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Application of Quantitative Phosphorous Nuclear Magnetic Resonance Spectroscopy to Chemical Warfare Agents

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ABSTRACT

This report outlines the development of an inverse-gated phosphorous nuclear magnetic resonance (NMR) spectroscopy method for determining the purity of chemical warfare agents using reference standards contained within a glass stem coaxial insert. The stem coaxial insert prevents any possible reaction of the reference standard and analyte by segregating the two solutions. The method was determined to be accurate to 1.1% and was employed to determine the purity of the V-series nerve agent VX using proton-decoupled pulse parameters. The method was found to be equal to or better than modern chromatographic techniques in terms of precision, accuracy and analysis time. The operational simplicity of this method enables both quantitative and qualitative information to be rapidly gleaned from a single sample.

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Application of Quantitative Phosphorous Nuclear Magnetic Resonance Spectroscopy to Chemical Warfare Agents

Executive Summary

Phosphorous quantitative Nuclear Magnetic Resonance (NMR) spectroscopy is a non-destructive technique that can be used for quantitation of chemical species with absolute errors generally below 2%. This report outlines the development of a quantitative phosphorous NMR spectroscopy method for determining the purity of CWAs using reference standards contained within a glass stem coaxial insert. The stem coaxial insert prevents any possible reaction of the reference standard and analyte by segregating the two solutions. The method was determined to be accurate to 1.1% and was subsequently employed to determine the purity of the V-series nerve agent VX using proton-decoupled pulse parameters. The method was found to be equal to or better than modern chromatographic techniques in terms of precision, accuracy and analysis turnaround time. The operational simplicity of this method enables both quantitative and qualitative information to be rapidly gleaned from a single sample.

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Contents

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Glossary

bp	boiling point
$CDCl_3$	chloroform-d_1
CWA	chemical warfare agent
DSTO	Defence Science and Technology Organisation
FID	free induction decay
GC	gas chromatograph
LC	liquid chromatograph
LOD	limits of detection
LOQ	limits of quantitation
M	molarity (moles per litre)
mg	milligrams
MHz	megahertz (10^6 Hz)
mL	millilitres
mm	millimetre
MPA	methylphosphonic acid
NOE	nuclear Overhauser effect
qHNMR	quantitative proton nuclear magnetic resonance spectroscopy
RSD	relative standard deviation
S/N	signal-to-noise
T_1	spin lattice relaxation time
T_2	spin spin relaxation time
TEP	triethyl phosphate
TPP	triphenyl phosphate

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1. Introduction

Nuclear magnetic resonance (NMR) spectroscopy is a technique that provides information on the chemical shift (δ), dipolar coupling (*J*), through-space interactions (NOE), spin-spin coupling (*J*) and relaxation parameters (T_1/T_2) of molecular systems.[1] These parameters can be exploited in one or multiple dimensions using multiple nuclei to provide insight into molecular structure and conformation, reaction kinetics and mechanisms. A fundamental drawback of NMR spectroscopy is poor sensitivity relative to other common laboratory techniques such as gas and liquid chromatography. Despite lower relative sensitivity and high cost of purchase and upkeep, NMR spectroscopy is beneficial as it is a non-destructive technique that enables the direct analysis of complex mixtures. Importantly, samples are fully contained during analysis, which prevents contamination of instrumentation and minimises exposure of personnel to solvents and toxic chemicals.

