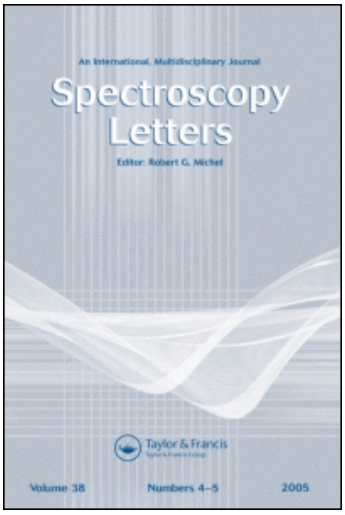

Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

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To cite this Article McGarvey, David J. , Stuff, John R. , Williams, Barry R. and Durst, H. Dupont(2000) 'Vapor-Phase Infrared Spectral Study of Analogs of the Nerve Agent Sarin', Spectroscopy Letters, 33: 6, 795 — 819
To link to this Article: DOI: 10.1080/00387010009350158
URL: http://dx.doi.org/10.1080/00387010009350158

SPECTROSCOPY LETTERS, 33(6), 795–819 (2000)

VAPOR-PHASE INFRARED SPECTRAL STUDY OF ANALOGS OF THE NERVE AGENT SARIN

Keywords: FTIR, infrared, chemical warfare agents, Sarin, spectra, gas chromatography

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ABSTRACT

Analogs of the chemical warfare agent Sarin were synthesized using a microscale technique and analyzed with a gas chromatograph equipped with a light pipe Fourier Transform infrared spectrometer. Produced as byproducts of the chemical warfare agents, a variety of related organophosphonate byproducts were often also observed. Similarities and differences among the spectra within the classes are noted, including some distinguishing characteristics of the infrared spectra not previously cited in the literature.

INTRODUCTION

Laboratory protocols for the Chemical Weapons Treaty (CWT), which went into effect in April 1997, specify the use of at least two independent techniques to confirm the presence of

relevant compounds in samples. In this case, *independent* has been defined as different spectrometric techniques, the use of chromatographic columns with different phases, or one spectrometric method and retention index monitoring.

Research in the past on detection and identification of chemical warfare agents (CWA) focused primarily on a relatively small number of compounds involved historically in large-scale production and stockpiling. Schedule 1 of the Chemical Weapons Treaty, however, addresses the production not only of these "standard" agents, but also the so-called "designer agents," which differ slightly in their chemical structures."[1] Sarin (O-isopropyl methylphosphonofluoridate, CAS RN 107-44-8), with the chemical formula $CH_3PF(O)CH(CH_3)_2$, is one such example of a standard chemical agent for which many possible homologues can be obtained by varying the alkyl side chains. Under the definition of the treaty, an organic ester of phosphonofluoridic acid is restricted if its formula can be described by $R^1P(O)(F)OR^2$, where R^1 is methyl, ethyl, n-propyl, or isopropyl, and R^2 is any alkyl or cycloalkyl with a carbon number ≤ 10. Gas chromatography with mass spectrometry (GC-MS) is most commonly used to identify these compounds. Large gaps currently exist, however, in the available libraries of mass spectra of the hundreds of potential compounds controlled under the Treaty.[2] Additionally, it can be difficult to obtain definitive structural information on the basis of the mass spectra alone due to their similarities.

For the above reasons, the combination of gas chromatography with Fourier Transform infrared spectroscopy (GC-FTIR) has been used by a number of laboratories to assist in the identification of the schedule compounds.[3] The available computerized infrared spectral libraries are more limited in scope than mass spectral databases. L. C. Thomas is well known for his work with phosphorous compounds, resulting in an extensive reference with correlations for many different functional groups.[4] Recently, M. T. Söderström, et al., published several studies of the IR spectra of nerve agents, including 24 methyl- and ethylphosphonofluoridates.[5,6] The analyses were made with a direct deposition FTIR spectrometer, and the spectra were in the condensed phase. Spectral data for the other alkylphosphonofluoridates series, which include the n-propyl

and isopropylphosphonofluoridates, are noticeably lacking. Vapor phase infrared spectral data for the organophosphorous nerve agents are even more limited.

The study by this laboratory was performed using a light pipe spectrometer. In the light pipe technique, the vaporized sample components, after separation in the GC column, are passed through a length of gold coated glass, quartz or steel tubing, and the spectra are collected dynamically.[7] Because the compounds are introduced into the sample compartment in a gaseous state, the resulting spectra are relatively free from matrix effects such as hydrogen bonding or dipolar interactions. The widths and shapes of absorption bands in vapor-phase spectra can be quite different from those in the condensed-phase, and band positions can shift significantly.[7,8] R.A. Nyquist cites frequency differences as large as 400 cm^{-1} where bands are strongly affected by intermolecular hydrogen bonding between molecules or between solute and solvent.[9] Although data from compounds in a solid or liquid state can be used for making generalized correlations, vapor phase data should be considered more reliable for assigning a structure to an unknown.

Recently, a simple, rapid method of synthesizing large numbers of analogs of Sarin (GB, isopropyl methylphosphonofluoridate, CAS RN 107-44-8) was demonstrated.[10] It involved the addition of milligram amounts of an alcohol with the desired O-alkyl functionality to 1 ml of a solution of $CH_3P(O)F_2$ (methylphosphonic difluoride, CAS RN 676-99-3) at a concentration of 1-2 mg/mL in dichloromethane in a standard GC autosampler vial. Resulting in a maximum final concentration of the target compound of 2000 μg/mL, below the level at which the most stringent regulatory and safety requirements begin to apply, the solutions were relatively easy to handle. (Researchers are cautioned, however, that, with LD_{50}'s as low as a few milligrams, no chemical warfare agent is benign. For examples of MSDS's for some nerve agents, refer to http://in1.apgea.army.mil/RDA/ecbc/services/msds/.) Rather than using standard distillation techniques to purify the reaction products, the solutions were analyzed in-situ, relying upon the capillary column of the gas chromatograph to separate the components for analysis.

Procedures used for preparing the analogs during the prior work had to be modified to include the other members of the series. Among the alkylphosphonic difluorides, only the methyl can be obtained locally, and none of the compounds are available commercially. For this reason, a process was developed using the corresponding alkylphosphonic dichlorides as starting materials, which were reacted with sodium fluoride in an intermediate step to form the required difluorides.

