid 5.8 ppm [11], hypophosphorous acid 12.2 ppm [11] and phosphoric acid 0.04 ppm [12]). The coupling constants for hypophosphorous acid and phosphorous acid were 566 and 683 Hz, respectively, and were also in agreement those reported in the literature (*J*-coupling hypophosphorous acid 566 Hz and phosphorous acid 690 Hz). [11]

The chemical shifts for phosphorous acid (phosphite), hypophosphorous acid (hypophosphite) and phosphoric acid (phosphate), as the basic anion, were 2.8, 6.9 and 3.6 ppm, respectively. These values were in agreement with those reported in the literature (phosphorous acid 3.3 ppm [11], hypophosphorous acid 8.1 ppm [13] and phosphoric acid 5.06 ppm [14]). The coupling constants for hypophosphorous acid and phosphorous acid, as the basic anion, were 517 and 569 Hz, respectively, and were also in agreement with those reported in the literature (J-coupling hypophosphorous acid 510 Hz and phosphorous acid 570 Hz). [11]

No phosphorus species were observed when red phosphorus was extracted with water. Red phosphorus was not analysed directly in this investigation as the appropriate solvents were not available. Using ^{31}P NMR spectroscopy (16 scans with a total acquisition time of 2.67

minutes), the phosphoric acid peak was still able to be detected at a concentration of 0.85% in water. It was expected that high field NMR spectroscopy would be much more sensitive than benchtop NMR. Multiple analyses of the phosphorus oxyacids over a two week period showed no change to the chemical shifts.
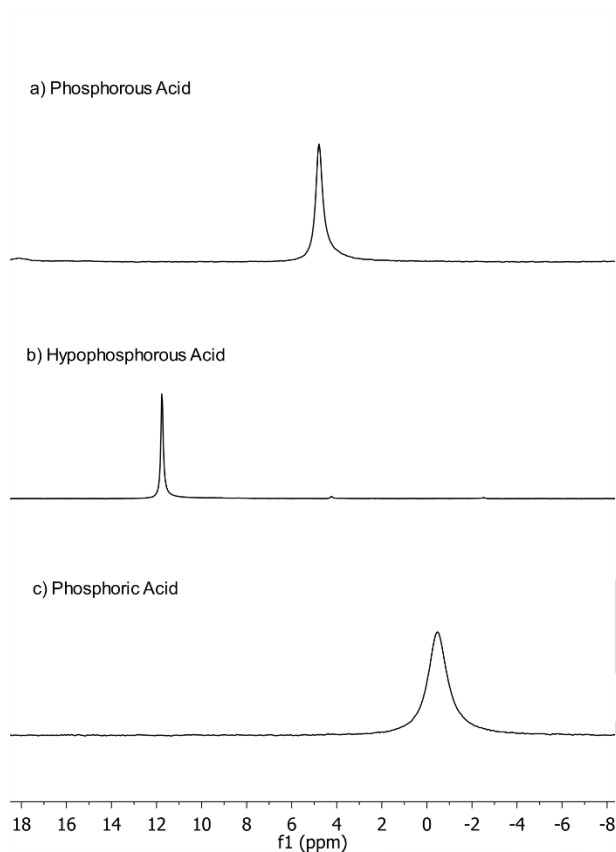

Figure 5: ^{31}P NMR spectra of a) phosphorous acid, b) hypophosphorous acid and c) phosphoric acid in water.
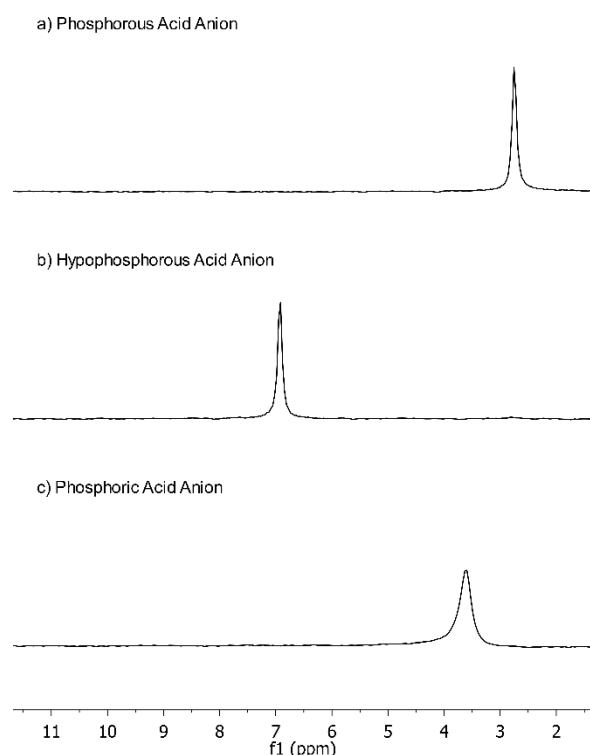
Figure 6: ^{31}P NMR spectra of a) phosphorous acid, b) hypophosphorous acid and c) phosphoric acid as the basic anion in water.

