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Journal:	*Chemical Reviews*
Manuscript ID:	cr-2013-006999.R5
Manuscript Type:	Review
Date Submitted by the Author:	21-Mar-2015
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Chemical derivatization processes applied to amine determination in samples of different matrix composition

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1. INTRODUCTION

Compounds containing an amino group are widely found in nature[1,2] and may be formed from industrial processes, with important examples being amino acids, triethylamines, anilines and biogenic amines. Biogenic amines are formed as a result of neutral and basic amino acid decarboxylation or by amination of aldehydes and ketones and include catecholamines (dopamine, norepinephrine and epinephrine), imidazoleamines (histamine), indoleamines (serotonin and melatonin) and polyamines (putrescine, spermidine and spermine)[3,4]. These amines are neurotransmitters, hormones, bio-modulators in the Animalia kingdom. It is known that both strong tastes and smells associated with decomposing organisms or with certain plants and fungi may originate from amines. For example, fungi and flowers release a specific smell whose role is to attract insects or other species[5] and the smell coming from decaying fish is associated with trimethylamine due to the breakdown of amino acids in the protein rich tissue[5]. Amines are also found in aquatic environment, soil and air where many organisms are capable of producing and releasing amines. For instance, in the freshwater environment, putrescine and phenethylamine can occur in phytoplankton. Many precursors to amines (including amino acids) are released by aquatic organisms either while alive, or during decomposition of deceased plants and animals[6]. These processes are likely to represent an important *in situ* source of amines to aquatic ecosystems.

Biogenic amines are found in a broad range of food products; particularly in protein-rich foods of both animal and plant origin but also in fermented products generally[7]. For instance, in wine, biogenic amines arise from two sources: raw materials and fermentation processes with the main source being of microbial origin, produced during malolactic fermentation by the decarboxylation of amino acid precursors[7]. Although, many biogenic amines including histamine, putrescine and tyrosine are needed for many essential functions in humans and

animals, consumption of food containing high amounts of these amines can have toxicological effects.

Amines are also important components of the plant kingdom and many are relevant to human health. Nicotine derived from tobacco plants (e.g. *Nicotiana tabacum L.,Nicotiana sylvestris*, *Nicotiana rustica L.*), is a prime example. It is a nicotinic acetylcholine receptor agonist and by a variety of mechanisms nicotine is both addictive and a mild antidepressant. Cocaine is a serotonin – norepinephrine – dopamine re-uptake inhibitor. Accordingly it is a powerful stimulant, addictive and the basis of the drug trade. Ephedrine from *Ephedra sp* and *Taxus sp* is a sympathomimetic stimulant that is found in many over the counter decongestants.

In addition to natural source of amines released into the environment, anthropogenic source should also be mentioned. While critical to living things, amines are also used and produced by the chemical industry[1,2]. For example, they are used as components in personal care products (e.g. aminomethyl propanol), detergents for laundry and dishwashing, disinfectants and degreasers (e.g. monoethanolamine)[8]. Amines are also used in chemical herbicides and pesticides. For example, monoethanolamine is used as an organic chelating agent used to reduce activity of elevated antioxidant enzyme levels in bi-pyridylium resistant plant species biotypes to overcome herbicide resistance. Amines including methylamine, ethylamine, n-butylamine are important raw materials in the production of pigments, medicines, corrosion inhibitors and polymers. The majority of these compounds are characterized by toxicity and allergenic properties. Moreover, they show adverse influence on eye mucus membrane, skin and the respiratory system. Additionally, amines can react with nitrites to form carcinogenic nitrozo amines[1].

The previous discussions show the relevance of amines to the well-being of both animals and humans. There is a need for analytical methods that detect these analytes in biological, environmental, forensic and food samples. High sensitivity and selectivity are a prime

requirements of such methods. These requirements, however, have to be met under the constraints of costs and environmental stewardship.

In practice, a variety of analytical methods are used in order to determine amine content in biological or environmental samples[9]. Gas and liquid chromatography have been used to a greater extent than other analytical techniques[1]. However, as many amines are polar, gas chromatography is not suitable for determination for this class of compounds. In addition many important amines do not possess structural features the enable detection by HPLC with a variety of detectors such as a ultraviolet absorption, fluorescence, electrochemical reduction/oxidation or even mass spectrometry. These characteristics give rise to the need for transformation into corresponding derivatives with desirable chromatographic or detection properties[10]. Derivatization process is known for many years and is often used for amine compounds. The milestones of derivatization is presented in Table 1.

A review of different methods of the derivatization process (at particular stages of analytical procedures) using common derivatizing reagents is presented here. The application of microextraction techniques coupled with derivatization of amines is also discussed. On derivatization, the analyte polarity is decreased resulting in an increase in the partition coefficient, while at the same time, the chemical conversion process allows for an increase in performance with respect to chromatographic techniques.

Table 1. Milestones in development of field of application of derivatization in analytical practice

Year	Description	Ref.
1957	The preparation of derivatives from quantities of substances down to one milligram reported	11
1961	The trimethylsilyl group introduced for the GLC analysis of amino acids	12
1961	Trimethylsilyl ethers for derivatization of steroids reported	13
1963	The trimethylsilyl group applied in carbohydrate chemistry	12
1963	First C-Derivatization of Amino Acids reported	14
1963	Derivatization using hexamethyldisilazane reported	15
1964	Derivatization using Chlorotrimethylsilane reported	16
1964	Preparation and decarbonylation of acyl derivatives of cyclopentadienyl metal	17

	carbonyls reported	
1966	Derivatization of thiols with trichloroacetyl isocyanate for NMR analysis reported	18
1967	Derivatization using bis-trimethylsilvy acetamide reported	19
1968	Determination of amino acids present in nanomolar quantities in biological samples after its derivatization using GC reported	20
1968	N,O-Bis(trimethylsilyl)trifluoroacetamide introduced	15
1969	Derivatization using N-Methyl-N-(trimethylsilyl)trifluoroacetamide reported	21
1969	The 9-H-hexadecafluorononanoate and 11-H-eicosafluoroundecanoate derivative for electron capture - GC of steroids reported	22
1970	Preparation of volatile derivatives of amino acids on a solid support followed by direct injection into the gas chromatography column reported	23
1970	The utilization of dansylation methods for quantitative determination of free amino acids reported	24
1970	Preparation of steroid heptafluorobutyrates for gas liquid chromatography utilizing vapor phase derivatization reported	25
1973	Fluorescamine first time used as a derivatization reagent for primary amines detected by MS	26
1974	Fluorimetric derivatization for pesticide residue analysis reported	27
1974	(R)-(+)-trans-chrysanthemoyl chloride for the gas-phase analytical resolution of enantiomeric amines and alcohols introduced	28
1976	Derivatization using trimetylsilyimidazole reported	29
1977	First handbook of derivatives for chromatography published	30
1983	Determination of amino acids with 9-fluorenylmethyl chloroformate and reversed-phase high-performance liquid chromatography reported	31
1985	Quantitative HPLC determination of amikacin in pharmaceutical formulations using precolumn derivatization first time described	32
1989	Dragendorff reagent introduced	33
1997	SPME was coupled with derivatization	34
2006	FMOC-Cl was introduced into derivatization of glucosamine sulfate in human plasma	35
2006	SBSE in combination with in situ derivatization	36
2006	Liquid phase microextraction coupled with in situ derivatization reported	37
2006	Dual derivatization–stir bar sorptive extraction–thermal desorption–gas chromatography–mass spectrometry reported	38
2006	Dynamic hollow-fiber liquid-phase microextraction coupled with derivatization reported	39
2007	Simultaneous dispersive liquid–liquid microextraction and derivatization combined with GC-electron-capture detection first time used	40
2008	Miniaturized hollow fiber assisted solvent microextraction with in situ derivatization first time reported	41
2010	Dispersive liquid–liquid phase microextraction coupled with derivatization first time reported	42
2011	Ionic liquid-based microwave-assisted dispersive liquid–liquid microextraction and derivatization of sulfonamides in river water, honey, milk, and animal plasma	43
2012	Molecularly imprinted-solid phase extraction combined with simultaneous derivatization and dispersive liquid–liquid microextraction for selective extraction and preconcentration of methamphetamine and ecstasy from urine samples followed by gas chromatography first time reported.	44
2013	Ultrasound assisted dispersive liquid-liquid microextraction followed by injector port silylation for rapid determination of quinine in urine by GC-MS first time reported.	45
2013	One-step headspace dynamic in-syringe liquid phase derivatization–extraction technique for the determination of aqueous aliphatic amines by liquid chromatography with fluorescence detection first time reported.	46
2013	Derivatization and dispersive liquid–liquid microextraction based on	47

	solidification of floating organic droplet method for analysis of amino acids in tobacco samples first time rported.	
2014	In situ derivatization combined with ultrasound-assisted emulsification microextraction followed by GC-MS for determination of non-steroidal anti-inflammatory drugs in surface water first time reported.	48

2. IMPROVEMENT OF CHROMATOGRAPHIC PROPERTIES BY ANALYTE STRUCTURE CHANGE

The low amounts of amines present in different kind of sample (e.g. ng/g), the complex sample matrix, and the need for several isolation steps makes accurate quantification difficult. Therefore it is necessary to select an appropriate method of sample preparation for analysis (e.g. type of extraction), and a final determination technique. One should also take into account the fact that a large group of amines do not possess structural properties which enable determination by means of gas or liquid chromatography. Conversion allows for a significant increase in the possibilities and scope of application of both techniques, for example, it is possible to decrease polarity and reactivity, and increase volatility of amine compounds which is desirable in the case of GC analysis. This contributes to an increase in the sensitivity and selectivity and therefore, a lowering of the detection limit[1].

