Derivatization chemistries for the determination of inorganic anions and related compounds by gas-chromatography

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Abstract

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1. Abbreviations

BSA = *N*,*O*-bis(trimethylsilyl)acetamide
BSTFA = *N*,*O*-bis(trimethylsilyl)trifluoroacetamide
DMF = Dimethylformamide
HMDS = Hexamethyldisilazane
MPA = Methylphosphonate
MTBSTFA =
N-*tert*-Butyldimethylsilyl-*N*-methyltrifluoroacetamide
PFB = Pentafluorobenzyl
RMPA = Alkyl methylphosphonate
SIM = Single Ion Monitoring
TBDMSCl = *tert*-butyl dimethylchlorosilane
TBDMS = *tert*-butyl dimethylsilyl
TECS = Triethylchlorosilane
TMCS = Trimethylchlorosilane
TES = Triethylsilyl
TMS = Trimethylsilyl

2. Introduction

gas chromatogrpahy for compounds termally stable volatile. chemical derivatization has exanded the scope of the aplication enormusly
also anionic compounds can be measured by gas chromatography.
not a standard technique, but for certain applcaiton (difficult matricie, need of sensistivity specificity is critical) GC can play a major role in anion determination.
for example most of no2 and no3 speciation in biological fluids is today attained with GC.
Advantages: miglior controllo dell effetto matrice avendo possibilita di misurare matrici biologiche dove gli analiti sono presenti a livello di tracce high resolution of complex matrices. Having ortogonal methods. very high chrom resolution with GC
move here the part of calibration and yield of derivatization.

3. Derivatization Chemistry for Anions

In this section, three general derivatization chemistries employed for inorganic anions are presented with attention to the molecular aspects of the reactivity. Silylation is firstly discussed for the conversion of oxyanions and fluoride to the corresponding R_3Si derivatives. Alkylation strategies are presented in Paragraph 3.2 and stable alkyl derivaties were prepared for analyte such as halides, azide, cyanide, thiocyanate, sulfide, nitrite and nitrate. A certain complementarity between silylation and alkylation strategies could be observed. The last paragraph of this section is dedicated to hydride generation with aqueous tetrahydroborate. This derivatization chemistry, which is widely utilized with atomic spectroscopy for the vapor generation of metalloids, has been employed with gas chromatography for trace metal determination and speciation.

3.1. Silylation

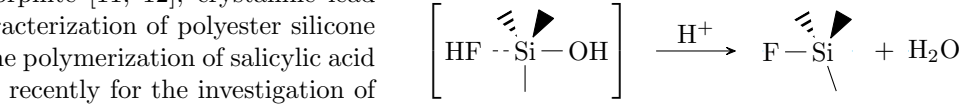
Silylation is the most versatile derivatization technique available for gas chromatographic applications, and it has been used since the fifties for the conversion of protic functional groups in the corresponding silyl-derivatives:

$$R_3Si\text{-}X + R^1\text{-}H \rightarrow R_3Si\text{-}R^1 + HX$$

Replacement of active -H with the $-SiR_3$ moiety has been reported for -OH, -SH, -COOH, -POH, -SOH, -NOH, -BOH, $-NH_2$, =NH, and $-CH_2C{=}O$ functional groups [1, 2]. The usefulness of this derivatization technique for gas chromatography is primarily related to better thermal stability, enhanced volatility, and reduced polarity character of the silyl-derivatives respect to the native analytes. Such properties contribute for better chromatographic figure-of-merits in terms of separation and peak shape. Furthermore, the use of silylation in conjunction with mass spectrometry has the advantage of providing diagnostic fragmentation patterns that can be used for identification purpose and for quantitation in select ion monitoring mode. Due to the importance of this topic for gas chromatography, an extensive mole of literature has been devoted to the fundamentals of silylation. A list of publications describing the general aspects of this topic includes the *Handbook of Analytical Derivatization Reactions* (Knapp 1979 [3]), the *Handbook of Derivatives for Chromatography* in its first (Blau and King 1977 [4]) and second edition (Blau and Halket 1993 [1]), and several review papers [5–7] where the most recent is one presented by Poole in 2013 [7]. In this last publication the reactivity aspects of the trialkylsilyl derivatization were discussed. The silylation reaction proceed accordingly to S_N2 mechanism with the formation of a transition state deriving from the nucleophilic attack of the analyte to the silicon atom of the reagent [1]:

The kinetic aspects of this reaction are dictated by the nucleophilic character of both analyte (HR^1) and leaving group (X), use of acid/basic catalysts and nature of the solvent [7]. Despite most of analytical applications described in literature are devoted to organic molecules (such as alcohols, phenols, carboxylic acid, amino acids, etc.), the use of silyl-chemistry has been proposed in early days for the analysis of inorganic anions as well. Already in 1964 Lentz [8] prepared TMS derivatives of several silicates from geological samples for a structural study. On the base of this first investigation, Wu et al. [9] resolved five silicates (SiO_4^{4-}, $Si_2O_7^{6-}$, $Si_3O_9^{6-}$, $Si_3O_{10}^{8-}$, and $Si_4O_{12}^{8-}$) on a dimethylpolysiloxane column at a temperature lower that 290 °C after reaction of the sample with HMDS for one hour at room temperature. A better control on unwanted condensation/hydrolytic side reactions was obtained using

a stronger silylating agent like BSA [10]. This approach found qualitative applications in the analysis of silicate minerals such as hemimorphite [11, 12], crystalline lead silicates [13], for the characterization of polyester silicone resins [14], for studying the polymerization of salicylic acid in solution [15] and more recently for the investigation of the ageing process of waterglass [16]. For the analysis of silicate the use of TMS chemistry has also the advantage of conferring chemical stability to unstable silicic acids [8, 17]. Several other oxyanions has been identified by gas chromatography after trimethylsilylation [4, 18]. Preparation of the TMS derivatives of BO_3^{3-}, CO_3^{2-}, $C_2O_4^{2-}$, PO_3^{3-}, SO_4^{2-}, AsO_3^{3-}, PO_4^{3-}, VO_4^{3-}, and AsO_4^{3-} was achieved by reaction of 5-10 mg of the corresponding ammonium salts with BSTFA in DMF [19, 20]. NO_3^- and CrO_4^{2-} did not respond to the test, resulting in the discoloration of the solution [20]. The reaction was carried out at room temperature overnight and complete solubilisation of the ammonium salts was observed. The silylation yield was strictly dependent on the nature of the analyte counter-cation: Na^+ or K^+ salts resulted in poor signals as compared to the NH_4^+ ones. Butts and Rainey [20] explained this evidence with the lack of solubility of such salts with the BSTFA/DMF mixture (a precipitate was in this case observed). This issue was solved when the Na^+ or K^+ salts were first eluted on a cation exchange resin in NH_4^+ form. TMS derivatives of oxyanions, however, undergoes fast hydrolysis at room temperature and only phosphate and oxalate derivatives are sufficiently thermally stable and resistant to hydrolysis for GC analysis [21]. Since the TBDMS derivatives are several orders of magnitude more stable toward hydrolysis then the TMS ones [7], Mawhinney [21, 22] overcame the issue of TMS chemistry using MTBSTFA derivatization. TBDMS derivatives of CO_3^{2-}, SO_3^{2-}, SO_4^{2-}, SeO_3^{2-}, SeO_4^{2-}, BO_3^{3-}, PO_3^{3-}, PO_4^{3-}, VO_4^{3-}, AsO_3^{3-}, AsO_4^{3-}, and $P_2O_7^{4-}$ were prepared accordingly to a similar reaction scheme as already proposed by Butts and Rainey [19, 20]. *t*BDMS derivatives were proved to be stable for six months when kept at 4 °C. Even for the MTBSTFA derivatization the nature of the analyte counter-ion was important: only the ammonium salts underwent quantitative derivatization, whereas the Na^+ and K^+ salts were poorly reacted. Up to date the only oxyanions that received extensive attention belongs to the phosphate family (Paragraphs 4.2 and 4.3). The major limitation of silyl-chemistry lies in the disposition to hydrolysis of the silyl-derivatives. For this reason, the analytes must be extracted in an organic solvent at first. In case of inorganic anions this operation is delicate and go against the hydrophilic nature of inorganic anions. Occasionally this phase transfer has been achieved, for example Matthews et al. [23] pre-concentrated ortho-phosphate from an aqueous solution into toluene using Adogen-464-HCO_3^- as catalyst. However, such operation can be challenging when complex matrix are analyzed. The only analyte that disobey the hydrophilic pathway common to most silyl-derivative is fluoride. In fact F^- can react directly with silanols in aqueous/acidic medium to give stable Si-F bond (D(Si-F) = 552 kJ/mol [24]):



These family of derivatives do not hydrolyze and therefore can find interesting analytical applications as discussed in Paragraph 4.8.

3.2. Alkylation

Silylation is a very useful method for GC derivatizations and several inorganic anions has been analyzed with this approach. However, silylation is moisture sensitive, requires a dry organic reaction medium and is active primarily toward oxyanions. In order to circumvent these issues, carbon-based chemistries have also been employed to convert inorganic anions into volatile alkyl-derivatives. A wide collection of alkylating agents is available for GC applications, including dialkylacetals, diazoalkales, pentafluorobenzyl bromide, benzylbromide, boron trifluoride in methanolic or butanolic solution, tetrabutylammonium hydroxide and alkyl halides [25]. Alkylation reagents can be used alone or in conjunction with acylation or silylation reagents, and the experimental conditions can vary from strongly acidic to strongly alkaline [26]. A general review on non-silylation derivatization techniques for gas chromatographic applications was presented in 1999 by Wells [25]. A first attempt for halides determination by alkylation was proposed in 1970 by MacGee and Allen [27]. The cations of an aqueous halide solution were exchanged with a tetraalkylammonium ion on a cation exchange column. The resulting R_4N^+ halides were vaporized at 360 °C in the injector port of the GC. The high-temperature promoted alkylation of the analyte:

$$R_4N^+ + X^- \rightarrow \text{R-X(g)} + R_3N \text{ (360 °C)}$$

Moore in 1982 improved this procedure increasing the yield of alkylation by using the *n*-butyl tosylate as alkylating agent [28] at a lower injection temperature:

$$n\text{-BuOTs} + X^- \rightarrow n\text{-BuX(g)} + TsO^- \text{ (210 °C)}$$

where $X^- = Cl^-$, Br^-, I^-. In another on-column approach halogens were extracted from aqueous solutions into toluene-alcohol with tetraheptylammonium carbonate [29]:

$$n\text{-Hp}_4N^+ + X^- \rightarrow n\text{-HpX(g)} + n\text{-Hp}_3N \text{ (150 °C)}$$

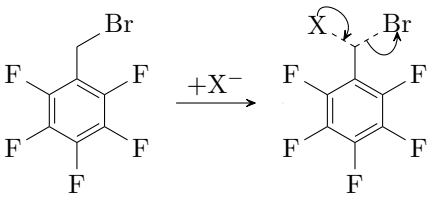
Trialkylsulfonium ions are another set of reagents applied for on-column alkylation. Jacob et al. [30] treated plasma samples with tributylsulfonium perchlorate. The resulting ion pair n-$Bu_3S^+[SCN]^-$ was extracted in ethyl acetate and analyzed by GC with a nitrogen-phosphorus detector with detection limit of 5 µM and a precision of 5.9% at the 20 µM level:

n-$Bu_3S^+ + SCN^- \rightarrow n$-Bu-SCN(g) + n-Bu_2S (325 °C)

This method was also effective for the conversion of $SeCN^-$ in the corresponding butyl-derivative. The major limitation of on-column reagents lies in their highly-caustic effect with rapid deterioration of the GC column [25]. Other reagents have been employed for the alkylation of inorganic anions directly in solution. The first reported methods used sulphate esters such as dimethyl [31], diethyl sulphate [32], and haloalkanens like butyl iodide [33]. However, the risk of handling these reagents which are volatile, toxic and carcinogenic poses serious concerns for the safety of the analyst. For this reason, other reagents such as methyl tosylate and trimethyl phosphate were also employed for alkylation of inorganic anions [34]. Mulligan et al. [35] used ethyl tosylate mixed with 18-Crown-6 for aqueous ethylation of Cl^-, Br^-, I^-, CN^-, SCN^-, N_3^-, and NO_3^- followed by static headspace GC-MS. In SIM mode, quantitation was achieved in the 0.001-1 mM range. Faigle and Klockow [36] derivatized Cl^-, Br^-, I^-, CN^-, SCN^- and NO_3^- with n-decyl methanesulphonate after extraction of the analytes in a non-aqueous solvent with n-Bu_4N^+ as phase-transfer catalyst. Funazo et al. [37] performed butylation in of Br^-, I^-, SCN^-, and NO_3^- with n-butyl tosylate. In this case a mixture of aqueous analyte with n-$Bu_4N^+HSO_4^-$ (phase transfer catalyst), TsOBu (alkylating reagent), KOH (pH control), and CH_2Cl_2 was held at 28 °C following GC-FID analysis of the organic phase. The reported derivatization yield were close to 100% for Br^-, I^-, SCN^- and 54% for NO_3^-. Other than these classic approaches, other two alkylation strategies have been lately applied for the conversion of inorganic ion into volatile compounds. In this regard, the pentafluorobenzyl alkylation will be treated in Paragraph 3.2.1, whereas the ethylation with triethyloxonium tetrafluoroborate in Paragraph 3.2.2. A general summary of alkylation reaction employed for GC determination of inorganic anions is presented in Table 1. Note that Table 1 omits alkylation reactions specific for phosphates which will be examined in Paragraph 4.3 (Table 5).