The reaction mixture of a completed methamphetamine synthesis using red phosphorus, hypophosphorous acid or phosphorous acid to generate HI was measured using ^{31}P and ^{1}H NMR spectroscopy (Figure 7 and 8). At the completion of the manufacture of methamphetamine using red phosphorus, four phosphorus containing species were detected in the ^{31}P NMR spectrum. Phosphoric acid was the major phosphorus containing species present at 0.2 ppm, while hypophosphorous acid at 20.8 ppm, phosphorous acid at 8.1 ppm and an unknown phosphorus containing species at 47 ppm (not shown in Figure 7a) were present in minor amounts. Person et al.[5] reported that phosphine, produced during the manufacture of methamphetamine using red phosphorous, can react with hydriodic acid (HI) to form phosphonium iodide and is released as phosphine when basified. No chemical shift data of phosphonium iodide is reported in the literature. However, a similar compound, tetramethyl-phosphonium fluoride, was reported to have a ^{31}P NMR chemical shift of 23-31 ppm. [14] Further research into identifying the unknown phosphorous containing species was not carried out.

When hypophosphorous acid was used three phosphorus containing species were detected in the ^{31}P NMR spectrum. Phosphorous acid was the major phosphorus containing species present at 6.5 ppm, while hypophosphorous acid at 17.4 ppm was present at smaller amounts and phosphoric acid was formed in very minor amounts at -0.3 ppm. When phosphorous acid was used, two phosphorus containing species were detected in the ^{31}P NMR spectrum. Phosphoric acid was the major phosphorus containing species present at -0.3 ppm, while phosphorous acid was present in smaller amounts at 7.3 ppm. The chemical shifts of the phosphorous compounds varied slightly for each reaction due to the differences in pH and temperature of the reaction mixtures. The phosphorous species identified were in agreement

with results obtained by Person et al.[5], who monitored the phosphorus containing species in methamphetamine reactions using capillary electrophoresis. The ratio of the starting materials, and the subsequent HI concentration and reducing potential, was shown to have an effect on what phosphorus containing species were observed at the completion of the reaction. For example, excess hypophosphorous acid resulted in only very minor production of phosphoric acid.
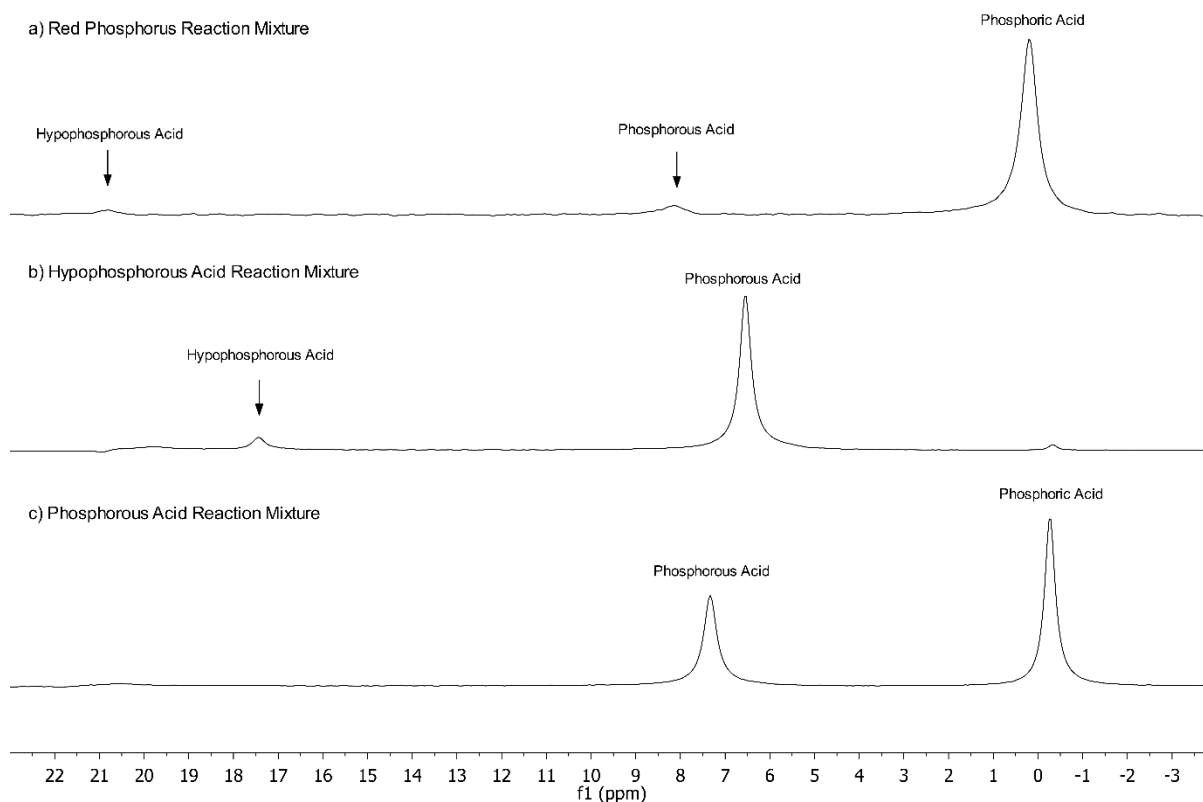

Figure 7: ^{31}P NMR spectra of completed reaction mixtures using a) red phosphorus, b) hypophosphorous acid and c) phosphorous acid.