EXPERIMENTAL SECTION

Chemicals

Table 1 lists the alcohols that were available to prepare the target compounds. All alcohols were commercially available and, unless otherwise noted, were obtained from Aldrich Chemical Company. Methyl- (CAS RN 676-97-1), ethyl- (CAS RN 1066-50-8), and n-propylphosphonic dichloride (CAS RN 4708-04-7) were obtained from Aldrich Chemical Company. Isopropylphosphonic dichloride (CAS RN 1498-46-0) was obtained from Digital Specialty Chemicals, Inc, Nashua, NH. HPLC grade dichloromethane (CAS RN 75-09-2) and reagent grade sodium fluoride (CAS RN 7681-49-4) were purchased from Aldrich Chemical Company.

Equipment and Chromatographic Conditions

A Hewlett-Packard (HP) Model 5890 Series II gas chromatograph was interfaced in series to a BioRad Model 5969B Fourier transform infrared spectrometer and a HP Model 5971A mass selective detector. The gas chromatograph was fitted with a 25 m x 0.32 mm I.D. HP-5 (cross-linked 5% phenyl methyl silicone) fused-silica capillary column with a film thickness of 0.25 μm.

Helium was used as a carrier gas at a linear velocity of 32 cm/s with electronic pressure programming. During the earlier phases of the project, the GC was outfitted with a standard split/splitless injector, with the injector port temperature set to a constant temperature of 250°C.

TABLE 1

Alcohols Available to Prepare Sarin Analogs

	Alcohol	CAS #
C1	methanol	67-56-1
C2	ethanol	64-17-5
C3	1-propanol	71-23-8
	2-propanol	67-63-0
C4	1-butanol	71-36-3
	2-butanol	15892-23-6
	2-methyl-1-propanol	78-83-1
	2-methyl-2-propanol	75-65-0
	cyclopropane methanol	2516-33-8
	cyclobutanol	2919-23-5
C5	1-pentanol	71-41-0
	2-pentanol	6032-29-7
	3-pentanol	584-02-1
	2-methyl-1-butanol	137-32-6
	3-methyl-1-butanol	123-51-3
	2-methyl-2-butanol	75-85-4
	3-methyl-2-butanol	598-75-4
	1-cyclopropylethanol [A]	765-42-4
	2-cyclopropylethanol [B]	2566-44-1
	cyclobutanemethanol	4415-82-1
	cyclopentanol	96-41-3
	1-methylcyclopropanemethanol	2746-14-7
	2-methylcyclopropanemethanol	6077-72-1
C6	1-hexanol	111-27-3
	2-hexanol	626-93-7
	3-hexanol	623-37-0
	2-ethyl-1-butanol	97-95-0
	2,3-dimethyl butanol [C]	1259-08-2
	2-methyl-1-pentanol	105-30-6
	3-methyl-1-pentanol	589-35-3
	4-methyl-1-pentanol	626-89-1
	4-methyl-2-pentanol	108-11-2
	2-methyl-2-pentanol	590-36-3
	3-methyl-2-pentanol	565-60-6
	2-methyl-3-pentanol	565-67-3
	cyclobutylethanol [C]	7515-29-9
	cyclopentanemethanol	3637-61-4
	trans-2-methylcyclopentanol	21544-04-1
	3-methylcyclopentanol	18729-48-1
C7	1-heptanol	111-70-6
	2-heptanol	543-49-7
	3-heptanol	589-82-2
C7	4-heptanol [A]	589-55-9
	4,4-dimethyl-2-pentanol	6144-93-0
	3-ethyl-2-pentanol [C]	609-27-8
	3-ethyl-3-pentanol	597-49-9
	2-methyl-2-hexanol	625-23-0
	5-methyl-2-hexanol	627-59-8
	5-methyl-3-hexanol [C]	623-55-2
	2-methyl-3-hexanol	617-29-8
	cis-2-methylcyclohexanol	7443-70-1
	trans-2-methylcyclohexanol	7443-52-9
	3-methylcyclohexanol	591-23-1
	cis-4-methylcyclohexanol	7731-28-4
	trans-4-methylcyclohexanol	7731-29-5
	cyclohexylmethanol	100-49-2
	1-cyclopentylethanol [C]	766-00-7
C8	dicyclopropylcarbinol [B]	14300-33-5
	1-octanol	111-87-5
	2-octanol	4128-31-8
	Norbornanemethanol	5240-72-2
	2-propyl-1-pentanol	58175-57-8
	2,5-dimethyl-3-hexanol [B]	19550-07-3
	2-ethyl-1-hexanol	104-76-7
	4-ethyl-3-hexanol [C]	19780-44-0
	2-methyl-4-heptanol [C]	21570-35-4
	4-methyl-3-heptanol	14979-39-6
	6-methyl-2-heptanol	4730-22-7
	4-ethylcyclohexanol	4534-74-1
	2,3-dimethylcyclohexanol	1502-24-5
	3-cyclopentyl-1-propanol	767-05-5
	1-cyclohexylethanol	1193-81-3
	2-cyclohexylethanol	4442-79-9
	cycloheptanemethanol	4448-75-3
C9	1-nonanol	143-08-8
	2-nonanol	628-99-9
	3-cyclohexyl-1-propanol	1124-63-6
C10	decyl alcohol	112-30-1
	2-decanol	1120-06-5
	4-decanol	2051-31-2
	2-tert butylcyclohexanol	13491-79-7
	4-tert butylcyclohexanol	98-52-2
	4-cyclohexyl-1-butanol	4441-57-0

A Chemical obtained from Fluka Chemie AG, CH-9470, Buchs.

B Chemical obtained from Lancaster Synthesis, Inc., Windham, NH.

C Chemical obtained from Chemsampco, Gray Court, SC.

Subsequently, the GC was outfitted with a Gerstel® high-volume injector system. This system combines cryogenic cooling with rapid temperature programming, venting solvent, and allowing introduction of large sample volumes, up to several hundred microliters, while maintaining analyte focusing in the column. The Gerstel injector was temperature programmed from 15-250°C in splitless mode, with injection volumes ranging from 1-6 μL.