3.2.1. Pentafluorobenzyl alkylation

Pentafluorobenzyl reagents have been employed to generate volatile derivatives with a wide variety of compounds, such as phenols, thiols, carboxylic acids, and inorganic anions [25]. The most employed reagent is the commercially available pentafluorobenzyl bromide (PFB-Br) which is a colourless to yellowish liquid, having a melting point of 19-20 °C and a density of 1.728 g/mL at 25 °C. The reaction between an inorganic anion (X^-) and PFB-Br follows S_N2 mechanism:



This scheme, however is not sufficient to fully explain PFB-Br reactivity toward anions. For example, we recently found a more complex chemistry between PFB-Br and CN^- [42]. Depending upon experimental conditions, multiple alkylation on the same CN^- anion led to single [N≡C-$CH_2(PhF_5)$], double [N≡C-$CH(PhF_5)(BnF_5)$], and triple [N≡C-$C(PhF_5)(BnF_5)_2$] PFB-derivatives. Formation of these multi-alkylated species was favored in an alkaline environment where the triple-PFB specie was most abundant. PFB derivatives are easily formed, highly stable, have excellent GC properties and are extremely sensitive with both ECD and MS detector in negative chemical ionization [43]. Two procedures for anions derivatization with PFB-Br are reported in the literature: the *extractive alkylation* and the *direct alkylation*. The extractive alkylation is the most common approach. In this case, the analytes are transferred as an ion pair with a quaternary ammonium cation to an organic solvent containing PFB-Br. Dichloromethane, acetophenone, cyclohexanone, 1-pentanol, 2-octanol or methyl isobutyl ketone have been used. The organic phase is then separated from the aqueous and analyzed by gas chromatography. Funazo et al. [44] applied extractive alkylation to prepare PFB-derivatives of Br^-, I^-, CN^-, SCN^-, NO_2^-, NO_3^-, and S^{2-} by reacting for 30 minutes at room temperature 1.0 mL of aqueous standard with 0.2 mL of 0.1 M n-$Pe_4N^+Cl^-$ and 1.0 mL of 0.1 M PFB-OTs in CH_2Cl_2. Detection was attained by mass spectrometry [44] and ECD detector [45]. Kage et al. [38] employed a similar approach for the determination of azide in whole blood and urine: 0.2 mL of sample were treated with a solution of PFB-Br in ethyl acetate (extraction solvent) using aqueous tetradecyldimethylbenzylammonium chloride as phase transfer catalyst. The reaction mixture was saturated with sodium tetraborate for pH control and held at 60 °C for 30 minutes:

PFB-Br + N_3^- → PFB-N_3 + Br^-

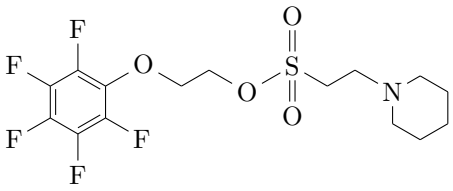
GC-MS analysis in negative ionization mode provide detection limit of 0.5 µM with a linear range of 1.0 – 200 µM. The nature of quaternary ammonium salt can influence the performance of extractive alkylation [46]. It was reported that n-hexadecyltrimethylammonium bromide was more suitable for simultaneous derivatization of I^-, SCN^-, NO_2^-, and S^{2-} then n-$Pe_4N^+Cl^-$ [47]. R_4N^+ salts with longer alkyl chains has also been preferred in earlier methods [38]. The increased lipophilic character of the phase transfer catalyst results in a better transportation efficiency of the anion from aqueous to organic phase. In this condition however, the degradation of PFB-Br, favored by an alkaline medium, proceed faster [48]. R_4N^+ salts have two major drawback: they promotes formation of unwanted emulsions which complicate phase separation and their migration into the organic phase is detrimental for GC columns [49]. In this regard, Chen et al. [49] replaced R_4N^+ salts with a polymer based phase-transfer catalyst, the Kryptofix 222 B. The solid-bounded particles of this polymer were not injected in the GC and no

Table 1: Alkylation chemistries for the conversion of inorganic ion in volatile derivatives

Analyte	Reagent	Derivative	Notes (year)	Ref.
Cl^-, Br^-, and I^-	*n*-$(Hp_4N)_2CO_3$	*n*-HpCl, *n*-HpBr, and *n*-HpI	On-column alkylation at 150 °C (1973)	[29]
Br^-, I^-, CN^-, SCN^-, S^{2-}, and NO_2^-	$(MeO)_3P{=}O$ TsOMe $(MeO)_2S{=}O$	MeBr, MeI, MeCN, MeSCN, Me_2S, and EtONO	1 mL of aqueous sample + 0.1 mL reagent; heating at 70 °C (1981-82)	[31] [34]
Br^-, I^-, CN^-, SCN^-, and S^{2-}	$(Et_2O)_2S{=}O$	EtBr, EtI, EtCN, EtSCN, and Et_2S	Aqueous derivatization at 70 °C (1982)	[32]
SCN^-, and $SeCN^-$	*n*-$Bu_3S^+[ClO_4]^-$	BuSCN, and BuSeCN	Extraction of analyte in ethyl acetate with *n*-Bu_3S^+ followed by on-column alkylation at 325 °C. Applied for blood and urine (1984)	[30]
Br^-, I^-, SCN^-, and NO_3^-	*n*-BuOTs	BuBr, BuI, BuSCN, and $BuONO_2$	1 mL aqueous standard + *n*-$Bu_4N^+HSO_4^-$ + KOH + *n*-BuOTs + CH_2Cl_2. Yield: 92% Br^-, 100% I^-, 95% SCN^-, and 54% NO_3^- (1985)	[37]
Cl^-, Br^-, I^-, CN^-, SCN^-, N_3^-, and NO_3^-	EtOTs with 18-Crown-6	EtCl, EtBr, EtI, EtCN, EtSCN, EtN_3, and $EtONO_2$	Aqueous derivatization buffered to alkaline pH followed by headspace GC-MS (1995)	[35]
N_3^-	PFB-Br	PFB-N_3	Extractive alkylation with ethyl acetate at 60 °C for 30 min (2000)	[38]
NO_2^-, and NO_3^-	PFB-Br	PFB-NO_2, and PFB-ONO_2	Direct derivatization in acetone for 60 min at 50 °C following reduction to dryness under N_2 stream and reconstitution with toluene (2000)	[39]
F^-, Cl^-, Br^-, I^-, CN^-, CNO^-, N_3^-, NO_2^-, and NO_3^-	PFB-OTs	PFB-F, PFB-Cl, PFB-Br, PFB-I, PFB-CN, PFB-OCN, PFB-N_3, PFB-NO_2, and PFB-ONO_2	Extractive alkylation with 18-crown-6-ether and 15-crown-5-ether catalysts (2006)	[40]
Cl^-, Br^-, I^-, CN^-, SCN^-, S^{2-}, NO_2^-, and NO_3^-	$R_3O^+[BF_4]^-$ R = Me, Et	RCl, RBr, RI, RCN, RSCN, R_2S, RONO, and $RONO_2$	Direct aqueous alkylation at room temperature followed by headspace GC-MS (2009)	[41]

emulsions were observed during extraction. More recently Sakayanagi et al. [40] used extractive alkylation assisted by 18-crown-6-ether and 15-crown-5-ether for the determination of F^-, Cl^-, Br^-, I^-, CN^-, CNO^-, N_3^-, NO_2^-, and NO_3^- with a detection limit better than 30 ng in negative chemical ionization mode GC-MS. In the same study it was proved that SO_4^{2-}, $S_2O_3^{2-}$, ClO_3^-, and ClO_4^- do not generate PFB derivatives amenable to gas chromatography. PFB derivatization has been also employed to perform *direct alkylations*. In this case the reaction is generally carried out on a one-phase system. The aqueous sample is diluted with a water miscible organic solvent, such as acetone or acetonitrile, following reaction with the PFB reagent at temperature that can vary from ambient to 90 °C. After alkylation the reaction medium is reduced to dryness under a stream of N_2 and the derivatives are reconstituted in an organic solvent like toluene or CH_2Cl_2. The direct alkylation with PFB reagents can be improved using crown ethers such as the 18-crown-6 which can chelate potassium and ammonium cations leaving the bare anionic counterpart more active toward alkylation [50]. This approach found applications for the determination of several alkyl phosphates/phosphonates [51–53] along with CN^-, I^-, NO_2^-, NO_3^-, S^{2-}, SCN^-, and CO_3^{2-} with interesting biomedical and forensic applications [39, 54–58]. More details about these methods will be provided in Paragraph 4. Despite the most common PFB reagent is the PFB-Br [43], other pentafluorobenzylating agent have been reported. PFB-OTs was synthesized from TsCl and PFB-OH [44] and it was preferred to PFB-Br because it allowed the determination of Br^- in biological samples [59] and several anions pro-

viding cleaner chromatography: PFB-OTs was fully separated from the analyte derivatives whereas the PFB-Br eluted at similar retention time as the analyte derivatives. due to its limited solubility in organic solvents other than chloromethanes, PFB-OTs was unsuitable for direct alkylation [60] and was replaced by Tanaka et al. [60] with the pentafluorobenzyl methanesulphonate, and employed it with both extractive alkylation in dichloromethane (using tetra-namylammonium chloride as a phase-transfer catalyst) and direct derivatization in acetone. More recently, 2-(pentafluorophenoxy)ethyl 2-(piperidino)-ethanesulfonate was synthesized and used to react I^-, CN^-, NO_2^-, and SCN^- by extractive alkylation in toluene with tetra-*n*-hexyl ammonium bromide as phase transfer [61]:



where the unreacted excess could be salinized by aqueous acid treatment and removed from the toluene phase, minimizing its interferences during gas chromatography. The 2-(pentafluorophenoxy)ethyl 2-(piperidino)-ethanesulfonate was not active toward alcohols and amines showing some selectivity. Other PFB reagents were mainly employed in the derivatization of organic compounds. *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine hydrochloride [62] and pentafluorophenylhydrazine [63] were used for the derivatization of carbonyls with low molecular weight under mild reaction conditions and pentafluorobenzyl chloroformate was proposed for the determination of amino acids and alcohols [64]. As a general safety remark, care should be paid when handling PFB reagents. In particular PFB-Br is corrosive and a potent lachrymator [65] which should be used in a vented fumehood with adequate PPEs.

3.2.2. Trialkyloxonium alkylation

The first preparation of trialkyloxonium salts ($R_3O^+[X]^-$, R = Me, Et; X = BF_4, $FeCl_3$, $SbCl_6$, etc.) dates back to 1937 with the work of Meerwein and colleagues [66, 67]. Since then a significant mole of organic and inorganic literature has been devoted to study the properties of this class of alkylating agents [68–70]. The possibility of using trialkyloxonium salts to perform alkylation of simple inorganic anions directly in aqueous solution is known since 1986 [71]. However, only in 2009 such derivatization chemistry was employed in conjunction with GC-MS for the determination of Cl^-, Br^-, I^-, CN^-, SCN^-, S^{2-}, NO_2^-, and NO_3^-[41]. $Me_3O^+[BF_4]^-$ and $Et_3O^+[BF_4]^-$ (both commercially available) could perform alkylation of these inorganic anions accordingly to the following scheme:

$$n\mathrm{Me_3O^+(aq)} + \mathrm{A}^{n-}\mathrm{(aq)} \rightarrow \mathrm{Me}_n\mathrm{A(g)} + n\mathrm{Me_2O}$$
$$n\mathrm{Et_3O^+(aq)} + \mathrm{A}^{n-}\mathrm{(aq)} \rightarrow \mathrm{Et}_n\mathrm{A(g)} + n\mathrm{Et_2O}$$

King et al. described these reactions as first-order nucleophilic substitutions S_N1 [71]:

$$\mathrm{R_3O^+ \rightarrow R^+ + X^- \rightarrow R\text{-}X(g)}$$

For the determination of inorganic ions an aqueous based chemistry is ideal because avoids the extraction of these polar analytes in organic solvents as other alkylation methods require. Both methyl and ethyl derivatives of the target analytes are volatile and can be sampled in the headspace allowing for their first order separation from the matrix. This key feature of the method results in baseline clean chromatography even for complex matrices like seawater [72] or biological fluids [73]. For analytical applications, ethylation with $Et_3O^+[BF_4]^-$ has been preferred over methylation. In fact, Et_3O^+ is more stable toward hydrolysis [69] and the Et-derivatives demonstrate better GC-MS figures of merits (higher mass and retention time). The method entails a simple sample preparation. An aqueous solution of triethyloxonium tetrafluoroborate is prepared just before use and it is added directly to the sample at room temperature following headspace GC-MS analysis. $Et_3O^+[BF_4]^-$ solutions undergoes acid hydrolysis within 80 minutes at 18 °C [69], therefore the reaction is quenched by the solvent:

$$\mathrm{Et_3O^+(aq) + 2H_2O \rightarrow EtOH + H_3O^+ + Et_2O}$$

In some cases the reaction medium should be buffered with ammonium hydroxide to prevent it turning acidic. For example an acid pH is undesiderable when bromide is measured in a sample containing bromate [74]:

$$\mathrm{BrO_3^- + 5Br^- + 6H^+ \rightarrow 3Br_2 + 3H_2O}$$

or when nitrite and nitrite are measured simultaneously [72, 75]:

$$\mathrm{2NO_2^- + O_2 \rightarrow 2NO_3^-}\ \text{(acid catalyzed)}$$

Et_3O^+ can perform ethylation of halides and, therefore it can react F^- into EtF. Commercially available Et_3O^+ salts include tetrafluoroborate, hexachloroantimonate or hexafluorophosphate. None of these is a viable option for fluoride derivatization: $[BF_4]^-$ and $[PF_6]^-$ salts are blank limited whereas the application of Et_3O+$[SbCl_6]^-$ would pose severe environmental concerns. To circumvent the issue we prepared Et_3O+$[FeCl_4]^-$ [76] accordingly to a known procedure [67]:

$$\mathrm{2Et_2O{\cdot}FeCl_3 + C_2H_3(O)CH_2Cl \rightarrow Et_3O{+}[FeCl_4]^- + FeCl_2[(OCH(CH_2Cl)CH_2OEt]}$$

This reagent was successfully employed for the determination of fluoride in several matrices like seawater and urine with detection limits in the part-per-billion range. In this case, the conversion of F^- to EtF was carried out an alkaline ammonia buffer for the precipitation of Fe(III) and other cations that could complex fluoride ions interfering

with the alkylation. Despite possible health hazard associated with alkylating agents, the risks handling Et_3O^+ salts are restrained by the non-volatile nature of these chemicals. As many tetrafluoroborates, $Et_3O^+[BF_4]^-$ is hygroscopic and moisture sensitive, therefore it should be kept at -20 °C and handled in a fumehood for the shortest period of time.