^{1}H NMR of the completed reaction mixtures using red phosphorus, hypophosphorous acid and phosphorous acid are presented in Figure 8. Species that were identified in the spectra include methamphetamine, common by-product 1-phenyl-2-propanone, hypophosphorous acid and phosphorous acid. These species were identified by comparing with reference materials. Methamphetamine was observed as the major product in all three reactions, with a characteristic doublet at 1.6 ppm with a *J*-coupling of 7 Hz for the protons at 4, an unresolved multiplet between 3 and 4 ppm for protons at 2, 3 and 5, and the aromatic signal at 7.5 ppm. The terminal methyl group of 1-phenyl-2-propanone was observed in the hypophosphorous acid and phosphorous acid reactions as a singlet at 2.45 ppm. Hypophosphorous acid and phosphorous acid were also observed in the ^{1}H NMR spectra as large doublets, due to the coupling of the directly bonded phosphorus atoms and protons. Phosphoric acid does not have direct P-H bonds and can therefore only be identified in the ^{31}P NMR spectra. Phosphorous acid was observed in each of the three reaction mixtures as a doublet with a *J*-coupling of 707-724 Hz, centred at the water peak (pH dependant). Hypophosphorous acid was observed in the red phosphorus and hypophosphorous acid reaction mixtures as a doublet that was also centred at the water peak with a *J*-coupling of 595-603 Hz. The coupling

constants discussed above were dependant on pH, concentration and temperature, however they were similar to those reported in the literature (*J*-coupling phosphorous acid 690 Hz, hypophosphorous acid 566 Hz). [11] The difference in pH between the various reactions was also the reason for the variation in the chemical shift of water, with the water peak shifting downfield in the more acidic hypophosphorous acid and phosphorous acid reactions.
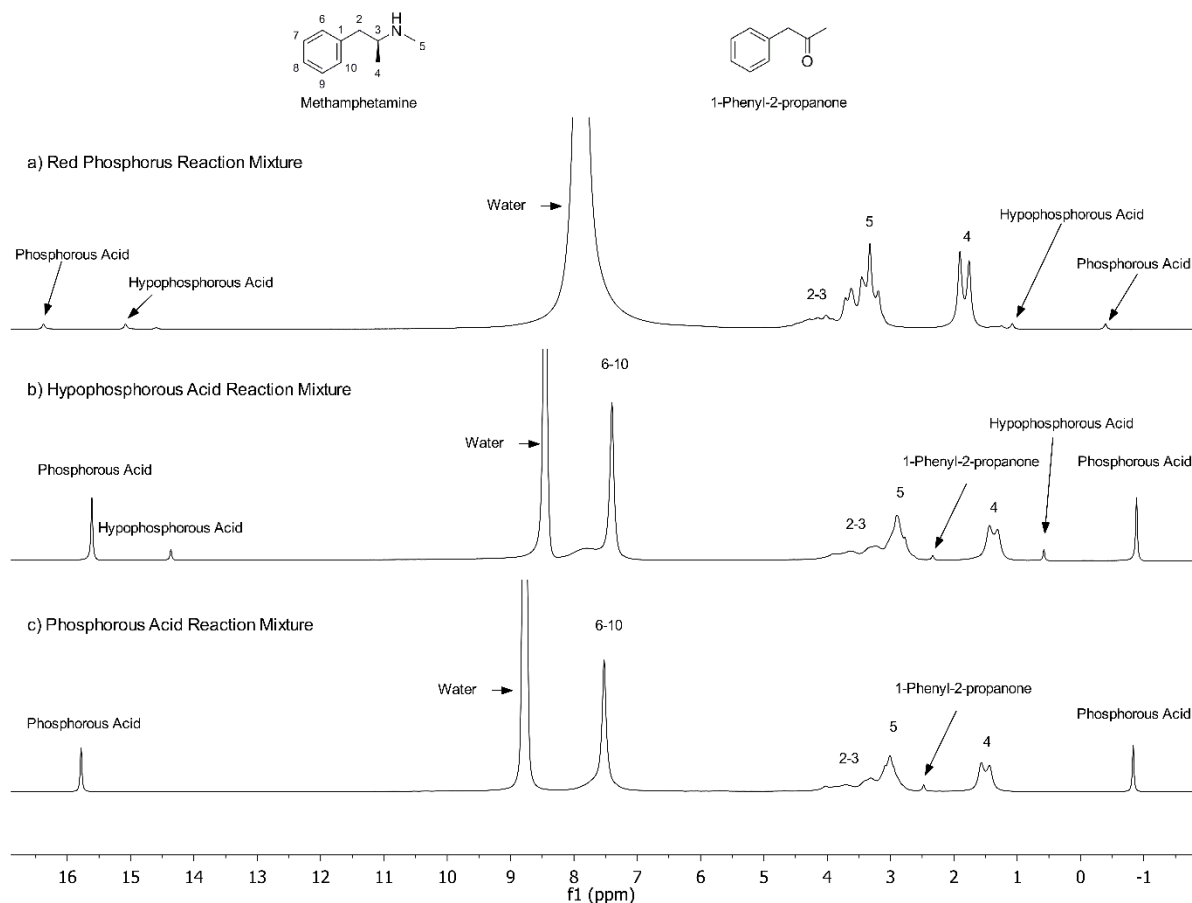

Figure 8: ^{1}H NMR spectra of completed reaction mixtures using a) red phosphorus, b) hypophosphorous acid and c) phosphorous acid.