The oven temperature was set initially at 35°C, ramped from 35 to 100°C at 40°C/min., to 200°C at 10°C/min., then to 280°C at 20°C/min. The infrared spectrometer transfer line was maintained at 300°C and the infrared light pipe at 280°C. The infrared scan rate 1.5 scans/sec., with 4 scans co-added per final spectrum, at 8 wavenumber (cm^{-1}) resolution from 4000-550 cm^{-1}.

The mass spectrum of each sample component was also collected in order to verify compound identities and for addition to a database of CW compounds for the National Institute of Standards and Technology. The design of the system, with a 1-meter length of capillary column between the FTIR spectrometer and the MSD, gives a delay of about 15 seconds between the time the component peaks appear in the infrared and their elution in the mass spectrometer. The transfer line of the mass selective detector was set to 280°C, and spectra were acquired from 40-400 AMU.

Preparation of Analogs

Very simple equipment and procedures were used to prepare the target compounds. Because the goal was not to maximize the yield of the final product, but rather to obtain a sufficient concentration to give useable spectra, volumes, and masses of starting materials, as well as reaction times and temperatures, were not critical.

Stock solutions of the alkylphosphonic dichlorides were prepared by adding two drops of each to 5 mL of dichloromethane in separate screw cap vials. Because the alcohols were used a minimum of four times to prepare the respective analog from each dichloride, solutions of these were also prepared by adding several drops of to 5 mL of dichloromethane. An excess of sodium

fluoride (approximately 10 mg) was added to a 2 mL crimp top GC autosampler vial. To the vial were then added 150 μL of the appropriate alcohol solution, followed by 50 μL of the desired alkylphosphonic dichloride solution, along with an additional 300 μL of dichloromethane. The vial was then capped and placed in a dry heating block to react at 55°C until analysis showed that the reaction to form the G-analog was sufficiently complete to provide good spectra.

The products were often a mixture of the target analog, sometimes with a small amount of the phosphonochloridate, and usually with varying amounts of the diester, and the diphosphonate (pyrophosphonate), which are easily separated chromatographically from the main product. In analysis of Treaty-related samples, it is, in fact, useful to have data for these other compounds, since they are considered precursors and are listed in Schedule 2 of the Treaty. The time necessary to produce a useable product varied from, as little as 6 hours in the case of the reaction of the primary alcohols with the methylphosphonic dichloride to, as long as 48 hours for the more sterically hindered products.

RESULTS AND DISCUSSION

Types of Compounds

Esters of methyl- and ethylphosphonofluoridic acid represent the majority of compounds prepared to date, including nearly all of the alcohols in Table 1. The smallest group of compounds analyzed are represented by the isopropylphosphonofluoridate esters. Even in this category, however, spectra of 24 compounds have been obtained. These represent a cross section of all of the chemical compounds specified in Schedule 1a(1) of the Chemical Treaty. It has thus been possible to correlate spectral features to molecular structure in some novel ways. Equally as important, since nearly all previous studies have been performed with the compounds in the condensed-phase, was the opportunity to compare the vapor-phase spectra to the former. In addition to the expected shifts in frequencies of bands, at least one spectral feature, usually cited as occurring in compounds with phosphorous bonded directly to ethyl, could not be observed in this study.

Phosphoryl Stretch Mode

Pentavalent phosphorous compounds containing a P=O are normally characterized by one or more prominent bands in the general region 1100-1400 cm^{-1}. It has long been known that the position of this band varies according to the electronegativity of the substituents in the molecule.[11] Thomas and Chittenden developed an equation enabling the prediction of the position of the phosphoryl stretching mode vibration.[12] Their equation states that $\upsilon(P=O) = 930+40*\Sigma\pi$, where π is a factor representing the electronegativity of the functional group. The equation generally predicts the phosphoryl stretching frequency within ± 12 cm^{-1} for compounds in the condensed-phase, although not accounting for rotational isomers or steric effects upon the bond angles around the phosphorous atom.[13]

In an attempt to account for the differences in the phosphoryl stretching frequencies in the vapor-phase, as much as 50 cm^{-1} higher than in the condensed-phase, Nyquist modified the π factors in the Thomas equation rather than the 930 cm^{-1} constant. Although recognizing that electronegativity values should not differ between the two states, this step seemed to fit the more limited vapor-phase data available. A comparison between the π values from Thomas and Nyquist is provided in Table 2. The latter values predict average phosphoryl frequencies of 1309 cm^{-1} for the alkylphoshonofluoridic acid esters and 1267 cm^{-1} for the corresponding diesters. It can be noted in the table that the Thomas PI values are further refined for alkyl and alkoxy substituents on phosphorous, with a reduction from CH_3 to CH_2 and a further reduction in CH. If a similar change in the phosphoryl stretching frequency with changes in the character of the R and OR groups were to hold true in the vapor-phase, this effect could aid in the elucidation of the structure of the molecule.

At least for the P-R functionality, the variation in the P=O band was not nearly so clear. Changes of a magnitude similar to that noted by Thomas would result in average values for the ethyl-and propylphosphonofluoridate esters approximately 5 cm^{-1} lower than for the methyl series and 15 cm^{-1} lower in the case of the isopropyl series. A similar change should also be

TABLE 2

Phosphoryl Stretching Frequencies for Selected Alkylphosphonofluoridic Acid Esters

OR	R			
	Methyl	Ethyl	n-Propyl	Isopropyl
Methyl	1324	1317	1313	1311
Ethyl	1315	1313	1308	1309
1-Propyl	1313	1313	1307	1309
2-Propyl	1308	1311	1305	1307
1-Pentyl	1308	1313	1307	1309
2-Pentyl	1307	1310	1303	1306
1-Heptyl	1306	1313	1306	1308
2-Heptyl	1304	1310	1303	1306
1-Nonyl	1306	1313	1306	1308
2-Nonyl	1303	1310	1303	1306
4-Methylcyclohexyl	1302	1310	1303	1306