Another pertinent challenge is the compliance of the derivatization process with the rules of green chemistry[49] and green analytical chemistry[50], which result from the principles of balanced development.

There are many known derivatization techniques for amine compounds, the easiest division being a chemical conversion based on the analytical procedure stage. This process can be carried out in a sample matrix, the measuring device dispenser chamber as well as in or behind the chromatographic column (*in situ*, *pre-column derivatization, on-column derivatization* and *post-column derivatization*)[51,52] (Figure 1). For example, in the case of post-

column derivatization, an extracted analyte is introduced together with the derivatizing reagent to a high temperature dispenser and the conversion is performed rapidly. This method reduces the loss of analyte since extraction is performed before the derivative is formed[51]. However, *post column* derivatization also dilutes the analyte.

The most frequently used derivatization technique for amine compounds is pre-column derivatization, that is, at sample collection or preparation for transport, or directly before analysis (*in situ* or in the dispenser of a control-measuring device within a laboratory environment)[51].

Figure 1. Schematic representation of analyte transformation method into derivatives depending on the process site[53]: A) *Pre-column* derivatization: 1) on SPME fiber; 2) directly in the sample taken or during sample-taking stage (*in situ*); B) In chromatograph dispenser chamber or on chromatographic column; C) *Post-column* derivatization.

One method of *pre-column* derivatization occurs within the hot injection port of the GC. This procedure simplifies the sample preparation process by injecting the sample/reagent mixture directly or separately, thus avoiding the need for extra apparatus, e.g. a heater to assist the reactions (however, the term *pre-column* derivatization may not apply to capillary columns where the sample is introduced into the column and presents different challenges that have to be acknowledged). Compared with *off-line* methods, injection port derivatization shows advantages in terms of convenience and "green" operability, high reaction efficiency and low cost.

Another method of derivatization is the direct conversion of the substance within the sample at or after the collection stage[54]. In the determination of amine compounds, *in situ* derivatization is often coupled with the extraction process. Among the "green" extraction techniques, the most commonly used for amines are SPME and SBSE. For example, these procedures are carried out on:

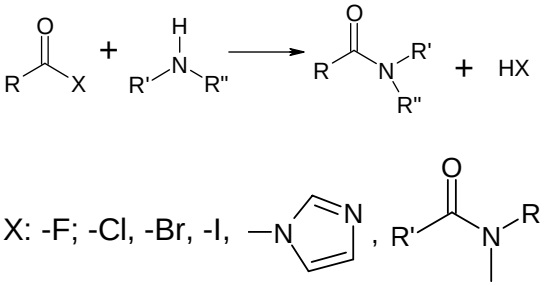
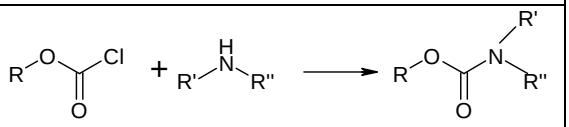
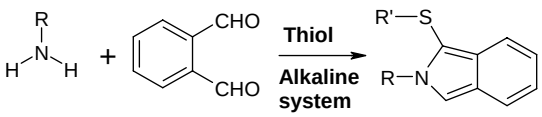
- a fiber for an SPME device which is used for analyte sampling from a medium and its introduction into the dispenser of a control-measuring device (HPLC, GC, etc.),

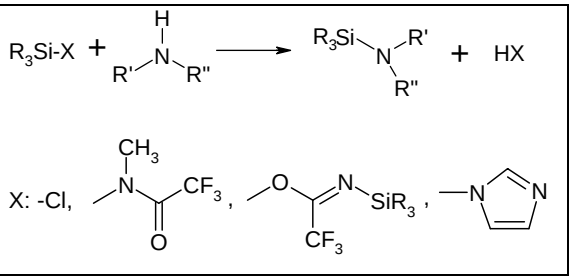
- a glass magnetic mixer covered with a thick layer of polydimethylsiloxane which constitutes a sorption element for analytes. After extraction (SBSE), the sorption element undergoes chromatographic analysis desorption.

Although not as frequently used, other extraction techniques which deserve attention, are hollow-fiber liquid-phase microextraction (HF-LPME) and single drop microextraction (SDME).

The greatest influence on efficiency and efficacy in the derivatization process is the appropriate choice of reagent. Among the many groups of derivatization reagents for amines, the most commonly used are acylation, silylation, Schiff base formation and carbamate formation. Information on these reagents groups is summarized in Table 2.

Table 2. Commonly used amine derivatizing reagents and their characteristics[1,55]

Derivatization method	**Characteristics**	**Reaction**
Acylation	Replacement of H with an acyl group. Typical reagents: • acid anhydrides, • acyl halides, • other reagents including acylimidazoles and acylamides. Occurs readily in mild conditions, often in the presence of bases e.g. pyridine, triethylamine (as a catalyst and scavenger of acidic by-products).	
Carbamate formation	Replacement of H with an alkyl group. Easily performed in aqueous alkaline medium/presence of catalyst (eg sodium carbonate) but yield is generally low. Tertiary amines can also be converted with alkyl chloroformate after dealkylation	 R: methyl-, ethyl-, propyl-, butyl-, trichloroethyl-, pentafluorobenzyl-
Schiff base formation	Performed rapidly in aqueous solution at room temperature using a range of aldehydes and ketones, which are selective to primary amines. The water by-product does not undergo secondary reactions in the reaction systems involved. Excess reagents, which often disturb the amine analysis, have to be removed in a separate clean-up step.	 Reaction with *o*-phthaldialdehyde (OPA) reagent: 

Silylation	Replacement of H with an alkylsilyl group. The most effective derivatizations are performed under anhydrous conditions (moisture sensitive reagents and derivatives). Reagents containing sterically crowded groups (e.g. tert-butylmethylsilyl) are more stable to hydrolysis and have greater reactivity towards amines.	

Considering the properties and range of applications of the derivatizing reagents mentioned above, the choice of reagent must take into account the requirements of the chromatographic technique or detector to be used.

3. MODES OF DERIVATIZATION OF AMINE COMPOUNDS IN CHROMATOGRAPHY

There are three types of derivatization modes commonly used in chromatography and applied to amine derivatization: *pre-column*, *on-column* and *post-column* derivatization[56-60]. The chemical conversion of amines can also be performed during sample collection and is termed *in situ* derivatization. The appropriate column derivatization mode strongly depends on the characteristics of the reaction (e.g., experimental conditions, rate, yield and stability of reagent and derivatives)[56].

It is also necessary to differentiate between *off-line* and *on-line* arrangements. In the *off-line* mode the derivatization process occurs away from the chromatographic system. However, in certain situations the method could be described as either *off-line* or *on-line*, for example, when a sample vial is in a carousel as part of an automated derivatization-injection system[61]. *Off-line* derivatization is simple and readily automated via 96 well plate technology and/or robotics and so it is not labor intensive[51]. In the *on-line* derivatization mode, the process is integrated into the

instrumentation and analysis, and is time constrained and controlled[61]. *On-line* derivatization can eliminate the time-consuming sample preparation step as well as decrease the use of valuable and/or toxic reagents and solvents that would otherwise be needed, thus increasing the speed and efficiency of the analysis. A specific on-line derivatization called injection port derivatization is when derivatization reaction occurs in the hot GC injection port.[62] Injection port derivatization may be performed in two ways, i.e. ion-pair extraction followed by injection port derivatization and direct injection port derivatization.[62] In the first mode, the derivatization reagent plays an additional role as the ion-pair reagent, and is firstly added into the sample solution to form ion-pair complexes with the analyte of interest to promote partition of them to the extractant phase.[62] Later on, the extractant phase enriched with the ion-pair complexes is introduced into a hot injecton port after appropriate treatment.[62] The ion-pair complexes would be converted to their corresponding volatile derivatives, which are amenable to analysis.[62] In the case of direct injection port derivatization, the analytes and derivatization reagents are injected separately or combinatorially into the hot injection port for derivatization analysis. It need to be mentioned that there are various injection modes in GC as follows:

- split/splitless mode,
- cold on-column injection,
- programmed temperature vaporization injection,
- large volume injection and valve injection,
- large volume injection coupled with programmed temperature vaporization injection technique, and
- cold on-column large volume injection injection.

Developments in injection port derivatization in excellent reviewed by Wang et al. [62]

Information on *off-line* and *on-line* derivatization modes is presented in Table 3. The chemical conversion process could also be described as an *at-line* system in cases where theanalysis device is transported to the sampling site.