Quantitative NMR methods rely on summing the components of a mixture to 100%, or comparing the integrated peak area of an analyte with that of a reference. The later approach requires calibration, which is achieved by addition of an internal, external or electronic standard.[2] Recently we confirmed that the purity of CWAs could be determined by quantitative proton NMR spectroscopy where the CWA and internal standard were dissolved in a deuterated lock solvent.[3] Method accuracy was determined to be better than 1% and was suitable for quantitation of degradation and by-products above 0.2 mM. Given the usefulness of this approach, we became interested in exploiting other nuclei for the quantitation of CWAs. Our interest in the quantitation of nerve agents led us to consider the phosphorous nucleus as it is a common element of the G and V-series agents. Quantitative ^{31}P NMR spectroscopy has been widely used for the analysis of phospholipids and pesticides. The reported methods generally rely upon the addition of a homogeneous reference standard to a solution of analyte.[4-6] An improvement to this quantitation process was developed by Henderson who demonstrated that the purity of CWAs containing the phosphorous nucleus can be determined using segregated reference standards.[7] In his work, a stem coaxial insert was used to separate the reference standard from the analyte in the NMR sample tube (Figure 1). As a key design feature, the stem coaxial insert has a tapered end that extends to the lower section of a conventional NMR sample tube, which sits between the NMR receiver coils during analysis. By segregating the two solutions, the stem coaxial insert prevents the reaction of the reference standard and the analyte, or any other impurities, and prevents contamination of the analyte with reference standards or deuterated lock solvents.

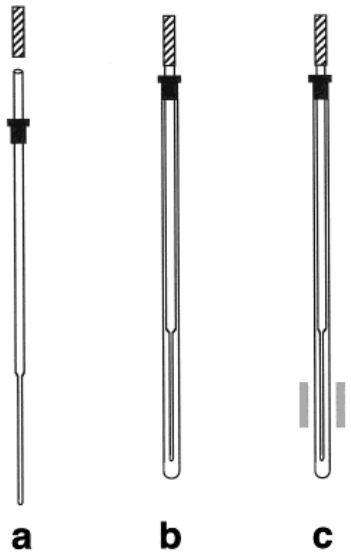

Figure 1. Schematic illustrations of (a) a stem coaxial insert with NMR cap (black) and insert cap (black and white stripes); (b) a capped stem coaxial insert nested in a NMR sample tube; (c) a capped stem coaxial insert with NMR sample tube positioned between the NMR spectrometer receiver coils (grey).[8]

Quantitative NMR strategies generally use a homogeneous solution of a test substance and a reference standard for purity determinations. As the solution is homogeneous, the test substance and reference standard occupy the same sample volume as observed by the NMR receiver coils. In this scenario, the purity of the test substance (P(wt%)) can be determined by Equation 1:

Equation 1

$$P(wt\%) = (\frac{I_T}{I_R})(\frac{N_R}{N_T})(\frac{FW_T}{FW_R})(\frac{m_R}{m_T})(P_R)$$

where I_T and I_R are the integrated peak areas of the test substance and reference solutions respectively; N_R and N_T are the number of spins of the reference and test substance solutions respectively; FW_T and FW_R are the molecular weights (g/mol) of the reference and test substance respectively; m_R and m_T are the measured masses of the refernce and test substance (g) respectively and P_R is the purity of the reference substance.[9] Stem coaxial inserts prevent the reference standard and test substance from occupying the same sample volume, thus quantitation requires an approach that accounts for the differing relative sample volumes of the reference standard and test substance. Henderson showed that when the test and reference substances contain an equal number of spins, the molar concentration of a test substance can be determined by using the relationship described by Equation 2:

Equation 2

$$C_T = (\frac{I_T}{I_R})(\frac{V_R}{V_T})(\frac{d_R}{FW_R})$$

where I_T and I_R are the integrated peak areas of the test substance and reference solutions respectively; d_R is the density (g/L) of the reference solution; FW_R is the molecular mass (g/mol) of the reference substance; and (V_R/V_T) is the ratio of the relative volumes of the sample tube and the stem coaxial insert as observed by the NMR receiver coils.[7] This relationship can be extended to determine test substance purity (P(wt%)) simply by considering the molecular mass (FW_T) and density (d_T) of the test substance.

Equation 3

$$P(wt\%) = (\frac{I_T}{I_R})(\frac{V_R}{V_T})(\frac{d_R}{FW_R})(\frac{FW_T}{d_T})(100\%)$$

In order to properly implement a quantitative ^{31}P NMR methodology using stem coaxial inserts, there are a number of important considerations which are discussed below.