3.3. Hydride Generation

Chemical generation of volatile hydrides (CHG) has been recognized for more than 45 years as a valuable tool for the analysis of trace and ultra-trace elements such as As, Se, Sn, Sb, Te, Bi, and Ge [77–81]. Despite hydride generation is a typical sample introduction technique for atomic spectroscopy, also gas-chromatography has been applied in conjunction with CHG. Hydride generation is performed by aqueous phase reaction of the analytes with a strong excess ($> 10^3$ mole/mole) of tetrahydroborate (THB) salts ($NaBH_4$, KBH_4) or, less frequently, amine borane complexes BH_3X (X = NH_3, *t*-$BuNH_2$, Me_2NH) [82, 83]:

$$EL_n(aq) + BH_3X(aq) \rightarrow EH_n(g)$$

Molecular aspects of aqueous THB chemistry for analytical determinations have been recently reviewed [84–87]. The generation of volatile hydrides is the results of two competitive processes: the hydride formation and the THB hydrolysis. CHG does not necessarily entail reduction of the element: for example when arsenite is converted into AsH_3, arsenic oxidation state remains +3. Under ideal analytical conditions, the final hydride is formed stepwise, by direct transfer of the hydride from borane to analyte atom. The chemical identity of CHG products depends on analyte concentration and on THB/analyte molar ratio. Under analytical condition (analyte $< 10^{-5}$ M, $10^{-2} <$ THB < 1 M) formation of a single derivatives (the binary hydride EH_n, E = Ge, Sn, Pb, As, Sb, Bi, Se, Te, and Hg) is observed (Table 2). The stability of metal hydrides decreases with higher atomic weight elements [84]. Furthermore, the increase of analyte concentration may lead to formation of dimeric and polymeric hydrides and other solid reaction byproducts which remains in the condense phase [88]. Anionic species are not reactive in CHG, but their reactivity can be enhanced by protonation, and the activation toward hydride attack increases in the order A^-, AH, AH^++. Anionic species arising from dissociation of strong mineral acids are not reactive to THB derivatization. Anionic species of the weak oxoacids of hydride forming elements reported in Table 3 are the less reactive then cationic ones. Since the efficiency of CHG is strongly dependent on the acidity of the solution, for simultaneous determination a compromise has to be made in regard to the choice of acid concentration. Sample aliquots can be derivatized at different pH and analyzed separately with a non-chromatographic setup [89]. Alternatively, species-specific CHG can be attained by progressive variation of the reaction condition. Diaz-Bone and Hitzke [90] created a pH-gradient, by lowering the pH from 7 to 1 while continuously adding $NaBH_4$. By doing so, all investigated analytes (methylated Ge-, As-, Sn-, Sb-, Te- and Hg-species) were successively derivatized at the highest pH possible in order to minimize rearrangement reactions. An additional issue in CHG is represented by the interferences which can affect both reaction yield and molecular mechanism of derivatization [77, 87]. Interference mostly arises from interaction between analyte/interferent/THB; for example, THB can convert transition metals in nanoparticle which can adsorb/degrade the hydride and promote competitive THB hydrolysis [91–93]. Furthermore, hydride forming elements can also interfere with the analytical substrate [94, 95]. Interference control can be attained by modulation of reaction conditions (pH and type of acid, reagent concentration, geometry and design of CHG apparatus), and by the use of additives [86]. When these measures fails, separation techniques, such as extraction, coprecipitation and ion chromatography, can be employed to alleviate interference effects [77]. Artifacts from hydride generation have been reported from organometallic substrates containing element-carbon bonds (R_xEL_{n-x}: R= alkyl, phenyl; L is a ligand). In some cases the aqueous borane reagent could perform the breakdown of E-C bonds leading different R_xEL_{n-x} species to the same derivative [96–99] resulting in issues when speciation is required. Despite a successful hydride generation experiment requires a careful control of reaction conditions, this technique is widely employed for trace metal determination and speciation. Due to the volatile nature of the derivatives, gas-chromatography is a suitable separation technique for stable hydrides-forming elements which in combination with MS and ICPMS detection can provide high selectivity and sensitivity. Several methods have been proposed in literature for classical element forming hydride by gas-chromatography [90, 97, 100–127]. Furthermore also phosphate in seawater has been measured by hydride generation [128]. For this purpose, a mixed solution of an equal amount of sample and 6% $NaBH_4$ was dried at 40 °C with an infrared lamp. The dried mixture was inserted in a reaction tube heated at 460 °C, and the generated phosphine was trapped in a cooled U-tube before introduction into the GC with a flame photometric detector. The procedure was validated against the molybdenum-blue colorimetric method with persulfate digestion, obtaining a good agreement. The CHG method eliminates the problems of interference from arsenic, silica, or other materials that can affect colorimetric determination of phosphate. In the last twenty years, most of the CHG-GC applications have been focused on the speciation of arsenic oxoacids, mostly occurring in anionic form. Paragraph 4.5 is focused on discussion of late GC applications for determination of such compounds.

Table 2: Reaction products obtained in CHG under analytical conditions for some inorganic and organometallic substrates

Element	Derivative	b.p.	Comments	Ref.
Ge(IV)	GeH_4	-88 °C	Stable covalent hydride. With high Ge concentration, or under non analytical conditions, H_3Ge-GeH_3 and polymeric germanes are formed	[77, 87]
Sn(II) Sn(IV)	SnH_4	-52 °C	Stable covalent hydride. With high Sn concentration, or under non analytical conditions, H_3Sn-SnH_3 and polymeric stannnes are formed	[77, 87]
Pb(II)	PbH_4	-13 °C	PbH_4 is obtained in good yield only in the presence of oxidants. Thermally unstable	[77, 87]
As(III) As(V)	AsH_3	-62 °C	Stable covalent hydride. At high As concentration, or under non analytical conditions, H_2As-AsH_2 and polymeric arsane are formed	[88]
$MeAsO(OH)_2$ $MeAs(OH)_2$	$MeAsH_2$	-18 °C	Stable covalent hydrides. Mono-methyl As(III) and As(V) yield same derivative. Under certain conditions demethylation was observed. With high As concentration, or under non analytical conditions, polymeric (methyl)arsanes are formed.	[99, 129]
$Me_2AsO(OH)$ $Me_2As(OH)$	Me_2AsH	16 °C	Stable covalent hydrides. Di-methyl As(III) and As(V) yield same derivative. Under certain conditions demethylation was observed. With high As concentration, or under non analytical conditions, Me_3As and Me_4As_2 are the main products.	[99, 130]
Me_3AsO	Me_3As	32 °C	Risk of demethylation during derivatization	[99]
Sb(III) Sb(V)	SbH_3	-17 °C	Stable covalent hydride. Lower reaction yield from Sb(V); Sb(III) is the preferred form for CHG.	[77, 87]
Bi(III)	BiH_3	17 °C	Thermally unstable. Forms black Bi precipitate at high analyte concentration.	
Se(IV)	H_2Se	-41 °C	Acid hydride: $H_2Se + H_2O \rightleftharpoons HSe^- + H_3O^+$ $pK_1 = 3.0$. At high Se concentration Se(0) is formed. Se(VI) is not reactive in CHG	[131, 132]
R_2SeO R_2SeO_2 R_3SeO^+	R_2Se		Dialkylselonoxides and dialkilselenones are reduced to stable, volatile R_2Se. Trialkyl selenonium species are dealkylated to R_2Se	[97, 132]
RSe-SeR RSeO(OH)	RSeH		Dialkylsenides and seleninic acids are reduced to selenols.	[132]
Te(IV)	H_2Te	-2 °C	Acid hydride: $H_2Te + H_2O \rightleftharpoons HTe^- + H_3O^+$ $pK_1 = 2.6$. Thermally unstable. Forms black Te precipitate at high analyte concentration. Te(VI) is not reactive in CHG	[131, 132]

4. Applications

In this section, several GC applications for anions determination are described with attention to the performance attained using various derivatization approaches. The use of GC-MS has been particularly beneficial for quantitative determination of nitrite and nitrate in biological fluids (Paragraph 4.1) and for qualitative confirmation of mono and di- alkyl phosphates and phosphonates listed in the Chemical Welfare Convention (Paragraph 4.3).GC has was also applied for the determination of cyanide, sulfide and thiocyanate (Paragraph 4.4), arsenic and selenium oxyanions (Paragraphs 4.5 and 4.6), and halides (Paragraph 4.8).

4.1. Nitrite and Nitrate

The determination of nitrite and nitrate is of great interest in many fields. For example, speciation of NO_2^- and NO_3^- have been attained in clinical samples for understanding the so-called NO_3^-, NO_2^- NO pathway [133, 134]. NO_2^- and NO_3^- analysis is also relevant in oceanography [135] for monitoring variations of marine biogeochemistry [136–

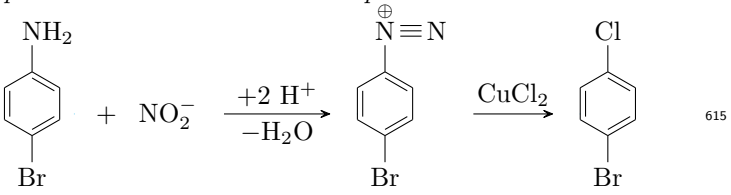
Table 3: Equilibrium constants for some analytical species involved in CHG [131]

Element	Aqueous form	pK_1	pK_2	pK_3
Ge(IV)	O=Ge(OH)$_2$ Ge(OH)$_4$	9.02	12.83	-
As(III)	H_3AsO_3	9.4	13.5	-
As(V)	H_3AsO_4	2.19	6.94	11.50
	$MeAsO(OH)_2$	3.6	8.2	-
	$Me_2AsO(OH)$	6.2	-	-
Sb(III)	$SbO^+ + H_2O \rightleftharpoons HSbO_2 + H_3O^+$	0.82	-	-
	$HSbO_2 + H_2O \rightleftharpoons [Sb(OH)_4]^- + H_3O^+$	-	11.0	-
Sb(V)	$H[Sb(OH)_4] + H_2O \rightleftharpoons [Sb(OH)_6]\text{-} + H_3O^+$	2.55	-	-
Se(IV)	O=Se(OH)$_2$	2.62	8.32	-
Se(VI)	H_2SeO_4	strong	1.66	-
Te(IV)	O=Te(OH)$_2$	2.7	7.7	-
Te(VI)	H_6TeO_6	7.70	10.95	-

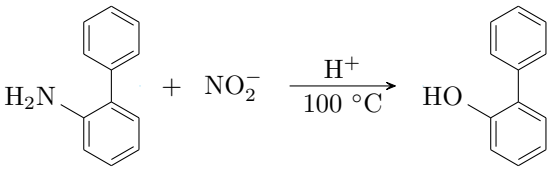
140] and for determination of residual fertilizers or additives in food [141]. In such variety of samples, NO_3^- and NO_2^- levels are widespread and they can range from nM in oligotrophic seawaters [135] to µM-mM levels in biological fluids [142] and up to several mM in food samples [141, 143]. For these reasons, many analytical methods have been developed for the determination of NO_2^- and NO_3^- in complex matrices. The historical approach for NO_2^- and NO_3^- measurement is based on the Griess assay which employs the diazotisation with sulphanilamide followed by reaction with *N*-(1-naphthyl)-ethylenediamine in acid medium to form a colored azo-dye detected at 540 nm. This reaction is specific for nitrite but does not work for nitrate which first needs to be reduced. $NO_2^- \rightarrow NO_3^-$ conversion is usually attained on a Cd/Cu column whose limited efficiency and reproducibility are the first concerns for precision work [144–146]. For example, with this method biases up to 60% were observed for nitrate analysis in vegetable extracts [145]. Several other approach have been published and reviews for nitrate and nitrate detection were presented in 2001 by Moorcroft et al. [147] and in 2017 by Wang et al. [148]. Most literature methods for NO_2^- and NO_3^- determination rely on spectrophotometry, chemiluminescence, or electrochemical detection with eventual hyphenation with separation techniques like ion chromatography [149] or capillary electrophoresis [150]. However, such approaches have limitations when complex matrices are analyzed and the implementation of GC-MS can be beneficial when the classical methods cannot reach the necessary sensitivity and selectivity or need validation [151]. Reviews focused on measurement of nitrite and nitrate by GC-MS in clinical samples were published by Smythe and Matanovic in 2002 [152] and by Helmke et al. [153] in 2007. In the following paragraph our discussion will be focuses on derivatization approach used for nitrite and nitrate conversion into molecules suitable for gas chromatography with applications to complex matrices (Table 4).

4.1.1. NO_2^- and the diazotisation reaction

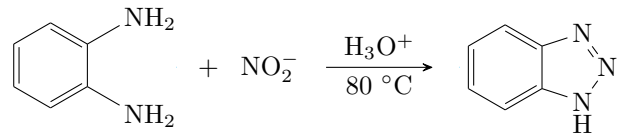
The diazotization reaction is a milestone in the analytical chemistry of nitrite. First proposed by Peter Griess in 1858 [154], this reaction has been widely applied for the determination of nitrite and here we will review gas chromatography methods which make use of such reaction. Already in 1980 Funazo et al. converted NO_2^- with *p*-bromoaniline and Cu^{2+} into *p*-bromochlorobenzene:



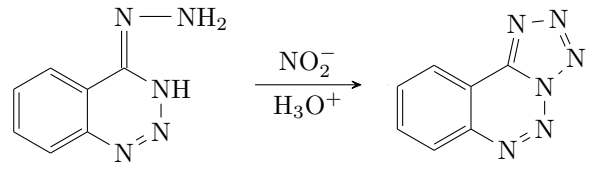
This aqueous reaction was performed on 1 mL of sample with 1 mL *p*-bromoaniline 1 mM in HCl 1N and 1 mL toluene with internal standard. After few minutes the diazonium salt was react with Cu^{2+} at room temperature for 2 h under shaking following analysis of the derivative extracted in toluene with a 100% conversion yield. The method was employed for analysis of river water, saliva, and food samples with detection limit of 10 ppb with a GC-ECD. A similar approach was proposed by the authors two years later by converting nitrite and *m*-nitroaniline into nitrobenzene with detection limit of 0.5 ppb with a dinamic range up to 1.00 ppm on the GC-ECD. Such approach however, produce a derivative that does not contain the molecular signature of the analyte making the method unsuitable for isotope dilution GC-MS [155]. Similarly, conversion of nitrite with 2-aminobiphenyl in aqueous acidic medium into 2-phenylphenol was employed for the determination fo nitrite in water samples:



In this case the water sample (0.5-3 mL) was reacted with 500 µL of 2-aminobiphenyl 30 mM in 1:1 H_2SO_4:H_2O keeping the reaction mixture at room temperature for 3 min. Resulting diazonium ion was hydrolized at 100 °C for 5 min to the corresponding 2-phenylphenol. With this technique detection limits in the low part-per-trillion were reported with both GC-FID [156] and GC-MS-MS [157]. Aromatic vicinal diamines have also been employed for nitrite derivatization. In this case the diazonium group, formed upon reaction of NO_2^- with the amine, reacts with the second aminic group on the aromatic ring to yield a triazole derivative. In 1980 Tanaka et al. employed such reactivity starting from 1,2-diaminobenzene [158]:



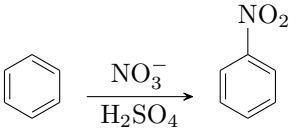
The 1H-benzotriazole was formed after 10 min at 80 °C at pH 1.0-1.5. Such derivative was extracted in ethyl acetate after saturation of the aqueous solution with NaCl. The organic phase was then evaporate to dryness and reconstituted in BSA for silylation of the -NH group on the triazole ring. With a GC-FID the method was applied for the determination of NO_2^- in food with detection limit of 0.31 ppm. The gas chromatographic properties of thirteen benzotriazole prepared from nitrite were discussed by Dilli and Patsalides in 1983 [159]. The use of 1,2-diaminobenzene as reagent for nitrite has the disadvantage of resulting in a compound which is still polar and need further silylation. This drawback could be bypassed by using a higher molecular weight compound. For example the 1-hydrazinophthalazine was use in acidic medium to convert nitrite in tetrazolophthalazine which could be extracted in organic solvent and analyzed by GC-ECD with a detection limit of 2 ng/mL:



In this derivative there are no hydrogens that need to be silylated. This derivatization was applied for the determination of nitrite in milk [160] with good spike recoveries. The most recent application that uses an aromatic vicinal diamines to convert NO_2^- was proposed by Akyüz and Ata in 2009 [161]. In a similar fashion, the 2,3-diaminonaphthalene reacted NO_2^- in 2,3-naphthotriazole in an acidic environment. The method was applied for the determination of nitrite and nitrate in biological, food and environmental samples with instrumental detection limits of 0.02 and 0.03 pg/mL for NO_2^- and NO_3^- with a linear range of 2.5–100 pg/mL. In this case, the analysis of nitrate was indirect and based on the its enzymatic reduction to nitrite. Finally, diazotisation was employed for conversion of nitrite in an azo-dye known as Sudan-1 [162]. A reagent solution of 4 g/L aniline sulphate was prepared weekly in 3M HCl and stored at 4 °C. An aliquot of sample was then treated with this 200 µL of this reagent (pH $\sim$ 2) and after 5 minutes with 200 µL of 2.08 g/L 2-naphthol in NaOH 3M following extraction of the Sudan-1 on a SPE C-18 cartridge. This derivative was then eluted with ethyl acetate and following air drying. Due to the polarity given by an hydroxyl group, the Sudan-1 needed further derivatization before analysis. Silylation was in fact obtained with 5 µL MTBSTFA in 45 µL of ethyl acetate at 75 °C for 30 min. Detection was attained in EI GC-MS monitoring in SIM mode the typical $[M\text{-}59]^+$ fragment. The method was employed for the determination of nitrate in seawater. The authors proposed first reduction of NO_3^- to NO_2^- with a copper/cadmium column. Even if reduction was not quantitative (30% to 60% efficiency), the isotope dilution approach corrected for analyte loss. Since the method respond to nitrite, this modus operandi is acceptable only for samples that do not contain significant amount of nitrite. In fact, nitrite is a positive interference to this assay which is most significant when NO_3^- to NO_2^- reduction is attained with poor yield. The Sudan-1 method was used by Clark et al. in 2007 [163] for NO_2^- and NO_3^- speciation in oligotrophic seawaters where NO_2^- and NO_3^- levels were <2 nmol/kg and <5 nmol/kg respectively and by Houben et al. in 2010 [164] for ^{15}N-nitrate determination in urine by gas chromatography combustion isotope ratio mass spectrometry. The method was applied for monitoring in vivo ^{15}N-arginine metabolism and endogenous NO production. The major limitation of this approach lies with the need to reduce NO_3^- to NO_2^- which is difficult to control and makes nitrate estimation indirect.

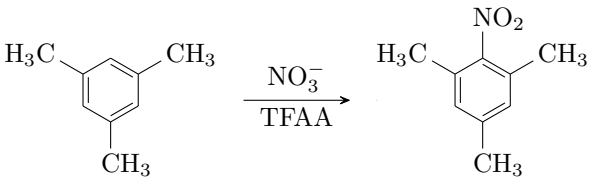
4.1.2. NO_3^- and the nitration reaction

Nitration of an aromatic rings is a specific reaction for nitrate which has been used in conjunction with gas chromatography. Already in 1974 Glover and Hoffsommer employed the following reactivity [165]:



This is an electrophilic aromatic nitration which proceed through the attach of NO_2^+ on the benzene ring [166]. Formation of NO_2^+ from NO_3^- is promoted by H_2SO_4 and resulting nitro-derivative contains nitrogen from native NO_3^- which could be used for isotope dilution quantitation (^{15}N-labeling). Since NO_2^+ rapidly exchange oxygen with the

solvent, isotopic labeling on oxygen cannot be proposed for isotope dilution. The authors treated 5 mL of water sample with 5 mL of benzene following addition of 15 mL H_2SO_4:H_2O 3:1 under stirring [165]. Reaction mixture was placed in a water bath at 75 °C for 5 min and resulting nitrobenzene (> 90% conversion efficiency) was analyzed by GC-ECD. Due to the massive amount of H_2SO_4 required, the detection limit of the method was penalized by its high blank (0.12 ppm). Such an approach was later used by Tesch et al. [167] for the determination of NO_2^- and NO_3^- in saliva and blood with quantitation limit of 0.1 ppm nitrate in a single drop of sample by GC-ECD. Similarly, Johnson et al. [168] measured nitrate in serum and urine by GC with nitrogen-phosphorous detector (0.06 ppm detection limit). Variations on this chemistry have been proposed in order to avoid using toxic benzene in a highly acidic medium. Gutzki et al. [169] replaced benzene with 2,4,6-trimethoxybenzene. Detection of 1-nitro-2,4,6-trimethoxybenzene was obtained by GC-MS/MS in negative chemical ionization mode with a low detection limit of 200 pg absolute (2 µL injection volume). The method was suitable for the measurement of NO_2^- + NO_3^- by isotope dilution ($^{15}NO_2^-$ internal standard) and it was applied to biological samples. Nitration of 2-methylphenol or 2,6-dimethylphenol in H_2SO_4 medium was proposed for nitrate determination in water samples [170]. The derivative was preconcentrated on a SPE cartridge obtaining 100-fold enrichment with a detection limit of 3 µg/L. Smythe et al. [171] proposed an alternative approach based on trifluoroacetic anhydride (TFAA) catalyzed nitration of toluene. The use of TFAA instead of H_2SO_4 allowed for milder reaction conditions avoiding degradation of nitroarginine to nitrate which was quantitative in H_2SO_4 medium. Nitration of toluene however, give rise three nitrotoluene isomers. Reported relative ratio between such isomers was 57:3:40 for *ortho*:*meta*:*para* with a detection limit better then 100 fmol on column. The reaction was held in a non-aqueous medium with 200 µL TFAA and 1 mL of toluene at 70 °C for 60 min. The solution was then washed with water and 1% sodium bicarbonate before GC-MS analysis. The method was applied for plasma and urine. A similar approach was proposed in 2008 by Jackson et al. [172] who replaced toluene with 1,3,5-trimethylbenzene. As an advantage, only one derivative was detected:



Nitration of the aromatic ring is a reaction specific only for nitrate. However, in an acidic medium, endogenous nitrite can be partially converted to nitrate giving positive interference. To avoid such effect the analyst could eliminate nitrite with sulfamic acid before derivatization or convert all NO_2^- to NO_3^- using an oxidant like H_2O_2 or $KMnO_4$.

4.1.3. NO_2^- and NO_3^-: the alkylation approach

Alkylation is a very popular approach for the determination of nitrite and nitrate by gas chromatography. The use of PFB-Br has been proposed by several authors [39, 47, 49, 54, 56, 173–179] with publications on the topic already in 1984 [173]. The use of PFB-Br for gas chromatographic determination of nitrite and nitrate was recently reviewed by Tsikas [43] who was among the first to apply PFB-Br chemistry for simultaneous determination of nitrite and nitrate in biological fluids [39]. Tsikas' method entails direct alkylation of NO_2^- and NO_3^- in acetone medium. For this purpose 100 µL of aqueous sample with internal standards ($^{15}NO_2^-$ and $^{15}NO_3^-$) were diluted with 400 µL of acetone and reacted with 10 µL of PFB-Br. This mixture was held at 50 °C for 60 min allowing formation of PFB derivatives:

$$\text{PFB} + NO_2^- \rightarrow \text{PFB-}NO_2 + Br^-$$
$$\text{PFB} + NO_3^- \rightarrow \text{PFB-}ONO_2 + Br^-$$

The reaction medium was then evaporated under a stream of nitrogen and the residue was solubilized in toluene following GC-MS analysis in negative chemical ionization. When 100 µL of 1 µM $^{15}NO_2^-$ and $^{15}NO_3^-$ aqueous standard where analyzed, a signal-to-noise ratio of 870 and 95 was obtained respectively. The method was sensitive and specific for simultaneous analysis of nitrite and nitrate in biological fluids [39, 177–179]. A significant improvement of this method was recently proposed by Yang et al. [56]. Tetraoctylammonium bromide was employed to catalyze the pentafluorobenzylation of NO_2^- and NO_3^-. The procedure entails dilution of 350 µL of aqueous sample and internal standards ($^{15}NO_2^-$ and $^{15}NO_3^-$) with 500 µL of 8.0 mM tetraoctylammonium in acetone and 50 µL 20% PFB-Br in acetone following reaction for 30 min at 50 °C. Sample were reconstituted in isoctane after evaporation under a stream on N_2. Respect to the non-catalyzed method, this approach allowed an increase of derivatization yield of 4.5 times for nitrite and 55 times for nitrate. The mechanistic aspect of this catalysis however, are not clear and will need further investigation. Another variation to the theme was proposed in 2002 by Kage et al. [54]. The authors preferred the extractive alkylation scheme for simultaneous determination of nitrite and nitrate in blood. With GC-MS in negative ionization mode a detection limit of 5 µM was proposed for both nitrite and nitrate, higher than thus reported with direct alkylation [39].

Despite the PFB method has a number of qualities such as good sensitivity and specificity, one drawback is the timely sample preparation. For this reason we implemented an alternative derivatization chemistry for nitrite and nitrate base on triethyloxonium tetrafluoroborate alkylation [72, 75, 180]:

$$Et_3O^+(aq) + NO_2^-(aq) \rightarrow EtONO(g) + Et_2O$$
$$Et_3O^+(aq) + NO_3^-(aq) \rightarrow EtONO_2(g) + Et_2O$$

A 3 mL sample aliquot was treated with 0.3 mL isotopically enriched internal standard ($N^{18}O_2^-$ and $^{15}NO_3^-$) following direct aqueous derivatization with 1 mL freshly prepared $Et_3O^+[BF_4]^-$ solution (1 g of reagent was dissolved in 10 mL of water at 4 °C with 700 µl of 25% NH_3 aqueous solution). After 30 min at room temperature, GC-MS analysis of the vial headspace was performed in negative chemical ionization mode with detection limits in the part-per-billion range. The NH_3/NH_4^+ buffer kept the pH of the reaction between 9 and 10. This condition is essential in order to avoid oxidation of nitrite to nitrate and oxygen exchange between nitrite and water which can occur in acidic medium. This sample preparation can be modified for the determination of nitrate. In this case the sample was spiked with $^{15}NO_3^-$ and treated with sulfamic acid to remove NO_2^-. At this point the blend was reacted with $Et_3O^+[BF_4]^-$ without the need for an alkaline buffer which cause a reduction in the derivatization efficiency due to a faster hydrolysis rate of the reagent. When compared to the direct alkylation with PFB-Br, the derivatization with $Et_3O^+[BF_4]^-$ has important procedural advantages: $Et_3O^+[BF_4]^-$ is a single stage aqueous derivatization which allow separation of the derivative form the matrix under gaseous form (headspace sampling). Pentafluorobenzylation is achieved in several steps resulting in an organic extract which can contain still matrix components that can deteriorate the chromatographic column (Figure 1). The $Et_3O^+[BF_4]^-$ method was employed

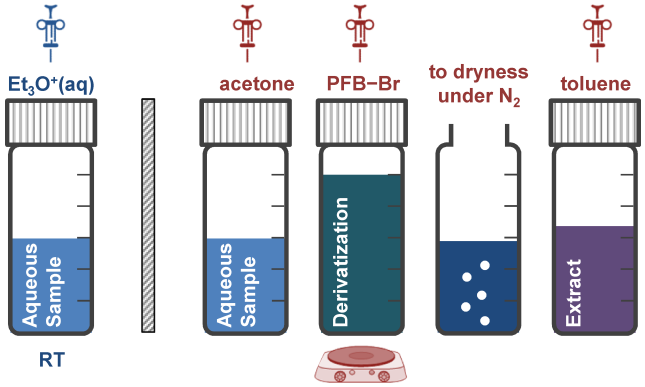


Figure 1: Procedural advantages of $Et_3O^+[BF_4]^-$ over PFB-Br derivatization. The first (on the left) is a single stage aqueous reaction resulting in gaseous derivatives separated from the matrix. The second (on the right) is a non-aqueous alkylation in acetone which requires heating at 50 °C for 60 min, evaporation under nitrogen of the reaction medium and reconstitution in toluene

for the simultaneous determination of nitrite and nitrate in seawater sample and applied for the characterization of MOOS-3 Certified Reference Materials (CRMs) for nutrients in seawater. The use of isotope dilution formalism for quantitation allowed collection of high-precision data: results from a 19 months study of the MOOS-3 are proposed in Figure 1 and demonstrate the ability of our method to perform NO_2^- and NO_3^- determination within a relative standard uncertainty of 1%. Recently we adapt the

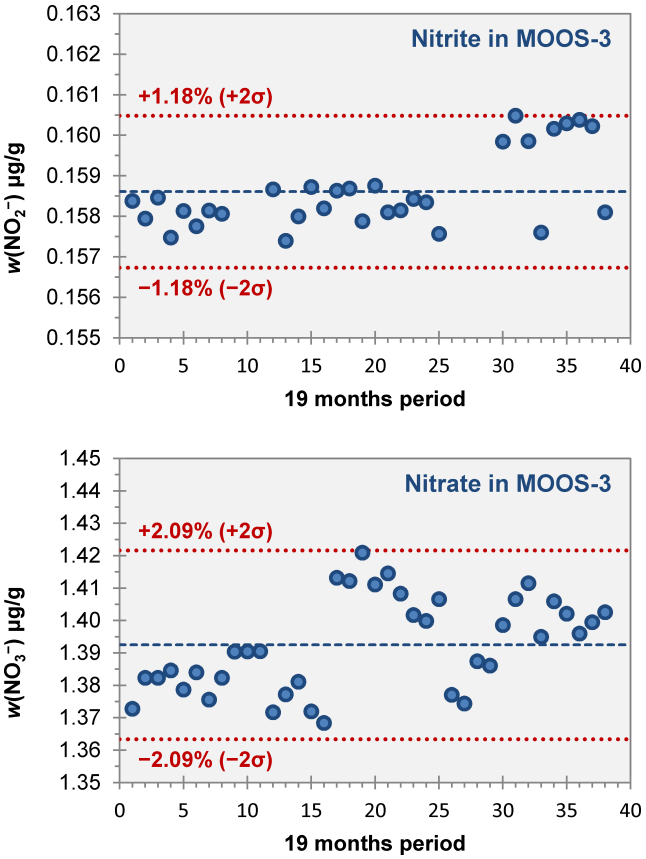


Figure 2: Determination of NO_2^- and NO_3^- in MOOS-3 by isotope dilution GC-following aqueous ethylation with $Et_3O^+[BF_4]^-$: a 19 months study

$Et_3O^+[BF_4]^-$ method for the determination of nitrate in vegetables by gas chromatography [181]. The analyte was extracted from the matrix in water at 70 °C and spiked with the $^{15}NO_3^-$ internal standard. After centrifugation, a 2 mL volume of supernatant was treated with 100 µL 1% sulfamic acid and derivatived with 50 µL of $Et_3O^+[BF_4]^-$ prepared in acetonitrile by mixing the 1 g of solid reagent with 1 mL of solvent at -20 °C. The reaction was left for 30 min at room temperature following manual sampling of the headspace and GC-MS analysis. Chromatography was completed within 1.8 min on a DB-5.625 and it was applied to quantify nitrite in vegetables in the range 10–10,000 µg/g with a detection limit of 2 µg/g on the fresh vegetable matrix in EI mode.