While the chemical shifts and *J*-coupling of the various phosphorous oxyacids in both the ^{1}H and ^{31}P NMR spectra may vary due to pH and concentration. In an acidic or basic environment, in which these species will most commonly be encountered, each species has a well-defined region of the spectrum distinct from each other. Common screening tests for acidic liquids, such as pH and acid colour precipitate tests (using silver nitrate and barium nitrate), can be used in conjunction with ^{1}H and ^{31}P NMR spectroscopy to positively identify phosphorous oxyacids present for forensic purposes.

^{1}H and ^{31}P NMR spectra of the two layers produced, when a hypophosphorous acid reaction mixture was basified, are shown in Figures 9 and 10. The oil layer was assumed to be mainly methamphetamine (free base). The phosphorus containing species present at the completion of the reaction were only present in the caustic layer, which is generally discarded as waste. No phosphorus containing species were detected in the oil layer containing the extracted methamphetamine. Peaks of species consistent with methamphetamine were observed in small quantities in the ^{1}H NMR spectrum of the caustic (aqueous) layer.
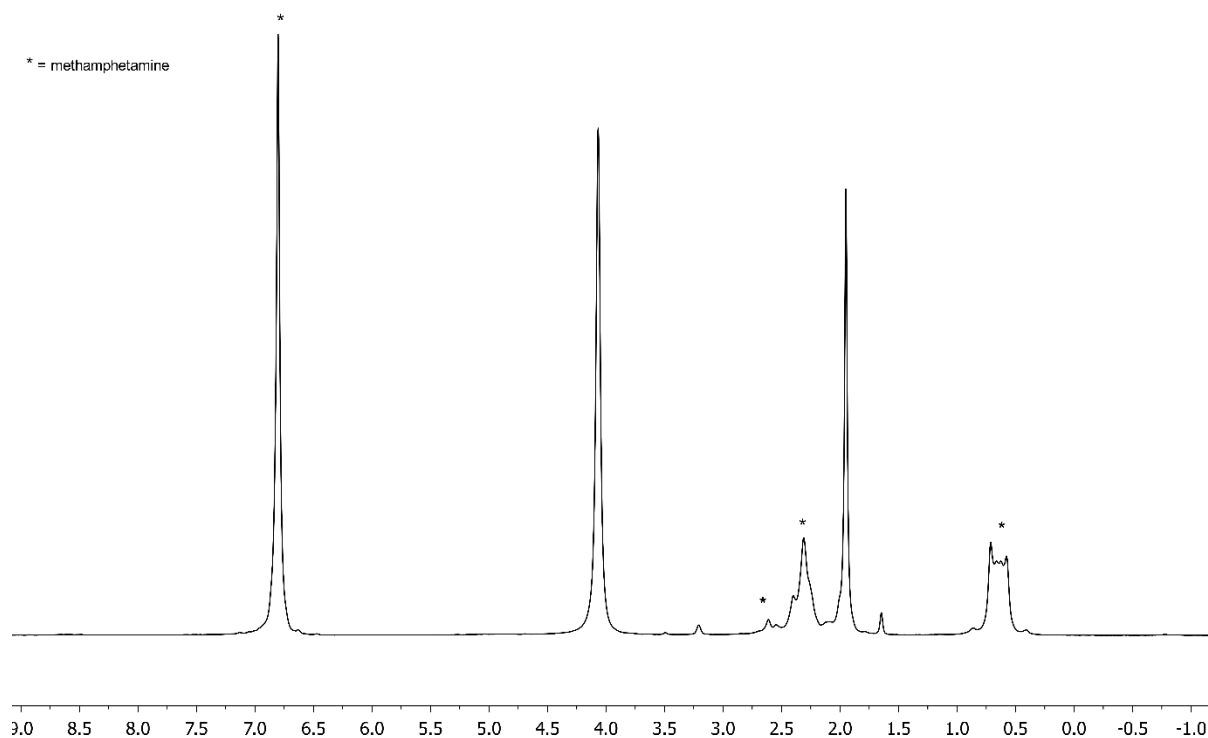
Figure 9: ^{1}H NMR spectrum of oil layer after addition of NaOH to a hypophosphorous acid reaction mixture.
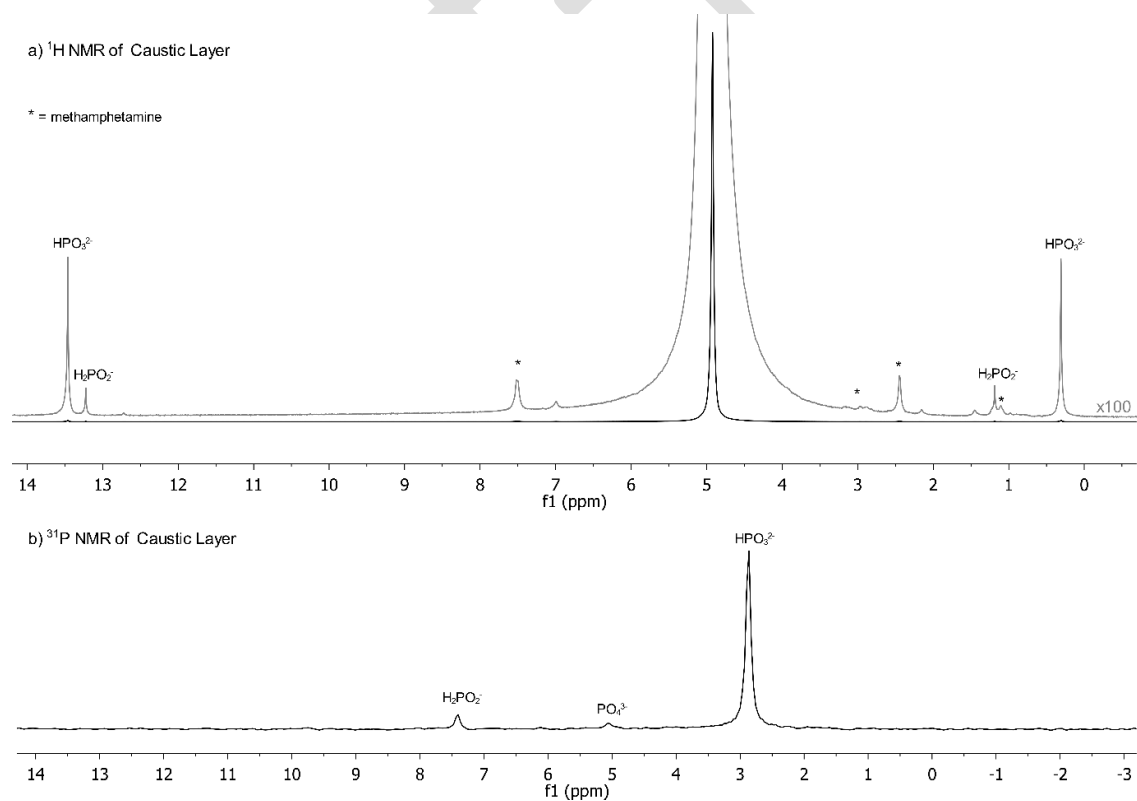