The Nucleus

^{31}P NMR experiments have only approximately 7% of the sensitivity of ^{1}H NMR experiments but are approximately 40 times more sensitive than typical ^{13}C experiments. The ^{31}P nucleus is the only naturally occurring isotope of phosphorous and the corresponding spectra are generally referenced to H_3PO_4 at 0.0 ppm.

The Reference Standard

For precise and accurate quantitation, the reference standard must have a known purity and at least one resolved peak in the NMR spectrum. Ideal reference standards are non-volatile, non-hygroscopic and have a limited number of peaks in an NMR spectrum.

Relaxation and Pulse Parameters

During acquisition of qNMR data, a long interpulse delay is required to ensure the complete spin relaxation prior to application of the next RF pulse. Relaxation rates for phosphorous in small organic molecules are not as widely reported as for protons. Whilst full relaxation for protons usually requires less than 60 s, the phosphorus nucleus may require a longer delay to account for relaxation mechanisms significantly influenced by the NOE.[7] Interpulse delays of approximately 80-90 s are generally adequate to ensure that all ^{31}P spin systems have time to equilibrate.

NMR Data Processing

A qHNMR spectrum should be carefully processed to obtain spectral characteristics suitable for quantitation. Crucial characteristics include flat baseline, sharp and phased peaks, and an absence of spectral artefacts. In order to achieve these objectives, the raw FID should be multiplied by an exponential window function with a line-broadening factor prior to Fourier transformation. The chemical shift scale is referenced to the reference standard and then the spectrum is phased and baseline corrected prior to integration.

2. Results and Discussion

As an extension of our programme dealing with purity determinations by NMR spectroscopy, we set out to develop a quantitative ^{31}P NMR spectroscopy procedure for determining the purity of CWAs containing the phosphorous nucleus. This report outlines the development of a quantitative NMR method that utilises stem coaxial inserts to introduce a reference standard to the test substance without mixing of the solutions. This document outlines the evaluation of precision and accuracy but does not include a complete method validation describing user-to-user effects in NMR spectroscopy as this topic has been dealt with in detail elsewhere.[9] It was decided that although the method would ultimately be applied to the analysis of G-series and V-series agents, this study would focus on determining the purity of the V-series nerve agent VX.

2.1 Experimental

2.1.1 Materials

Triethyl phosphate (99.8%, Sigma), triphenyl phosphate (99%, Sigma) and methylphosphonic acid (98%, Sigma) were used in the development of this method. All solutions are in chloroform-d_1 (D 99.8%, CIL) unless specified otherwise.

2.1.2 Procedures

A Sartorius CP2245 balance was used for weighing neat CWAs and a Sartorius ME5 analytical scale (microbalance) was used for weighing all other chemicals. Solutions were prepared in Class A volumetric glassware that had been thoroughly rinsed with distilled water and heated at 200^{o}C overnight to assist in removal of phosphorous. ^{31}P NMR spectra were acquired on a Bruker Avance Ultrashield 500 MHz spectrometer at 202.46 MHz with a 5 mm BBI Z-GRD probe using Topspin software (V2.1). NMR tubes were purchased from Novachem (Australia). Table 1 outlines the parameters used for data acquisition.

Table 1. Acquisition and processing parameters for quantitative ^{31}P NMR

Parameter	Value
Spin rotation	0 Hz
Measurement temperature	25 ºC
Pulse Angle	90º
Preacquisition delay	6.5 µs
Acquisition time	0.81 s
Relaxation delay	84 s
Number of scans	32
Sweep width	200 ppm
FID points	64k
Line broadening	5 Hz
Frequency of excitation	23 ppm

Raw FIDs were multiplied by an exponential window function with a line-broadening factor of 5 Hz and Fourier transformed to give frequency domain spectra. The phase and baseline parameters were adjusted manually. Peak integration was extended symmetrically from the peak apex and terminated prior to reaching the ^{13}C satellites, which may be observed in $^{31}P\{^{1}H\}$ spectra with high S/N ratios.