A For CH_3, CH_2, and CH, respectively
B For OCH_3, OCH_2, and OCH, respectively

noted for the phosphonate diesters. In fact, the average phosphoryl frequency for more than 40 ethylphosphonofluoridates studied, at 1311 cm^{-1}, was actually higher than that observed for the methyl series, at 1305 cm^{-1}. Data for the propyl series, with a total of 36 compounds studied, resulted in an average frequency of 1305 cm^{-1}, identical to that of methyl compounds. In fact, at 1307 cm^{-1}, the average for 24 compounds in the isopropyl series resulted in a number higher than that seen for the methyl and n-propyl compounds. It should be noted that the determination of the position of this band in the case of the P-methyl analogs is affected by its proximity to another medium intensity band arising from the symmetric deformation of the methyl.[14] According to Thomas, the frequency range for this band in the condensed-phase spectra of the Sarin analogs is 1312-1328 cm^{-1}. For the compounds in this study, the observed range was 1310-1323 cm^{-1}, although at the 8 cm^{-1} resolution, the band was not well resolved from the phosphoryl stretching frequency. Because it appears on the shoulder of the P=O, the P-methyl band was often nearly as intense as the phosphoryl band.

In discussing the phosphonate diesters, Nyquist cites a range for phosphoryl in O,O-dialkyl alkylphosphonates of 1265-1291 cm^{-1}. The upper end of that range is inhabited by

compounds with phosphorous bonded to more polar groups such as chloromethyl, cynanomethyl, and vinyl. The data do not include P-ethyl, P-propyl, or P-isopropyl.

Data for a more limited number of the diesters than the fluoridates was available from this study, since as previously noted, these were obtained only as byproducts of the primary reaction. As in the case of the phosphonofluoridates, the systematic reduction of phosphoryl frequencies between members of the series cited by Thomas was not observed. With at least 10 members of each species, the average frequency for the methylphosphonate diesters was 1267 cm^{-1}, while the ethylphosphonates were seen at 1265 cm^{-1}, and the n-propyl compounds at 1267 cm^{-1}. The only dramatic differences observed were for the isopropylphosphonates, at an average of 1251 cm^{-1}. Although the latter number is based upon the average of only 4 compounds, all of the members of the other three types lie within the relatively narrow range of 1261-1268 cm^{-1}.

The limited data available appears to indicate, in the case of a phosphonate diester, that a vapor-phase phosphoryl frequency significantly below 1260 cm^{-1} is probably indicative of a dialkyl isopropylphosphonate species. For a laboratory doing analysis of Treaty related samples, where additional information is usually available from gas chromatography-mass spectrometry, this fact may prove most useful for its apparent ability to distinguish between the n-propyl and isopropyl forms of two phosphonate diesters, which produce nearly identical mass spectra. With the data from this study, therefore, the range of P=O in $(RO)_2P(O)R$ can apparently be extended from 1251-1291 cm^{-1}.

Data from the diphosphonates was available for a number of compounds with methyl and ethyl directly bonded to phosphorous. These compounds, however, showed an effect similar to that of the corresponding phosphonofluoridates and the diesters. Average phosphoryl stretching frequency for the 13 dimethyldiphosphonate esters was 1280 cm^{-1} and 1284 cm^{-1} for the 17 diethyldiphosphonates. Using the Thomas π value for OP^{V} with the Nyquist values for R and OR predicts a phosphoryl valence frequency of 1279 cm^{-1}, a number close enough to the observed data to be useful for diagnostic purposes. Only 3 dipropyldiphosphonate compounds were obtained. These showed bands between 1277 and 1279 cm^{-1}.

In contrast to P-R, the effect of the P-O-R substituent on the phosphoryl valence frequency for all the types of compounds was more similar to that noted by Thomas. A difference of approximately 7% in PI values between methyl and secondary alkoxy esters would be expected to result in a reduction in frequency in the vapor-phase of about 8 cm^{-1}, with a smaller shift in going from methyl to ethyl and higher n-alkyl esters. In each case, the actual shift in values observed was in the expected direction and approximately the right magnitude.

The effect upon the phosphoryl frequency from chlorine bonded to phosphorous could also be studied. The majority of compounds observed were esters of alkylphosphonochloridic acid. Structurally and chemically they are similar to the phosphonofluoridates, although only two, isopropyl methylphosphonochloridate (chlorsosarin, CAS RN 1445-76-7) and 1,2,2-trimethylpropyl methylphosphonochloridate (chlorosoman, CAS RN 7040-57-5) are Schedule 1 compounds. Nevertheless, the data are potentially useful because of the possibility of the occurrence of them as byproducts or intermediates in the synthesis of the phosphonofluoridates. A number of these compounds were obtained during the earlier part of this work as a result of the direct reaction of methylphosphonic dichloride with the alcohol, while the ethylphosphonochloridates, propylphosphonochloridates, and isopropylphosphonochloridates were seen as reaction byproducts. Using only the Nyquist π factors for the functional groups yields a predicted band at 1279 cm^{-1}, while a prediction made using Thomas' value for Cl and Nyquist's factors for OR and R gives a 1283 cm^{-1} location. Because the actual data in this study showed an average frequency of 1286 cm^{-1} for the methyl-, 1289 cm^{-1} for the ethyl-, 1283 cm^{-1} for the propyl-, and 1286 cm^{-1} for the isopropyl- compounds, the π factor for Cl provided by Thomas appears to better predict the actual position of the phosphoryl bands in these compounds. Furthermore, Thomas' factor for Cl comes closer, at 1283 cm^{-1}, than Nyquist's, at 1279 cm^{-1}, to predicting the observed phosphoryl band in the alkylphosphonic dichlorides, which range from 1294-1299 cm^{-1}. For $EtOP(O)Cl_2$, however, the phosphoryl is seen at 1311 cm^{-1}, very close to the predicted value of 1314 cm^{-1} if the PI value given by Nyquist is used. The slightly higher factor from Thomas raises the prediction to 1322 cm^{-1}. It does appear, however, that at

TABLE 3

Phosphoryl Stretching Frequencies for Selected Alkylphosphonofluoridic Acid Esters

