

NRC Publications Archive Archives des publications du CNRC

Chemical vapor generation by aqueous phase alkylation
Gajdosechova, Zuzana; Pagliano, Enea

Publisher's version / Version de l'éditeur:

Vapor Generation Techniques for Trace Element Analysis: Fundamental Aspects,
2022-03-25

NRC Publications Archive Record / Notice des Archives des publications du CNRC :
<https://nrc-publications.canada.ca/eng/view/object/?id=db8b3c4f-de8b-4541-bc76-73ae9b3d1332>
<https://publications-cnrc.canada.ca/fra/voir/objet/?id=db8b3c4f-de8b-4541-bc76-73ae9b3d1332>

Access and use of this website and the material on it are subject to the Terms and Conditions set forth at
<https://nrc-publications.canada.ca/eng/copyright>

READ THESE TERMS AND CONDITIONS CAREFULLY BEFORE USING THIS WEBSITE.

L'accès à ce site Web et l'utilisation de son contenu sont assujettis aux conditions présentées dans le site
<https://publications-cnrc.canada.ca/fra/droits>

LISEZ CES CONDITIONS ATTENTIVEMENT AVANT D'UTILISER CE SITE WEB.

Questions? Contact the NRC Publications Archive team at
PublicationsArchive-ArchivesPublications@nrc-cnrc.gc.ca. If you wish to email the authors directly, please see the first page of the publication for their contact information.

Vous avez des questions? Nous pouvons vous aider. Pour communiquer directement avec un auteur, consultez la première page de la revue dans laquelle son article a été publié afin de trouver ses coordonnées. Si vous n'arrivez pas à les repérer, communiquez avec nous à PublicationsArchive-ArchivesPublications@nrc-cnrc.gc.ca.

Chapter 4 – Chemical vapor generation by aqueous phase alkylation

Zuzana Gajdosechova · Enea Pagliano

National Research Council Canada, 1200 Montreal Road, K1A 0R6 Ottawa, Ontario, Canada

zuzana.gajdosechova@nrc-cnrc.gc.ca

enea.pagliano@nrc-cnrc.gc.ca

Summary

As an alternative to classical tetrahydroborate ($[\text{BH}_4]^-$), chemical vapour generation (CVG) can also be attained using alkylation-based derivatization chemistries. In paragraphs 4.2 and 4.3, two classes of alkylating reagents are presented: the tetraalkylborates ($[\text{BR}_4]^-$) and the trialkyloxonium (R_3O^+) salts. The first have been applied for metal speciation, whereas the latter have found applications for headspace GC-MS analysis of several inorganic anions. Properties and reactivity of these two chemicals are presented under typical analytical conditions, i.e. conversion of trace amount of analyte with a large excess of reagent in an aqueous medium. We also report possible interferences, side reactions and ways to tackle them. Most notably, these alkylation chemistries allow the separation of the derivative from the matrix providing for clean sample introduction and very competitive detection limits. In most applications, potential matrix effects and other perturbation of the analytical signal have been addressed by the use of isotope dilution quantitation. Finally, paragraph 4.4 is a brief discussion about Grignard reagents used in metal speciation. Such applications of Grignard chemistry typically require injection of a solvent extract in a GC system, therefore they cannot be properly classified as CVG techniques. However, Grignard chemistry applied to metal speciation is closely related to the tetraalkylborates and we retained useful to mention it in this chapter.

Keywords: Tetraalkylborates, trialkyloxonium salts, Grignard reagents, metal speciation, inorganic anions, headspace analysis

List of contents

4.1 Introduction	4
4.2 CVG with tetraalkylborates	5
4.2.1 <i>Historical background</i>	5
4.2.2 <i>Reaction products and applications</i>	6
4.2.3 <i>Properties and reactivity of tetraalkylborates</i>	8
4.2.3.1 Interferences.....	9
4.2.3.2 Side reactions and trans-alkylation	9
4.3 CVG with Trialkyloxonium salts	12
4.3.1 <i>Historical background</i>	12
4.3.2 <i>Reaction products and applications</i>	13
4.3.3 <i>Properties and reactivity of trialkyloxonium</i>	16
4.3.3.1 R_3O^+ acid hydrolysis and pH adjustment.....	16
4.3.3.2 Manipulating R_3O^+ salts.....	17
4.3.3.3 Reaction medium: aqueous or non-aqueous?.....	18
4.3.3.4 Interferences and other effects	18
4.4 Metal speciation with Grignard reagents	19
4.4.1 <i>Historical background</i>	19
4.4.2 <i>Properties and reactivity of Grignard reagents</i>	19
4.4.2.1 Interferences and transalkylation	20
4.5 Future trends and perspectives	21
4.6 References	22

4.1 Introduction

Alkylation reactions are widely employed in analytical chemistry for derivatization. For example, in the gas chromatography world, alkylation is used to convert polar compounds (like carboxylic acids) into volatile and thermally stable derivatives (like carboxylate esters). Common alkylating reagents include alkyl halides, dialkylsulfates, diazoalkanes, and pentafluorobenzyl bromide; a large number of papers can be found on their general use in analytical chemistry [1-4].

Within CVG techniques, there are two main classes of alkylating reagents that have found application: the tetraalkylborates ($[\text{BR}_4]^-$) and the trialkyloxonium (R_3O^+) salts. As shown in Fig. 4.1, to some extent these reagents can be considered equal and opposite. The $[\text{BR}_4]^-$ anion is a formal carboanion (R^-) donor and has found applications for metal speciation, primarily for Hg, Sn, and Pb analysis. Conversely, R_3O^+ is a formal carbocation (R^+) donor and it has been used for the determination of several inorganic anions such as NO_2^- , NO_3^- , Br^- , Cl^- , SCN^- , and SeCN^- . Although both reagents show disposition to hydrolysis, the kinetics is favorable for their use in a buffered aqueous medium; since most relevant samples for metal speciation and inorganic anions are water based, the possibility of using these chemicals directly in water offers great procedural advantages. From a health and safety perspective, we must remark that alkylation reagents are toxic and potential carcinogens, therefore the analyst must avoid any exposure.

In classical CVG with $[\text{BH}_4]^-$, most derivatives have a boiling point well below 0 °C; in these cases there is no doubt that chemical *vapour* generation properly describes the technique. When replacing $[\text{BH}_4]^-$ with an alkylating agent, the boundaries of CVG become blurred: many alkyl-derivatives have boiling points well above 50 °C and are significantly less volatile with respect to metal hydrides. Table 4.1 summarizes the properties of major alkylation systems used for CVG. Although some derivatives could be extracted into solvents, the use of headspace analysis remains advantageous in providing matrix separation and cleaner chromatography. Particularly for those applications requiring low detection limits (such as Hg and Sn speciation), the use of pre-concentration techniques – such as SPME, purge and trap, and in-tube extraction (ITEX) – has favoured the shift of the $\text{A(l)} \rightleftharpoons \text{A(g)}$ equilibrium toward the gas phase, a necessary step for derivatives with higher boiling points.

On a final note, we would like to emphasize that within the applications discussed in this chapter, the use of isotope dilution quantitation [5-7] is paramount. In fact, conversion yield can be

hampered by matrix effects and the efficiency of the headspace transfer/sampling can depend on a number of parameters, including temperature, degradation of the SPME/ITEX phase and so forth. Such effects can be described as analyte losses during sample preparation but are well accounted for when using an isotopically enriched form of the analyte as internal standard. For certain applications, isotope dilution is essential for high-precision quantitation.

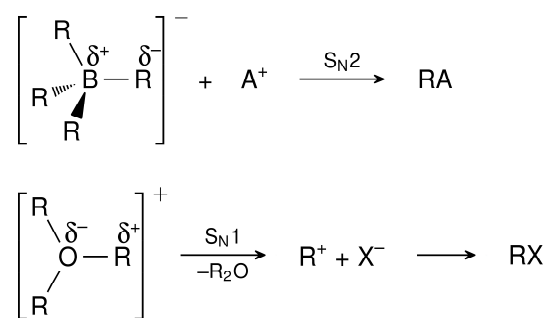


Figure 4.1 Comparison between Et_3O^+ and $[\text{BR}_4]^-$ reagents. The $[\text{BR}_4]^-$ is a formal carbanion (R^-) donor, reacting with non-volatile cations to create neutral volatile derivatives. On the other hand, Et_3O^+ is a formal carbocation (R^+) donor reacting with non-volatile anions to yield neutral volatile derivatives. The volatility of the derivative is influenced by the nature of R for both reagents, most CVG applications use $\text{R} = \text{ethyl}$.

Credit: No credit necessary.

4.2 CVG with tetraalkylborates

4.2.1 Historical background

The earliest reference to synthesis of alkylborates dates to the 1930s [8]. However, it wasn't until 1960 when Honeycutt and Riddle reported alkyl group transfer from R_3B compounds to mercury and lead with suitable alkylation yield [9]. They specified that the alkylation takes place in a stepwise manner and suggested that all three alkyl groups might partake in the reaction. Looking for improved alkylation efficiency, Honeycutt and Riddle synthesised several tetraalkylborates ($[\text{BR}_4]^-$) and reported on their physical and chemical properties [10]. Soon after, in-depth analytical studies of $[\text{BR}_4]^-$ synthesis and reactivity paved the way for novel alkylation reactions which now dominate metal speciation protocols [11, 12]. The first application of lead speciation using $[\text{BEt}_4]^-$ [12] was followed by speciation of mercury [13-15], tin [16-19], determination of cadmium [20, 21], and publications on volatilization of thallium [22], germanium, and selenium

[16]. Because $[\text{BR}_4]^-$ alkylation could be performed in aqueous solutions, it provided a convenient alternative to Grignard alkylation, eliminating several sample preparation steps, thus reducing the risk of analyte loss and sample contamination.

4.2.2 Reaction products and applications

Alkylation can replace hydride generation whenever the hydride-derivative (EH_n) presents unsuitable stability for analytical applications. In fact, for heavy elements, the E–C bond is more stable than the E–H bond. Alkylation is especially useful for Pb and Hg, whose hydrides are very unstable; the stability scale for lead and mercury hydrides can be summarized as follow: $\text{R}_3\text{PbH} > \text{R}_2\text{PbH}_2 > \text{PbH}_4$, and $\text{RHgH} \gg \text{HgH}_2$, the latter being highly unstable and decomposing to Hg^0 even at low temperatures (see also Chapter 2).