2.2 Method Evaluation

This section outlines the evaluation of accuracy and also presents comparison data for proton-coupled and proton-decoupled phosphorous spectra. All spectra were acquired with an interpulse delay of 84 s as described by Henderson.[7]

2.2.1 Determination of Stem Coaxial Insert Volumes Relative to NMR Tubes

The accurate determination of coaxial insert volumes is central to the quantitation process as the ratio of reference substance volume to test substance volume (V_R/V_T) is required for purity calculations using Equation 3. The value of V_R/V_T is constant for a stem coaxial insert and its matched NMR sample tube and is required to be determined prior to conducting purity determinations. The volume of two stem coaxial inserts was determined by analysing two aqueous solutions of MPA, each with identical MPA concentration but different hydrogen ion concentrations.[7] The preparation of these solutions is described in Appendix A.1. The volumes were determined by placing an alkaline MPA solution (pH 10.5) in the stem coaxial insert and an acidic MPA solution (pH 1.6) in the NMR sample tube and acquiring spectra under quantitation conditions at 25 ºC. The solutions were then swapped, and data was acquired under the same conditions. The protonated and deprotonated species of MPA in D_2O were observed to resonate at 30.5 ppm and 21.0 ppm, respectively. Given the concentration of the two MPA solutions were identical, the relative integrated peak area represents the volume of the stem coaxial inserts relative to the matched NMR sample tubes (assigned a volume of 1.000). In each case, the results obtained through use of the acidic and alkaline solution are in agreement, with no

statistically significant differences detected. The ratio of V_R/V_T was thus determined to be 0.1083 and 0.1091 for insert 1 and 2, respectively.

Table 2

Insert solution[a]	Insert 1 Volume[b]	Insert 2 Volume[b]
alkaline MPA	0.1078	0.1105
	0.1078	0.1094
	0.1081	0.1099
acidic MPA	0.1091	0.1048
	0.1091	0.1100
	0.1079	0.1073
mean	**0.1083**	**0.1091**
RSD	0.55	2.0

[a]alkaline MPA (pH 10.5) and acidic MPA (pH 1.6); [b]NMR tube assigned a relative volume of 1.0000

2.2.2 Comparison of Proton-Coupled (^{31}P) and Proton-Decoupled ($^{31}P\{^1H\}$) Phosphorous NMR Spectra

Proton-coupled ^{31}P spectra are often used when quantitation of a compound containing phosphorous is required. However, the proton-coupled ^{31}P spectra are more complex than the corresponding decoupled spectra and increase the likelihood of peak overlap in multi-component or complex samples. The inverse-gated $^{31}P\{^1H\}$ pulse program is an alternative option that provides fully decoupled ^{31}P spectra as well as accurate integration data for quantitation. The inverse-gated pulse program applies low power decoupling during acquisition of the FID and turns it off at other times. This inverse gated approach minimises the impact of NOE enhancements, which are generally observed when decoupling is applied for the entire duty cycle. In order to confirm the applicability of the inverse-gated pulse sequence to a quantitation procedure, we acquired an additional data set for insert 1 (see Section 2.2.1) with the inverse-gated $^{31}P\{^1H\}$ pulse programs using the alkaline MPA solution employed in Section 2.2.1. The difference in integrated peak area between data sets was observed to be less than 1%. Although an increase in RSD was observed for data acquired with the inverse-gated program, the data was suitable for quantitative applications. Comparison data is presented in Table 3 below.