4.1.4. Other derivatization for NO_2^-

Another couple of methods are reported for nitrite analysis by gas chromatography. In 1993 Mitsuhashi [182] used the 3-oxobutanoate to convert NO_2^- in aqueous HCl to 2-hydroxyimino-3-oxo-butanoate. The derivative was produced with quantitative yield and it was extracted in ethyl acetate before GC-ECD analysis. Nitrite determination in

river and human saliva was attained with a detection limit of 2 ng/mL. In 2010 Tsikas et al. [183] proposed a method for the determination of nitrite in biological fluids using an on-column derivatization approach. The sample were acidified with HCl to reach pH 2. In this condition, the acid-base equilibrium of nitrite ($pK_a = 3.29$) was shifted toward the nitrous acid which could be extracted in ethyl acetate. The reaction mixture was injected in the GC-MS system working in negative chemical ionization and a signal at m/z 46 Da was detected (m/z 47 Da for the internal standard $^{15}NO_2^-$). The derivative could not be identified and the reaction efficiency was dependent on the injector temperature which was set at 300 °C. The method was applied for nitrite determination in biological fluids, but only saliva and urine could be successfully analyzed: plasma and serum contain endogenous nucleophilic compounds which react HONO before extraction.

4.2. Orthophosphate

The determination of orthophosphate is generally performed using molybdenum chemistry [258] followed by spectrophotometry detection. PO_4^{3-} is firstly reacted with ammonium molybdate to form $H_3PO_4(MoO_3)_{12}$ which is then reduced with ascorbic acid to a colored blue product detectable at 890 nm [258]. This century-old method remains the reference for the determination of phosphate in water and seawater [135, 144]. The use of spectrophotometry however, presents limitations when complex matrices are analyzed and alternative methods based on gas chromatography are reported in the analytical literature. The first attempt to convert orthophosphate in a volatile TMS-derivative was described in the sixties [259, 260] with the idea of applying gas chromatography for the analysis of sugar phosphates and nucleotides. Hashizume et al. [261] measured total phosphorus in nucleotides by digesting the sample with perchloric acid following conversion of resulting PO_4^{3-} to TMS_3PO_4 by trimethylsilylation. For this purpose the dry digested sample (10 mg) was suspended in pyridine (0.2 mL) and reacted with HMDS (0.2 mL) and TMCS (0.1 mL) at 140-150 °C for 1 hour. As noted by other authors [23], the silylation yield depended on the nature of the phosphate salts analyzed: alkali-phosphates like sodium or potassium were associated with a low silylation yield whereas with ammonium salts the derivatization was almost quantitative [261]. Matthews et al. used the silylation approach for the determination of orthophosphate in water after analyte extraction in toluene-octanol mixture using Adogen-464-HCO_3^- as phase transfer catalyst. The derivatization of the organic phase was performed at room temperature for 15 minutes with BSTFA - 1% TMCS with a detection limit of 100 ppb PO_4^{3-} using a flame-photometric detector. Smillie et al. [262] measured both phosphite and phosphate in plant extracts by GC-MS under the form of TBDMS ester. The plant extract sample (50-100 µL) was dried under vacuum following the addition of pyridine (50 µL) and MTBSTFA (100 µL). The derivatization was complete within 4 hours at room temperature. The reported detection limit with mass spectrometry detection was 100 pg. Bierhanzl et al. [263] employed the HMDS and BSTFA for the full silylation of orthophosphate (and other organo-phosphates) and applied the method for the GC-MS determination of PO_4^{3-} in aqueous fraction of the cell membrane lysate of textitBacillus subtilis. Alternatives approaches for phosphate analysis are generally based on alkylation. n-butyl iodide was employed to react PO_4^{3-} to $n Bu_3PO_4$ [33]. The preparation of trimethyl phosphate by diazomethane was reported by Brunengraber [264] in a study dedicated to the determination of ^{18}O enrichement of water in biological fluids after reaction with phosphorus pentachloride and by Hardy [200] for the determination of phosphate, mono- and di- alkyl phosphate in tri-n-butylphosphate.

4.3. Mono-, di- alkylphosphates and phosphonates

Organophosphate compounds have been widely used to produce insecticides, herbicides, warfare agents, plasticizes and EP additive. Mostly employed compounds includes the alkyl esters of phosphoric acid, phosphonates and corresponding thio-analogues. The stability of these compounds in environment and human body is limited by disposition of PO-R and PS-R bounds to hydrolysis. For this reason, target analytes which demonstrate exposure to these contaminants include their degradation byproducts such as dimethylphosphate, diethylphosphate, dimethylthiophosphate, diethylthiophosphate, dimethyldithiophosphate, and Diethyldithiophosphate [226–228]. A significant mole of literature has been devoted to the development of methods for their determination. Traditionally these contaminants have been analyzed by gas chromatography after derivatization [185]. As for orthophosphate, derivatization is necessary because such compounds are acidic with low pK_a at least for the first dissociation (diethyl phosphoric acid $pK_a = 1.3$; methylphosphonic acid $pK_{a1} = 2.3$ and $pK_{a2} = 7.76$) [265, 266] and in physiological conditions they are deprotonated. In order to convert such analytes in derivatives amenable to gas chromatography, several approaches have been proposed. The most popular methods are based on alkylation and silylation. In 2003, Black and Muir [267] reviewed derivatization methods employed for the analysis of warfare agents by-products with attention to silylation, methylation and pentafluorobenzylation. In 2016 Tsikas [43] reviewed recent literature dedicated to the use of PFB-Br for the determination of dialkyl phosphates in biological fluids. In this paragraph, derivatization strategies proposed for conversion of the anionic -PO^- moiety into a thermally stable nonpolar derivative are discussed and summarized in Table 5.

4.3.1. P-OH silylation

Most of silyl chemistry applications for conversion of the P-OH group are related to identification of warfare agents degradation by-products in environmental samples [267].

Table 4: Derivatization chemistries for the conversion of nitrite and nitrate in volatile derivatives

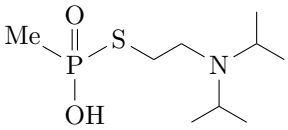
Derivative	Reagents	Notes (Year)	Ref.
Aryl-N≡N$^+$ → hydrolysis or further reaction to triazole or Sudan-I	Aryl-NH_2/aqueous acid	Diazotization reaction of NO_2^- which is fully converted into a diazonium ion. The Aryl-N≡N$^+$ intermediate can be hydrolyzed or further reacted. Aromatic vicinal diamines yields the corresponding triazole. Formation of Sudan-I dye has been proposed recently. Late studies on GC-MS reported detection limits in the low ppt (1980-2010)	[155–164, 184]
Aryl-NO_2	Aryl-H/acid	Nitration of the aromatic ring (Ar) in acidic conditions: Ar-H + H_2SO_4 + NO_3^- → Ar-NO_2. NO_2^- can interfere in this assay and need to be removed or converted to NO_3^-. Applied to biological fluids and environmental samples (1974-2008)	[165, 167–172]
PFB-NO_2^- and PFB-ONO_2^-	PFB-Br	Simultaneous determination of NO_2^- and NO_3^-. Direct alkylation in acetone media at 50 °C 60 min. Suitable for NO_2^- and NO_3^- speciation in biological fluids With NCI GC-MS (1984-2017)	[39, 47, 49, 54, 56, 173–179]
Et-ONO and Et-ONO_2^-	$Et_3O^+[BF_4]^-$	Simultaneous determination of NO_2^- and NO_3^-. Direct alkylation in water medium at RT following matrix separation by headspace sampling. Suitable for NO_2^- and NO_3^- speciation in seawater with NCI GC-MS and NO_3^- determination in vegetable with EI GC-MS (2011-2017)	[72, 75, 180, 181]

For this purpose both TMS and TBDMS derivatives have been prepared [268], but the latter are more stable toward hydrolysis and a better choice for such applications [7]. Kataoka et al. [193] reported the determination of alkyl methylphosphonate (RMPA) and methylphosphonate (MPA) in soil. For this purpose an aqueous soil extract were first dried at 50 °C under vacuum and then derivatized with MTBSTFA in acetonitrile at 60 °C for one hour following GC-MS analysis. Single and double TBDMS derivatives were observed for RMPAs and MPA rFor soil analysis however, sensitivity issues related to extraction and derivatization have been reported [193]. Interference of divalent cations such as Ca^{2+} and Mg^{2+} reduced silylation yield [193, 197]. This observation is consistent with the results reported on the silylation of inorganic phosphate [23, 261] where complete derivatization was attained only with ammonium phosphates. In this regard, phosphates and phosphonates can combine with metal cations to give insoluble complex which are inert toward silylation, resulting in negative interference that can span from 10% to 98% [193]. For this reason, sample pretreatment with strong anion exchange (SAX) column was beneficial. Noami et al. [194] further improved this approach by eluting a sample sodium hydroxide aqueous extract in a SAX column with the presence of a high concentration of ammonia in methanol. The use of ammonia support conversion of phosphonates in the corresponding ammonium salts increasing the derivatization yield to the 90% level for both MPA and RMPA. Richardson and Caruso employed TBDMS derivatives for the determination of alkylphosphonates in soil and water by GC-ICPMS with detection limits better than 5 pg absolute and linear response in the 0.2 to 20 ng range [196]. In this case the derivatization was achieved with MTBSTFA with 1% of TBDMSCl in a 1:2 mixture of acetonitrile:reagent at 80 °C for 45 minutes. The TBDMSCl acts as activator of the MTBSTFA increasing both reaction rate and extent [7]. Gravett et al. [198] further improved this approach by adding pyridine as proton scavenger. MTBSTFA has been also employed for in-situ derivatization of alkylphophonates on SPME [192], on diatomaceous sorbents [199], and with the hollow fiber-protected liquid-phase microextraction technique [195] with detection limits in the sub part-per-billion range. The silylation of phosphonic acids has also been achieved by trimethylsilylation. Dubey et al. [185] used the BSTFA to react alkylphophonates (R = methyl, ethyl, *n*-propyl and isopropyl) and corresponding alkylthiophosphonates into the bis(trimethylsilyl) esters. The derivatization was performed in acetonitrile medium (50 µL) by reaction with 200 µL of BSTFA at 70 °C for 1 hour. This approach has been used in other studies [187, 191, 269]. Dubey et al. [185] discussed resulting EI mass spectra, concluding that double TMS alkylphosphonate derivatives exhibited a main signal at [M-15]$^+$, whereas the alkylthiophosphonates at [M-R]$^+$. TMS approach was also implemented for the determination of nerve agent degradation products in human plasma with detection limits better than 22 ng/mL [186]. Terzic et al. [189, 268] employed the BSTFA for the in-situ derivatization of several compounds related to chemical warfare agents followed by thermal desorption GC-MS; the procedure entailed the preparation of tubes packed with Tenax TA 60/80 mesh that were used to adsorb the target analytes which were then derivatized with 3 µL BSTFA at 50

Table 5: Derivatization chemistries for the conversion of phosphates/phosphonates in volatile derivatives

Derivative	Reagents	Notes (Year)	Ref.
PO-TMS	BSTFA	Derivatives sensitive to moisture. Analyte multiple silylation are possible. TMCS is used as catalyst with pyridine as proton scavenger. Applications includes qualitative screening of environmental samples for chemical warfare agents markers (2005-2015)	[185–191]
PO-TBDMS	MTBSTFA	Similar chemistry and application reported for BSTFA, with better stability toward hydrolysis. Interference of Ca^{2+} and Mg^{2+} is limited by SAX elution with NH_3. Used in conjunction with SPME with detection limits in the part-per-billion range (1999-2014)	[192–199]
PO-Me	Diazomethane	Highly toxic and explosive. Used for analysis of dialkylphospahtes in urine with detection limit of 4-20 µg/L. Interference of orthophosphate and poor chromatography (1964-2012)	[200–206]
	MeI	Used for quantitation of dialkyl phosphates in urine after exposure to organophosphorus pesticides (2002)	[207]
	Me_3PhN^+	On-column derivatization. Limited column life due to caustic effects of the reagent but safer than previous strategies. Detection limit in the part-per-billion for quantitation of dialkyl phosphate in urine (1978-2007)	[208–212]
PO-R	Diazoalkane	Ethyl, pentyl, benzyl derivatives showed better chromatography then methyl ones. Recently 3-pyridyldiazomethane was employed for structural determination of alkyl methylphosphonates by EI GC-MS (1967-2013)	[213–220]
	Tolyltriazenes	Less toxic then diazoalkanes can perform multiple benzylations of monoalkyl phosphates in 15 min (1979)	[221, 222]
	PeBr, PrBr	Derivatization at 100 °C in less then 2 h with no interference from Ca^{2+} and Mg^{2+}. Alkylphophonates screening in water with 0.1-0.75 µg/mL detection limits (2006-2017).	[223, 224]
PO-$(CH_2)_3$Cl	I-$(CH_2)_3$Cl	Single alkylation of dialkyl phosphates in urine with part-per-trillion detection limit (2002-2013)	[225–228]
PO-PFB	PFB-Br	Single alkylation of dialkyl phosphates in urine and alkyl alkylphosphonates in environmental samples with sub part-per-billion detection limit (1981-2015).	[229–254]
PO-Bn(CF_3)	N=N-Bn(CF_3)	Rapid derivatization (5 min at RT) of 25 µL aqueous samples by dilution in ACN (475 µL) with 4 µL reagent. Quantitation of alkylphosphonates (mono and diprotic) in urine and water with sub part-per-billion detection limits (2010-2013)	[255, 256]
P-F	HF	Dehydroxy-fluorination of dialkylphospahtes for the conversion of P-OH into P-F (1980)	[257]

°C for 5 minutes. Due to the limited contact time with the reagent, compounds with two silylable moieties lead to the formation of both mono- and di- TMS derivatives. The use of BSTFA has also been proposed for the determination of dialkyl phosphate ester in petroleum samples. Rossé and Harynuk [188] proposed trimethylsilylation of dibutyl and bis(2- ethylhexyl) phosphate for their determination in oil. For this purpose a 100 µL of] BSTFA:pyridine:TMCS mixture (10:5:2) was employed to react 500 µL of hexane extract at room temperature for 30 minutes with detecti-FID system. An interesting application of TMS chemistry was reported by Subramaniam et al. [190] for the GC-MS identification of S-2-(N,N-diisopropylaminoethyl) methylphosphonothiolate known as EA-2192:



This molecule exhibits a high toxicity and is associated to the hydrolysis of VX nerve agent. Until 2012 it was believed that the silylation of this phosphonate was not feasible due to its zwitterionic character [267]. However, Subramaniam et al. [190] proved that the issues encountered for the silylation of EA-2192 were due to the presence of salt that can interfere with the derivatization chemistry. This results is consistent with the founding of Kataoka et al. which report strong interference of Ca^{2+} and Mg^{2+} during derivatization of alkyl phosphonate and justifies sample preparation strategies aimed to remove the ionic component from the sample.