Table 3. *Off-line* and *on-line* derivatization modes

Characteristics		Advantages	Drawbacks	Ref.
PRE-COLUMN DERIVATIZATION				
Off-line	Process occurs away from chromatographic system, prior to analysis.	No solvent or kinetic limitations. Conducted under flexible reaction conditions or with harsh reagents. Optimization possible for high yields/ minimal by-product formation.	Non-automated *off-line pre-column* derivatizations are time-consuming. Experimental errors: • loss of analyte through evaporation and re-suspension; contamination during work up.	52, 56, 58
On-line	Incorporation of a derivatization reagent into the flow scheme of a chromatographic system.	No solvent dilution problems. Where the extraction and clean-up of complex samples is necessary, it can be automatically performed via the switching of valves. Preliminary sample handling is minimized and automated derivatization gives better reproducibility.	Several requirements exist for application of this mode in LC: • good solubility in the mobile phase; • compatibility of derivatization solvent with mobile phase; • formation of precipitate or gas in the derivatization should not occur; • good chemical and/or pressure stability of derivatizing reagents in organic solvent; • minimum volume of derivatization solvent or well packed solid-phase derivatization column.	52, 56, 58
POST-COLUMN DERIVATIZATION				
Off-line	The least used technique. Involves separation of analyte from the mobile phase prior to detection and performing a derivatization process remotely.	Derivatization process not affected by sample matrix during reaction.	Automation is difficult. low reproducibility, accuracy and precision.	56, 58, 63

On-line	Injection-separation steps are followed by *on-line* derivatization, using automatation. Utilization of *post-column* reactors. The derivatives formed and any excess reagent are introduced into the detector.	Many reactions have been employed *post-column on-line*: solid phase/ catalytic enhanced reactions, photochemical reactions, etc.	Several requirements/contraints for application in LC: • transparency of reagents in detector; • nature of the reagent solvent; • prevention of derivative precipitation before detection; • lack of mixing noise; • mixing of reagents with the analyte. Need for additional instrumentation.	56, 58, 63, 64

3.1. *In situ* derivatization

Many of the derivatization reactions reported in the literature occur in an organic medium. *In situ* derivatization can be carried out in aqueous media[65] and offers a simplified procedure that is readily automated. It requires water compatible reagents[54] such as S-(−)-N-(trifluoroacetyl)prolyl chloride[66,67] and S-heptafluorobutyrylprolyl chloride[68,69]. *In situ* derivatization is performed to improve GC separation, detection and the extractability of the target compound into a non-polar sorbent improving the extraction efficiency[65]. The process is frequently also applied to LC-MS techniques in order to increase the sensitivity by adding on moieties that improve ionization and reduce matrix effects[70]. Moreover, by modification with a defined structural element, derivatization often enables the prediction of specific fragmentation reactions in tandem MS (MS-MS), which enhances the specificity of the method[54].

Although, *in situ* derivatization in LC is not as commonly used as in GC, there are several articles present this mode of derivatization as a simple and fast method of choice when applied to amine compounds determination[71-74].

In situ aqueous derivatizations offer many advantages. There are very well described by Casas Ferreira et al.[54] in a review focused on the application of in situ aqueous derivatization as

sample preparation technique for gas chromatographic determinations. First of all, because the chemical reaction occurs directly in the aqueous medium, no previous extraction of the compounds is required reducing the errors associated with sample manipulation[54]. Moreover, removal of water soluble hydrolysis products may not be necessary due to their solubility, which allows them to remain in the aqueous sample. In the case when derivatization is coupled with extraction, the aqueous medium is clearly advantageous compared with organic solvents because this contributes to the reduction or elimination of organic, toxic, and non environmentally friendly solvents in the analytical procedures. Moreover, as was previously mentioned, depending on the analytical technique chosen for the amine determination, it is possible to automate the whole sample preparation step[54]. Therefore, from the mixture of reagents in a suitable vessel the whole process occurs on-line[75].

An excellent example showing the advantages of *in situ* aqueous derivatization coupled with extraction procedure was presented by Llop et al.[2]. The authors proposed automated determination of aliphatic primary amines in wastewater by simultaneous derivatization and headspace solid-phase microextraction followed by gas chromatography–tandem mass spectrometry. The proposed method avoids the use of organic solvents, achieves low LODs (between 10 and 100 ng/L) and offers satisfactory precision (RSD ≤11%). In addition, the entire analytical process, including sample preparation and determination, is fully automated and performed in less than 30 min, which enables high sample throughput. Moreover, the use of MS–MS rather than single MS detection provides high selectivity for the determination of primary amines in very complex matrices such as industrial wastewater samples.

On the other hand, there are limited reagents that can be used for amine derivatization, since many of them react or decompose in water, for example silylation reagents (these reagents are sensitive to water, making it necessary to perform a prior extraction step, which complicates

the process). Additionally, a high excess of reagent should be added to the aqueous medium and the optimized target analyte/reagent ratio is usually high. This reduces the possibility of low reaction yields when reactive matrix compounds are also present[54].

The examples of application of in situ aqueous derivatization with presentation of it advantages and drawbacks are presented by Ferreira et al.[54]

In past, the most often techniques used for introducing derivatives into the chromatographic system when the reaction takes place directly in the aqueous medium have been solid phase extraction (SPE)[76-78] and liquid-liquid extraction (LLE)[79-81]. However, these techniques present some drawbacks including high level of organic solvent consumption (especially LLE) and considerable manipulation of the sample (SPE, LLE). Moreover, the automation of either technique has been scarcely addressed. In the era when it is recommended to apply the principles of green chemistry in analytical laboratories, it is difficult to justify extraction methods which use large quantities of toxic, organic solvents in the sample preparation stage[79-80]. Therefore, sample preparation techniques where solvent consumption is reduced are preferred, for example hollow-fiber liquid phase microextraction (HF-LPME) or single drop microextraction (SDME). These techniques resolve many aspects of green chemistry while keeping advantages of using the well understood long used liquid-liquid extraction. In 2013, the first proposal was published for a quantitative comparative assessment of the impact on the environment and analysts' health from different stages or whole analytical procedures[50].

Solventless sample preparation techniques based on the extraction of analytes in sorption processes have become effective and environmentally friendly alternatives compared with traditional solvent extraction techniques. These techniques include solid phase microextraction (SPME) and stir bar sorptive extraction (SBSE). Both techniques are successfully applied to the *in situ* derivatization of amine compounds. As was previously mentioned, other techniques that

meet the criteria of green chemistry and can be coupled with in situ derivatization and successfully applied for amine compounds are HF-LPME and SDME. However, it must be mentioned that optimization of sample preparation will involve the chemistry of the sample matrix. Once SPME, SBSE, or solvent extraction techniques are employed then these extraction medium may play a role in the reaction as catalysts or media for co-concentration of the analyte and reagent. In this case, optimizing the sample preparation will require investigation of the extraction medium.

Two limiting cases that describe the combination of derivatization and extraction are characterized by Pawliszyn[82]. The first occurs when mass transfer to the fiber is slow in comparison with the reaction rate. Under these conditions, the accumulation rate of the analytes can be described by equation 1, assuming that the derivative is trapped in the extraction phase.

$$n(t) = \frac{B_3 A D_s}{\delta} \int_0^t C_s(t) dt \qquad (1)$$

where:

- n is the mass of analyte extracted (ng) in a sampling time (t),
- D_s is the phase molecular diffusion coefficient,
- A is the outer surface area of the sorbent,
- δ is the thickness of the boundary layer surrounding the extraction phase,
- B_s is a geometric factor, and
- C_s is the analyte concentration in the bulk of the sample.

In the second limiting case, the situation is reversed in that the reaction rate is slow in comparison with transport of analytes to the extraction medium. In other words, at any time during the extraction process the extraction phase is at equilibrium with the analyte of interest in a well-agitated sample, resulting in a uniform reaction rate throughout the coating.

Here, the accumulation rate of the product in the extraction phase *n/t* can then be defined by:

$$n = V_e k_r K_{es} \int C_s(t) dt \qquad (2)$$

where:

- C_s is the initial concentration of analytes in the sample,
- k_r is chemical reaction rate constant
- V_e is the volume of the extraction phase,
- K_{es} is the distribution constant of the analyte between the extraction phase and the sample matrix.

Thus, in the case when volume of the sample is large, the reaction and accumulation of analyte in the extraction phase proceeds with the same rate as long as the reagent is present in excess (the rate is also propotional to the extraction phase/sample matrix distribution constant). In the case of a limited sample volume, however, the analyte concentration in the sample phase decreases with time as it becomes partitioned into the coating and converted to trapped product, resulting in a gradual decrease of the rate. The time required to extract analytes exhaustively from a limited volume can be estimated from the experimental conditions.

The extraction techniques coupled with *in situ* derivatization, as well as other methods, are described in Section 4.

3.2. Pre-column derivatization

Nowadays, the optimal separation of a wide range of amine compound derivatives (aliphatic and aromatic amines; primary, secondary, tertiary amines) in different matrices, including food, wastewater or biological samples, can be achieved with the aid of *pre-column* derivatization[56, 83-95].