OR	R			
	Methyl	Ethyl	n-Propyl	Isopropyl
Methyl	1324	1317	1313	1311
Ethyl	1315	1313	1308	1309
1-Propyl	1313	1313	1307	1309
2-Propyl	1308	1311	1305	1307
1-Pentyl	1308	1313	1307	1309
2-Pentyl	1307	1310	1303	1306
1-Heptyl	1306	1313	1306	1308
2-Heptyl	1304	1310	1303	1306
1-Nonyl	1306	1313	1306	1308
2-Nonyl	1303	1310	1303	1306
4-Methylcyclohexyl	1302	1310	1303	1306

TABLE 4

Phosphoryl Frequencies (cm^{-1}) for ROPR(O)X

R	X			
	F	Cl	OR	OP^{V}
CH3	1302-1324	1283-1292	1264-1268	1278-1284
Ethyl	1309-1317	1287-1290 (6)	1260-1268	1272-1290
Propyl	1302-1313	1281-1284 (3)	1264-1268	1277-1279 (3)
Isopropyl	1305-1311	1285-1287 (4)	1251-1252 (4)	

Number of compounds (if <10)

least for the groups of compounds studied here, using the Thomas PI factor of 3.4 does give a better overall prediction of the phosphoryl band in the vapor phase. It also gives a good illustration that the equation, at best, yields only an estimate of the position of the band.

Table 3 gives the phosphoryl frequencies for selected alkylphosphonofluoridates. Table 4 summarizes, by functional group, the range of frequencies observed for all of the categories of compounds observed.

P-O-R Modes

Acyclic esters

The presence of a P-O-C group in a molecule is nearly always accompanied by one or more bands in the 1000 cm^{-1} region of the infrared spectrum, and they are often the strongest in

the spectrum.[4,5,15] It has long been recognized that these bands arise from complex stretching modes in the P-O-C bonds and that their position and appearance can provide indications of the nature of the group bonded to the oxygen.[11] Here also, the previously published condensed-phase data can provide a starting point in the interpretation of the spectra, but more detailed correlations require data obtained from compounds in the vapor phase.

Perhaps the most distinctive effect upon the spectrum in the phosphorous-alkoxy region is played by the presence of branching at the carbon adjacent to the oxygen. For noncyclic side chains, for example, the presence of a P-O-CHR_2 lowered the frequency of the strongest band in the phosphonofluoridate by 19-37 cm^{-1} versus an alkyl group with the same carbon number unbranched at the alpha position. The C_3 esters were an exception to this rule. The n-propyl phosphonofluoridates were characterized by a very strong band at 1014-1019 cm^{-1} and a second band, nearly as strong, at 1043-1051 cm^{-1}. The strongest band in the isopropyl esters was seen as 1009-1015 cm^{-1}. As a group, the strongest bands in the esters formed from secondary alcohols were seen in the relatively narrow range from 1003-1015 cm^{-1}. This compares with 950-1018 cm^{-1} cited by Thomas for P-O-CHR_2 in condensed-phase spectra, a range which includes a much wider variety of esters of pentavalent phosphorous than that included in this study.

The strongest bands in the spectra of the methyl alkylphosphonofluoridates were observed at 1055-1060 cm^{-1}, versus 1010-1088 cm^{-1} cited for the overall range of this functionality reported by Thomas. The esters formed from the other primary alcohols, were seen at 1021-1051 cm^{-1}, with the exception of the propyl ester, as previously noted. In the condensed phase, the corresponding bands in compounds with primary alkoxy side chains are seen at 987-1042 cm^{-1}. The ethyl esters have a second strong band at 958-966 cm^{-1}. This is similar to their appearance in the condensed-phase.

For the same alkoxy functionality within the four homologous alkylphosphonofluoridates, a pattern was observed in the effect of the alkyl group directly bonded to the phoshorous upon the frequency of the P-O-C bands. Compared to the methylphosphonofluoridates, for example, the position of the bands in the P-ethyl and P-propyl

TABLE 5

Band Positions for P-O-R in Selected $R^1OP(O)R^2F$

R^1	R^2 methyl	ethyl	n-propyl	isopropyl
methyl	1060	1059	1056	1055
ethyl	1051	1050	1047	1046
propyl	1019	1017	1016	1014
butyl	1037	1031	1034	1032
pentyl	1046	1044	1043	1040
hexyl	1032	1024	1027	1024
heptyl	1036	1028	1032	1029
octyl	1038	1030	1034	1032
nonyl	1039	1031	1035	1032
decyl	1040	1031	1036	1033
2-propyl	1015	1013	1010	1009
2-pentyl	1012	1011	1008	1006
2-heptyl	1009	1009	1005	1003
2-nonyl	1011	1009	1007	1005
2-methylpropyl	1040	1036	1036	1034
2-methylpentyl	1036	1036	1032	1029
2,4,4-trimethylpentyl	1034	1029	1030	1028

compounds averaged approximately 4 cm^{-1} lower, while the average for the P-isopropyl compounds was 6 cm^{-1} lower than the P-methyl analogs. Furthermore, although the differences within the groups were not large, there were few exceptions noted to the general observation that for the same O-R functionality, the band position was highest for P-methyl, and lowest for P-isopropyl. Table 5 lists these characteristic frequencies for 68 compounds.

Esters with cyclic groups

The position of the strongest P-O-C band in alkylphosphonofluoridic acid esters involving cyclic groups not directly bonded to oxygen was similar to that of the primary alkyl esters. Unsubstituted cycloalkanol derivatives with the cyclic group directly bonded to oxygen displayed spectral characteristics in the 1000 cm^{-1} region similar to that of the other secondary esters.

TABLE 6

Primary P-O-C bands in Cyclohexyl and 2- and 4-Methylcyclohexyl Alkylphosphonofluoridates

	P-R			
P-O-R	methyl	ethyl	n-propyl	isopropyl
cyclohexyl	1017	1015	1013	1012
cis-2-methylcyclohexyl	1015	1011	1009	1006
trans-2-methylcyclohexyl	1022	1019	1020	1017
cis-4-methylcyclohexyl	1012	1009	1006	1005
trans-4-methylcyclohexyl	1030	1028	1028	1027

Among the classes of phosphonofluoridates observed, the substituted cyclohexyl derivatives provided the most unexpected results. Although the spectra of this group of compounds have been collected previously, typically they have been obtained using liquid IR cells with the products of mixed *cis* and *trans* isomers. The products of the two forms of these alcohols can differ significantly in their toxicities, however.[16] For this reason, an ability to distinguish between them is important.