Therefore, $[\text{BR}_4]^-$ reagents are often used for speciation analysis of Pb [23-25], Hg [26-29], and Sn [30-32] in a large variety of matrices and, to a lesser extent, for the determination of Cd [20, 21], Se ($\text{Se}^{\text{IV}}/\text{Se}^{\text{VI}}$ speciation) [33], and Bi [34]. When reacted with $[\text{BEt}_4]^-$, both Se^{IV} and Se^{VI} compounds give Et_2Se as the volatile derivative, whereas only Se^{IV} reacts with $[\text{BH}_4]^-$ to yield H_2Se [35].

The complexity of sample preparation depends on the sample matrix but generally consists of sample solubilisation, i.e. analyte extraction, pH adjustment and derivatization. Formation of volatile derivatives allows for the headspace sampling which could be used for direct analysis or pre-concentrated. Alternatively, if the analysis cannot be performed immediately, alkylated analytes can be extracted into a small volume of organic solvent and stored for later analysis. Either the headspace or organic extract are analysed by gas chromatography which can be coupled to various detectors.

Since $[\text{BR}_4]^-$ reagents are not analyte specific, they are frequently used in multi-elemental speciation studies: several metal(loid) species can be alkylated, preconcentrated and quantified simultaneously. In such instances, an optimum pH condition for individual analytes has to be identified and particular attention paid to impurities in the reagents, which may introduce bias. Additionally, the significant differences in the polarity and volatility of individual alkylation products can add complexity to optimization of preconcentration and headspace sampling conditions. Nonetheless, several recent studies reported successful simultaneous quantitation of Pb and Sn in urine [36], Hg and Sn in biological tissues [37, 38] and sediments [39], Hg, Pb and

Sn in waters [40-42] biological tissues [43] and sediments [44], Hg and Pb in river waters [45]. In most cases, Hg and Sn speciation is performed by combining a headspace pre-concentration technique with GC-ICP MS detection. For example, in Fig. 4.2 sub-ng/kg detection of Hg and Sn species is achieved. Such analytical capability can be reproduced even when working with difficult matrices such as bitumen extracts, as illustrated in Fig. 4.3.

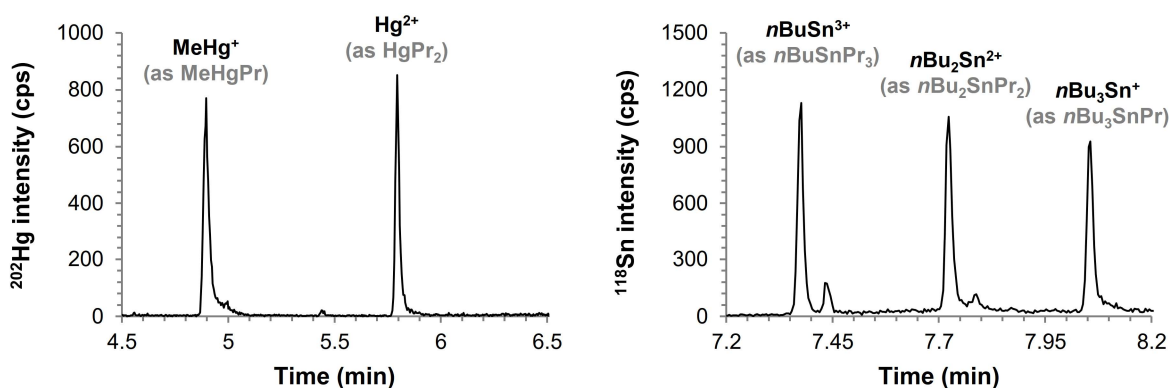


Figure 4.2 Speciation of mercury (MeHg^+ and Hg^{2+}) and tin ($n\text{BuSn}^{3+}$, $n\text{Bu}_2\text{Sn}^{2+}$, and $n\text{Bu}_3\text{Sn}^+$) using propylation with NaBPr_4 . ITEX GC-ICP MS of a 5 ng/kg aqueous standard.

Credit: Adapted from Ref. [46] with permission from The Royal Society of Chemistry.

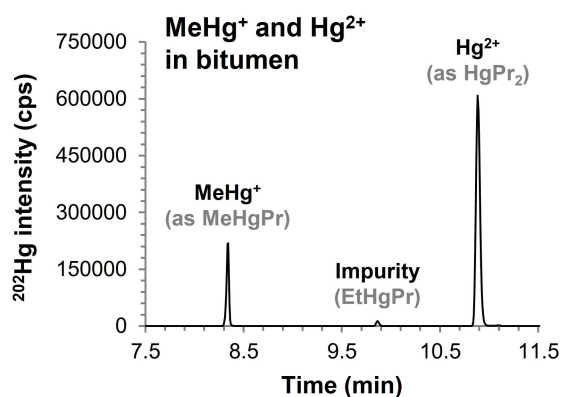


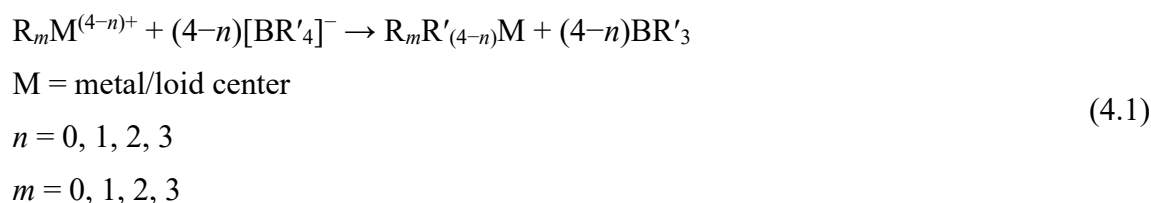
Figure 4.3 Speciation of mercury (MeHg^+ and Hg^{2+}) in an aqueous-extracted bitumen sample. The analytes were derivatized with NaBPr_4 and measured by GC-ICP MS using ITEX pre-concentration. Small quantities of EtHgPr were found due to impurities in the derivatization reagent.

Credit: Adapted with permission from Ref. [47]. American Chemical Society, 2018.

4.2.3 Properties and reactivity of tetraalkylborates

Tetraalkylborates are formed by addition of an alkyl (R) or aryl (Ar) group to an organoborane (BR_3), leading to the formation of $[\text{BR}_4]^-$. The polarization of the carbon-boron bond, $\text{B}^{\delta+}-\text{C}^{\delta-}$, favors the transfer of a carbanion to a metal(loid) center [48]. This represents an analogy with the behavior of aqueous boranes, where the polarization of the boron-hydrogen bond $\text{B}^{\delta+}-\text{H}^{\delta-}$, favors the hydride transfer to the metal(loid). In spite of the large number of applications to speciation analysis of selected classes of metals and semimetals (Hg, Pb, Sn, Cd, Se), dedicated studies on the mechanism involved in CVG by $[\text{BR}_4]^-$ are not well explored, as in the case of CVG by aqueous boranes (see Chapter 2).

A general reaction scheme is shown in Eq. 4.1, where $[\text{BR}_4]^-$ donates a carbanion to a metal or metalloid cation:



An exception to Eq. 4.1 is given by inorganic Pb^{2+} which forms PbEt_2 , an unstable derivative that dismutates into PbEt_4 and Pb^0 [12].

The most commonly used $[\text{BR}_4]^-$ are sodium tetraethylborate (NaBEt_4) and sodium tetra(*n*-propyl)borate (NaBPr_4). However, other reagents such as NBu_4BBu_4 [49, 50] and NaBPh_4 [29, 51] have been used for analytical purposes. $[\text{BR}_4]^-$ salts are hygroscopic and air sensitive; a 20% solution of $[\text{BR}_4]^-$ in tetrahydrofuran maintained its derivatization efficiency over 4 weeks when stored at 4 °C in the dark [52]. NaBPr_4 prepared in water showed sufficient stability at 35 °C for 16 h [11], however its stability can be prolonged by storage at sub-zero temperature. Similarly, NaBEt_4 in 2% KOH at -18 °C maintained its stability over 18 months [53].

The alkylation reactions are obtained in buffered acidic solutions; the exact experimental conditions in terms of buffer molarity and pH are specific for individual $[\text{BR}_4]^-$ and metal(loid) species [44, 47, 54]. Nonetheless, a $\text{pH} \leq 2$ causes rapid decomposition of $[\text{BR}_4]^-$ [11, 44].

4.2.3.1 Interferences

Similarly to hydride generation, alkylation reactions are complex and suffer from several interferences or other unwanted effects. In the first place, the derivatization yield may vary among various metal(loid) species. Secondly, the alkylation may be affected by matrix components (see Chapter 2). Major interferences can be caused by heterogeneous phase components such as particles or by other inorganic compounds such as transition and noble metals. In comparison with CVG by aqueous $[\text{BH}_4]^-$, little is reported on the effects of concomitant species in CVG by aqueous $[\text{BR}_4]^-$. The interferences of hydride forming elements (Cu^{II} , Ni^{II} , Co^{II} , Fe^{II} , Ag^{I} , Au^{III}) and high chloride content has been investigated for the ethylation (NaBEt_4) of Bi^{III} [34], Cd^{II} [20-22], Se^{IV} and Se^{VI} [33], Pb^{II} [55], and Hg^{II} [53, 56]. In general, interferences from foreign elements which are observed with CVG by $[\text{BR}_4]^-$ appear to be less severe than those observed with $[\text{BH}_4]^-$ derivatization.

Some interferences are easier to control than others. Sedimentation or filtration are efficient for removal of particles and sample dilution can reduce matrix interferences. Nonetheless, if the analyte concentration is already at trace levels, sample dilution may not be suitable. In such case, an increased amount of the reagent has been suggested to compensate for its degradation by matrix components [52]. However, in saline samples such as seawater, it was reported that the efficiency of MeHg^+ alkylation by NaBEt_4 starts to decrease above 7.5 mg/L NaBEt_4 at pH 4.0-4.1 [53]. This effect was not observed in high purity waters wherein the efficiency remained constant over the range of 0.5-15 mg/L NaBEt_4 [57, 58].

4.2.3.2 Side reactions and trans-alkylation

When the alkylation reaction takes place in an acidic medium, $[\text{BR}_4]^-$ is rapidly hydrolysed, generating several by-products [44]. For example, trialkylboroxin ($\text{R}_3\text{B}_3\text{O}_3$), a six-angle ringed alkyl borane, was one of the by-products identified after derivatization with $[\text{BR}_4]^-$ [59, 60]. It has very high reactivity towards the bonded phase in GC columns, impacting their efficiency and lifetime. The synthesis of trialkylboroxin suggests that the alkylation reaction is accompanied by a rather complex set of alkyl cleavage and rearrangement side reactions.