Figure 10: a) ^{1}H (with 100x magnification) and b) ^{31}P NMR spectra of the caustic layer after addition of NaOH to a hypophosphorous acid reaction mixture.

The ^{1}H and ^{31}P NMR spectra of the two liquids resulting from toluene extraction of the basified reaction mixture are presented in Figures 11 and 12. The ^{1}H NMR spectrum of the toluene extract showed two strong resonances at 7.02 and 2.10 ppm due to the aromatic and methyl resonances, respectively, of toluene (protonated solvent) and methamphetamine signals. There were no phosphorus containing species observed in the ^{31}P NMR spectrum of the toluene extract. All of the phosphorus containing species resulting from the reaction were observed in the caustic waste layer. A small amount of methamphetamine was identified in the ^{1}H NMR spectrum of the caustic waste, which was extracted into deuterated chloroform for confirmation (Figure 13).
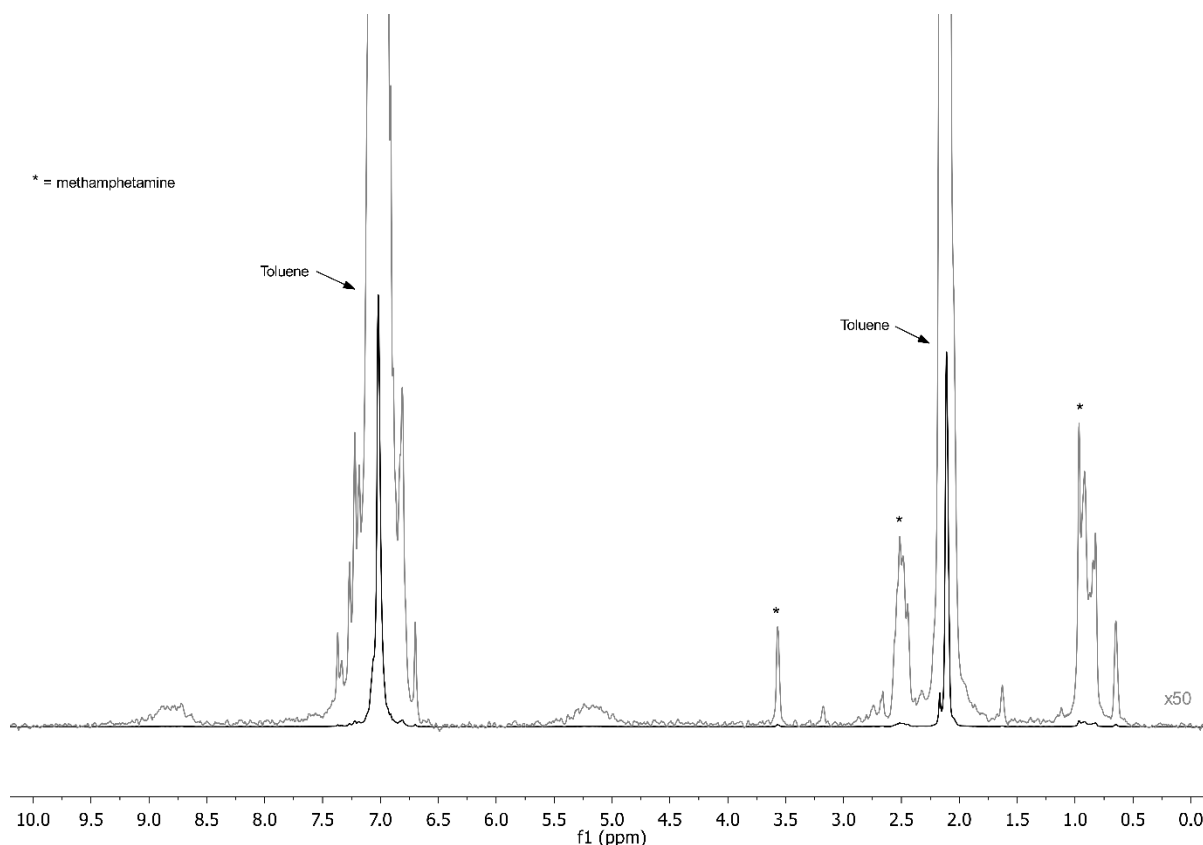