During the course of the work in this laboratory, two of the cyclohexanols, 2-methylcyclohexanol and 4-methylcyclohexanol, were obtained in the separate *cis* and *trans* forms, enabling the separate synthesis of the individual isomeric forms of the esters. For each of the two forms of the phosphonofluoridate esters, there were significant differences in the P-O-C region of the IR spectra, with the *cis* forms displaying bands approximately 10-20 cm^{-1} lower than the *trans*. Table 6 lists the frequencies of the main bands of these compounds, along with those of the unsubstituted cyclohexyl products. This effect of a reduction of the P-O-C stretching bands is apparently similar to that observed in some non-phosphorous compounds with C-O functionalities.[17,18] The prior work with non-phosphorous compounds indicated that the change in the C-O stretch depends upon whether the substituent on the ring is axial or equatorial. Substitutions equatorial to the ring plane increase the frequency, while axial groups result in a reduction, consistent with the data observed for the 2- and 4-methylcyclohexyl esters.

TABLE 7

Primary P-O-C Bands in Alkylcyclohexyl Alkylphosphonofluoridates

	P-R			
P-O-R	methyl	ethyl	n-propyl	isopropyl
3-methylcyclohexyl	1013, 1023	1011, 1020	1009, 1020	
4-ethylcyclohexyl	1011, 1031	1005, 1028	1006, 1028	1005, 1026
3,3,5-trimethylcyclohexyl	1011, 1020			
3,3,5,5-tetramethylcyclohexyl	1016			

Note: The frequency of the P-O-C band in the earlier eluting peak is given first

Other subsituted cyclohexanols were available, although not as the purified isomers. Nevertheless, because the phosphorous in the compounds is also chiral, the molecules produced from the alcohols have two chiral centers, resulting in pairs of diastereomers with slight differences in their boiling points, thus allowing their chromatographic separation.[19] With the gas chromatographic column used for this study, compounds with lower boiling points normally elute earlier than similar compounds with higher boiling points. As expected, the phosphorous compounds from 3-methylcyclohexanol did give two chromatographic peaks, with the earlier eluting peak having the lower frequencies in the 1000 cm^{-1} region of the spectrum. In contrast to the 2- and 4-methylcyclohexanols, in which the *cis* isomer, and presumably the resulting phosphonofluoridate, has the lower boiling point, the boiling point of the *trans*-3-methylcyclohexanol is lower than that of the *cis*. It would seem reasonable, therefore, that the *trans* isomer of the phosphorous compounds, in which the methyl substituent is presumably axial, would have the lower frequencies. The products of 4-ethylcyclohexanol and 3,3,5-trimethylcyclohexanol showed similar characteristics, with lower frequencies in the P-O-C region of the spectrum for the earlier eluting peak. As expected, 3,3,5,5-trimethylyclohexyl methylphosphonofluoridate gave only one chromatographic peak, with an apex in the IR spectrum at 1016 cm^{-1}. Data for these additional substituted cyclohexyl compounds is summarized in Table 7.

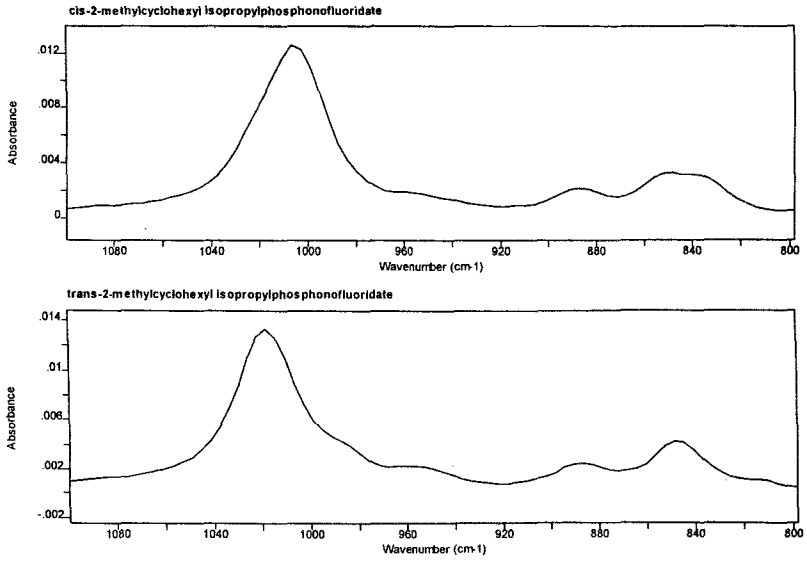
In addition to the strongest band, other weaker spectral features can often be associated with the P-O-C functionality in phosphorous molecules, and, in fact, both the appearance and intensity of the bands in the general region between 840-1050 cm^{-1} in the *cis* and *trans* isomers of the substituted cyclohexyl analogs were different. Although pronounced, the effect was less predictable than in the case of the much stronger primary band. In some cases, the possibility of interaction with the strong P-F stretching band, seen between 840-850 cm^{-1}, could not be excluded. Furthermore, an additional prominent band is seen at around 900 cm^{-1} in the P-methyl compounds that can obscure other bands in that area of the spectrum. Figure 1 shows the region between 800-1100 cm^{-1} for the 2- and 4-methylcyclohexyl derivatives of isopropylphosphonofluoridic acid, highlighting the differences in this spectral region. It is noteworthy that although a number of acyclic derivatives were prepared that give at least two chromatographic peaks, their IR spectra were very similar to one another.