In several studies it has been reported that alkylation of Hg^{2+} yields a number of alkylated by-products [60-62]. Both $[\text{BEt}_4]^-$ and $[\text{BPr}_4]^-$ reagents seem to promote complex transalkylation reactions involving the analytes, the derivatives, the alkylboranes (and the corresponding

hydrolysis by-products) and other organometals potentially present in the reaction medium. Transalkylation reactions associated with $[\text{BEt}_4]^-$ and $[\text{BPr}_4]^-$ are usually complex and may result in a larger number of by-products [60]. The individual variables controlling the degree of transalkylation have been the subject of numerous studies; however, agreement has not been reached, mainly due to the poor reproducibility of artifact formation. Some studies suggested that competitive alkylations can arise due to the presence of alkyl donors in the sample matrix, including the acetate buffer [63]. Furthermore, it has been reported that unwanted transalkylations can occur when organometals are present in the sample matrix [64, 65]. However, Huang [60] showed that changes in experimental conditions, such as a change in buffering agent and introduction of Et_3Sn^+ , induce very little variation in the yield of Hg by-products, whose concentration increased linearly with increase of Hg^{2+} . Hence, it was concluded that transalkylations can also be induced by side reactions involving alkyl borates. Other studies suggested that transalkylation may be driven by impurities found in $[\text{BR}_4]^-$ and on-column conversion [61, 66].

Transalkylation reactions at a rate above 2% can have a significant impact on Hg speciation in soil, sediments or natural waters. In fact, in these samples, the concentration of alkylated Hg species is generally below 1% with respect to Hg^{2+} . Similar issues have been reported for speciation of Sn. Since these transalkylation reactions can induce significant quantitation bias, several approaches, such as double [67, 68] and triple [69] spike isotope dilution, have been proposed to account for potential issues.

Table 4.1 Examples of alkylation reactions used in CVG applications

Analyte	Reagent	Derivative	b.p. ^a	Matrix	LODs	Ref.
Hg ²⁺	NaBEt ₄ , NaBPr ₄	Et ₂ Hg, Pr ₂ Hg	≥ 159 °C	natural waters	0.04-0.4 ng/L	[41, 46, 70]
MeHg ⁺	NaBEt ₄ , NaBPr ₄	MeHgEt, MeHgPr	≥ 93 °C ≤ 159 °C	natural waters	0.2-80 pg/L	[41, 46, 71- 73]
<i>n</i> Bu ₃ Sn ⁺	NaBEt ₄ , NaBPr ₄	<i>n</i> Bu ₃ SnEt, <i>n</i> Bu ₃ SnPr	> 178.5 °C ^a	natural waters	11-80 pg/L	[41, 46, 72, 74, 75]
<i>n</i> Bu ₂ Sn ²⁺	NaBEt ₄ , NaBPr ₄	<i>n</i> Bu ₃ SnEt ₂ , <i>n</i> Bu ₃ SnPr ₂ ,	> 178.5 °C ^a	natural waters	20-200 pg/L	[41, 46, 76]
<i>n</i> BuSn ³⁺	NaBEt ₄ , NaBPr ₄	<i>n</i> Bu ₃ SnEt ₃ , <i>n</i> Bu ₃ SnPr ₃ ,	> 178.5 °C ^a	natural waters	20-250 pg/L	[41, 77]
Me ₃ Pb ⁺	NaBPr ₄	Me ₃ PbPr,	Note ^a	natural waters	0.01-0.4 ng/L	[41, 78]
Et ₃ Pb ⁺	NaBPr ₄	Et ₃ PbPr	Note ^a	natural waters	0.01-0.2 ng/L	[41, 78]
Cd ²⁺	NaBEt ₄	Et ₂ Cd ^b	n/a	natural waters	0.02-1 ng/mL	[20, 22]
Se ^{IV}	NaBEt ₄	Et ₂ Se	108 °C	natural waters	8 ng/L	[33]
Bi ³⁺	NaBEt ₄	Et ₃ Bi ^b	107 °C (79 mmHg)	urine	1.6 ng/mL	[34]
F ⁻	Et ₃ OFeCl ₄	EtF	-38 °C	natural waters	3.2 µg/L	[79]
Cl ⁻	Et ₃ OBF ₄	EtCl	15.8 °C	crude oil	0.03-0.2 mg/kg	[80, 81]
Br ⁻	Et ₃ OBF ₄	EtBr	38.4 °C	natural waters	0.25 ng/g	[6]
I ⁻	Et ₃ OBF ₄	EtI	72.3 °C	standards	1.2 µg/L	[82]
NO ₂ ⁻	Et ₃ OBF ₄	EtONO, EtNO ₂	17 °C, 114.5 °C	seawater, meat	0.15 ng/mL, 0.05 µg/g	[83, 84]
NO ₃ ⁻	Et ₃ OBF ₄	EtONO ₂	87.3 °C	seawater, meat	0.6 ng/mL, 1.0 µg/g	[83, 84]
SCN ⁻	Et ₃ OBF ₄	EtSCN	146.1 °C	biological fluids	0.3-0.6 ng/g	[85, 86]

^a b.p. = boiling point of the alkyl-derivative. If not otherwise specified, data were obtained from the NIST webbook on 2021-05-26 (<https://webbook.nist.gov/>); b.p.(Et₂Hg) = 159 °C, b.p.(Me₂Hg) = 93 °C [87]; b.p.(Et₃Bi) = 107 °C at 79 mmHg [88]; b.p.(Et₂Se) = 108 °C [89]; b.p.(Et₄Pb) = 183 °C; b.p.(Et₄Sn) = 178.5 °C, b.p.(Pr₄Sn) = 222-225 °C [90].

^b Although Et₂Cd and Et₃Bi are assumed to be the cadmium and bismuth ethyl-derivatives, they have not been identified so far.

4.3 CVG with Trialkyloxonium salts

4.3.1 Historical background

In the 1930s, Meerwein and coworkers synthesized a series of trialkyloxonium salts for the first time, including trimethyloxonium tetrafluoroborate ($\text{Me}_3\text{O}^+[\text{BF}_4]^-$) and triethyloxonium tetrafluoroborate ($\text{Et}_3\text{O}^+[\text{BF}_4]^-$) [91, 92]. This class of strong alkylating agents has found notable applications in organic chemistry, especially for undertaking difficult alkylations requiring mild experimental conditions. A systematic study of the reactivity of trialkyloxonium salts with organic functional groups can be found in “*Onium ions*” by Olah et al. [93] or other published literature [94, 95]. In organic chemistry, reactions involving trialkyloxonium salts are usually conducted in organic solvents such as dichloromethane. However, it is important to remark that the use of organic solvents is not the only option when working with trialkyloxonium salts. For example, in 1986 King et al. [96] published an interesting study concerning the use of $\text{Et}_3\text{O}^+[\text{BF}_4]^-$ for aqueous ethylation of inorganic compounds. The only drawback of using water as the reaction solvent was identified as being the disposition to hydrolysis of trialkyloxonium salts:

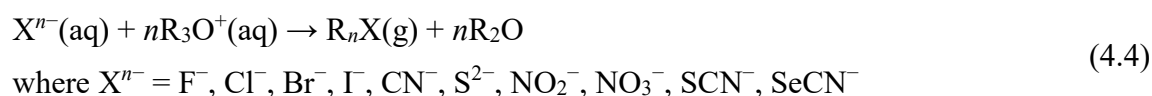


This side reaction results in the degradation of the reagent and needs to be accounted for when high conversion yields are targeted. Notably, King et al. reported that in the $4 < \text{pH} < 9$ range, the hydrolysis of $\text{Et}_3\text{O}^+[\text{BF}_4]^-$ is pH-independent (half-life 7.4 min at 25 °C) and that the alkylation follows an $\text{S}_{\text{N}}1$ mechanism (Fig. 4.1) [96]. The possibility of using trialkyloxonium salts in aqueous media has significant implications for analytical chemistry where most applications are water based.

In the past ten years, the use of R_3O^+ chemistry for qualitative and quantitative applications has grown significantly, including the determination of organic acids, chemical warfare agents, protein post-translational modifications, and inorganic anions [97]. Within all these applications, the only ones that belong to the realm of CVG techniques are those involving the quantitation of inorganic anions [82]. In several cases, a non-volatile aqueous anion X^- (aq) can be converted by R_3O^+ into a thermally stable volatile $\text{RX}(\text{g})$ molecule which can be sampled from the headspace (Table 4.1).

4.3.2 Reaction products and applications

CVG applications of trialkyloxonium salts are limited to the analysis of those inorganic anions that can be converted into stable alkyl derivatives [98]. Commercially available $\text{Et}_3\text{O}^+[\text{BF}_4]^-$ has been the most used reagent for derivatization of inorganic anions. With respect to $\text{Me}_3\text{O}^+[\text{BF}_4]^-$, the $\text{Et}_3\text{O}^+[\text{BF}_4]^-$ is more resistant towards hydrolysis and easier to handle in aqueous solutions. High-precision methods based on this derivatization include quantitation of nitrite and nitrate in seawater [99], vegetables [100], and meats [83]; fluoride [79] and bromide [6] in freshwaters, thiocyanate in saliva [85] and other biological fluids [86], chloride in crude oil [80, 81] and selenocyanate in wastewaters [101]. The reaction of anions with Et_3O^+ can be illustrated as follows:



For the determination of fluoride, $\text{Et}_3\text{O}^+[\text{FeCl}_4]^-$ was used instead of $\text{Et}_3\text{O}^+[\text{BF}_4]^-$. In fact, the tetrafluoroborate anions can liberate large amounts of fluoride, making its detection impracticable at trace levels [79].

For all analytes mentioned above, the only one that could not be associated with a CVG technique is the SeCN^- : its derivative (EtSeCN) is not sufficiently volatile for static headspace sampling and needs to be extracted into an organic solvent.

Sample preparations involving aqueous ethylation with Et_3O^+ are very simple and fast: typically, the samples are spiked with an isotopically labeled internal standard following pH adjustment and reacted with Et_3O^+ at room temperature. This single-pot chemistry can be performed directly in a vial, avoiding consumption of single-use labware for sample clean-up and extraction. In most applications, the volatile ethyl-derivatives have been sampled from the headspace and analyzed using a GC-MS platform. The first-order separation of the ethyl-derivatives from the matrix results in very clean chromatograms, even for challenging samples such as meat extracts and crude oils, as exemplified in Figs. 4.4 and 4.5. Furthermore, the GC-MS analysis of a gas offers the possibility for fast chromatography. For example, nitrate in spinach extracts could be detected by GC-MS on a standard DB-5.625 column (30 m length x 0.250 mm ID x 0.25 μm film) within only 2 min of isothermality at 30 °C. In this regard, high sample throughput and mass spectrometric detection

are two competitive advantages that headspace GC-MS methods with Et_3O^+ derivatization owns with respect to traditional ion chromatography.