Table 3. Insert volume calculations using proton coupled and decoupled ^{31}P NMR

	Alkaline MPA[a]	Alkaline MPA[b]
	0.1078	0.1066
	0.1078	0.1059
	0.1081	0.1085
mean	**0.1079**	**0.1070**
RSD	0.1605	1.2573

[a]Determined using ^{31}P NMR; [b]determined using inverse-gated $^{31}P\{^{1}H\}$ NMR; sample tube assigned a relative volume of 1.0000

Inverse-gated proton decoupled spectra yield improved S/N ratios compared to proton coupled spectra, largely due to a consolidation of peak area. For example, a S/N improvement of approximately 30% was observed by switching from fully-coupled to inverse gated-decoupled acquisition for the analysis of a mixture of TEP and TPP in $CDCl_3$ (Figure 2). These improvements facilitate significant reductions in the acquisition time required for the detection and quantitation of low level components containing phosphorous.

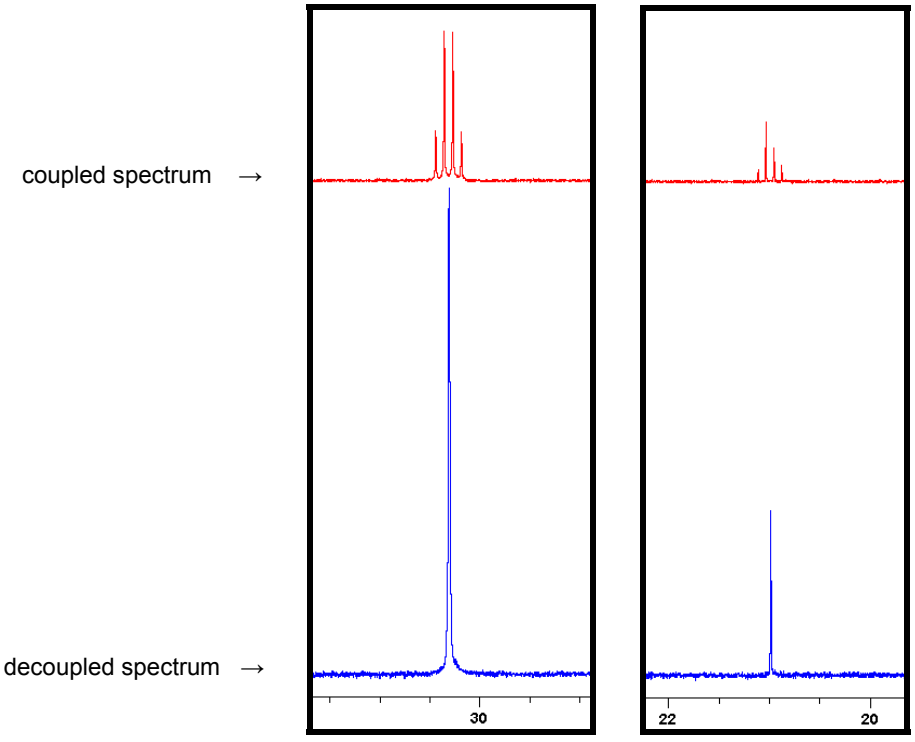

Figure 2. Comparison of ^{1}H coupled (top) and ^{1}H inverse gated decoupled (bottom) ^{31}P NMR spectra (scale is ppm). In this case, the signal-to-noise is enhanced by 30% for the inverse gated spectrum.

2.2.3 Accuracy

Accuracy is a combination of the bias and precision of a method and describes the closeness of a measured value and a true value, as described by Equation 4:

Equation 4

$$accuracy = \sqrt{p^2 + b^2}$$

where p is precision (RSD) and b is bias (difference between the measured and expected values). In order to estimate method accuracy, a solution of TPP with TEP reference standard was analysed at 25 °C using the standard quantitative inverse gated $^{31}P\{^1H\}$ NMR pulse parameters. Under these conditions, TEP and TPP were observed to resonate at -1 ppm and -17 ppm, respectively (see A.2.). The purity of TPP was calculated according to Eq. 3 and is given in Table 4 below. The accuracy of the procedure was determined to be 1.1% based on precision and bias values of 0.7% and 0.8%, respectively.