4.3.2. P-OH methylation

Methylation of the P-OH group has been proposed in early days with with diazomethane derivatization [200–206]:

$$CH_2N_2 + \text{OH-P} \rightarrow H_3CO\text{-P} + N_2$$

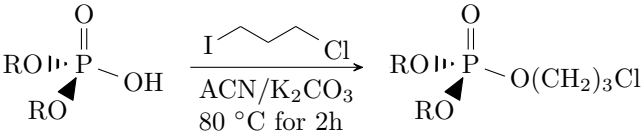
CH_2N_2 however is explosive and highly toxic; furthermore this approach suffer orthophosphate interference which produces the same derivative as the mono and dimethyl phosphate:

$$O{=}P(OH)_3 + CH_2N_2 \rightarrow O{=}P(OMe)_3$$
$$O{=}P(OH)_2(OMe) + CH_2N_2 \rightarrow O{=}P(OMe)_3$$
$$O{=}P(OH)(OMe)_2 + CH_2N_2 \rightarrow O{=}P(OMe)_3$$

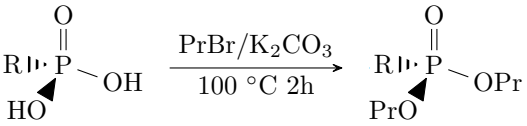
For these reasons, other milder methylating agents has been used. Lin et al. [207] isolated four alkylphosphates on a SAX disk and performed the methylation directly on the disc with methyl iodide in acetonitrile at 80 °C for one hour. On-column methylation with trimethylphenylammonium hydroxide has also been proposed [208–212]. However, methyl derivatives of phosphoric and phosphonic acids are still polar compounds with limited chromatographic properties [267] and are prone to hydrolysis. Therefore, alkylation with higher alkyl chain is more popular.

4.3.3. P-OH alkylation

The use of alkylation reaction for the derivatization of phosphates and phosphonates has the advantage to provide more stable derivatives with better GC figure-of-merits as compared to methylation. For this purpose ethylation and amylation reactions based on the use of diazoalkanes are reported [213–218]. For example the amyl derivatives of dialkyl phosphates were prepared by Shafik et al. in 1973 [215] with diazopentane. The alkylating reagent was prepared in-house starting from the *N*-amyl-*N*-nitro-*N*-nitrosoguanidine and used for reacting dialkyl phosphates previously acid-extracted in organic solvent. Due to health and safety concerns associated with diazoalkanes, Daughton et al. [221] and Takade et al. [222] used a non-aqueous reaction with triazene derivatizing agents for the benzylation (3-benzyl-1-*p*-tolyltriazene) and nitrobenzylation (1-(4-nitrobenzyl)-3-(4-tolyl)triazene) of mono- and di- alkyl phosphate at the ppb level. The reaction was accomplished in acetone for 20 min at 60-70 °C. Both reagents are considerably safer that diazoalkane. In fact they are solid, non-volatile, non-explosive, do not need to be prepared in-house, and are stable in solution [222]. However, they are potential carcinogens [221]. An alternative benzylation approach was proposed by Kupfermann et al. [219] using diazotoluene as derivatizing agent. Despite the use of this reagent did not give evident procedural advantages respect to the triazenes, the authors proved that benzyl derivatives of dialkyl phosphates produced a significant molecular ion which give an advantage for EI mass spectrometric detection. More recently another diazo compound, the 3-pyridyldiazomethane, was utilized for the derivatization of alkyl methylphonic acids related to the Chemical Weapon Convention. Pyridyl derivatives have the advantage to provide unique EI fragmentations making possible the GC-MS identification of structural related compounds [220]. Another alkylation approach employed to derivatiz ed phosphate ester was based on the use of 1-chloro-3-iodopropane. Bravo et al. [225, 226] proposed a GC-MS/MS method for the determination of six dialkylphosphate at the part-per-trillion level in urine samples (MRM in positive CI). The samples were spike with isotopically enriched internal standard and concentrated under evaporation. The residue was then suspended in acetonitrile and reacted with 1-chloro-3-iodopropane at 80 °C for two hours. The reaction was favored by adding potassium carbonate grains directly in the non-aqueous reaction medium:

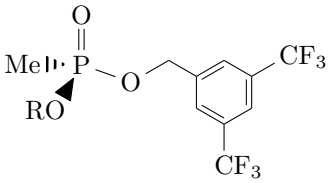


The presence of chlorine on the molecular structure of the derivatives was used to prove the selectivity of the method by monitoring the ^{35}Cl to ^{37}Cl ratio. This interesting derivatization approach has been employed by De Alwis et al. in 2006 [227] with an SPE method for isolation of dialkyl phosphates from urine samples and by Wang et al. in 2013 [228] on the same matrix for monitoring human exposure to organophosphate pesticides. In a similar fashion, other haloalkanes were proposed for the derivatization of the P-OH moiety. Pardasani et al. employed the reactivity of both pentyl bromide [223] and propyl bromide [224]:



for the derivatization of di-protic phosphonic acid connected with the Chemical Weapon Convention. With the

use of the hollow fiber liquid phase microextraction detection limits of 0.5-0.75 µg/mL were obtained. A very popular derivatization scheme applied for both phosphates and phosphonates is based on the alkylation with PFB-Br. This strategy was recently reviewed [43] and 26 research papers over the 1982-2015 time frame are summarized in Table 5. This reagent has been applied for determination of dialkylphosphates, dialkylthiophosphates, dialkyldithiophosphates, alkyl alkylphosphonates in biological fluids and environmental samples [229–254]. As a general reaction scheme, the direct alkylation of the analytical substrate with PFB-Br has been proposed in acetone or acetonitrile with a base like K_2CO_3 at 40-90 °C for 0.5-16 hours following dissolution in hexane after evaporation of the reaction media to dryness [230, 247]. Most of the applications of PFB chemistry encompass phosphates/phosphonates with only one protic group. Due to the steric hindrance of the PFB group it is expected that molecule with multiple P-OH groups would react incompletely with PFB-Br [43]. The major advantage of PFB derivatives is their disposition to undergo chemical ionization in negative mode (NCI) which brings the detection limits below the part-per-billion range [241]. This great advantage is counterbalanced by the timely preparation of PFB esters which make this approach unsuitable for fast screening. For this reason, Subramaniam et al. [255, 256] proposed a novel fluorinated phenyldiazomethane for the conversion of the P-OH moiety in the following derivative:



This approach maintains the advantage of NCI high-sensitivity, but overcome the timely procedure for the preparation of PFB esters [255]. The direct derivatization of an aqueous sample (25 µL) was attained in 475 µL acetonitrile with 4 µL of a fluorinated phenyldiazomethane prepared in house within 5 min at room temperature in a ultrasonic bath. Resulting solution could be analyzed directly by GC-MS and the method was implemented for the screening of nerve agents degradation by-products in both biological and environmental samples.

4.4. Thiocyanate, cyanide and sulfide

Cyanide (CN^-) is a potent toxic agent able to inhibiting cell respiration by binding Fe(III) of cytochrome oxidase. Cyanide is widely used in industry and regulation have been established in several countries to ensure minimum standard of quality [270]. Thiocyanate (SCN^-) is its major metabolites in mammals, and it is regarded as a long-term biomarker for CN^- exposure and for assessment of the internal smoking dose [271]. Most of analytical applications are focused on simultaneous determination of CN^- and SCN^- in biological samples. Normal blood cyanide level averages from 0.015 to 0.030 µg/mL in non-smokers, and from 0.03 to 0.08 µg/mL in smokers where it becomes toxic at concentration above 0.5 µg/mL. Normal plasma thiocyanate levels ranges from 1 to 4 µg/mL (3 to 12 µg/mL in smokers) [272]. Sulfide ion (S^{2-}) is in acid equilibrium with H_2S which is an asphyxiant, irritant and neurotoxic gas. Hydrogen sulfide poisoning is a common occupational hazard, with an incidence that is second only to carbon monoxide poisoning and a mortality rate that is the first among occupational poisoning incidents [273]. Analysis of blood sulfides is diagnostic of acute hydrogen sulphide poisoning. Because of the extreme H_2S toxicity along with its relevant biological role [274], very low detection limits are required for its quantitation. Traditional methods for CN^- [275], SCN^- [276] and S^{2-} [277] include spectrophotometry upon conversion of the analytes in colored derivatives [278–280]. These approaches however, may lack specificity when complex matrices are analyzed. This issue is also common to electrochemical methods. For example, amperometric methods are affected by the presence of large amount of chloride and organic compounds, like fatty acids, sugars, aldehydes and polysulphides. Moreover, pre-concentration is usually required to obtain limits of detection in the µg/L range. Sensitive voltammetric methods are reported for S^{2-}, but issue with the identification of the analytical peak are known for complex matrices like seawater [281]. Liquid chromatography, ion chromatography and electrophoresis have been widely employed for separation of inorganic anions, but typically such methods are interfaced with UV (210 nm) and conductivity detectors which suffer limited specificity and detection power [282–284]. Methods based on gas chromatography that overcome issues of the classical ones have been proposed for the determination of CN^-, SCN^- and S^{2-}. In the following paragraphs we will discuss major derivatization chemistries that have been applied for the conversion of these anions into volatile compounds suitable for gas chromatography. Derivatization chemistries recently applied for GC determination of these analytes are also summarized in Table 6.

4.4.1. Generation of HCN by acidification

Simple aqueous acidification with sulfuric or phosphoric acid has been proposed for the conversion of CN^- in gaseous HCN:

$$CN^-(aq) + H^+(aq) \rightarrow HCN(g)$$

This approach has been used for over 40 years for cyanide determination by headspace gas chromatography using nitrogenphosphorus specific detector (NPD) or mass spectrometry [285–294]. Variations on this technique include fully automated procedures [293], cryogenic oven trapping [288, 295] and sampling of the headspace via SPME fibers [292, 296–298]. In the cited studies detection limit between 2 and 50 µg/L are reported, and acetonitrile or propionitrile were proposed as internal standards with the NPD

detector. Acetonitrile however, is widely used in most laboratories as an extraction solvent or mobile phase for liquid chromatography, therefore it is not an ideal choice [289, 297]. Among recent studies the implementation of automated headspace GC-MS methods has allowed high-precision isotope dilution quantitation of cyanide in blood with detection limits of 3-8 µg/L [295, 299]. Furthermore, this approach was proven to generate data statistically equivalent to the a classic spectrophotometric method [300]. Although acid generation of HCN is simple to implement, such an approach has some limitations. When biological samples are analyzed, artifactual formation of CN^- from SCN^- in the presence of oxyhemoglobin in acidic medium has been observed [301]. Furthermore, HCN is a low-molecular-weight molecule which is detected at m/z of 27 Da; this region of the MS spectrum is dominated by air gases like N_2 (m/z of 28 Da) which can cause interference. Another issue working with gaseous HCN is related to the injection mode. In this regard, some authors reported that HCN could be measured without cryogenic cooling [294, 299], but others could not obtain reliable results without cryogenic cooling [295, 302].

4.4.2. Gas chromatography of H_2S

In aqueous samples sulfide ion has not been detected at substantial concentrations even in alkaline medium: Meyer et al. [303] reported that starting from 8.9 N NaOH with 0.6 M S^{2-} and 0.1 M $NaClO_4$ a 0.5± 0.1 M HS^- solution was obtained, proving that even in such extreme alkaline conditions the major sulfide portion was bisulfide:

$$S^{2-}(aq) + H^+(aq) \rightarrow HS^-(aq)$$

This observation with reported values of H_2S second dissociation constant ($pK_{a2} = 17 \pm 1$ as measured by Raman spectroscopy [303] or $pK_{a2} = 17.6 \pm 0.3$ as measured with a pH-electrode [304]). Bisulfide ion itself is in equilibrium with H_2S:

$$HS^-(aq) + H^+(aq) \rightarrow H_2S(g)$$

The first dissociation constant of H_2S ($pK_{a1} = 7.06\pm 0.02$ [305]) suggests that in physiological condition (pH 7.4) H_2S, HS^- and S^{2-} are present at the 30:70:0.000002 ratio [274]. Despite H_2S is not the most abundant species, several study are focused on its determination which can be attained directly by gas chromatography. At very low concentration H_2S is of concern for its unpleasant odor and it has been analyzed by GC with flame phometometric detector in gaseous industrial effluents (with detection limit in the µg/m^3 range) [306], in hyper-eutrophic freshwater sample [307], and in wine samples (with a detection limit of 0.50 µg/L) [308] as part of its aroma [309]. In all methods a PDME-Carboxen fiber was employed for sampling from the vial headspace. Other examples of direct determination of H_2S by headspace gas chromatography include pharmaceutical formulations [310], seawater [311], biological [312] and atmospheric samples [313]. In analogy with CN^- analysis (Paragraph 4.4.1), the determination of total dissolved sulfides could be attained by gas chromatography upon acidification:

$$S^{2-}(aq) + 2H^+ \rightarrow H_2S(g)$$

Radford-Knoery et al. [314] reported a method for total sulfides where 300 mL aliquots of water sample were treated with 12 mL of H_3PO_4 1.5 M following stripping/cryogenic trapping of H_2S. With a flame photometric detector a an absolute detection limit of 0.06 pmol was reported. On the 300 mL sample volume as low as 0.2 pmol/L of total sulfides could be measured. In this study total sulfides was defined as the summation of free sulfide (H_2S, HS^-, and S^{2-}) and dissolved metal sulfide complexes.