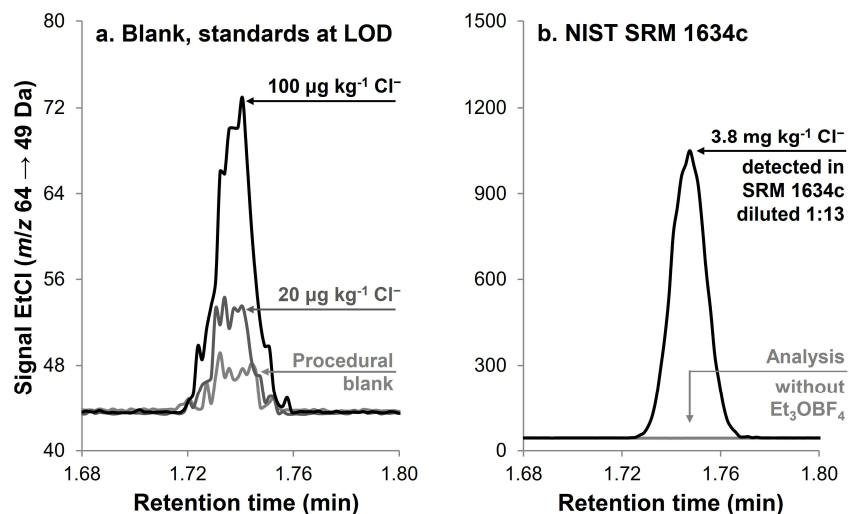


Figure 4.4 Isotope dilution headspace GC-MS/MS (m/z 64→49) for the determination of chloride in crude oil: $\text{Cl}^- + \text{Et}_3\text{O}^+ \rightarrow \text{EtCl}$. (a) Overlaid chromatograms of procedural blank with two Cl^- standards prepared at 20 and 100 $\mu\text{g}/\text{kg}$. (b) Chloride in NIST SRM 1634c crude oil (diluted 1:13). 45 mg/kg Cl is reported by NIST as information value (INAA, undiluted sample).

Credit: Reprinted from Ref [80], Crown Copyright 2019, with permission from Elsevier.

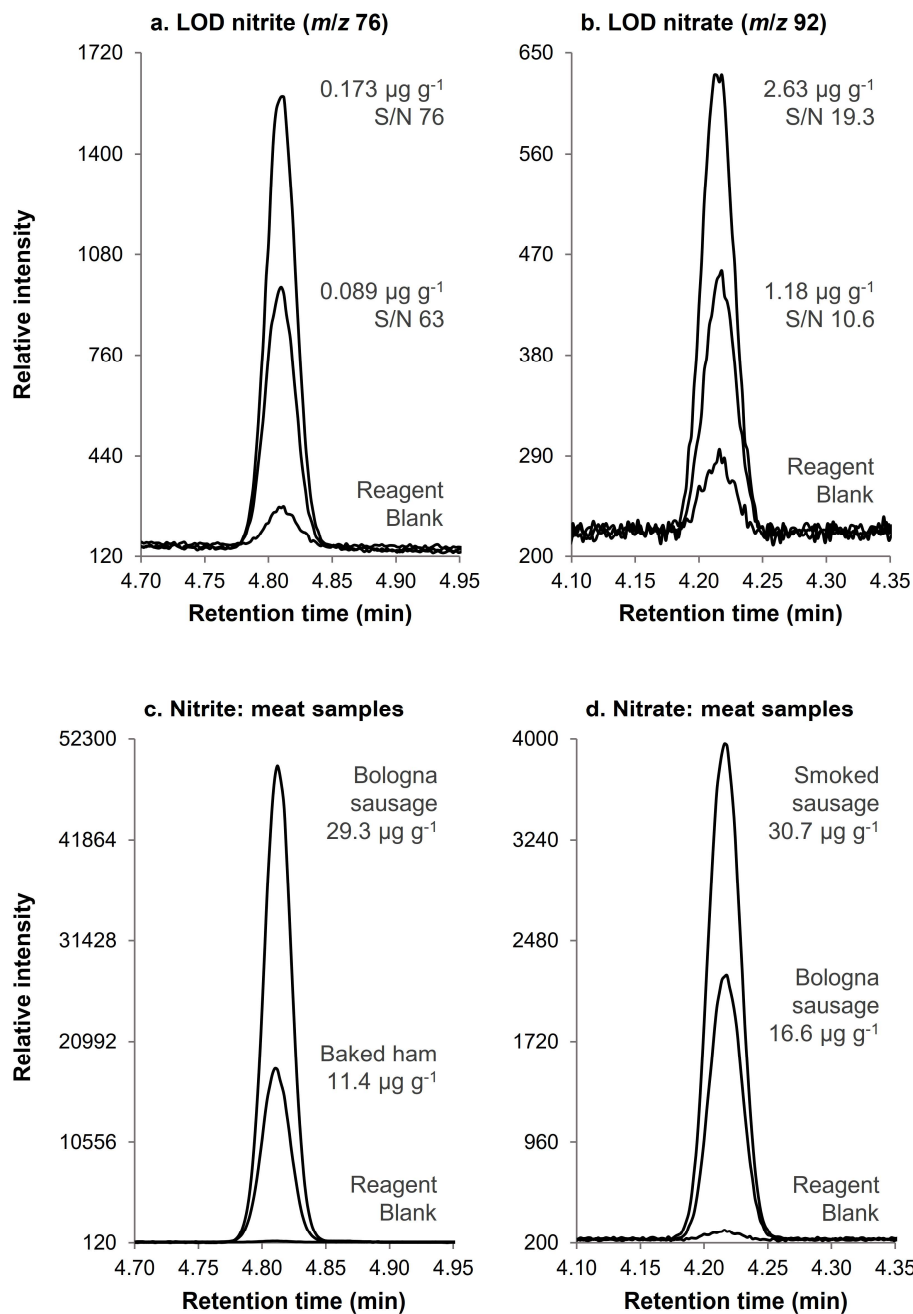


Figure 4.5 Isotope dilution headspace GC-MS for the determination of nitrite and nitrate in meat extracts: NO_2^- and $\text{NO}_3^- + \text{Et}_3\text{O}^+ \rightarrow \text{EtNO}_2$ and EtONO_2 . Positive chemical ionization mode for nitrite (m/z 76) and nitrate (m/z 92). (a) Overlaid chromatograms of procedural blank with two NO_2^- standards prepared at 0.089 and 0.173 $\mu\text{g/g}$. (b) Overlaid chromatograms of procedural blank with two NO_3^- standards prepared at 1.18 and 2.63 $\mu\text{g/g}$. (c) Nitrite chromatograms observed in meat samples. (d) Nitrate chromatograms observed in meat samples.

Credit: Reprinted from Ref. [83], 2019 Her Majesty the Queen in Right of Canada, with permission from Wiley.

4.3.3 Properties and reactivity of trialkyloxonium

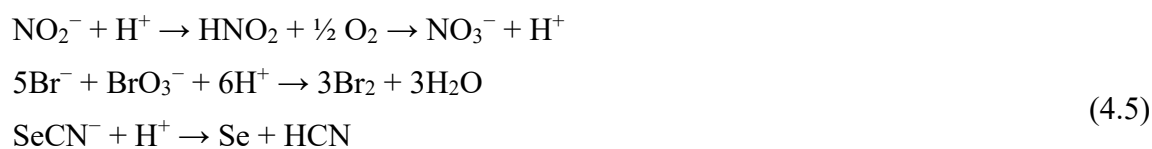
Most analytical studies involving alkylation with trialkyloxonium salts have been written with the purpose of describing and promoting novel analytical methods. Therefore, most of the knowledge in this emerging area was generated from a practical perspective: dedicated studies designed to understand the reactivity of trialkyloxonium salts under analytical conditions are still missing. Nevertheless, in many published methods information about R_3O^+ hydrolysis, optimal pH, use of buffers, reagents manipulation, possible interferences, and so forth can be found. In the following paragraphs, a brief summary of these fundamentals aspects is undertaken.

4.3.3.1 R_3O^+ acid hydrolysis and pH adjustment

Although R_3O^+ salts can be utilized in aqueous media, the analyst must consider that trialkyloxonium cations undergo hydrolysis according to Eq. 4.2. Therefore, water competes with the alkylation and promotes the acidification of the sample. As reported by Granik et al. [94], the hydrolysis of R_3O^+ depends on the nature of the alkyl moiety: for Me_3O^+ , Et_3O^+ and nPr_3O^+ tetrafluoroborates, complete degradation is reported after 8, 80, and 120 min, respectively [94]. A thorough investigation of Et_3O^+ hydrolysis was recently proposed by Linthwaite et al. [102] who reported a rate constant for hydrolysis of $2.23 \cdot 10^{-3} \pm 1.22 \cdot 10^{-3} \text{ s}^{-1}$ in the pH range 2-9 ($t_{1/2} \approx 6$ min, in fair agreement with $t_{1/2} \approx 7.4$ min reported by King et al. [96]).

To tackle the competition of water, a large reagent-to-analyte molar ratio (10^3 - 10^4) is generally used. Even under these conditions, analyte conversions could be partial, as in the case of fluoride (8% conversion efficiency [79]). Since most determinations using R_3O^+ derivatization are not detection limit driven, partial conversions can still be suitable for quantitation.

Upon contact with water, the R_3O^+ salts release H^+ which, in certain cases, can be undesirable. For example, the determination of certain anions, an acid media can promote analyte degradation and interconversion:



Eq. 4.5 shows that an acidic medium is undesirable when the R_3O^+ method is used for speciation of nitrite and nitrate, or for analysis of bromide in the presence of bromate, or for the determination of selenocyanate.

Furthermore, an acidic pH could contribute to protonation of those analytes conjugated with weak acids:



We can postulate that alkylation is more favourable when the analytical substrate is in the form of an aqueous anion (X^-) and not as a “deactivated” neutral molecule (HX).

For these reasons, many applications require buffering: organic amines, ammonium hydroxide, sodium carbonate, and sodium bicarbonate have been used to remove the excess acid. In aqueous media, trialkyloxonium salts have been used over the $0 < \text{pH} < 10$ range for analytical applications.