In this process analytes are derivatized before injection, and thereafter the reaction products are separated and detected. *Pre-column* derivatization offers the advantage of increasing sensitivity using reagents that provide lower background levels than *post-column* derivatization. Moreover, it allows an increase in hydrophobicity of analytes sufficient to retain the reversed-phase stationary phase conditions while minimizing reagent consumption rates using a small reaction system. When unreacted derivatizing reagent is present this does not generally cause a problem provided separation has been achieved in the column[96]. However, in some cases possible interferences from the excess reagent and the formation of artifacts mean a post-reaction step may be required to obtain cleaner chromatograms, especially with UV–VIS and fluorescence detection. When mass spectrometry detection is used, interferences may be avoided by specific monitoring of selected ions and, thus, clean-up operations may be minimized or avoided[56]. As the derivatization reagent is added directly to the sample, reaction efficiency is strongly influenced by the sample matrix (e.g. coexisting substances) and *pre-column* derivatization can be considered appropriate when analysis is required of a limited variety of samples with high sensitivity[56].

Pre-column derivatization is also applied for enantiomer determination of chiral compounds[97]. The difficulty of derivatization procedures varies widely, from simple mixing at room temperature for fast reactions, to processes that require heating, post-reaction cleaning, and so on[56,96].

3.3. On-column derivatization

On-column derivatization is where modification of analytes is carried out during elution through the column. This is accomplished using a mobile phase containing an appropriate derivatizing reagent. In the case of *on-column* derivatization in an HPLC system, the analyte

interacts with the stationary and mobile phases during the analysis. In this process, the derivatizing reagent which is available in the mobile phase, modifies the analyte into its derivatives and therefore enhances chromatographic behavior[52]. Underivatized analytes adsorb light in different wavelength range that derivatives and this knowledge is used to differentiating from the signal from the derivatives. In the case of injection-port or on-column derivatization before GC analysis, the analytes and the derivatization reagent are mixed and injected together into the GC system and the derivatization reaction occurs in hot GC-injection port[62].

A two-step auto-injector has been developed for the automated on-column derivatization and subsequent GC–MS of amine-type drugs and metabolites by Miki et al.[98] For effective reaction, this injector has been designed to inject the reagent several seconds after the sample using the following procedure: The derivatization reagent was drawn into the syringe, followed by air (creating a gap between the sample and reagent). The next step involves positioning the sample, and finally 1 μL of air, closer to the needle than the derivatization reagent. The use of a gas-tight syringe minimizes cross-contamination. After sample injection the derivatization reagent was injected after a predetermined time period. To optimize the performance of the injector, several operation parameters were set (amount of reagent/ sample solution, volume of air gap, injection speed of the derivatization reagent, and the interval between the injections of sample and reagent). When the vaporized sample enters the column, the analyte is retained on the inner wall of the column over an area close to the injection port, while the solvent is carried away faster. Then the vaporized derivatization reagent flows into the column and comes in contact with the bands of analytes adsorbed over a certain area, thereby efficiently reacting at a certain column temperature. The yield of trifluoroacetic acid (TFA) derivatives were calculated by comparing to the standard approach using trifluoroacetic anhydride (TFAA). However, the yield of mono-*N*-TFA derivative of amphetamine type compounds possessing a hydroxyl group,

which cannot be prepared by using TFAA, was estimated by comparing its peak area with that of bis-*N*,*O*-TFA derivative obtained by the ordinary method using TFAA, on the total ion chromatogram.

The mechanism of the two-step injector and on-column trifluoroacetylation proposed by authors of this work is presented in Figure 2.

Figure 2. Mechanism of on-column trifluoroacetylation using the two-step injector and *N*-methyl bis(trifluoroacetamide) (MBTFA) (Reprinted with permission from ref 98. Copyright 2008 Elsevier.)

The *on-column* derivatization mode is an attractive technique because it has several advantages such as greatly minimizing the consumption of samples and labeling reagents, which reduces the operating cost and can improve the precision of analysis of nanomolar or micromolar samples. These advantages make *on-column* derivatization a useful technique for analysis where only small amounts of sample are available. Moreover, this technique does not require any additional or specialized instrumentation[52, 99].

Despite these advantages, *on-column* derivatization has not attained widespread acceptance until recently due to the fact that the derivatization reaction has to be completed during separation[51]. This is in contrast with the current trend to reduce the separation time.

3.4. Post-column derivatization

Post-column derivatization has been proposed to overcome the drawbacks associated with *pre-column* modes dealing with, for instance, reaction completeness and stability of reagent and derivatives. In the *post-column* procedure, separation occurs within the column, derivatizing reagent is then mixed with the analytes in a *post-column* reactor[45] and finally, the derivatives are

transferred to the detector. Therefore, the conversion reaction of analytes into their derivatives should be rapid. A reagent that generates a low background signal is required. Moreover, it is necessary to minimize certain parameters, including band broadening, dead volume associated with connecting tubing, mixing device, and detection flow cell[51]. With the *post-column* reactors, band broadening could be greatly reduced by using segmented-flow procedures. Recently, a wide range of *post-column* reactors for different detection systems has become commercially available.

A specific advantage of the *post-column* derivatization mode is that the process can be automated and therefore offers excellent quantitative performance and reproducibility. Because analytes are separated before the derivatization process, reaction efficiency is less prone to matrix effects, enabling use in a wide range of samples. On the other hand, this derivatization mode cannot be used for high-sensitivity analysis. Also, further pumps to dispense the derivatizing reagents are required and in addition to this the *post-column* reactor can lead to peak-broadening and to a decrease in sensitivity[100]. Another disadvantage is the high consumption of the reaction reagent, which is kept flowing constantly. *Post-column* derivatization does not permit the detection of unreacted reagent, which limits the type of reagents that can be used.

4. Derivatization coupled with microextraction techniques

Although the main goal of current derivatization approaches is not to obtain greener developments, the fact remains that it can be considered under this perspective[101]. Automation and miniaturization are both key in the design of greener derivatization procedures[101]. When these are applied, the amount of reagents used and waste generated are reduced what also brings financial benefits (cost savers). Particular effort has been made towards the elimination and/or

reduction of organic solvent consumption via developments in the field of miniaturization such as SPME, SBSE or different liquid-phase microextraction all with the possibility of simultaneous extraction and derivatization. Table 4 presents different derivatization approaches that are often used in amine compounds conversion, assessed according to the achieved green benefits.

Table 4. Some greener derivatization approaches in analytical laboratories

Green solution	**Approaches**	**Reference**
Reduction in toxic reagents and less harsh conditions.	In aqueous media	54
	In ionic liquids	102
	In supercritical fluids	103
Derivatization in the instrument. Reduction of labor, time, energy and reagents.	In-port	104
	On-column/in-capillary	105
Automation.	On-line	106
Reduction of analytical steps and work scale. Simultaneous derivatization and extraction. Elimination or reduction of organic solvents.	Solid-phase In-fiber In-drop In-hollow fiber In-membrane	107-111

The application of microextraction combined with derivatization process of amine compounds has been found to be attractive due to many advantages including analyte recovery, improvement of separation, detectability and compound identification. Among the known extraction modes, HS-based methods such as HS-SPME and HS-SDME, are preferable as the extraction phase containing the derivatization reagent is not in contact with the aqueous phase. However, in the case of the silylation reaction the reagents and their derivatives are moisture sensitive and hydrolyzed in aqueous medium, therefore, drying SPME fibers under a nitrogen stream before derivatization, or derivatizing analytes in the syringe barrel after extraction are possible solutions to this sensitivity. Other derivatization processes including acylation or Schiff base formation may proceed rapidly in the aqueous medium at room temperature, and therefore, can be coupled with fast extraction techniques.

4.1. Solid Phase Microextraction

Solid phase microextraction (SPME) has been known for over twenty years. There are many types of SPME devices along with their corresponding methodologies. The solventless technique should be treated as a classical example with two important stages[101]:extraction of analyte; and introduction of the sample to the instrument (GC, LC, etc.).

SPME fulfills all the requirements of green chemistry and green analytical chemistry (GAC) rules during analytical procedures[7]. The technique is increasingly important in everyday laboratory practice because it has many advantages which are listed and described throughout the scientific literature[112-117].

Currently, combining analyte collection and derivatization with the use of an SPME device is widely used for samples of different matrix composition and different origins. Since no organic solvents are used (or their use is minimal), it is possible to use different approaches to sample collection with the help of an SPME device combined with derivatization[107,118] (Figure 3). The most popular method is the direct transformation of the sample into its derivative during collection or within the sample studied (*in situ*), followed by extraction using the SPME technique[54]. Another option is derivatization on the fiber of the SPME device[119]. In this case two approaches can be used. In the first, the derivatizing reagent is adsorbed onto the fiber and then the analyte is directly extracted from the solution (direct immersion-solid phase microextraction, DI-SPME) or from the headspace (headspace-solid phase microextraction, HS-SPME). In the second, the analyte is extracted from the sample on the fiber surface and then converted chemically using immersion, exposure to vapor phase or spraying the fiber with the mixture containing the derivatizing reagent[120].

This approach has advantages when compared with conventional derivatization procedures, such as ease of use, rate, relatively low cost (per sample) and low solvent use, all desirable when considering GAC principles[50].

In Figure 4 the headspace sampling (HS-SPME) of the analyte with simultaneous derivatization is shown.