Phosphonate diesters

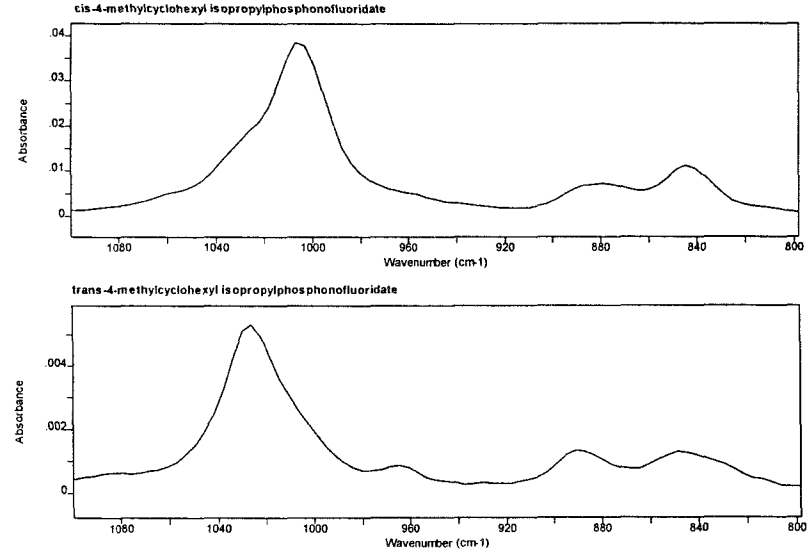
The spectra of the diesters tend to be more complex in the 1000 cm^{-1} region. In general, however, the strongest bands deriving from the P-O-C functionalities in the molecule tend to be 10 to 20 cm^{-1} lower in frequency than in the corresponding phosphonofluoridates.

Phosphorous-Fluorine Modes

The prior study of methylphosphonofluoridates had indicated a vapor-phase range for the P-F stretch of 840-846 cm^{-1}.[10] This is within and narrower than the 833-849 cm^{-1} compiled by Thomas for these compounds. Thomas reports a range of 841-858 cm-1 for the band in the phosphonofluoridates excluding the P-methyl compounds. If these showed a similar narrow range in the vapor-phase, the phoshorous-fluorine band could be useful diagnostically to aid in structure determination. The observed data for the four categories of compounds are in Table 8. The three additional groups of compounds studied showed a combined range of 847-865 cm^{-1}.



cis-2-methylcyclohexyl (upper) and *trans*-2-methylcyclohexyl (lower)



cis-4-methylcyclolhexyl (upper) and *trans*-4-methylcyclohexyl (lower)

FIGURE 1

lR Spectra of the 2- and 4-Methylcyclohexyl Esters of lsopropylphosphonofluoridic Acid in the 1000 cm-1 Region

TABLE 8

Phosphorous-Flourine Stretching Band in RO-P(O)R'F

R'			
methyl	ethyl	propyl	isopropyl
840-846	853-866	853-870	847-865

Despite significant overlapping of the P-F band within the ethyl-, n-propyl-, and isopropylphosphonofluoridates, the frequencies noted for the P-methyl compounds are outside of those noted for the other compounds. It does appear, therefore, that a strong band at 840-846 cm^{-1} in the spectrum of a suspected Sarin analog is useful in identification of a methylphosphonofluoridate.

Phosphorous-carbon

P-methyl

The infrared spectra of phosphorous compounds with a methyl group directly bonded to the central phosphorous atom are characterized by a band around 1300 cm^{-1} (CH_3 symmetric deformation) and 900 cm^{-1} (CH_3 rocking).[15] Unlike some of the other functionalities within the phosphorous molecules, the change from the condensed-phase to the vapor-phase would be expected to have less effect upon the position of these bands. As previously noted, the range of frequencies observed in this study with the Sarin analogs, at 1310-1323 cm^{-1}, was close to the reported condensed-phase range of 1312-1328 cm^{-1} . Because of the higher frequency of the phosphoryl band in the vapor-phase, the 1300 cm^{-1} band was not always well resolved. The lower band, medium in intensity, was seen at 917-928 cm^{-1}, within the 900-934 cm^{-1} cited by Thomas. This vibration was readily identifiable in the compounds in this study. The observation of this prominent band in a compound combined with the P-F vibration would appear to be highly diagnostic of a P-methyl phosphonofluoridate even in spectra in which the 1300 cm^{-1} band is difficult to distinguish.

In the methyphosphonate diesters and the diphosphonates, in which the phosphoryl frequency is lower than in the fluoridates, the P-methyl band was better separated from the stronger P=O absorption and was, thus, readily identified. In these compounds the absorption due to the methyl group was found within the extremely narrow limits of 1310-1311 cm^{-1} for the diesters and 1314-1316 cm^{-1} for the diphosphonates.

P-ethyl, P-propyl, and P-isopropyl

Compounds with a P-CH_2 functionality can be distinguished in the condensed-phase by bands at 1405-1440 cm^{-1}.[15] If the group directly bonded to phosphorous is an ethyl, two weak bands are often seen at around 1250 cm^{-1}. Where these bands are close to the phosphoryl stretch, splitting of that band may occur.[4]

The more recent work by Söderström and Ketola indicated the presence of a double band at 1295 and 1309 cm^{-1} in the ethylphosphonofluoridic acid esters. A prominent doublet did not appear at those frequencies in the samples analyzed during our study. It is possible that the bands are not well resolved from the stronger phosphoryl, which appears at higher frequencies in the vapor-phase. This would not be surprising, given that the average phosphoryl frequency in the ethyl analogs was 1311 cm^{-1}. More surprising was the absence of a band at 1250 cm^{-1} in all of the samples, which should have been adequately resolved from the strong P=O. Nearly all spectra did, however, exhibit a poorly resolved band as a shoulder on the lower frequency side of the phosphoryl, although not at the expected position. Bessel deconvolution of a number of the spectra appeared to indicate that the frequency may lie between 1275-1280 cm^{-1}. A similar band was also observed at approximately 5-10 cm^{-1} lower in the spectra of the isopropylphosphonofluoridates.

Analysis of the ethylphosphonate diesters showed these to be more consistent with the observations from condensed-phase studies. The spectra were apparently more complex in the phosphoryl stretching region than the methylphosphonates, with several partially resolved bands on either side of the phosphoryl. Deconvolution of a number of the spectra indicated the expected presence of a band at about 1250 cm^{-1} and one or more bands at about 1290 cm^{-1}.