4.3.3.2 Manipulating R_3O^+ salts

In most analytical applications, either $\text{Me}_3\text{O}^+[\text{BF}_4]^-$ or $\text{Et}_3\text{O}^+[\text{BF}_4]^-$ is used. The first has a very high disposition to hydrolysis, therefore the solid salt is usually added to the samples with a spatula. The $\text{Et}_3\text{O}^+[\text{BF}_4]^-$ survives longer in water, therefore an aqueous solution can be prepared and quickly used for derivatization. Since this solution is not stable for long periods of time, leftovers must be discarded. More stable $\text{Et}_3\text{O}^+[\text{BF}_4]^-$ solutions have been prepared in acetonitrile; 1 g $\text{Et}_3\text{O}^+[\text{BF}_4]^-$ has been solubilized in 1 mL acetonitrile pre-cooled at $-20\text{ }^\circ\text{C}$ and used for derivatization. When stored at $-20\text{ }^\circ\text{C}$, the alkylation power of $\text{Et}_3\text{O}^+[\text{BF}_4]^-$ solutions in acetonitrile was retained for over a month [100]. In the organic literature, it is reported that the interaction between R_3O^+ and $R'\text{CN}$ can produce the nitrilium ion $[\text{R}'\text{CN-R}]^+$, an intermediate that can be converted to other functional groups such as imines, amides, and amines [103, 104]. Dedicated experiments to evaluate if such organic by-products can be generated when solutions of $\text{Et}_3\text{O}^+[\text{BF}_4]^-$ in acetonitrile are kept at $-20\text{ }^\circ\text{C}$ have not been conducted so far. The $\text{Et}_3\text{O}^+[\text{BF}_4]^-$ solutions (either in water or acetonitrile) can be delivered to the sample using a precision pipet, ensuring that all samples and standards are treated with the same amount of reagent.

4.3.3.3 Reaction medium: aqueous or non-aqueous?

The use of the R_3O^+ salts in aqueous media comes at the cost of reduced alkylation power. If the rate of alkylation of the analyte is lower than that of water, competition with the solvent reduces the alkylation yield of the analyte. For example, alkylation of phosphate and sulfate in water has not yet been obtained, but the reaction between phosphonic/sulfonic acids with $Me_3O^+[BF_4]^-$ was successful in dichloromethane [105, 106]. The use of a non-aqueous solvent could also be beneficial for those analytes that produce alkyl-derivatives which can undergo aqueous hydrolysis: this could be the case for alkyl-derivatives of certain oxyanions such as borate [107].

4.3.3.4 Interferences and other effects

CVG applications of trialkyloxonium chemistry are limited to a number of inorganic anions (Eq. 4.4) whose alkyl-derivatives have been detected by headspace GC-MS. The matrix separation offered by CVG combined with GC separation and MS detection results in very specific methods: even with very complex matrices, it is rare to find overlapping interferences at the detection stage (Figs. 4.4 and 4.5). Most of the interference effects that may be encountered using trialkyloxonium salts are related to chemistry. As noted in section 4.3.3.1, the alkylation of the analyte is in competition with that of the solvent and of any other potential substrates present in the sample. For example, for the determination of nitrate in seawater at $\mu\text{g/g}$ levels, the presence of chloride can reduce the analytical signal up to 60 %. This type of aqueous phase interference results in a reduced yield of derivatization. As long as the reduction in signal intensity does not critically impact detection, the effect of incomplete derivatization can be accounted for by isotope dilution quantitation [5-7].

Finally, another interesting effect that has been encountered with certain analytes is the possible production of more than one derivative. As shown in Fig. 4.6, Et_3O^+ can alkylate nitrite on both nitrogen and oxygen to yield nitromethane and ethyl nitrite: both derivatives have been used for quantitation purposes [83, 99]. Likewise, ethylation of thiocyanate can yield both ethyl thiocyanate and ethyl isothiocyanate with the signal intensity of the second only 7 % of that of the EtSCN [82].

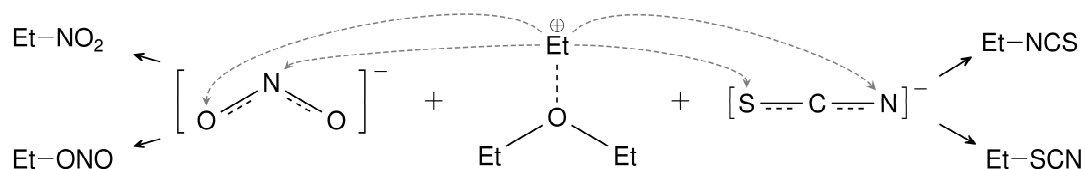


Figure 4.6 The triethyloxonium cation is a strong ethylating agent. For analytes that offer multiple attacking sites, more than one derivative can be produced. In the case of nitrite, both ethyl nitrite and nitroethane can be used for quantitation [83, 99]. Similarly, thiocyanate can be converted in both ethyl thiocyanate and ethyl isothiocyanate [82].

Credit: No credit necessary.

4.4 Metal speciation with Grignard reagents

4.4.1 Historical background

Grignard reagents react with almost all functional groups which have an electrophilic center. In metal analysis, methylmagnesium and *n*-butylmagnesium bromide were used in the late 1970s for speciation of Sn [108] and methods for organolead analysis were published soon after [109]. Grignard alkylation has been applied for speciation of Pb in water, sediments and biological samples [110-112], for speciation of both Sn in water [113-115], and Hg in biological tissue [116] and gas condensates [117, 118]. The Achilles' heel of Grignard reagents can be found in their violent reactivity with water: this class of chemicals can only be used in dry, aprotic organic solvents. Nonetheless, Grignard reagents are still being used for alkylation of metals in organic matrices, such as petroleum hydrocarbons.

4.4.2 Properties and reactivity of Grignard reagents

Reaction between alkyl halides (RX) and metallic magnesium in diethyl ether or tetrahydrofuran results in organomagnesium halides (RMgX), compounds commonly known as Grignard reagents. The chemistry of Grignard reagents is characterised by a polarised $\text{Mg}^{\delta+}-\text{C}^{\delta-}$ bond yielding an alkyl moiety having the characteristics of a nucleophilic carbanion, able to react with metals and metalloids.

As noted, Grignard reagents are moisture sensitive and undergo rapid exothermic hydrolysis: their use is restricted to dry aprotic solvents. Analytes in aqueous solutions have to be extracted into a suitable organic solvent prior to derivatization, resulting in lengthy sample preparation with possible contamination and/or analyte losses. However, analytes already present in organic

solvents can be directly alkylated by addition of a small volume of Grignard reagent (generally in a 10:1 mole ratio). After a short reaction time, the excess Grignard reagent is hydrolysed by addition of dilute acid and the alkylated analytes present in the organic phase are determined by GC coupled to a detector of choice. Although the products of this reaction are not suitable for CVG, Grignard alkylation provides a necessary alternative to $[\text{BR}_4]^-$ alkylation for samples in non-aqueous matrices (cf. Chapter 6).

4.4.2.1 Interferences and transalkylation

Ideally, the Grignard reagent should completely convert the species of interest into the desired derivative(s) without otherwise changing their chemical forms. However, there are several interferences which have to be carefully considered: *i*) trans-alkylation during derivatization, *ii*) matrix interference and *iii*) matrix-induced product decomposition.

Typically, the Grignard reagent is added in excess in order to compensate for competitive alkylation reactions with matrix components. Additionally, the selection of suitable reaction time is also critical for controlling unwanted transalkylation reactions. Several studies showed that reaction times greater than 5 minutes promote substitution of endogenous metal-alkyl groups by the derivatizing alkyl group. The rate of this conversion for Me_2Hg and MeHgCl standards was up to 10 % [119, 120] and increased up to 50 % for PhHgCl [119]. Therefore, to minimise trans-alkylation, detailed studies of the reaction time for given matrices and analyte concentrations should be part of method validation.

Matrix interferences are mainly induced by moisture present in the sample. Several protocols advise working under an inert atmosphere and include extra steps to dry the organic solvent in which the derivatization takes place [121, 122]. Matrix induced product decomposition can occur either during the derivatization reaction or on the GC column. Free iodine has been found to interfere with alkylation of Hg species, causing complete dealkylation after prolonged time [120]. Similar degradation was observed when the reaction was conducted in the presence of NaI and NaBr ; however, de-alkylation was not observed when chloride was introduced into the reaction mixture. De-alkylation has also been observed on GC columns caused by halides retained from previous injections. Currently, Grignard reagents are mostly used for alkylation of metals in organic matrices [123-125], whereas $[\text{BR}_4]^-$ is used for all other applications.

4.5 Future trends and perspectives

Tetraalkylborates are standard derivatizing agents used for metal speciation by headspace GC ICP MS, particularly for analysis of mercury and tin. A substantive collection of methods for ultra-trace quantitation can be found in the literature for a wide variety of matrices, including natural waters, sediments, and biota. Although this research area has produced consolidated analytical methods, some aspects related to the alkylation chemistry are yet to be fully understood. For example, trans-alkylation effects are often reported, but the factors that govern this unwanted side-effect need to be elucidated. Trans-alkylation can alter metal speciation, leading to systematic errors in quantitation. To date, the most effective way to compensate for trans-alkylation issues entails the use of sophisticated multi-spike isotope dilution approaches. For future work, it could be useful to explore whether slight modifications of the reagents – such as partially fluorinated $[\text{BR}_4]^-$ – might be beneficial to understand the origin of these reactions. For most applications, tetraalkylborates have replaced Grignard reagents whose analytical use for metal speciation remains limited to some non-aqueous samples, typically petroleum hydrocarbons.

The second class of reagents discussed in this chapter is the trialkyloxonium salts, particularly useful for the CVG of simple inorganic anions. These reagents have been used in both aqueous and non-aqueous media, under both acidic and alkaline conditions. Since these are non-volatile salts, they are easy to handle and can tolerate difficult matrices. Considering that only Me_3O^+ and Et_3O^+ salts are commercially available, it may be of analytical interest to study the properties of trialkyloxonium salts having longer alkyl chains. Furthermore, the availability of fluorinated R_3O^+ could be useful for identification work and to enhance detection power for negative chemical ionization GC-MS. Most analytical applications of this chemistry appeared in the literature within the last decade, making this field relatively novel. Considering the importance of alkylation reactions for derivatization and the practical advantages offered by trialkyloxonium, more developments using this chemistry are expected [97].