Figure 3. Schematic representation of SPME device with simultaneous analyte derivatization[118]: A) Analyte absorption with the use of an extraction fiber (SPME) after the chemical conversion process is carried out in the sample; B) Analyte sampled with the use of an SPME device, after derivatizing reagent adsorption on the extraction fiber; C) Extraction of analytes from the sample on the surface of the fiber before derivatization on the fiber.

Figure 4. Schematic representation of analyte sampling stage from HS-SPME with simultaneous derivatization. Reprinted with permission from ref 118. Copyright 2004 Wiley and Sons.)

4.2.Stir Bar Sorptive Extraction

Stir bar sorptive extraction (SBSE) was introduced in 1999 by Baltussen et al.[121] in order to overcome some limitations of existing techniques including SPME. This is a solventless extraction technique, developed for the enrichment of analytes from aqueous matrices. SBSE is based on the same principles as SPME, but instead of a polymer-coated fiber, stir bars are coated with PDMS, an apolar polymeric phase used for hydrophobic interactions with target molecules (commercially available as ***Twister®***, ***Gerstel GmbH***). The retention process in the PDMS phase is based on Van der Waals forces as well as the hydrogen bonds that can be formed with oxygen atoms of PDMS depending on the molecular structure of the analytes[108].

The SBSE technique offers several advantages that have been described in many review papers[108, 122-124]. Some limitations are described[108,122], for example since a single apolar polymer covers the stir bar, it may only be applied to semi-volatile thermo-stable compounds when thermal desorption is used as a back-extraction mode. However, the SBSE technique coupled with a derivatization process can address this limitation and expand the application of the SBSE technique to more polar and thermally labile compounds.

Different derivatization modes can be employed including *on-stir*, *post-extraction* and the most commonly used *in situ* strategy. *In situ* mode derivatization (Figure 5A) is the simplest way to convert analytes to appropriate derivatives and occurs in aqueous matrices before or simultaneously with the enrichment step[108, 125]. After the derivatization process, analytes are extracted by the PDMS phase in both direct immersion (DI) and headspace (HS) modes. However, this derivatization mode is not applicable to moisture-sensitive reactions since the analyte has an affinity for the PDMS phase and the subsequent GC separation is increased. In the case of amine derivatizations, many reagents are used but the most popular are ethyl chloroformate, 9-fluorenylmethyl chloroformate (FMOC), (+)-fluorenylethyl chloroformate (FLEC), acetic anhydride, and 2,3,4,5,6-pentafluorobenzaldehyde[108, 125]. Acetic anhydride is mainly used for GC with flame ionization detection, while the 2,3,4,5,6-pentafluorobenzaldehyde is mainly used for electron capture detection or mass spectrometry with negative ion chemical ionization.

The on-stir bar derivatization can be performed in two ways:

- preloading the polymeric coating with a derivatization reagent before exposure to the sample (simultaneous extraction and derivatization, Figure 5B), or
- preconcentration of the analytes in the PDMS phase followed by exposure of the stir bar to the vapor of the derivatization compound (extraction followed by derivatization).

The post-extraction mode can be performed with thermal desorption (Figure 5C) and this strategy is more suitable for silylating reagents. If thermal desorption is applied, a small glass capillary tube containing derivatization reagent is placed together with a stir bar in the desorption chamber. In the case of liquid desorption, the derivatization reagent is added to the organic solvent after stir-bar desorption.

Figure 5. Schematic representation of different derivatization modes using SBSE: A) *in situ*; B) *on-stir-bar* with the derivatization reagent preloaded before exposure to the sample; C) *in-tube* derivatization. Reprinted with permission from ref 125. Copyright 2008 Elsevier.)

4.3. Single drop microextraction

One of the most popular techniques in which the use of solvents has been significantly reduced compared to classical liquid–liquid extraction is a single-drop microextraction (SDME).

Single drop microextraction was developed by Jeannot and Cantwell[126] as an inexpensive alternative to SPME. In this methodology a syringe is used to suspend a microliter drop of an extracting solvent either directly immersed within or in the headspace above the sample[127,128] (Figure 6). Next, the syringe is used to inject the solvent together with extracted analytes into the chromatographic system. In the SDME technique, the analytes are extracted and concentrated in a single step[127].

Figure 6. Single drop microextraction[128]: A) direct immersion SDME (two-phase); B) direct immersion SDME (three-phase); C) headspace SDME. 1 Syringe; 2 Aqueous sample; 3 Stir bar; 4 Organic solvent layer; 5 Headspace; 6 Needle; 7 Solvent drop.

Single drop microextraction has emerged as one of the simplest and most easily implemented modes of micro-scale sample pre-concentration and clean-up[127,129]. Other advantages include low cost, high selectivity, good quantitation and a lowering of detection limits. Since in SDME only a microliter of solvent is used, it may be called a “green” technique[127,129]. Moreover, SDME is found to provide excellent clean-up for samples within complicated matrices (especially HS-SDME). In addition, the technique can be automated. On

the other hand, SDME is time consuming and significantly affected by the stirring rate, as demonstrated by the difficulty in attaining equilibrium in most cases[127,129].

Single drop microextraction is found in a variety of applications including sample preparation for amine determination in different matrices[127]. The applicability of this technique has been also extended by converting amines into extractable analogs through a derivatization process, what is attractive when for example GC technique is used for further analysis. Analytes of interest can be derivatized in four ways:

- in the donor aqueous phase,
- in the extractive solvent droplet,
- in the syringe needle barrel, and
- in the injection port.

In the last few years, many different derivatization methods of amine have been developed for SDME[109-111]. Previously, derivatization followed by SDME was the most commonly used for the analysis of amine compounds[130]. However, derivatization and simultaneous SDME for the analysis of amines has been also developed and extensively used. To avoid matrix interferences, HS-SDME for the extraction and concentration of volatile compounds in an aqueous solution has been developed[131] and recently applied to amine compounds, with in situ derivatization the most commonly used (Figure 7). For example, Deng et al.[110] applied the mixture of derivatization reagent and organic solvent as the accepter phase for HS-SDME with in situ derivatization of aliphatic amines in the samples. However, they found some disadvantages with this method such as instability of the microdrop, operational difficulties and air bubble formation during extraction. To overcome these drawbacks, Muniraja et al.[111] developed an automated one-step in-syringe simultaneous derivatization-extraction

method for the analysis of primary and secondary aliphatic amines in aqueous samples. The present method provides a simple, selective, automated, low cost and eco-friendly procedure to determine aliphatic amines in aqueous samples.

Figure 7. Schematic representation of analyte sampling stage from HS-SDME with simultaneous droplet derivatization[128].

4.4. Hollow fiber liquid phase microextraction

As noted above, during the extraction process by SDME there is a risk of detachment of the extractant drop. In addition, when the amine compounds are extracted from the aqueous sample, the choice of suitable organic solvent is limited. To overcome these disadvantages it is necessary to introduce the liquid extractant inside a porous, semi-permeable polymeric membrane. This is known as hollow fiber liquid-phase microextraction (HF-LPME) and was introduced in 1999 by Pedersen-Bjergaard and Rasmussen[132]. The technique utilizes a hollow fiber (HF) to stabilize and protect the extractant phase[81]. Next, the small pore size of hollow fibers in membrane methodologies allows both extraction and preconcentration of the analytes from the complex samples in a simple and inexpensive way[81]. The other advantages of HF-LPME include the possibilities of automation and miniaturization, high versatility and selectivity, immersion and headspace modes and coupling with derivatization procedures[129]. On the other hand, HF-LPME is a non-equilibrium procedure (as are other LPME techniques)as a result of the smallcontact surface between the sample and the extractant. In addition, pre-conditioning of the membrane, longer sampling time as well as higher temperature is necessary when compared to SDME because of the lower evaporation rate. In manual mode, only average precision is achieved.

Hollow-fiber liquid phase microextraction can be performed in two- and three-phase modes. The two-phase mode consists of the organic solvent (a few microliters) in the lumen as well as being immobilized in the wall pores of the hollow fiber. The extracting solvent (acceptor) is not in direct contact with the sample solution because the porous membrane of the hollow fiber serves as a barrier to the aqueous sample[127,133]. Hollow-fibre liquid-phase microextraction in the three-phase mode is a microscale sample preparation technique where target analytes are extracted from an aqueous sample through a supported liquid membrane (SLM) that is immobilized in the pores of a porous polymeric material and into a volume of acceptor solution (typically, 10–30 μL). In this context, the porous polymeric material is a hollow fibre[127,134].

HF-LPME can be coupled with a derivatization process and this combination can also be applied to amine analysis[134,135]. This coupling improved chromatographic separation, sensitivity and selectivity of analytes[127]. Generally, the coupling can be carried out in several ways[127,136]. The first mode is using HF-LPME coupled with injection port-derivatization[123]. In the second mode, pure solvent is used to extract the analytes of interest with derivatization on a GC column[136,137]. In the third mode, derivatizing reagent is added to the sample solution (*in situ*) for simultaneous derivatization and extraction of analytes[136,137] (Figure 8). In a further successful approach, a mixture of organic solvent and derivatizing reagent is used as the extraction medium, and this is held within a hollow fiber for both direct immersion as well as for headspace of LPME for the simultaneous clean up, extraction and derivatization of analytes[135-137] (Figure 9). This approach may bring several advantages including simplification of sample pretreatment step and reduction of solvent consumption[135]. Moreover, HF can exclude biomacromolecules and protect moisture-sensitive derivatizing reagents[135]. This approach was presented by Chia et al.[69] for the amine analysis in river water after their derivatization with pentafluorobenzaldehyde.