Figure 11: ^{1}H (with 50x magnification) NMR spectrum of toluene extract of the basified methamphetamine reaction mixture.
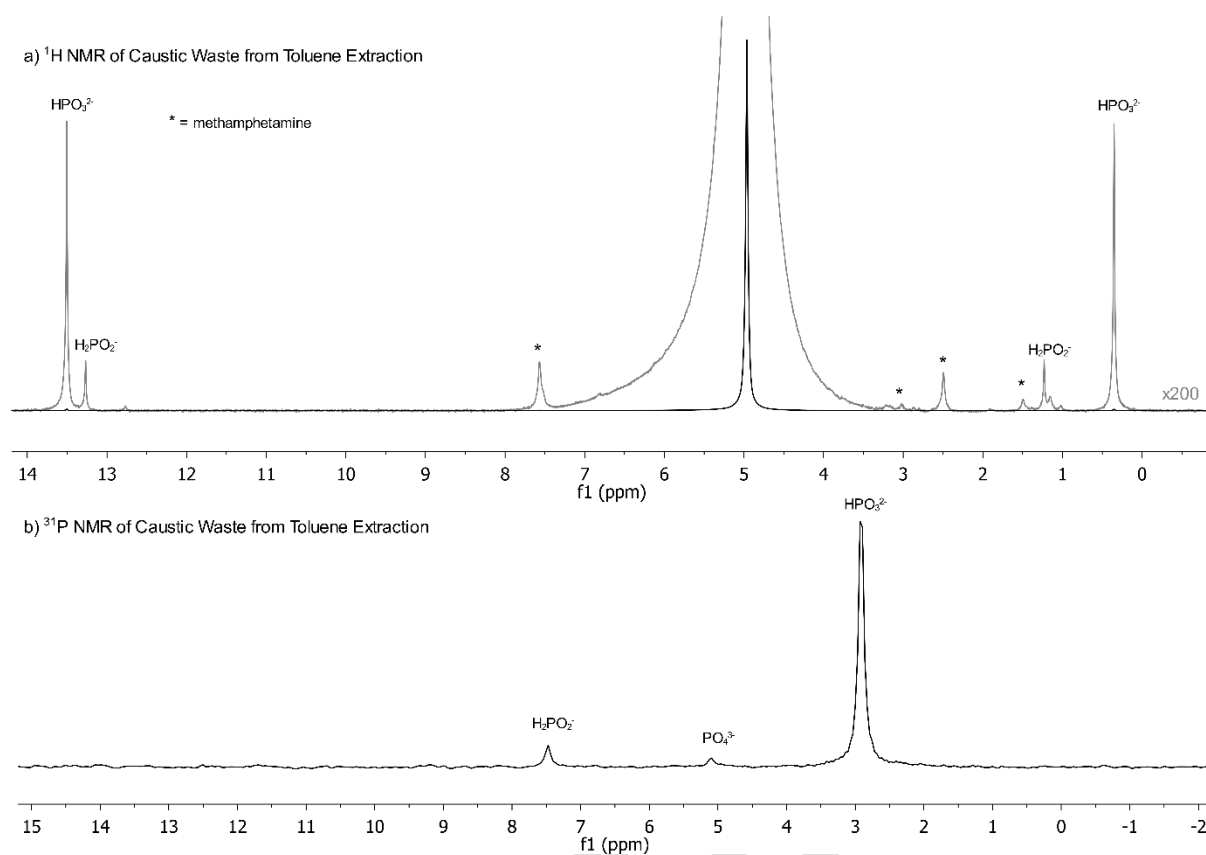
Figure 12: a) ^{1}H (with 200x magnification) and b) ^{31}P NMR spectra of caustic waste after toluene extraction of the basified methamphetamine reaction mixture.
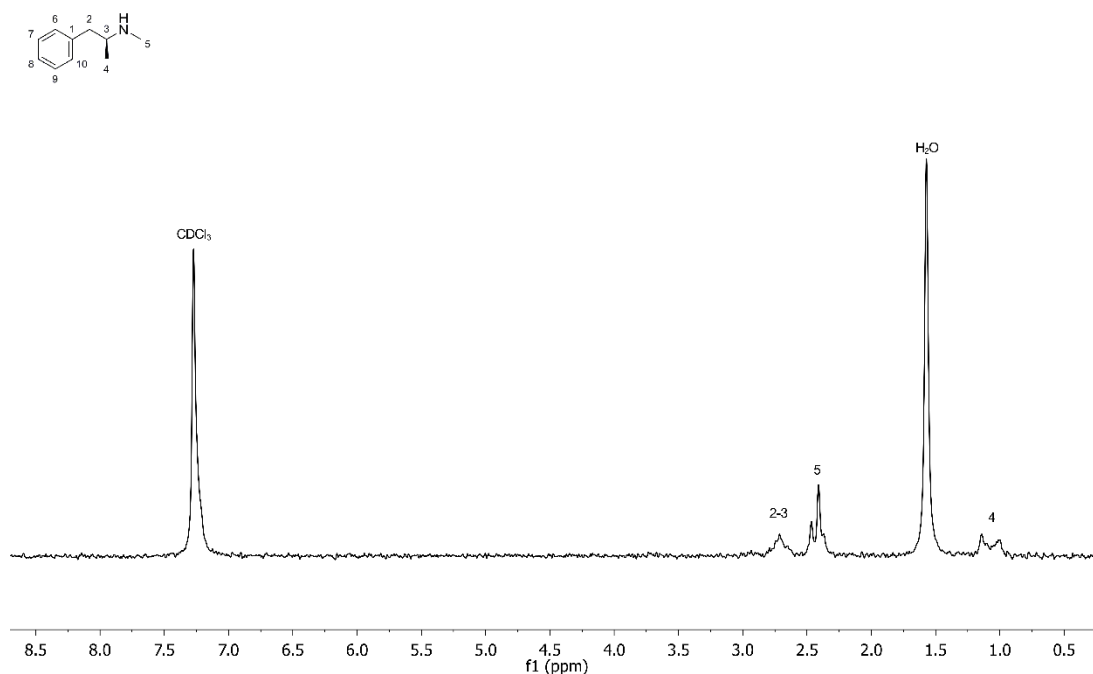