4.6 References

- [1] S. Moldoveanu, V. David, Chapter 13 - Chemical reactions used in analytical derivatizations, in: S. Moldoveanu, V. David (Eds.) *Modern Sample Preparation for Chromatography* (Second Edition), Elsevier, 2021, pp. 499-593.
- [2] C.F. Poole, Chapter 24 - Sample preparation for gas chromatography, in: C.F. Poole (Ed.) *Gas Chromatography* (Second Edition), Elsevier, Amsterdam, 2021, pp. 615-653.
- [3] D. Tsikas, Pentafluorobenzyl bromide - A versatile derivatization agent in chromatography and mass spectrometry: I. Analysis of inorganic anions and organophosphates, *J. Chromatogr. B* 1043 (2017) 187-201.
- [4] R.J. Wells, Recent advances in non-silylation derivatization techniques for gas chromatography, *J. Chromatogr. A* 843 (1999) 1-18.
- [5] J. Alonso, P. Gonzalez, *Isotope Dilution Mass Spectrometry*, The Royal Society of Chemistry, 2013.
- [6] E. Pagliano, Z. Mester, J. Meija, Reduction of measurement uncertainty by experimental design in high-order (double, triple, and quadruple) isotope dilution mass spectrometry: application to GC-MS measurement of bromide, *Anal. Bioanal. Chem.* 405 (2013) 2879-2887.
- [7] E. Pagliano, Z. Mester, J. Meija, Calibration graphs in isotope dilution mass spectrometry, *Anal. Chim. Acta* 896 (2015) 63-67.
- [8] J.R. Johnson, H.R. Snyder, M.G. Van Campen, Jr., Organoboron compounds. III. Reactions of tri-*n*-butylborine, *J. Am. Chem. Soc.* 60 (1938) 115-121.
- [9] J.B. Honeycutt, J.M. Riddle, Triorganoboranes as alkylating agents, *J. Am. Chem. Soc.* 82 (1960) 3051-3052.
- [10] J.B. Honeycutt, J.M. Riddle, Preparation and reactions of sodium tetraethylboron and related compounds, *J. Am. Chem. Soc.* 83 (1961) 369-373.
- [11] R. Damico, Preparation, characterization, and reactions of lithium and sodium tetraalkylboron compounds, *J. Org. Chem.* 29 (1964) 1971-1976.
- [12] S. Rapsomanikis, O.F.X. Donard, J.H. Weber, Speciation of lead and methyllead ions in water by chromatography/atomic absorption spectrometry after ethylation with sodium tetraethylborate, *Anal. Chem.* 58 (1986) 35-38.

[13] N. Bloom, Determination of picogram levels of methylmercury by aqueous phase ethylation, followed by cryogenic gas chromatography with cold vapour atomic fluorescence detection, *Can. J. Fish. Aquat. Sci.* 46 (1989) 1131-1140.

[14] S. Rapsomanikis, P.J. Craig, Speciation of mercury and methylmercury compounds in aqueous samples by chromatography-atomic absorption spectrometry after ethylation with sodium tetraethylborate, *Anal. Chim. Acta* 248 (1991) 563-567.

[15] R. Fischer, S. Rapsomanikis, O.A. Meinrat, Determination of methylmercury in fish samples using GC/AA and sodium tetraethylborate derivatization, *Anal. Chem.* 65 (1993) 763-766.

[16] J. Ashby, S. Clark, P.J. Craig, Methods for the production of volatile organometallic derivatives for application to the analysis of environmental samples, *J. Anal. At. Spectrom.* 3 (1988) 735-736.

[17] J.R. Ashby, P.J. Craig, New method for the production of volatile organometallic species for analysis from the environment; some butyl tin levels in U.K. sediments, *Sci. Total Environ.* 78 (1989) 219-232.

[18] J.R. Ashby, P.J. Craig, Speciation for analysis of organotin compounds by GC AA and GC MS after ethylation by sodium tetraethylborate, *Appl. Organomet. Chem.* 5 (1991) 173-181.

[19] Y. Cai, S. Rapsomanikis, M.O. Andreae, Determination of butyltin compounds in river sediment samples by gas chromatography-atomic absorption spectrometry following in situ derivatization with sodium tetraethylborate, *J. Anal. At. Spectrom.* 8 (1993) 119-125.

[20] L. Ebdon, P. Goodall, S.J. Hill, P.B. Stockwell, K.C. Thompson, Ultra-trace determination of cadmium by vapour generation atomic fluorescence spectrometry, *J. Anal. At. Spectrom.* 8 (1993) 723-729.

[21] M.C. Valdés-Hevia Y Temprano, M.R. Fernández De La Campa, A. Sanz-Medel, Sensitive inductively coupled plasma atomic emission spectrometric determination of cadmium by continuous alkylation with sodium tetraethylborate, *J. Anal. At. Spectrom.* 9 (1994) 231-236.

[22] A. D'Ulivo, Y. Chen, Determination of cadmium in aqueous samples by vapour generation with sodium tetraethylborate(III) reagent, *J. Anal. At. Spectrom.* 4 (1989) 319-322.

[23] M. Heisterkamp, F.C. Adams, Gas chromatography - inductively coupled plasma: time-of-flight mass spectrometry for the speciation analysis of organolead compounds in environmental water samples, *Fresenius J. Anal. Chem.* 370 (2001) 597-605.

[24] E.M. Krupp, C. Pécheyran, H. Pinaly, M. Motelica-Heino, D. Koller, S.M.M. Young, I.B. Brenner, O.F.X. Donard, Isotopic precision for a lead species (PbEt₄) using capillary gas

chromatography coupled to inductively coupled plasma-multicollector mass spectrometry, *Spectrochim. Acta B* 56 (2001) 1233-1240.

[25] A. Wasik, J. Namieśnik, Speciation of organometallic compounds of tin, lead, and mercury, *Pol. J. Environ. Stud.* 10 (2001) 405-413.

[26] O. Cavoura, C.C. Brombach, R. Cortis, C.M. Davidson, Z. Gajdosechova, H.E. Keenan, E.M. Krupp, Mercury alkylation in freshwater sediments from Scottish canals, *Chemosphere* 183 (2017) 27-35.

[27] Z. Gajdosechova, A. Brownlow, N.T. Cottin, M. Fernandes, F.L. Read, D.S. Urgast, A. Raab, J. Feldmann, E.M. Krupp, Possible link between Hg and Cd accumulation in the brain of long-finned pilot whales (*Globicephala melas*), *Sci. Total Environ.* 545-546 (2016) 407-413.

[28] Z. Gajdosechova, M.M. Lawan, D.S. Urgast, A. Raab, K.G. Scheckel, E. Lombi, P.M. Kopittke, K. Loeschner, E.H. Larsen, G. Woods, A. Brownlow, F.L. Read, J. Feldmann, E.M. Krupp, In vivo formation of natural HgSe nanoparticles in the liver and brain of pilot whales, *Sci. Rep.* 6 (2016) 34361.

[29] Y. Cai, S. Monsalud, R. Jaffé, R.D. Jones, Gas chromatographic determination of organomercury following aqueous derivatization with sodium tetraethylborate and sodium tetraphenylborate. Comparative study of gas chromatography coupled with atomic fluorescence spectrometry, atomic emission spectrometry and mass spectrometry, *J. Chromatogr. A* 876 (2000) 147-155.

[30] J. Muñoz, M. Gallego, M. Valcárcel, Speciation analysis of mercury and tin compounds in water and sediments by gas chromatography-mass spectrometry following preconcentration on C₆₀ fullerene, *Anal. Chim. Acta* 548 (2005) 66-72.

[31] W.M.R. Dirkx, R. Lobiński, F.C. Adams, Speciation analysis of organotin in water and sediments by gas chromatography with optical spectrometric detection after extraction separation, *Anal. Chim. Acta* 286 (1994) 309-318.

[32] J. Vercauteren, C. Pérès, C. Devos, P. Sandra, F. Vanhaecke, L. Moens, Stir bar sorptive extraction for the determination of ppq-level traces of organotin compounds in environmental samples with thermal desorption-capillary gas chromatography - ICP mass spectrometry, *Anal. Chem.* 73 (2001) 1509-1514.

[33] M.B. De La Calle Guntiñas, R. Łobiński, F.C. Adams, Interference-free determination of selenium(IV) by capillary gas chromatography-microwave-induced plasma atomic emission spectrometry after volatilization with sodium tetraethylborate, *J. Anal. At. Spectrom.* 10 (1995) 111-115.

- [34] J.P. Valles Mota, M.R. Fernández De La Campa, A. Sanz-Medel, Merging zones flow injection for the determination of ultratraces of bismuth by volatile species generation atomic absorption spectrometry using sodium tetraethylborate(III), *J. Anal. At. Spectrom.* 13 (1998) 431-435.
- [35] S. Clark, P.J. Craig, The use of sodium tetraethylborate for the derivatization and analysis of selenium containing compounds, *Mikrochim. Acta* 109 (1992) 141-144.
- [36] G.A. Zachariadis, E. Rosenberg, Speciation analysis of triethyl-lead and tributyl-tin compounds in human urine by liquid-liquid extraction and gas chromatography microwave-induced plasma atomic emission detection, *J. Sep. Sci.* 35 (2012) 1132-1137.
- [37] J. Cavalheiro, H. Preud'Homme, D. Amouroux, E. Tessier, M. Monperrus, Comparison between GC-MS and GC-ICPMS using isotope dilution for the simultaneous monitoring of inorganic and methyl mercury, butyl and phenyl tin compounds in biological tissues, *Anal. Bioanal. Chem.* 406 (2014) 1253-1258.
- [38] M. Monperrus, R.C.R. Martin-Doimeadios, J. Scancar, D. Amouroux, O.F.X. Donard, Simultaneous sample preparation and species-specific isotope dilution mass spectrometry analysis of monomethylmercury and tributyltin in a certified oyster tissue, *Anal. Chem.* 75 (2003) 4095-4102.
- [39] A. Delgado, A. Usobiaga, A. Prieto, O. Zuloaga, A. de Diego, J.M. Madariaga, Optimisation of the headspace-solid phase microextraction for organomercury and organotin compound determination in sediment and biota, *J. Sep. Sci.* 31 (2008) 768-774.
- [40] C. Moscoso-Pérez, V. Fernández-González, J. Moreda-Piñeiro, P. López-Mahía, S. Muniategui-Lorenzo, D. Prada-Rodríguez, Multivariate optimization of PTV-GC-MS method for simultaneous determination of organometallic compounds of mercury, lead and tin, *Anal. Methods* 8 (2016) 7702-7710.
- [41] J. Terán-Baamonde, S. Bouchet, E. Tessier, D. Amouroux, Development of a large volume injection method using a programmed temperature vaporization injector – gas chromatography hyphenated to ICP-MS for the simultaneous determination of mercury, tin and lead species at ultra-trace levels in natural waters, *J. Chromatogr. A* 1547 (2018) 77-85.
- [42] E. Beceiro-González, A. Guimaraes, M.F. Alpendurada, Optimisation of a headspace-solid-phase micro-extraction method for simultaneous determination of organometallic compounds of mercury, lead and tin in water by gas chromatography-tandem mass spectrometry, *J. Chromatogr. A* 1216 (2009) 5563-5569.
- [43] P. Jitaru, H.G. Infante, F.C. Adams, Simultaneous multi-elemental speciation analysis of organometallic compounds by solid-phase microextraction and multicapillary gas chromatography

hyphenated to inductively coupled plasma-time-of-flight-mass spectrometry, *J. Anal. At. Spectrom.* 19 (2004) 867-875.