Figure 8. Hollow-fiber liquid phase microextraction coupled with *in situ* derivatization[128]: A) U-shaped HF-LPME (three-phase) and in situ derivatization; B) U-shaped HF-LPME (two-phase) coupled with in situ derivatization; C) rod-shaped HF-LPME (two-phase) coupled with in situ derivatization. 1 Guiding tube; 2 HF with organic phase; 3 Aqueous acceptor; 4 Aqueous sample with derivatizing reagent; 5 Organic acceptor; 6 Syringe; 7 Stir bar; 8 Needle.

Figure 9. Schematic representation of HF-LPME using extraction medium contains both derivatizing reagent and organic solvent[128]: A) direct immersion; B) headspace of LPME. 1 Syringe; 2 Aqueous sample; 3 Stir bar; 4 Headspace; 5 Hot/Stir plate; 6 Needle; 7 HF with organic phase containing derivatizing reagent.

Another approach of *in situ* derivatization HF-LPME for the determination of biogenic amines in food samples was presented by Saaid et al.[73]. The analytes in the sample solution were derivatized with dabsyl chloride and then extracted into the organic phase residing in the pores and the lumen of the hollow fiber. After optimization of various parameters affecting the extraction efficiency the method was then evaluated and applied to the determination of biogenic amines in shrimp sauce and tomato ketchup with satisfying results (LOD: 0.0075 – 0.03 μg/mL, RSD: 2.7 – 7.5 %).

5. DERIVATIZATION REAGENTS FOR THE DETERMINATION OF AMINES BY GAS CHROMATOGRAPHY

As was previously mentioned, gas chromatography is a widely used analytical technique for the determination of amines because of its simplicity, high resolution and sensitivity, short analysis time and low cost. Analysis of free amines using GC has some inherent problems related to the difficulty in handling low-molecular-mass amines due to their high water solubility and high volatility, therefore derivatization process is a good resolution for these problems[1]. Derivatization of the amine compounds allows not only more volatile compounds of decreased

polarity and reactivity to be analyzed, but also improves selectivity, sensitivity and a degree of separation of analyte derivatives that leads to a decrease in the detection limit[54,70].

Taking into account all the derivatizing reagent, acylation is one of the most common derivatization techniques used for primary and secondary amines[97] (Figure 10). Acetamide, acetylimidazole, acyl chloride and acetic acid anhydride are excellent examples of acylating agents[1,54,97]. These reagents easily react with the amine group in mild reaction conditions ($5 < pH < 9$, 50 – 75 ^{o}C, 15 – 20 mins)[1,54,97]. In the chemical conversion of amines with acylated acids and chloride anhydrides, it is necessary to remove the excess reagent and acid by-products which destroy chromatographic columns[1]. Because of the acidic byproducts, the derivatization process is carried out in pyridine, triethylamine, tetrahydrofuran or another solvent capable of accepting the acid by-product.

One exception is the chemical conversion reaction of amine compounds with the use of acetylimidazoles, where there is no need to remove excess reagent and imidazole derivatives[97]. For example, N-methyl-bis**(**trifluoroacetamide) is a highly volatile reagent and the by-products formed during the derivatization reaction do not cause damage to the column. This reagent may be successfully used for selective acylation after trimethylsilylation of hydroxyamine compounds[54,97].

Figure 10. The number of publications concerning the application of GC technique and appropriate derivatization for amine compounds (calculated in Web of Science)

Fluorinated and chlorinated substituted reactants are popular among acylating reagents, which in the reaction with analytes form compounds capable of capturing low energy electrons and producing negatively charged ions[138]. In this case, an electron capture detector (ECD) is used which is selective for halogen derivatives, and at the same time increasing the sensitivity of the assay. Detection sensitivity differs depending on the type of halogen derivative (and their mass)

and increases in the following order: F < Cl < Br < I [1,139]. However, volatility and stability decrease in the same order and that is why fluorinated derivatizing agents are most frequently used in practice. It should be noted that in the case of determination of fluorinated (chlorinated) derivatives of acylated amines, there is a difference in analyte retention depending on the fluorinated (chlorinated) reactant. ECD detector sensitivity increases with the increase in number of fluorine (chlorine) atoms in the analyte molecule. That is why ECD detector shows greater sensitivity for pentafluorobenzyl derivatives than for trichloroacetyl derivatives. The ECD detector is also characterized by selectivity for derivatives which have a nitro group, but these are less volatile and consequently leads to unsymmetrical, strongly tailing peaks in chromatograms, thus their application in GC is limited[139].

Formation of carbamate derivatives is another example of an acylation reaction, useful for sample analysis in order to determine primary, secondary and tertiary amines content[1,54,97]. For this purpose alkylated chloroformates have been used [140-143]. An advantage of using these compounds is the fact that the reaction can be performed in an aqueous basic solution. The derivatives obtained are characterized by properties which can be used in analytical procedures based on GC techniques at the mixture separation, detection and quantitative determination stages[144]. Carbamate derivatives of primary and secondary amines are successfully determined using GC with the following detectors: electron capture (ECD), flame photometric (FPD), mass spectrometric (MS) and nitrogen-phosphorus (NPD)[1,145,146]. In tertiary amine determination, peak tailing due to the polar character of analytes is a significant problem, but can be overcome using analyte dealkylation, followed by derivatization with an alkylated chloroformate such as pentafluorobenzyl chloroformate[1,145,146].

Amine groups are not particularly reactive in relation to silylating reactants and their conversion into silyl derivatives is difficult. Using strong silylating reagents such as N, O-

bis(trimethylsilyl)acetamide (BSA), N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) or N-(tert-butyldimethylsilyl)-N-methyl-trifluoroacetamide (MTBSTFA) with an appropriate catalyst the process can be very efficient[145,146]. These reagents also react with hydroxyl and carboxyl groups in an anhydrous reaction environment. The use of trimethylchlorosilane as a catalyst ensures efficiency in the derivatization process[145,146].

Comparing trimethylsilylation reagents, BSTFA is a stronger reagent towards amine groups than BSA and additionally by-products formed in the reaction with BSTFA are characterized by volatility and do not interfere with the assay. Nevertheless, trimethylsilyl derivatives (N-TMS) formed as a result of the reaction with these reagents are unstable in a humid environment. Additionally, during primary amine silylation, the substitution of one or both protons may occur, resulting in the formation of mono- and di-trimethylsilyl derivatives, respectively. The use of MTBSTFA as a derivatizing reagent is an excellent solution in this case because the tert-butyldimethylsilyl (N-t-BDMS) derivatives formed are ten thousand times more stable than the corresponding N-TMS derivatives. This is the result of the protection of the silyl group from humidity by the expanded tert-butyl group[1].

In the determination of primary and secondary amines present in water samples, an excellent solution is the transformation of analytes into N-dinitrophenyl derivatives with the help of reagents such as 1-fluoro-2,4-dinitrobenzene (DNFB) and dinitrobenzene sulfonic acid (DNBS)[1, 145]. The ECD detector is sensitive for N-dinitrophenyl derivatives (particularly those of low molecular mass, characterized by short retention times). 1-Fluoro-2,4-dinitrobenzene is a water soluble compound and its dinitrophenyl amine derivatives are soluble in organic solvents[1], meaning that analyte derivatives are easily separated from excess of reagents by solvent extraction after derivatization[1].

However, it should be remembered that despite the easy derivatization of amines with DNBF, appropriate safety measure should be applied as it is a possible skin irritant and allergen.

The condensation reaction of primary amines is another example of the formation of analyte derivatives with favorable properties[1,2,54]. Primary long chain and alicyclic amines, aliphatic diamines and aromatic amines can be condensed using the following compounds: acetone, 1,1,1-trifluoroacetone, cyclopentanone, cyclohexanone and cycloheptanone. For the determination of short chain amine compounds the following are used: furfural, benzaldehyde and pentafluorobenzaldehyde (PFBA). The condensation process is performed rapidly even at room temperature in aqueous solution in the presence of acetic acid or alcohol. Any excess of reactants must be removed as it may adversely influence the course of further analytical procedures[1,2,54].

The formation of sulfonamides as amine derivatives in the reaction with sulfonyl chloride is also applied in order to achieve separation and identification using GC[1,2,147]. Benzenesulfonyl chloride (BSC)[148] and (p-toluenesulfonyl)chloride[147] are excellent reagents for derivatization of amines characterized by small molecular mass, both primary and secondary, producing the corresponding sulfonamide. With BSC as the derivatizing agent, benzosulfyl (BS) derivatives of secondary amines are formed, which during extraction are extremely soluble in a hexane-methanol mixture (with the addition of potassium hydroxide), and the BS derivatives of primary amines, which are present in the aqueous phase, may be extracted using diethyl ether under acidic reaction conditions. These derivatives can be determined using FPD, NPD and a chemiluminescence detector (CLD). ECD may also be used for primary amine determination, however, another derivatization process is required, this time with TFAA (BS-derivatives of secondary amines do not react with TFAA)[1].