Table 4

TPP Concentrations.[a] Determined by Quantitative $^{31}P\{^1H\}$ NMR Spectroscopy Using TEP Reference Standard at 25 ºC.

	replicate	insert	calculated purity (wt%)
	1	1	96.9
	2	1	98.9
	3	1	98.3
	4	1	98.7
	5	1	98.4
	6	1	97.8
	7	1	98.4
mean			**98.2**
RSD			0.7

[a]TPP solution prepared at 79.80 mM in $CDCl_3$; expected TPP purity ≥99.0%

2.3 Determination of VX Purity

The toxicity of VX is sufficiently high that handling and manipulation should be minimised. Thus, only one solution of VX (89.43 mM in $CDCl_3$ if VX is 100% pure) was prepared for this work. A 500 µL aliquot of the VX solution was added to NMR tube 1 and 50 µL of TEP solution (347.1 mM) was added to the stem coaxial insert as the reference standard. Insert 1 was then carefully nested within the NMR tube. The assembly was placed in the NMR spectrometer and four data sets were acquired using the quantitative NMR parameters described in Section 2.1.2. The process was then repeated using NMR

tube 2 and stem coaxial insert 2. The eight individual data sets were processed and the reference standard peak and VX peak were carefully integrated (See Supplementary Information Section A.3.). VX purity was calculated according to Eq. 3 and is reported as the mean purity of eight replicates with a 95% confidence interval (mean ± 1.96 standard deviations). As presented in Table 5, VX purity was determined to be 94.1 ± 0.8% in good agreement with a value of 95.4 ± 1.4%, which we determined previously using a quantitative ^{1}H NMR protocol.[3]

Table 5.

VX Purity.[a] Determined by Quantitative $^{31}P\{^{1}H\}$ NMR Spectroscopy Using TEP Reference Standard at 25 ºC.

	replicate	insert	purity (wt%)
	1	1	93.9
	2	1	93.7
	3	1	93.7
	4	1	94.1
	5	2	94.2
	6	2	93.7
	7	2	94.5
	8	2	94.6
mean			**94.1**
RSD			0.4

[a]89.43 mM solution in $CDCl_3$

3. Conclusion

This report outlines the development of an inverse-gated $^{31}P\{^{1}H\}$ pulse program for applications in quantitative NMR spectroscopy. Glass stem coaxial inserts were used to physically separate the reference standard and the analyte. Using certified NMR standards, method accuracy was determined to be 1.1% based on precision and bias values of 0.7% and 0.8%, respectively. The method was applied to determining the purity of VX and was found to be in good agreement with the value obtained previously using quantitative ^{1}H NMR spectroscopy. The primary benefits of this quantitative NMR method are the non-destructive analysis of samples, full containment of samples during analysis, no sample contamination during analysis, and reduced consumption of solvents and consumables. In addition, the operational simplicity of this method permits qualitative and quantitative information to be rapidly gleaned from a single sample with minimal manipulation.

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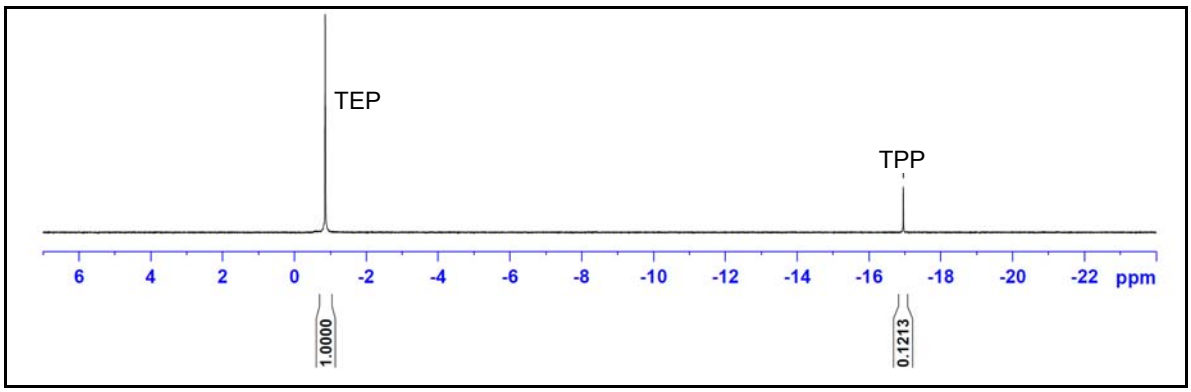
Appendix A: Supplementary Information