[44] T. De Smaele, L. Moens, R. Dams, P. Sandra, J. Van Der Eycken, J. Vandyck, Sodium tetra(*n*-propyl)borate: a novel aqueous in situ derivatization reagent for the simultaneous determination of organomercury, -lead and -tin compounds with capillary gas chromatography-inductively coupled plasma mass spectrometry, *J. Chromatogr. A* 793 (1998) 99-106.

[45] C. Zheng, L. Hu, X. Hou, B. He, G. Jiang, Headspace solid-phase microextraction coupled to miniaturized microplasma optical emission spectrometry for detection of mercury and lead, *Anal. Chem.* 90 (2018) 3683-3691.

[46] J. Hu, E. Pagliano, X. Hou, C. Zheng, L. Yang, Z. Mester, Sub-ppt determination of butyltins, methylmercury and inorganic mercury in natural waters by dynamic headspace in-tube extraction and GC-ICPMS detection, *J. Anal. At. Spectrom.* 32 (2017) 2447-2454.

[47] Z. Gajdosechova, E. Pagliano, A. Zborowski, Z. Mester, Headspace in-tube microextraction and GC-ICP-MS determination of mercury species in petroleum hydrocarbons, *Energy Fuels* 32 (2018) 10493-10501.

[48] S. Rapsomanikis, Derivatization by ethylation with sodium tetraethylborate for the speciation of metals and organometallics in environmental samples. A review, *Analyst* 119 (1994) 1429-1439.

[49] K. Bergmann, B. Neidhart, Speciation of organolead compounds in water samples by GC-AAS after in situ butylation with tetrabutylammonium tetrabutylborate, *Fresenius J. Anal. Chem.* 356 (1996) 57-61.

[50] M. Heisterkamp, F.C. Adams, Simplified derivatization method for the speciation analysis of organolead compounds in water and peat samples using in-situ butylation with tetrabutylammonium tetrabutylborate and GC-MIP AES, *Fresenius J. Anal. Chem.* 362 (1998) 489-493.

[51] Y. Cai, S. Monsalud, K.G. Furton, Determination of methyl- and ethylmercury compounds using gas chromatography atomic fluorescence spectrometry following aqueous derivatization with sodium tetraphenylborate, *Chromatographia* 52 (2000) 82-86.

[52] S.W.C. Chung, A.H.T. Wu, Determination of butyltins, phenyltins and octyltins in foods with preservation of their moieties: a critical review on analytical methods, *J. Chromatogr. A* 1505 (2017) 18-34.

- [53] C.R. Mansfield, F.J. Black, Quantification of monomethylmercury in natural waters by direct ethylation: interference characterization and method optimization, *Limnol. Oceanogr. Methods* 13 (2015) 81-91.
- [54] R. Peñalver, N. Campillo, M. Hernández-Córdoba, Comparison of two derivatization reagents for the simultaneous determination of organolead and organomanganese compounds using solid-phase microextraction followed by gas chromatography with atomic emission detection, *Talanta* 87 (2011) 268-275.
- [55] M.C.V.H.y. Temprano, M.R.F. de la Campa, A. Sanz-Medel, Comparison of plumbane and tetraethyllead for the determination of lead by inductively coupled plasma atomic emission spectrometry, *Anal. Chim. Acta* 309 (1995) 369-378.
- [56] L.R. Bravo-Sánchez, J.R. Encinar, J.I. Fidalgo Martínez, A. Sanz-Medel, Mercury speciation analysis in sea water by solid phase microextraction-gas chromatography-inductively coupled plasma mass spectrometry using ethyl and propyl derivatization. Matrix effects evaluation, *Spectrochim. Acta B* 59 (2004) 59-66.
- [57] L. Liang, N.S. Bloom, M. Horvat, Simultaneous determination of mercury speciation in biological materials by GC/CVAFS after ethylation and room-temperature precollection, *Clin. Chem.* 40 (1994) 602-607.
- [58] L. Liang, M. Horvat, N.S. Bloom, An improved speciation method for mercury by GC/CVAFS after aqueous phase ethylation and room temperature precollection, *Talanta* 41 (1994) 371-379.
- [59] F. Smedes, A.S. De Jong, I.M. Davies, Determination of (mono-, di- and) tributyltin in sediments. *Analytical methods, J. Environ. Monit.* 2 (2000) 541-549.
- [60] J.H. Huang, Artifact formation of methyl- and ethyl-mercury compounds from inorganic mercury during derivatization using sodium tetra(*n*-propyl)borate, *Anal. Chim. Acta* 532 (2005) 113-120.
- [61] M. Horvat, N.S. Bloom, L. Liang, Comparison of distillation with other current isolation methods for the determination of methyl mercury compounds in low level environmental samples. Part 1. Sediments, *Anal. Chim. Acta* 281 (1993) 135-152.
- [62] H. Hintelmann, R. Falter, G. Ilgen, R.D. Evans, Determination of artifactual formation of monomethylmercury (CH_3Hg^+) in environmental samples using stable Hg^{2+} isotopes with ICP-MS detection: calculation of contents applying species specific isotope addition, *Fresenius J. Anal. Chem.* 358 (1997) 363-370.

[63] N.S. Bloom, J.A. Colman, L. Barber, Artifact formation of methyl mercury during aqueous distillation and alternative techniques for the extraction of methyl mercury from environmental samples, *Fresenius J. Anal. Chem.* 358 (1997) 371-377.

[64] B. Rosenkranz, J. Bettmer, W. Buscher, C. Breer, K. Cammann, The behaviour of different organometallic compounds in the presence of inorganic mercury(II): transalkylation of mercury species and their analysis by the GC-MIP-PED system, *Appl. Organomet. Chem.* 11 (1997) 721-725.

[65] M. Hempel, J. Kuballa, E. Jantzen, Discovery of a transalkylation mechanism - identification of ethylmercury⁺ at a tetraethyllead-contaminated site using sodiumtetrapropylborate, GC-AED and HPLC-AFS, *Fresenius J. Anal. Chem.* 366 (2000) 470-475.

[66] C.M. Tseng, A. De Diego, J.C. Wasserman, D. Amouroux, O.F.X. Donard, Potential interferences generated during mercury species determination using acid leaching, aqueous ethylation, cryogenic gas chromatography and atomic spectrometry detection techniques, *Chemosphere* 39 (1999) 1119-1136.

[67] J. Ruiz Encinar, P. Rodriguez Gonzalez, J.I. García Alonso, A. Sanz-Medel, Evaluation of extraction techniques for the determination of butyltin compounds in sediments using isotope dilution-GC/ICPMS with ¹¹⁸Sn and ¹¹⁹Sn-enriched species, *Anal. Chem.* 74 (2002) 270-281.

[68] M. Monperrus, P. Rodriguez Gonzalez, D. Amouroux, J.I. Garcia Alonso, O.F.X. Donard, Evaluating the potential and limitations of double-spiking species-specific isotope dilution analysis for the accurate quantification of mercury species in different environmental matrices, *Anal. Bioanal. Chem.* 390 (2008) 655-666.

[69] P. Rodríguez-González, J.R. Encinar, J.I.G. Alonso, A. Sanz-Medel, Development of a triple spike methodology for validation of butyltin compounds speciation analysis by isotope dilution mass spectrometry Part I. Synthesis of the spike, characterisation and development of the mathematical equations, *J. Anal. At. Spectrom.* 19 (2004) 685-691.

[70] B. Jackson, V. Taylor, R.A. Baker, E. Miller, Low-level mercury speciation in freshwaters by isotope dilution GC-ICP-MS, *Environ. Sci. Technol.* 43 (2009) 2463-2469.

[71] S. Azemard, E. Vassileva, Rapid determination of femtomolar methylmercury in seawater using automated GC-AFS method: Optimisation of the extraction step and method validation, *Talanta* 232 (2021) 122492.

[72] J. Cavalheiro, C. Sola, J. Baldanza, E. Tessier, F. Lestremau, F. Botta, H. Preud'homme, M. Monperrus, D. Amouroux, Assessment of background concentrations of organometallic compounds (methylmercury, ethyllead and butyl- and phenyltin) in French aquatic environments, *Water Res.* 94 (2016) 32-41.

- [73] L.-E. Heimbürger, J.E. Sonke, D. Cossa, D. Point, C. Lagane, L. Laffont, B.T. Galfond, M. Nicolaus, B. Rabe, M.R. van der Loeff, Shallow methylmercury production in the marginal sea ice zone of the central Arctic Ocean, *Sci. Rep.* 5 (2015) 10318.
- [74] E. Alasonati, I. Fettig, J. Richter, R. Philipp, R. Milačič, J. Ščančar, T. Zuliani, M. Tunç, M. Bilsel, A.C. Gören, P. Fisticaro, Towards tributyltin quantification in natural water at the Environmental Quality Standard level required by the Water Framework Directive, *Talanta* 160 (2016) 499-511.
- [75] C. Devos, F. David, P. Sandra, A new validated analytical method for the determination of tributyltin in water samples at the quantification level set by the European Union, *J. Chromatogr. A* 1261 (2012) 151-157.
- [76] R.F. Cole, G.A. Mills, A. Bakir, I. Townsend, A. Gravell, G.R. Fones, A simple, low cost GC/MS method for the sub-nanogram per litre measurement of organotins in coastal water, *MethodsX* 3 (2016) 490-496.
- [77] G. Centineo, P. Rodríguez-González, E.B. González, J.I. García Alonso, A. Sanz-Medel, N.F. Cardona, J.L. Aranda Mares, S.B. Nebot, Isotope dilution GC-MS routine method for the determination of butyltin compounds in water, *Anal. Bioanal. Chem.* 384 (2006) 908-914.
- [78] G. Centineo, E. Blanco González, A. Sanz-Medel, Multielemental speciation analysis of organometallic compounds of mercury, lead and tin in natural water samples by headspace-solid phase microextraction followed by gas chromatography–mass spectrometry, *J. Chromatogr. A* 1034 (2004) 191-197.
- [79] E. Pagliano, J. Meija, J. Ding, R.E. Sturgeon, A. D'Ulivo, Z. Mester, Novel ethyl-derivatization approach for the determination of fluoride by headspace gas chromatography/mass spectrometry, *Anal. Chem.* 85 (2013) 877-881.
- [80] Z. Gajdosechova, Z. Mester, E. Pagliano, A rapid and sensitive method for the determination of inorganic chloride in oil samples, *Anal. Chim. Acta* 1064 (2019) 40-46.
- [81] Z. Gajdosechova, M. Dutta, F. Lopez-Linares, P. de Azevedo Mello, G. Dineck Iop, E.M. Moraes Flores, Z. Mester, E. Pagliano, Determination of chloride in crude oil using isotope dilution GC–MS: A comparative study, *Fuel* 285 (2021) 119167.
- [82] A. D'Ulivo, E. Pagliano, M. Onor, E. Pitzalis, R. Zamboni, Vapor generation of inorganic anionic species after aqueous phase alkylation with trialkyloxonium tetrafluoroborates, *Anal. Chem.* 81 (2009) 6399-6406.
- [83] N. Luckovitch, E. Pagliano, A reference isotope dilution headspace GC/MS method for the determination of nitrite and nitrate in meat samples, *Int. J. Food Sci. Tech.* 55 (2020) 1110-1118.