For determination of amines with steric hindrance, N,N-dimethylformamide dimethyl acetal (DMF-DMA) and di-tert-butylformamidedimethyl acetal (DMF-DBA) are very good reagents. These compounds react quickly with excellent efficiency in a non-aqueous environment[55]. Table 5 shows a summary of commonly used derivatizing reagents for the determination of amine compounds by gas chromatography.

Table 5. Derivatizing reagents used in the determination of amine compounds by gas chromatography

Analyte	Derivatizing reagent	Characteristics	Detection	Ref
1°, 2°	TFAA	Highly stable and volatile derivatives are easily formed. The use of catalysts triethylamine and trimethylamine speed up the reaction. Often used for the analysis of addictive amine substances such as amphetamine, ephedrine, etc.	FID, ECD, MS	1,54, 97
	PFPA		FID, MS, ECD, NPD	
	HFBA		ECD, FID, MS	
1°	Chloroacetic anhydride	Reacts rapidly under mild conditions. Necessary to remove excess reagent and acidic by-products which can damage the chromatographic column. Derivatization process performed with the addition of bases, i.e., pyridine, triethylamine or trimethylamine.	ECD, MS	
	Dichloroacetic anhydride			
1°, 2°	Trifluoroacetic acid	Derivatives of high stability and volatility. Also used as a catalyst in silylating reactions. In combination with hexamethyldisilazane it avoids the formation of ammonium chloride.	FID, ECD, MS	
2°	Pentafluorobenzyl chloride	Fast reaction and suitable for compounds with steric hindrance. A base (NaOH) is required in order to remove by-products (HCl).	NPD, ECD	1, 97, 138,139
2°, 3°	Imidazole heptafluorobutyryl	Reacts in mild conditions. By-products (imidazoles, methyl-trifluoroacetamide) are not acidic and do not damage the chromatographic column. Reacts rapidly with water.	ECD	1, 97
1°, 2°	N-Methyl-bis(trifluoroacetamide)	Reacts in mild conditions. By-products (imidazoles, methyl-trifluoroacetamide) are not acidic pH and do not damage the chromatographic column. Reacts rapidly with water. Recommended for the analysis of amine samples of addictive substances.	FID, MS, ECD	1, 54,97
2°	4-CB	Addition of a protonic solvent is recommended in order to remove excess reagent.	ECD, MS	1, 54,97
1°	Dimethyl dicarbonate	The products obtained are stable. No harmful by-products.	FID	1, 54,9, 140-144
1°, 2°, 3°	Ethyl chloroformate	The reaction is performed easily and rapidly. Aqueous sample analysis possible. Derivatization process takes place with the addition of bases, e.g. pyridine. Derivatization of tertiary amines requires dealkylation to a secondary amine and then derivatization with these reagents.	FID, NPD, MS	
1°, 2°	Isobutyl chloroformate			
1°, 2°	Amyl chloroformate		FID	

1°, 2°	2,2,2-trifluoroethyl chloroformate		MS, NPD	
1°, 2°, 3°	Pentafluorobenzyl chloroformate		ECD	
1°, 2°	BSA	Stable TMS derivatives are formed as a result of this reaction. The reaction is performed in mild conditions.		1, 97, 145
	BSTFA	Very reactive. More volatile than BSA.	MS	
	MTBSTFA	Substitutes active hydrogen atoms forming t-BDMS derivatives. MTBSTFA derivatives are 10K times more stable than corresponding TMS derivatives.	MS	
1°	Bis(trimethylsilyl)amine	Poor donor of TMS group. The reaction demands a catalyst. Ammonia is a by-product.	MS	1, 2, 97
1°, 2°	(Trimethylsilyl)diethylamine	Volatile by-products of derivatization reaction.	MS	
1°, 2°	DNFB	As well as amine group also selective towards hydroxyl, thiol and imidazole group.	FID, ECD, MS	1, 147
	DNBS	Very reactive and specific to amine group. Reacts slower than DNFB and requires longer reaction time or strongly basic reaction environment.	FID, ECD	
1°	Benzaldehyde	Appropriate for low molecular mass amines. Addition of acetic acid or alcohol is necessary.	FID	1, 2, 97
	Furfural		FID	
	PFBA		ECD, MS	
1°, 2°	BSC	Depending on the analyte order, the derivatives are soluble in different solvents at different pH.	FPD, CLD, MS, NPD	148
1°, 2°	p-toluenesulfonyl chloride	Appropriate for amines of low molecular mass	FID, MS	147
1°, 2°	DMF-DMA	The reaction is performed very quickly. No reaction in aqueous environment. For amines with steric hindrance	FPD, MS	1, 55, 97
	DMF-DBA			

1°-primary amines, 2°-secondary amines, 3°- tertiary amines
BSA, N, O- bis(trimethylsilyl)acetamide; BSTFA, N,O-bis(trimethylsilyl)trifluoroacetamide; CLD, chemiluminiscent detector; DMF-DBA, Ditertbutylformamide dimethyl acetal; DMF-DMA, N,N-Dimethylformamide; DNBS, 2,4-dinitrobenzenesulfonic acid; DNFB, 2,4-dinitrofluorobenzene; ECD, electron capture detector; FID, flame ionization detector; FPD, flame photometric detector; HFBA, Heptafluorobutyryl acid anhydride; MS, mass spectrometer; MTBSTFA, N-Methyl-N-tert-butyldimethylsilyltrifluoroacetamide; NPD, nitrogen–phosphorus detector;PFBA, Pentafluorobenzaldehyde; PFPA, Pentafluoropropionic acid anhydride; TFAA, Trifluoroacetic anhydride; 4-CB, 4-carboethoxyhexafluorbutyryl chloride

6. DERIVATIZATION REAGENTS FOR THE DETERMINATION OF AMINES BY LIQUID CHROMATOGRAPHY

Liquid chromatography is also commonly used for the determination of amine content in different types of samples. The popularity of this approach stems from its advantages, i.e., relative ease of sample preparation since analytes do not have to be volatilized and can be used at ambient temperature.

However, amine compounds do not have the functional groups (chromophoric or fluorescent) which are necessary for analysis by ultraviolet (UV) or fluorescence detectors, so derivatization is necessary in order to introduce desirable functional groups to the analyte structure[149]. Depending on the functional group introduced, derivatizing reagents can be grouped as follows[149]:

- Chromophores: Reagents that absorb UV-VIS light and impart this property to the derivatives;
- Fluorophores: Reagents that fluoresce and impart this property to the derivatives;
- Fluorogenics: Reagents that do not fluoresce but form fluorescent derivatives with the analytes;
- Redox reagents: reagents the reduce/oxidize analytes to show enhance detection.

Absorption detection in ultraviolet and visible light (UV-VIS) is one of the most frequently applied techniques in liquid chromatography[149]. In order to introduce the desirable function groups to the analyte structure for determination by HPLC-UV-VIS, a series of derivatizing reagents have been used. For the determination of primary and secondary amines, the best reagents are: nitrobenzenes, i.e., DNFB; 2,4,6-trinitrobenzene sulfonic acid (TNBS)[150]; 4-fluoro-3-dinitro-fluoromethylbenzene (FNBT, also reacts with polyamines)[151]; ninhydrin[152] and dabsyl chloride (DABS-Cl)[153,154]. For determination of aliphatic tertiary amines *post-column* derivatization is usually required, consisting of the reaction of the analyte with a mixture of acetic anhydride and citric acid. In the case of polyamine compound determination, benzoyl chloride, tosyl chloride and dansyl chloride are widely used. Benzoyl chloride is particularly convenient because of the short reaction time and long elution time of corresponding derivatives[149].

In addition to a UV-VIS detector, a fluorometric detector is also very popular and requires analyte derivatization of amine compounds. O-Phthalic aldehyde (OPA) is one of the most widely used reagents for determination of primary amines in different types of matrix such as water, biological and food samples (pH 9-11) [155-156]. This reagent reacts very rapidly in the presence of mercaptane forming fluorescent isoindole derivatives. Molnar-Perl has carried out much research into the use of OPA for the derivatization of biogenic amines and amino acids[157-161]. She focused on this reagent because it provides fast reactions, can be used in aqueous solutions, at ambient temperature, and produces derivatives of high selectivity and sensitivity suitable for use in a fluorescent detector[157]. Molnar-Perl published review of the advancement in the derivatizations of the amino groups with the o-phthaldehyde-thiol[157] where author states that certainly this derivatization protocol did have and it still have its uncertainties, limitations, shortages and advantages: however, in the last decade the overwhelming part of uncertainties were examined and cleared up: resulting in the trouble-free, conscious and reliable use the OPA technique[159-164].

Fluorescamine is another example of a fluorogenic compound reacting with primary amines in a basic environment at room temperature. This reaction occurs rapidly with the formation of fluorescent pirolidone derivatives[149].

Sulfonic acid chlorides are excellent derivatizing reagents in the determination of both primary and secondary amines[165]. The reaction is easily performed in a slightly alkaline environment with the formation of fluorescent sulfonamides which emit radiation of wavelengths 470 and 510 nm. One of the exemplary reactants from this group of compounds is dansyl chloride, which in the reaction with amines forms stable derivatives[166], however, it can have a long reaction time (30-120 minutes depending on the amine compound).