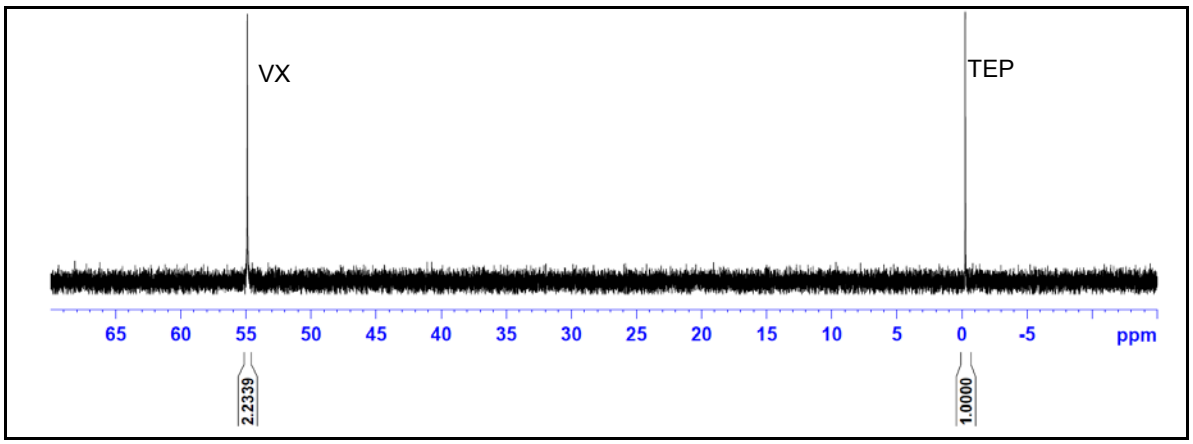
A.1 Preparation of Acidic and Alkaline MPA solutions for Volume Determinations

A stock solution of MPA was prepared by adding MPA (8.4974 g, 88.50 mmol) to 100 mL of distilled water and mixing to homogeneity. The acidic MPA solution was prepared by adding a 25 mL aliquot of the stock solution to 10 mL of deuterated water and diluting to 50 mL with distilled water. The pH of the final acidic solution was 1.6. The alkaline solution was prepared by adding 6 mL of 25% $NaOH_{(aq)}$ solution to a 25 mL aliquot of the stock solution prior to dilution to 50 mL with distilled water. The pH of the final alkaline solution was 10.5.

A.2 Example TPP Spectrum with TEP Reference Standard



A.3 Example VX Spectrum with TEP Reference Standard



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Nuclear Magnetic Resonance Spectroscopy; Phosphorous; Chemical Warfare Agent

19. ABSTRACT

This report outlines the development of an inverse-gated phosphorous nuclear magnetic resonance (NMR) spectroscopy method for determining the purity of chemical warfare agents using reference standards contained within a glass stem coaxial insert. The stem coaxial insert prevents any possible reaction of the reference standard and analyte by segregating the two solutions. The method was determined to be accurate to 1.1% and was employed to determine the purity of the V-series nerve agent VX using proton-decoupled pulse parameters. The method was found to be equal to or better than modern chromatographic techniques in terms of precision, accuracy and analysis time. The operational simplicity of this method enables both quantitative and qualitative information to be rapidly gleaned from a single sample.