Figure 13: ^{1}H NMR spectrum of methamphetamine extracted into deuterated chloroform from the caustic waste produced from toluene extraction of a basified methamphetamine reaction mixture.

^{1}H and ^{31}P NMR spectra of the distillation waste and distillate produced during the distillation extraction of the basified reaction mixture were measured (Figure 14). All the phosphorus containing species present at the end of the reaction were only present in the caustic distillation waste and not in the distillate (both layers) containing the extracted methamphetamine. In contrast to the toluene extraction, the distillation method did not leave any detectable residual methamphetamine in the caustic waste. This requires the distillation to be carried out for long enough to remove all of the methamphetamine from the basified reaction mixture and in clandestine laboratories this may not always be the case.
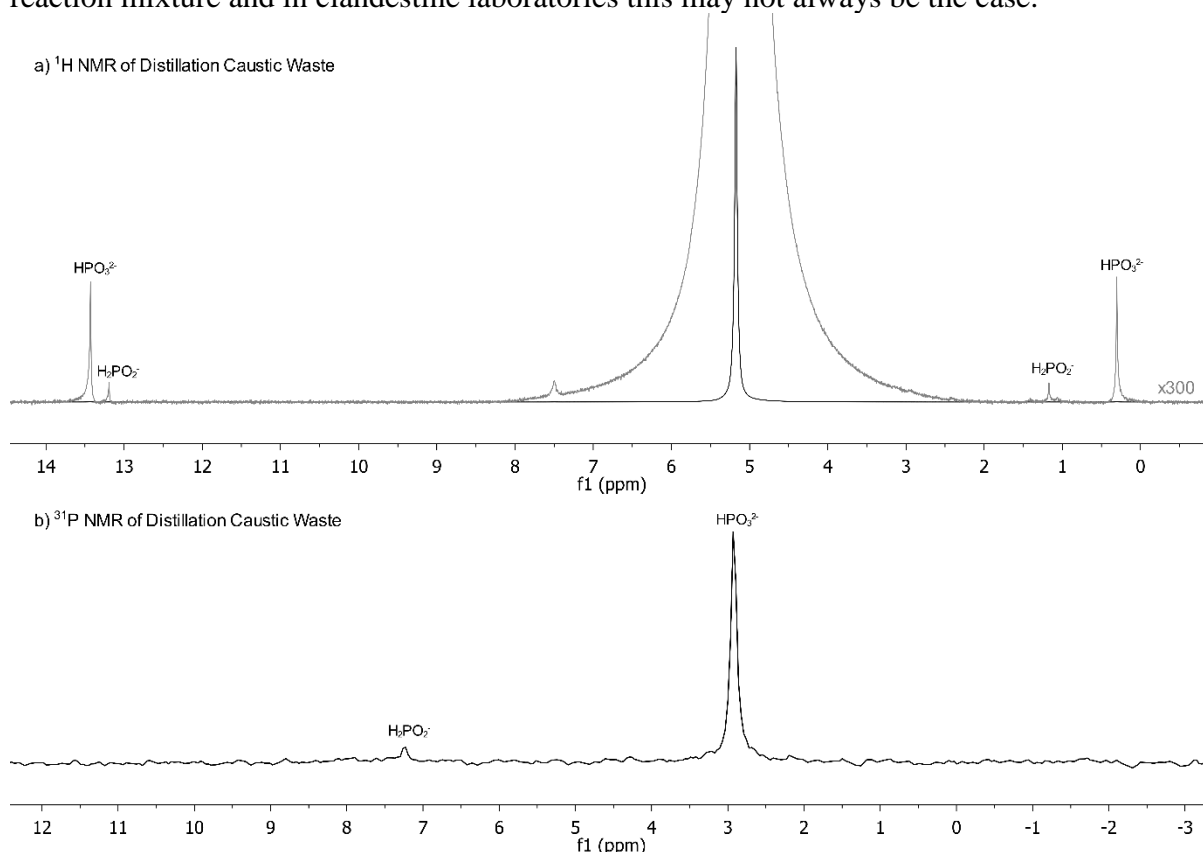