4.4.3. Generation of CNCl by chloramine-T

To overcome disadvantages associated to HCN detection, other derivatization approach have been proposed to convert CN^- into a higher molecular weight derivative. For example, Valentour et al. [315] reported first the use of chloramine-T (sodium *p*-toluene sulfonchloramide) to convert CN^- into cyanogen chloride (CNCl), a volatile gas readily detectable by ECD. This derivatization has been applied for the determination of cyanide in cigarette smoke [316] with a linear response from 25.0 ng/mL to 15.0 µg/mL (RSD = 0.07-3.30%) on a µECD detector. Cyanide was also measured in blood using both GC-MS detection in EI mode (working range 0.13-2.6 µg/mL [317]) and ECD (DL 10 µg/L [318]). The chloramine-T derivatization requires first separation of CN^- from the matrix which is commonly attained by acid conversion of the analyte into HCN. For this purpose, the use of a microdiffusion cell was proposed for the collection of HCN in diluted NaOH following extractive derivatization with a solution of chloramine-T in *n*-heptane or hexane [315–317]. Other authors avoided the lengthy microdiffusion step by injecting HCN(g) directly in a pre-column packed with chloramine-T [319]. Notably, Odoul et al. carried out HCN formation and chlorination in a single step and in the same reaction medium with a double vial system, the outer containing sample solution, the inner the derivatizing agent [320]. In the most recent study using this derivatization, the authors converted CN^- into HCN with nitric acid into a headspace vial containing a chloramine-T stick filter paper [318]. In the cited studies, chloramine-T concentration was 0.25-1.5%, and reaction was attained at 20-65 °C within 90 min.

4.4.4. CN^-, SCN^- and S^{2-} by alkylation

Alkylation is a common approach for derivatization of CN^-, SCN^- and S^{2-} before gas chromatography. Methylation of these analytes could be attained with dimethyl sulfate, methyl *p*-toluenesulfonate or trimethyl phosphate (Table 1) and in paragraph 3.2 is reported the proof of concept for these classical reagents. A recent application

of $(MeO)_2S{=}O$ chemistry was proposed for the determination of salivary thiocyanate by GC-FID with a detection limit of 0.2 ng/mL and a working range up to 80 ng/mL. The sample was pre-cleaned on a SPE column following derivatization with 100 µL dimethyl sulphate at 60 °C for 30 min in an ultrasonic bath. The methyl-derivative was extracted in CH_2Cl_2 and injected in the GC-FID [321]. Tanaka et al. compared methylation and ethylation with $(MeO)_2S{=}O$ and $(EtO)_2S{=}O$ [32] founding the second reagent more efficient to alkylate S^{2-}. For common laboratory practice however, the use of such very toxic reagents poses concerns. SCN^- ethylation was also attained with ethyl iodide in an immiscible aqueous phase-organic phase system with commercial Kryptofix 222B polymer as immobilized phase-transfer catalyst, and resulting ethyl thiocyanate was detected by a flame thermionic detector with a detection limit of 0.01 µg/mL [322]. Methyl iodide was employed for the alkylation of sulfide and polysulfides following their determination in drinking water by headspace SPME GC-MS with detection limits ranging from 50 to 240 ng/L [323]:

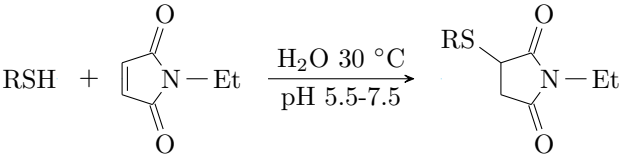
$$S_n^{2-} + 2MeI \rightarrow Me_2S_n + 2I^-$$

Me_2S however, is a compound that can be present endogenously in a water sample [314] which could result in an obvious positive interference for S^{2-} detection. On-column butylation of SCN^- ion paired with tributylsulfonium ion [30] was employed for plasma analysis. The ion pair was extracted into ethyl acetate and injected into a gas chromatograph, resulting in formation of volatile EtSCN. The method was suitable for quantitation of thiocyanate in 100 µL plasma samples from nonsmokers. Another alkylation strategy that we recently proposed for the determination of salivary SCN^- is based on aqueous ethylation with triethyloxonium tetrafluoroborate followed by headspace GC-MS [73]. The method was optimized for quantitation of saliva samples containing 1-400 µg/g SCN^- with a standard uncertainty of 2% relative for saliva samples with 25 µg/g SCN^-. The method was applied to discriminate between smokes and nonsmokers. A popular alkylation strategy for derivatization of CN^-, SCN^- and S^{2-} is based on PFB-Br. The first application of this reagent for anions dates back to 1981, when direct alkylation of S^{2-} allowed its quantitation in spring water by GC-ECD at the part-per-billion level [51]. An alkaline medium favor the double alkylation of S^{2-} to PFB_2S even if for NaOH concentrations above 0.06 M strong PFB-Br hydrolysis was observed. This method combined with extractive alkylation with tetradecyldimethylbenzylammonium chloride found forensic applications for the determination of S^{2-} (0.3 nmol/mL DL) [324] and polysulfides (5 nmol/mL DL) [325] in whole blood in cases of hydrogen sulfide poisoning. Later, Hyspler et al. [326] presented a method for determination of S^{2-} in whole blood with benzalkonium chloride as phase-transfer catalyst for PFB-Br extractive alkylation. Derivatization was completed in 4 hours under continuous shaking with a detection limit of 192 µg/L on GC-MS. Such method was suitable for quantitation of sulfide in blood of healthy volunteers (35-80 µmol/L) with a reproducibility better than 3%. Many inorganic anions and organic alcohols were checked as internal standards, and naphthalene was chosen to compensate for instrumental fluctuations. Alkylation of CN^- and SCN^- by PFB-Br was also reported in early eighties [52]. The derivatives formed after direct alkylation in a acetone/NaOH medium were directly analyzed by GC-FID or ECD, and identified by GC-MS. The effects of several reaction parameters (e.g., added base or acid, amount of PFB-Br, reaction temperature, solvent and reaction time) were optimized for each anion. In a second study, the interference of SCN^- with CN^- following PFB alkylation was reported [53]. While analyzing SCN^- a peak also appear at the retention time of CN^- derivative showing possible conversion of SCN^- to CN^- during the derivatization step. A counterintuitive reactivity of SCN^- with PFB-Br was also reported by Wu et al. [52] who identified PFB_2S (S^{2-} natural derivative) as the main reaction product. This chemistry artifacts were observed for direct PFB alkylation in acetone or ethanol medium suggesting that care should be taken when PFB chemistry is applied for speciation of CN^- and SCN^-. Paul and Smith [327] addressed this issue using the extractive alkylation in 2,5-dibromotoluene with tetrabutylammonium sulfate as phase-transfer catalyst. In these conditions, simultaneous determination of CN^- and SCN^- in saliva could be attained without formation of side product or SCN^- hydrolysis. Derivatization yield was 55-65% and with a GC-MS system in EI mode a linear response was collected in the 1-100 µmol/L for CN^- and 5-200 µmol/L for SCN^-. A similar extractive alkylation approach was also applied for CN^- and SCN^- speciation in blood [57]. Derivatization of CN^- was successful after protein precipitating. whereas SCN^- could be analyzed only on whole blood. Therefore, two different procedures were required for analysis of CN^- and SCN^-. Identification was attained by GC-MS and quantitation by GC-ECD with detection limits 0.26 µg/g CN^- and 1.7 µg/g SCN^-, while the gross recovery of both compounds was 80%. More recently, Bhandari et al. [328] employed extractive alkylation into ethyl acetate (tetrabutylammonium sulphate as phase-transfer catalyst) for the simultaneous determination of CN^- and SCN^- in plasma. With chemical positive ionization GC-MS, the authors reported detection limits of 1 µM and 50 nM for cyanide and thiocyanate with a linear dynamic range from 10 µM to 20 mM for CN^- and from 500 nM to 200 M for SCN^- (RSD $\leq$ 9%). Gross recovery of both anions from swine plasma was 90%. Extractive PFB alkylation was also proposed for the GC-MS determination of SCN^- in urine, saliva, and hair as a marker for smoke uptake (1.015 µg/mL quantitation limits) [329] and in plasma proteins to confirm cyanide exposure [330]. In this last study SCN^- bound to protein was extracted from swine plasma within 1 hour at room temperature in aqueous buffer at pH 10 and the derivatization strategy was the one proposed by Kage et al. in 1996 [57]. This study re-

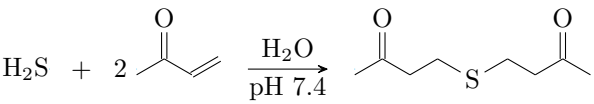
lied on the reactivity of free CN^- with disulphide bonds in proteins to form protein-bound thiocyanate. Because proteins have long half-lives, analysis of thiocyanate-protein adducts has the potential to be a long-term marker for CN^- exposure. In our recent study, we investigated the reactivity of PFB-Br with CN^- [42] and we found that direct derivatization in alkaline medium leads to multiple alkylation with formation of F_5Bn-CN, (F_5Bn)(F_5Ph)CH-CN, and (F_5Bn)$_2$(F_5Ph)C-CN. When a 100 mL volume of an aqueous CN^- standard in NaOH 0.1% was reacted with 700 mL of 1.3% PFB-Br in acetone, (F_5Bn)$_2$(F_5Ph)C-CN was the most abundant derivative. Such highly-fluorinated specie could be detected at 0.5 ng/g with negative chemical ionization GC-MS and the method was applied for the determination of total cyanide in soil.

4.4.5. Sulfide derivatization with α,β-unsaturated ketones

The reactivity of hydrogen sulfide with α,β-unsaturated ketones [331] has been employed for sulfides determination via gas-chromatography. Salgado-Petinal et al. [332] converted several alkanethiols and H_2S into volatile compounds by aqueous reaction with *N*-ethyl-maleimide (NEM) following immersion SPME GC-MS:



This reaction is very specific for thiols and in case of H_2S it can lead to the formation of NED-SH (single alkylation) and NED_2S (double alkylation). For H_2S quantitation, the first derivative was preferred being the second not reproducible. Under optimized conditions NED-SH was quantified at 6.9 ng/L. The authors also reported that H_2S could also react with alkenethiols to form R-S-S-NED resulting in potential analyte losses [332]. A similar approach was recently proposed using 3-buten-2-one [333]. Also in this case the reaction with H_2S could lead to multiple derivatives however, under strong excess of reagent and at pH 7.4 the reaction could be shifted to the double derivative:



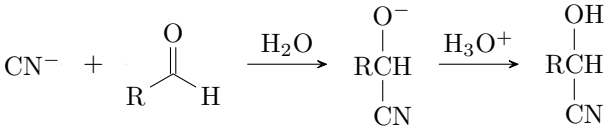
Stable isotope dilution was implemented for quantitation. The authors prepared a $Na^{34}S$ internal standard by reacting elemental $^{34}S_8$ with metallic sodium following a known procedure [334]. Detection was attained by two-dimensional heart-cut GC-MS using positive chemical ionization.

4.4.6. Other derivatization for CN^-

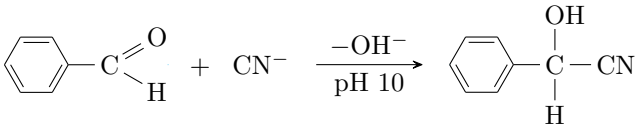
The interest behind CN^- quantitation has fuelled the development of derivatization methods other than conversion to HCN or alkylation. For example, Funazo et al. [335] described formation of benzonitrile from CN^- in presence of Cu^{2+} ion, aniline and sodium nitrile. 1 mL of aqueous sample was treated with 0.25 mL$NaNO_2$ 70 mM and 0.25 mL $CuSO_4$ 100 mM following addition of 1 mL of aniline 300 mM in chloroform and the reaction mixutre was shaken for 30 min at 55 °C. Detection limit of 3 µg/mL with GC-FID were obtained, but a non-linear calibration plot on the low concentration was observed. Reaction of CN^- with Br_2 was employed for CN^- determination by GC-ECD [336]:

$$CN^-(aq) + Br_2(aq) \rightarrow BrCN(g) + Br^-(aq)$$

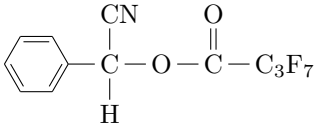
Resulting BrCN was sampled in the headspace. SCN^- is an interference to the assay since it is converted to the same BrCN derivative. Therefore this method returns the summation of CN^- and SCN^-. Another proposed approach for CN^- derivatization is based on reaction with formaldehyde or acetaldehyde to form cyanohydrin [337]:



Quantitative derivatization was attained without SCN^- interference. Concentrations of CN^- ranging from 0.05 to 50 ppm were determined with a nitrogen-phosphorus detector on water samples. The method was robust toward the presence of high amounts of proteins and metal cations whose decomposition was attained by UV irradiation of the sample solution, leaving CN^- free to react with the aldehyde. Among more recent work, a double derivatization approach was proposed for the determination of CN^- in plasma and urine [338]. The sample was buffered with sodium borate solution (pH 10) and treated with benzaldehyde:



Such reaction was completed within 30 s at room temperature. The mixture was then eluted on a diatomaceous earth column and after 1 min the analyte was eluteed with 5 mL *n*-hexane containing 0.4% heptafluorobutyryl chloride (HFB-Cl) for in situ derivatization to:



No protein precipitation was required. The method allows a complete analysis of biological samples in 25 min, with detection limits of 10 and 40 ng/mL CN^- for urine and blood on a GC-MS system in SIM mode. Despite the use of an isotopically enriched CN^- could have been

use for quantitation, the authors chose non-specific 1,3,5-tribromobenzene as internal standard. Another derivatization scheme was recently proposed by Kang et al. [339]. Cyanide derivatization in surface water was attained using 2-(dimethylamino)ethanethiol, to make a 2-(dimethylamino)ethyl thiocyanate. A 10 mL aliquot of water sample was pH adjusted to 6 with an acetate buffer and reacted for 20 min at 60 °C 20 min. The derivative was extracted in ethyl acetate and analyzed by GC-MS/MS with a limit of detection of 20 ng/L.