- [84] E. Pagliano, J. Meija, R.E. Sturgeon, Z. Mester, A. Dulivo, Negative chemical ionization GC/MS determination of nitrite and nitrate in seawater using exact matching double spike isotope dilution and derivatization with triethyloxonium tetrafluoroborate, *Anal. Chem.* 84 (2012) 2592-2596.
- [85] S. Ammazzini, M. Onor, E. Pagliano, Z. Mester, B. Campanella, E. Pitzalis, E. Bramanti, A. D'Ulivo, Determination of thiocyanate in saliva by headspace gas chromatography-mass spectrometry, following a single-step aqueous derivatization with triethyloxonium tetrafluoroborate, *J. Chromatogr. A* 1400 (2015) 124-130.
- [86] J.D. Chandler, H. Horati, D.I. Walker, E. Pagliano, R. Tirouvanziam, M. Veltman, B.J. Scholte, H.M. Janssens, Y.M. Go, D.P. Jones, Determination of thiocyanate in exhaled breath condensate, *Free Radical Biol. Med.* 126 (2018) 334-340.
- [87] H.W. Thompson, J.W. Linnett, The vapour pressures and association of some metallic and non-metallic alkyls, *Trans. Faraday Soc.* 32 (1936) 681-685.
- [88] E.Q. Adams, A simple relation between composition and boiling point, *J. Am. Chem. Soc.* 48 (1926) 870-872.
- [89] T. Tomai, M. Yanaka, I. Honma, Analysis of selenization in supercritical ethanol for the production of compound semiconductor films, *J. Supercrit. Fluids* 83 (2013) 41-46.
- [90] R.K. Ingham, S.D. Rosenberg, H. Gilman, Organotin compounds, *Chem. Rev.* 60 (1960) 459-539.
- [91] H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, E. Pfeil, Über tertiäre oxoniumsalze, I, *J. Prakt. Chem.* 147 (1937) 257-285.
- [92] H. Meerwein, E. Battenberg, H. Gold, Über tertiäre oxoniumsalze, II, *J. Prakt. Chem.* 154 (1939) 83-156.
- [93] G.A. Olah, K.K. Laali, Q. Wang, G.K.S. Prakash, *Onium ions*, Wiley, New York, 1998.
- [94] V.G. Granik, B.M. Pyatin, R.G. Glushkov, The chemistry of trialkyloxonium fluoroborates, *Russ. Chem. Rev.* 40 (1971) 747-759.
- [95] H. Perst, *Oxonium Ions in Organic Chemistry*, Verlag Chemie, 1971.
- [96] G.J. King, C. Gazzola, R.L. Blakeley, B. Zerner, Triethyloxonium tetrafluoroborate as an ethylating agent in aqueous solution, *Inorg. Chem.* 25 (1986) 1078.

- [97] E. Pagliano, Versatile derivatization for GC-MS and LC-MS: alkylation with trialkyloxonium tetrafluoroborates for inorganic anions, chemical warfare agent degradation products, organic acids, and proteomic analysis, *Anal. Bioanal. Chem.* 412 (2020) 1963-1971.
- [98] E. Pagliano, B. Campanella, A. D'Ulivo, Z. Mester, Derivatization chemistries for the determination of inorganic anions and structurally related compounds by gas chromatography - A review, *Anal. Chim. Acta* 1025 (2018) 12-40.
- [99] E. Pagliano, J. Meija, Z. Mester, High-precision quadruple isotope dilution method for simultaneous determination of nitrite and nitrate in seawater by GCMS after derivatization with triethyloxonium tetrafluoroborate, *Anal. Chim. Acta* 824 (2014) 36-41.
- [100] B. Campanella, M. Onor, E. Pagliano, Rapid determination of nitrate in vegetables by gas chromatography mass spectrometry, *Anal. Chim. Acta* 980 (2017) 33-40.
- [101] E. Pagliano, K.L. LeBlanc, Z. Mester, Selective gas chromatography mass spectrometry method for ultratrace detection of selenocyanate, *Anal. Chem.* 91 (2019) 12162-12166.
- [102] V.L. Linthwaite, J.M. Janus, A.P. Brown, D. Wong-Pascua, A.M.C. O'Donoghue, A. Porter, A. Treumann, D.R.W. Hodgson, M.J. Cann, The identification of carbon dioxide mediated protein post-translational modifications, *Nat. Commun.* 9 (2018) 3092.
- [103] R.F. Borch, Nitrilium salts. A new method for the synthesis of secondary amines, *J. Org. Chem.* 34 (1969) 627-629.
- [104] T. Van Dijk, J. Chris Slootweg, K. Lammertsma, Nitrilium ions-synthesis and applications, *Org. Biomol. Chem.* 15 (2017) 10134-10144.
- [105] C.A. Valdez, R.N. Leif, A. Alcaraz, Effective methylation of phosphonic acids related to chemical warfare agents mediated by trimethyloxonium tetrafluoroborate for their qualitative detection and identification by gas chromatography-mass spectrometry, *Anal. Chim. Acta* 933 (2016) 134-143.
- [106] C.A. Valdez, M.K. Marchioretto, R.N. Leif, S. Hok, Efficient derivatization of methylphosphonic and aminoethylsulfonic acids related to nerve agents simultaneously in soils using trimethyloxonium tetrafluoroborate for their enhanced, qualitative detection and identification by EI-GC-MS and GC-FPD, *Forensic Sci. Int.* 288 (2018) 159-168.
- [107] H. Steinberg, D.L. Hunter, Preparation and rate of hydrolysis of boric acid esters, *Ind. Eng. Chem.* 49 (1957) 174-181.

[108] H.A. Meinema, T. Burger-Wiersma, G.V.D. Haan, E.C. Gevers, Determination of trace amounts of butyltin compounds in aqueous systems by gas chromatography/mass spectrometry, *Environ. Sci. Technol.* 12 (1978) 288-293.

[109] S.A. Estes, P.C. Uden, R.M. Barnes, Determination of *n*-butylated trialkyllead compounds by gas chromatography with microwave plasma emission detection, *Anal. Chem.* 54 (1982) 2402-2405.

[110] Y.K. Chau, P.T.S. Wong, O. Kramar, The determination of dialkyllead, trialkyllead, tetraalkyllead and lead(II) ions in water by chelation/extraction and gas chromatography/atomic absorption spectrometry, *Anal. Chim. Acta* 146 (1983) 211-217.

[111] D. Chakraborti, W.R.A. De Jonghe, W.E. Van Mol, R.J.A. Van Cleuvenbergen, F.C. Adams, Determination of ionic alkyllead compounds in water by gas chromatography/atomic absorption spectrometry, *Anal. Chem.* 56 (1984) 2692-2697.

[112] R.J.A. Van Cleuvenbergen, D. Chakraborti, F.C. Adams, Occurrence of monoalkyllead species during the speciation of organolead, *Anal. Chim. Acta* 182 (1986) 239-244.

[113] R.J. Maguire, H. Huneault, Determination of butyltin species in water by gas chromatography with flame photometric detection, *J. Chromatogr. A* 209 (1981) 458-462.

[114] Y.K. Chau, P.T.S. Wong, G.A. Bengert, Determination of methyltin(IV) and tin(IV) species in water by gas chromatography/atomic absorption spectrophotometry, *Anal. Chem.* 54 (1982) 246-249.

[115] R.J. Maguire, Y.K. Chau, G.A. Bengert, E.J. Hale, P.T.S. Wong, O. Kramar, Occurrence of organotin compounds in Ontario lakes and rivers, *Environ. Sci. Technol.* 16 (1982) 698-702.

[116] E. Bulska, D.C. Baxter, W. Frech, Capillary column gas chromatography for mercury speciation, *Anal. Chim. Acta* 249 (1991) 545-554.

[117] J.P. Snell, W. Frech, Y. Thomassen, Performance improvements in the determination of mercury species in natural gas condensate using an on-line amalgamation trap or solid-phase micro-extraction with capillary gas chromatography-microwave-induced plasma atomic emission spectrometry, *Analyst* 121 (1996) 1055-1060.

[118] J. Snell, J. Qian, M. Johansson, K. Smit, W. Frech, Stability and reactions of mercury species in organic solution, *Analyst* 123 (1998) 905-909.

[119] W. Frech, J.P. Snell, R.E. Sturgeon, Performance comparison between furnace atomisation plasma emission spectrometry and microwave induced plasma-atomic emission spectrometry for

the determination of mercury species in gas chromatography effluents, *J. Anal. At. Spectrom.* 13 (1998) 1347-1353.

[120] H. Emteborg, J. Snell, J. Qian, W. Frech, Sources of systematic errors in mercury speciation using Grignard reagents and capillary gas chromatography coupled to atomic spectrometry, *Chemosphere* 39 (1999) 1137-1152.

[121] C. Liscio, M. Di Carro, E. Magi, Comparison of two analytical methods for the determination of organotin compounds in marine organisms, *C. R. Chim.* 12 (2009) 831-840.

[122] R. Łobiński, F.C. Adams, Ultratrace speciation analysis of organolead in water by gas chromatography-atomic emission spectrometry after in-liner preconcentration, *J. Anal. At. Spectrom.* 7 (1992) 987-992.

[123] F.V.M. Pontes, M.C. Carneiro, D.S. Vaitsman, M.I.C. Monteiro, A.A. Neto, M.L.B. Tristão, Investigation of the Grignard reaction and experimental conditions for the determination of inorganic mercury and methylmercury in crude oils by GC-ICP-MS, *Fuel* 116 (2014) 421-426.

[124] Z. Gajdosechova, M.S. Boskamp, F. Lopez-Linares, J. Feldmann, E.M. Krupp, Hg speciation in petroleum hydrocarbons with emphasis on the reactivity of Hg particles, *Energy Fuels* 30 (2016) 130-137.

[125] B. Bouyssiere, J. Szpunar, R. Lobinski, Gas chromatography with inductively coupled plasma mass spectrometric detection in speciation analysis, *Spectrochim. Acta B* 57 (2002) 805-828.