Figure 14: a) ^{1}H (with 300x magnification) and b) ^{31}P NMR spectra of caustic waste produced during the distillation extraction of methamphetamine from basified methamphetamine reaction mixture.

In both methamphetamine extraction methods, the phosphorus containing species were only detected in the caustic waste. Therefore, the detection (or absence) of hypophosphorous acid, phosphorous acid and phosphoric acid anions, in a caustic liquid, can assist in determining whether the liquid was produced during the manufacture of methamphetamine or one that was a result of methamphetamine salt being purified by base/solvent extraction or distillation.

Caustic liquids and two-layered liquids found at suspected clandestine laboratories in New Zealand were also analysed using ^{1}H and ^{31}P benchtop NMR spectroscopy. Previous analysis using GCMS showed that these liquids contained methamphetamine and by-products of the methamphetamine manufacturing process, and were consistent with liquids produced during the extraction of methamphetamine from reaction mixture. The ^{31}P NMR spectra of these caustic liquids were consistent with those obtained in this study, where the phosphorus containing species were detected in the caustic waste (or layer) suggesting they were produced during the manufacture of methamphetamine.

Benchtop NMR spectroscopy has good potential as an analytical technique in forensic drug chemistry. It was shown to produce reliable and reproducible results, which agreed with previous published research in non-forensic fields using the instrument. Compared to high field NMR, benchtop NMR was significantly less sensitive, which resulted in the requirement to have more concentrated samples and longer acquisition times. However, if the amount of sample available was not a factor this would not be a problem. Decreased sensitivity compared to high field NMR, also resulted in reduced peak resolution. Decreased resolution meant it was difficult to analyse mixtures, large complex compounds and carry out structural elucidation using 2D NMR (especially on more complex compounds). In this research we only discussed the use of ^{1}H and ^{31}P NMR spectroscopy, and not ^{13}C or ^{19}F NMR, qNMR and 2D experiments, which were also capable on various benchtop NMR. Given that only a limited number of NMR active isotopes can be analysed using the one instrument, choosing the right instrument with the right combination of isotopes would be important to potential users. Benchtop NMR is a relatively new technique and the technology will continue to develop. The development of stronger magnets will increase instrument sensitivity along with peak resolution and the number of isotopes that could be analysed using the one instrument is also likely to increase.

4.   Conclusion

The benchtop NMR was effective at analysing liquids and solids used and/or produced during the manufacture of methamphetamine. There were distinct spectral differences between pseudoephedrine hydrochloride and free base, ephedrine hydrochloride and methamphetamine hydrochloride and free base. The benchtop NMR was able to identify between phosphorus containing acids, or the equivalent basic anion, used or produced during the manufacture of methamphetamine (i.e. hypophosphorous acid, phosphorous acid and phosphoric acid), including samples taken from suspected clandestine laboratories in New Zealand.

The analysis of liquids produced during the extraction of methamphetamine from reaction mixture showed that when methamphetamine was extracted, by base/solvent extraction or distillation, the phosphorus containing species, used and/or produced during the manufacture of methamphetamine, were only detected in the caustic waste and not in either the extracted solvent or distillate. Therefore, the detection of methamphetamine along with specific phosphorus containing compounds in liquids found at a suspected clandestine laboratory can assist in determining whether a liquid was produced during the manufacture of methamphetamine and therefore if methamphetamine manufacture had occurred.

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