4.5. Arsenic oxyanions

Inorganic arsenic is commonly encountered in two stable redox states, As(III) and As(V), which may interconvert under certain conditions of pH and redox potential. At natural pH, arsenite is present in solution predominantly as H_3AsO_3 (pK_{a1} = 9.2 and pK_{a2} = 12.7) whereas arsenate occurs mainly as anionic $H_2AsO_4^-$ and $HAsO_4^{2-}$ (pK_{a1} = 2.3, pK_{a3} = 6.8, and pK_{a3} = 11.6. In living organisms inorganic As is usually metabolized to organoarsenic molecules like monomethylarsonic acid (MMA, $MeAsO(OH)_2$) and dimethylarsinic acid (DMA, $Me_2AsO(OH)$). Some As species, such as arsine (AsH3), are highly toxic whereas others, like arsenobetaine (AsB, $Me_3As^+CH_2CHOO^-$), arsenocholine (AsC, $Me_3As^+CH_2CH_2OH$), arseno-sugars (AsS), or arsenolipids (AsL), are organic compounds which remain unchanged in the body. The different toxicity of As containing compounds has fulled the interest for speciation of the element in several matrices such as food, drinking water, air and soil and several strategies have been employed [130, 340–347].

4.5.1. Hydride generation with $[BH_4]^-$

4.5.2. As-OH derivatization with thioglycolic acid alkyl esters

4.5.3. Other approach of As-OH derivatization

4.6. Selenite

4.6.1. Alkylation with aqueous $NaBR_4$ (R = Et, Pr, Ph)

4.6.2. Derivatization with aromatic o-diamines

4.7. Borate

Zeng et al. [348] proposed a derivatization method for the conversion of borate in a volatile derivative. A 20 mL aliquot of drinking water sample was dried at 55 °C under a stream of nitrogen and reacted with 2.4 mg of triethanolamine in 500 µL of acetonitrile at 50 °C for 1 hour. Formation of condensation product triethanolamine borate [$B(\text{-}OCH_2CH_2\text{-})_3N$] was observed. The reaction mixture was diluted to 2.0 mL with acetonitrile and analyzed by GC-MS. In SIM mode a linear response was obtained from 0.01 µg/mL to 10.0 µg mL. Like many alkyl borates, triethanolamine has a strong disposition to hydrolysis [349], therefore this derivatization requires non-aqueous medium.

4.8. Fluoride and other halides

Fluoride is an inorganic anions which has a role in human health and several countries perform drinking water fluoridation at the 0.7-1 mg/L level in order to prevent tooth decays. However adverse health effects are expected when fluoride levels rise above 1.5 mg/L [350, 351]. The very narrow concentration window where fluoride is beneficial for humans has justified development of several analytical methods for its monitoring. In 2016 Dhillon et al. [351] presented a review on fluoride methods highlighting that ion-selective electrode is the most employed technique and future trends include development of sensors. However, methods based on electrochemistry can suffer matrix effects and alternative more specific approaches - like gas chromatography - can have a role in their validation. The first GC methods for fluoride dates back to the sixties when silylation was employed for conversion of F^- in volatile F-SiR_3 [352–354]. A general study of this reaction was carried out by Yamamoto et al. [355] where formation of several fluoroalkylsilanes was attained with X-SiR_3 reagents (X = Cl, imidazole and R = methyl, ethyl, isopropyldimethyl, and *t*-butyldimethyl). For this purpose, a water F^- standard was diluted in 5 mL HCl 1.2 M following addition of 1 mL of 2% X-SiR_3 in *n*-hexane. The reaction time for the TECS (90 min) was longer than with TMCS (5min), but the sensitivity of TES derivative was twice higher [355]. Already in early days, the implementation of this derivatization chemistry allowed trace determination of fluoride in complex biological samples by GC [356]. Despite TECS seems to offer analytical advantages, in more recent studies TMS chemistry was preferred. Hui and Minami [357] used TMCS for GC-FID determination of fluoride in urine samples with detection limits of 0.01 ppm; 1,1,1-trichloroethane was used as internal standard and Me_3Si-F extraction was obtained in toluene. Me_3Si-F has a boiling point of only 16.4 °C and a favorable partition into gas-phase at room temperature. For this reason, in recent studies the liquid-liquid extraction of Me_3Si-F has been replaced by headspace sampling techniques which allow for a much cleaner chromatography for complex matrices. Static headspace was implemented for the determination of fluoride in milk with 0.01 µg/mL detection limit on FID detector [358]. Also SPME [359] and headspace single drop microextraction [360] were proposed for determination of F^- in toothpaste and water with detection limit in the low part-per-billion. Alternative carbon-based chemistry has also been employed for F^-. Kage et al. [361] converted F^- in PFB-F using direct alkylation in acetone with commercial PFB-Br at 80 °C. In positive EI the detection limit was only 0.5 mg/L, but a much higher sensitivity would be expected in negative chemical ionization mode. Alkylation with triethyloxonium tetrachloroferrate (III) was implemented for the F^- ethylation in aqueous solution:

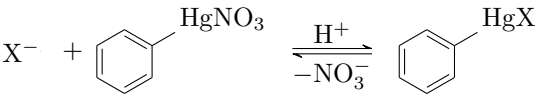
$$Et_3O^+(aq) + F^- \rightarrow Et\text{-}F(g) + Et_2O$$

Table 6: Derivatization chemistries recently employed for the conversion of thiocyanate, cyanide and sulfide in volatile derivatives

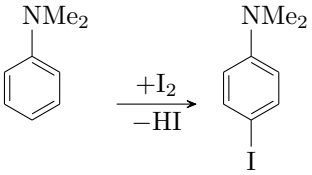
Derivative	Reagents	Notes (Year)	Ref.
HCN	Inorganic acid	$CN^- + H^+ \rightarrow HCN$. Direct headspace or SPME with cryogenic cooling. Employed for blood analysis with DL of 3–8 µg/L. Artifactual formation of CN^- from SCN^- is reported (1963-2008)	[285–299]
CNCl	Chloramine-T	Previous separation of CN- from the matrix as HCN via acidification is required. Reaction occurs at 20-65C within 90 min with 0.25-1.5% chloramine T (1974-2008)	[315–320]
MeSCN, MeCN, and Me_2S	$(MeO)_2SO_2$	Aqueous derivatization at 60 °C for 30 min with KOH. Quantitative conversion of SCN^-. Applied for quantitation of salivary SCN^- with a DL of 0.2 ng/mL (1982, 2014)	[31, 32, 321]
Me_2S and Me_2S_n	MeI	Methylation of sulfide and polysulfides following HS GC-MS with DL of 50-240 ng/L. Sulfide derivative (Me_2S) can be an endogenous compound in natural water (2010)	[323]
EtSCN	$Et_3O^+[BF_4]^-$	HS GC-MS determination of salivary thiocyanate (1-400 µg/g, RSD $< 2\%$) with direct aqueous derivatization at room temperature (2015)	[73]
PFB-SCN, PFB-CN, and PFB_2S	PFB-Br	Conversion of SCN^- to CN^- was observed with direct alkylation in acetone or ethanol, but not with extractive alkylation. Widely applied for clinical, forensic and environmental analysis for measurement at the part-per-billion (1981-2017)	[42, 51, 53, 57, 324–330]
NED-SH, NED_2S, and NED-SR	*N*-ethyl-maleimide (NEM)	Aqueous derivatization of volatile alkanethiols and H_2S followed by SPME GC-MS with detection at the low part-per-trillion (20005)	[332]
R_2S	3-buten-2-one	Overnight reaction in aqueous medium at RT, and extraction of the derivatives in organic solvent. At pH 7.4 double alkylation of H_2S was predominant resulting in $(CH_3(C{=}O)CH_2CH_2)_2$-S. $Na^{34}S$ was employed for isotope dilution GC-MS quantitation (2016)	[333]
Heptafluoro butyric acid alphacyanobenzyl ester	Benzaldehyde (1st step) HFB-Cl (2nd step)	Two-step derivatization, reaction time less than 5 min at RT. Proteins do not interfere with the assay. CN^- determination in urine and blood with DL of 10–40 ng/mL on GC-MS (2009)	[338]
$Me_2N(CH_2)_2SCN$	$Me_2N(CH_2)_2SH$	CN^- derivatization in aqueous medium at 60 °C for 20 min. Applied for water analysis by GC-MS/MS with a DL of 20 ng/L (2014)	[339]

The derivatization was held in alkaline ammonia buffer which limit the interference of aqueous cations like Fe^{3+} with detection limit of 3.2 µg/L for headspace GC-MS [76]. Recentely, fluoride has been determined in plasma and urine after derivatization with 2-(bromomethyl)naphthalene to 2-(fluoromethyl)naphthalene, using 2-fluoronaphthalene as internal standard [362]. The derivatization was conducted in aqueous environment at 70 °C for 70 min with 15-crown-5-ether as phase transfer catalyst, and the derivative extracted with dichloromethane. The method was successively improved for headspace analysis using SPME sampling (CAR/PDMS fiber) with detection limit of 9-11 µg/L on a GC-MS/MS setup for fluoride in plasma and urine [363]. For the other halides, use of silyl chemistry is unsuitable for analytical purpose: Si-X bound is only stable when X = F, but not for Cl, Br, and I where derivatives are moisture sensitive. For thus analytes, alkylation is a common strategy and the correspondent halocarbon derivatives are stable and can be sampled in the headspace providing clean chromatography even with complex matrices (see paragraph 3.2 and Table 1). Methylation with dimethyl sulphate was employed for quantitation of urinary bromide at 0.1-10 mM concentration range [364]. However such reagent is extremely toxic, carcino-

genic, and mutagenic therefore other alkylating agents are preferred. Recently we proposed the use of commercial triethyloxonium tetrafluoroborate salt for aqueous ethylation of halides [41]. The general aspects of this chemistry are outlined in paragraph 3.2.2 and applications includes the determination of iodine in starch [365, 366] and high-precision isotope dilution for measurement of bromide in groundwater with detection limit of 0.25 ng/g and relative standard uncertainty better then 0.5 % for quantitation of 100 ng/g (GC-MS detection in EI) [74]. The use of ethylene oxide has also been proposed for conversion of Cl^-, Br^-, and I^- in the corresponding 2-haloethanol with quantitative conversion [367]. Despite potential analytical interest for this chemistry, hazards handling this gaseous toxic reagent have posed limitation to the development of such technique. Another reaction scheme proposed for volatilization of Cl^-, Br^-, and I^- entails conversion into phenylmercury (II) compounds accordingly to the following scheme [368–371]:



Already in the seventies this derivatization allowed for the quantitation of as little as 8 ng/g of chloride in water samples by GC-FID [368]. This chemistry has not been employed to complex matrices and its applicability is penalized by the use of a mercury compounds whose presence poses health and environmental concerns. Another strategy common for Cl^-, Br^-, and I^- is based on their oxidation to X_2 form followed by reaction with an organic compounds. In 1972, Archer [372] measured bromide in blood (0.1-1.0 mg/ml with GC-FID) after its conversion to Br_2 (70% efficiency) by $KMnO_4$ in diluted H_2SO_4. Br_2 was then reacted with cyclohexene to yield 1,2-dibromocyclohexane. The author found that also chlorine, from chloride, reacts to give 1,2-dichlorocyclohexane, while organobromine compounds gave a negligible response. Mishra et al. [373] employed selective 2-iodobenzoic acid for oxidation $Br^- \rightarrow Br_2$ and resulting bromine was trapped by reaction with 2,6-dimethylphenol to 4-bromo-2,6-dimethylphenol with providing a detection limit of only 5 ng/L on GC-MS. In a similar fashion determination of iodine in milk was proposed after I^- conversion to I_2 and reaction with acetone to yield monoiodoacetone which was back-liquid extracted in *n*-hexane [374]. The method was modified by Maros et al. [375], which obtained the quantitative oxidation of iodide and bromide by chromate and permanganate in acidic solutions and in the presence of acetone with application to complex matrices such as seawater, urine, blood, and milk with a relative standard deviation of 1.9% and 3.0% for 100 nM Br^- and 10 mM I^- respectively. Such an approach is not only useful for halides (X^-), but also for determination of their oxidized forms (XO_3^-). Bromate was measured in drinking water after reduction to Br_2 and reaction with styrene [376] or ethyl acetate [377] with detection limits of 22 ng/L on GC-MS. Furthermore, Shin et al. [378] proposed a method for the iodine/iodide/iodate determination after conversion of these anions to I_2 following reaction with 2,6-dimethylphenol to 4-iodo-2,6-dimethylphenol within 20 min. With the Hewlett-Packard 5890/5971 GC-MS system the detection limit reported for $I_2/I^-/IO_3^-$ where of 0.5 ng/mL. Typically reduction $IO_3^- \rightarrow I^-$ was attained using ascorbic acid [379, 380] or sodium metabisulfite [381] whereas oxidation of $I^- \rightarrow I_2$ with 2-iodosobenzoate [379–381]. For a faster I_2 trapping reaction, the use of N,N-dimethylaniline allowed a complete reaction in only 1 min and was preferred in earlier studies:



The 4-iodo-N,N-dimethylaniline can be extracted in organic solvent and measured by GC-MS. Such and approach has found applications for speciation of iodide, iodate, iodine and organo-iodide in several matrices such as natural water and food with detection limit in the low part-per-trillion by GC-MS [379–381]. Furthermore the method was implemented for monitoring ^{129}I contamination in the Savannah River Site in South Carolina with detection limit of 0.08 nM for both $^{129}I^-$ and $^{129}IO_3^-$. In 2007 Reddy-Noone et al. [382] employed a similar reactivity for the determination of BrO_3^- and IO_3^- in seawater and table salt. Br^- and I^- were removed by ion exchange and the oxyhalides were reduced with ascorbic acid to X^- form, following conversion to 4-bromo-2,6-dimethylaniline and 4-iodo-2,6-dimethylaniline using 2,6-dimethylaniline. Detection limits in the tens of ppb are reported.

5. Health and safety consideration

Anions determination by gas chromatography can only be achieved using chemistries for the conversion of such analytes in volatile derivatives. When working with reagents on a regular basis, an important question to be addressed is about health and safety hazards related with manipulation of these substances. Among the plethora of reactions we reviewed, some are more friendly then others and in Table XX we recompiled all chemicals cited in the text with a health and safety angle. All information reported in Table XX were obtained from the Material Safety Data Sheets (MSDS) available on-line on the Sigma-Aldrich website and are therfore updated to current knowledge on such reagents.

6. Conclusion

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