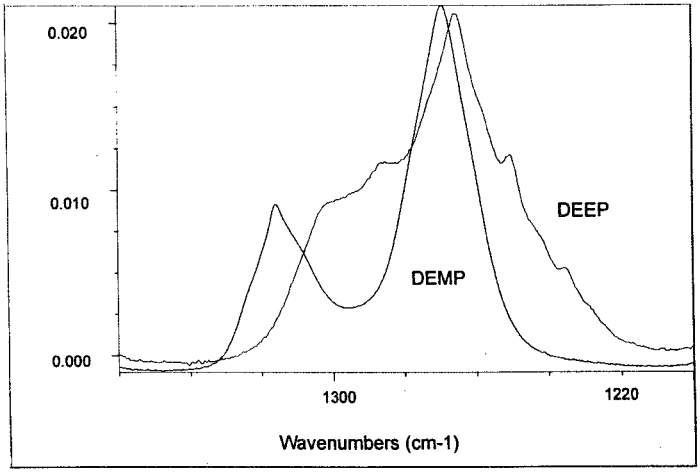


FIGURE 2

Vapor-Phase Infrared Spectra of Diethyl Methylphosphonate and Diethyl Ethylphosphonate

Further evidence of the complex nature of this region of the spectra of the ethylphosphonates versus the methylphosphonates was provided by a comparison of the vapor-phase spectra of diethyl methylphosphonate (DEMP) and diethyl ethylphosphonate (DEEP) acquired at 0.5 cm^{-1} resolution using a Nicolet Protégé® equipped with a 10-meter gas cell operated at 50°C (Figure 2). The spectra were obtained in a laboratory built to acquire quantitative vapor-phase spectra to be used in active open-path FTIR monitoring.[20] The technique requires a relatively pure compound and cannot be combined with a gas chromatograph to obtain individual spectra from a mixture. The strongest bands in the high-resolution spectrum of the DEEP were seen at 1285, 1266, and 1250 cm^{-1}, within ±3 cm^{-1} of those obtained through deconvolution of the GC-IR spectra.

The alkyl and cycloalkyl propylphosphonofluoridates were easily distinguished from the other analogs on the basis of a weak band at 1244-1245 cm^{-1}. There were no exceptions in the compounds analyzed, with this feature always sufficiently well resolved to be easily

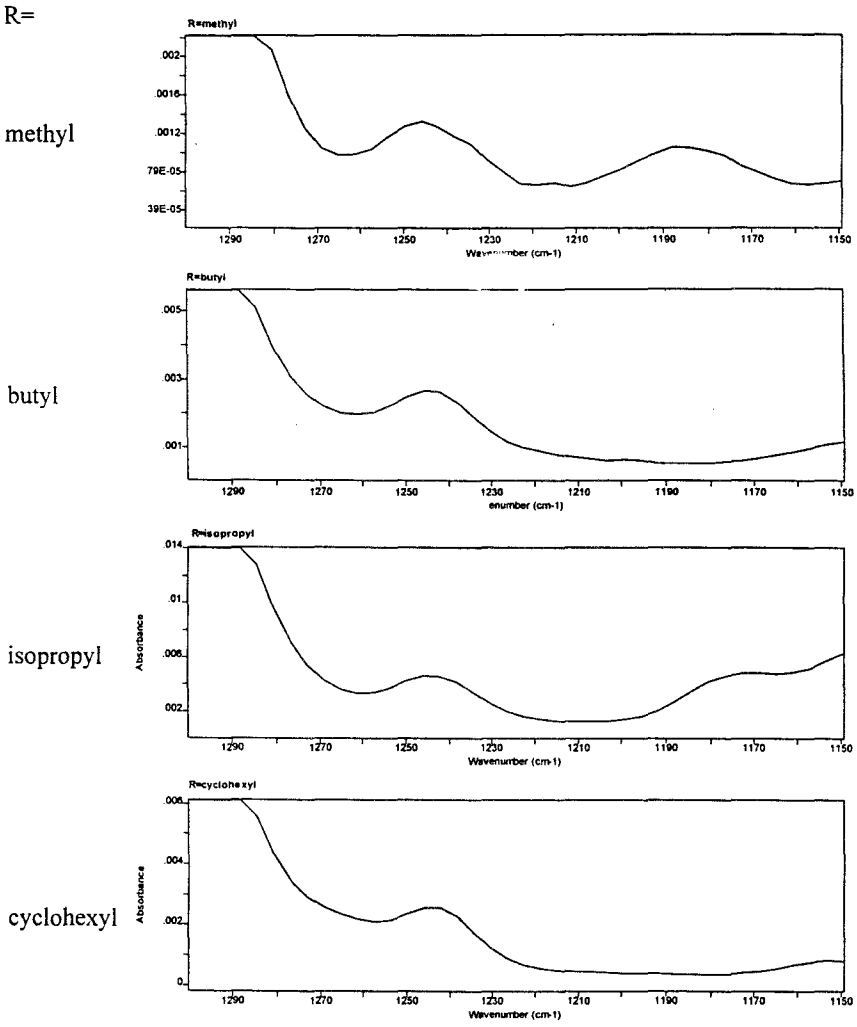


FIGURE 3

1150-1300 cm-1 Region of Several RO-P(O)$CH_2CH_2CH_3$

distinguished from other spectral features and with little variation in intensity. On the basis of the mass spectra alone, it is difficult to distinguish between the P-propyl and P-isopropyl isomers of two Sarin analogs with the same alkoxy functionality because of their similarities. The ability of infrared to distinguish between the two forms is potentially useful in obtaining a correct identification of an unknown sample without the necessity of synthesizing both compounds for confirmation. Figure 3 shows the spectra of several of these compounds, with the region between 1150 and 1300 cm^{-1} expanded to show the characteristic band. Deconvolution of the spectra of the corresponding diesters indicated that the corresponding band in those compounds most likely have a frequency close to 1238 cm^{-1}.

CONCLUSIONS

The microscale in-situ technique has proven extremely useful for rapid synthesis and analysis of a variety of chemical warfare agent related compounds. The approach has enabled the vapor-phase spectroscopic study of the characteristics of a broader cross-section of analogs of the nerve agent Sarin than has been possible in the past.

The ability of gas chromatography interfaced with light-pipe infrared spectroscopy to provide valuable information for the identification of CW-related compounds has been demonstrated.

ACKNOWLEDGEMENTS

This work was supported by contracts with the Edgewood Chemical and Biological Center and the National Institute of Standards and Technology.

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Date Received: May 31, 2000
Date Accepted: August 14, 2000