The formation of the corresponding carbamine derivatives from the reaction with carbonyl chlorides or fluorides is another derivatization method used for the introduction of a fluorescent group into a molecule. One of the commonly used reactants from this group of compounds is 9-fluorenylmethyl chloroformate (FMOC), which in a slightly alkaline environment reacts very quickly (2 minutes), resulting in stable derivatives showing fluorescent abilities[107,167,168]. The reactant can also be used for the final assay with a UV-VIS detector. Another derivatizing reagent appropriate for amine compounds is (+)-fluorenylethylchloroformate (FLEC)[169].

Less popular groups of compounds which form fluorescent derivatives with primary and secondary amines are: isocyanates[170](e.g. phenyl isocyanate); isothiocyanates (e.g. phenyl isothiocyanate) and benzofurazanes[171] (e.g. 4-chloro-7-nitro-2,1,3-benzoxadiazole, NBD-Cl and 4-fluoro-7-nitro-2,1,3-benzoxadiazole, NBD-F).

Basic information on the most frequently used reactants for the derivatization of amine compounds determined using liquid chromatography is summarized in Table 6.

Table 6. Derivatizing reagents used in the determination of amine compounds by liquid chromatography

Analyte	Derivatizing reagent	Characteristics	Ref.
Absorption detection in ultraviolet and visible light UV-VIS			
1°, 2°	DNFB	Amine derivative of 2,4-dinitrophenyl is formed in an alkaline environment.	150, 159
1°, polyamines	FNBT	A N-2'-nitro-4-trifluoromethylphenylpolyamine derivative is formed which absorbs radiation of wavelengths 242 nm and 410 nm.	151, 159
1°	TNBS	Performed in an aqueous environment of pH 8 at room temperature. N-Dinitrophenyl derivatives are formed, which absorb radiation of 280 nm.	150, 159
1°, 2°	DABS-Cl	Derivatives formed absorb radiation in the range 448-468 nm.	153,159
3°	Mixture of acetic anhydride and citric acid	Usually *post-column* derivatization is used. Reaction temperature is ca. 120°C. Derivatives formed absorb radiation of 550 nm.	159
Polyamines	Benzoyl chloride	Advantages include a short derivatization reaction time and long elution time.	149, 159
Aromatic	Dimethylaminobenzaldehyde	Schiff bases are formed.	159

amines (1°)			
Aromatic amines (1°, 2°)	Phenyl isocyanate	N-aryl-N'-phenyl urea derivatives are formed absorbing radiation of wavelength 255 nm. Excess reagent should be removed with the use of n-propanol.	159, 16
Fluorometric detection			
1° (2°)	OPA	Performed in aqueous basic solution (pH 9-11) in the presence of mercaptane at room temperature and fluorescent isoindole derivatives are formed. May be applied both for *pre-* and *post-column* derivatization. Possibility for secondary amine derivatization after the addition of sodium hypochlorite to the reaction mixture.	155, 156, 157, 162
1°	Fluorescamine	Performed in aqueous basic solution (pH 9.5-10) at room temperature. The reaction occurs rapidly with the formation of fluorescent pyrrolidone derivatives.	149, 159
1°, 2°	Sulphonic acid chlorides	Rapid reaction performed in a slightly alkaline environment resulting in the formation of fluorescent sulfonamides with emission wavelength 470 and 510 nm.	159, 165
1°, 2°	Dansyl chlorides	Long reaction time dependent on the type of amine (up to 120 minutes)	159, 166
1°, 2°	FMOC	Quick reaction in a slightly alkaline environment (pH 8) in the presence of an excess reactant. Derivatives determined by UV-VIS.	108, 159, 167
1°, 2°	Phenyl isocyanate	Rapid reaction requiring excess reactant.	159, 170
1°, 2°	Phenyl isothiocyanate	The reaction is performed in an acidic environment. Derivatives determined by UV-VIS.	159, 170
1°, 2°	SINC	The reaction is performed in an alkaline environment (pH 9.5) within 1 minute at room temperature. Carbamoyl naphthyl derivatives are formed. Hydrolysis used to remove excess reactant.	159
1°, 2°	CNB	Poor reaction in a slightly alkaline environment (pH 8-9) at 50-60°C. The reaction with FNB is performed 10 times quicker than with CNB. Used for *post-column* derivatization.	
	FNB		
Electrochemical detection			
1°, 2°	NDA	Reaction takes place in the presence of cyanide ions.	159
1°, 2°	acetylsalicylic acid chloride	The reactant used for *pre-column* derivatization. Performed in an alkaline environment.	

CNB, 4-chloro-7-nitro-2,1,3-benzoxadiazole; DNFB, 2,4- dinitrofluorobenzene; FNB, 4-fluoro-7-nitro-2,1,3-benzoxadiazole; FNBT, 4-fluoro-3-nitrotrifluoromethylbenzene; NDA, Naphthalene-1,2-dicarboxaldehyde; OPA, o-phthalic aldehyde; SINC, Succinimido naphthylcarbamate; TNBS 2,4,6 trinitrobenzenesulfonic acid

7. LITERATURE DATA ON AMINE COMPOUND DETERMINATION IN SAMPLES OFCHARACTERIZED BY COMPLEX COMPOSITION OF THE MATRIX

Amine compounds often have an unpleasant smell and are hazardous to health, i.e., as sensitizers and irritants to the eyes, skin, respiratory tract and mucous membranes. These amines

occur in a number of ambient environments such as air, foods, soil and water, and are a source of serious social and hygiene problems. Thus, their monitoring in different types of samples has become an important task for chemists resulting in a significant annual increase in the number of publications in the last few years on the determination of amine compounds in samples of materials from different sources (environmental, biological material, food, industrial product samples). Based on the literature data, the most frequently used techniques for this purpose are gas or liquid chromatography. Table 7 summarizes the literature information on the use of both techniques for determination of different types of amine compounds.

The results presented in the literature allow us to state that methods using microextraction techniques such as SPME, SBSE, SDME and HF-LPME coupled with derivatization, and gas/liquid chromatography combined with a corresponding type of detection, can be successfully used for both qualitative and quantitative determination of different types of amine compounds in different types of matrix. It is clear that not all analytical problems can currently be solved using available procedures based on derivatization processes and chromatographic techniques. Therefore, research on the modification of known methods and the quest for new methodologies in this field is ongoing. In this respect, a series of parameters should be taken into consideration, among which the most pertinent are:

- different source of samples for tests;
- diverse matrix composition;
- continuing improvement in the quantitative determination of amine compounds in samples from different media;
- aspects of natural environmental protection.

8. CONCLUSIONS

Amines are important biological compounds and so their analysis and monitoring in various matrices is worthy of investigation and development.

Due to the polar nature of amines, chromatographic analysis (in particular GC) of free amines is generally unsatisfactory owing to adsorption and decomposition of the solute on the column, resulting in peak tailing and losses. Therefore, many derivatization reactions are employed to reduce the polarity, improve chromatographic separation of analytes and increase selectivity and sensitivity of detection. In addition, the sample matrix contains other compounds at the same or higher concentration levels, making determination difficult and sometimes impossible. Animportant solution to this problem is derivatization of analytes, causing changes in their structures and properties, thus allowing differentiation of the analyte from other compounds present in the sample.

A number of derivatization reactions including acylation, silylation or carbamate formation can be applied to amine compounds. In a chromatographic system, these reactions can be performed as *pre-column*, *on-column* or *post-column*. Attempts have been made in both *off-line* and *on-line* approaches. *Off-line* derivatization is simple but time-consuming and labor intensive, particularly when large numbers of samples are involved and may increase the risk of loss or contamination. An alternative approach is to convert analytes by *on-line* derivatization using flow methods, so avoiding the drawbacks of *off-line* procedures. *On-line* derivatization can be performed prior to chromatographic separation. This offers advantages for analytes with poor separation due to strong adsorption on the stationary phase, or labile compounds, which may easily decompose or react with other components during chromatographic separation.

Derivatization reactions are mainly performed *off-line* in a reaction vessel that is separated from the GC analysis hardware. *In situ* derivatization may be applied in the case of aqueous samples and therefore water-compatible derivatization reagents are used. This derivatization procedure improves GC separation and detection as well as the extractability of the target compound into a non-polar sorbent. The *in situ* derivatization process is also popular in LC-MS methods in order to increase sensitivity by adding on moieties that improve ionization and reduce matrix effects, giving an excellent alternative to GC analysis.

Solventless sample preparation techniques based on the extraction of analytes in sorption processes are effective and an environmentally friendly alternative to solvent extraction procedures. This type of extraction includes solid phase microextraction (SPME) and stir bar sorptive extraction (SBSE), with both techniques having been successfully applied to *in situ* derivatization of amine compounds. SPME and SBSE in combination with chromatographic techniques enable selectiveand sensitive analysis of amine derivatives in various matrices. Both techniques are simple, economical, do not require preliminary sample preparation steps and reduce the volume of (toxic) solvents used. A number of studieshave demonstrated that the linearity and precision obtained by SBSE and SPME are similar, but SBSE has been shown to be more accurate and sensitive than SPME.

Meeting the criteria of “green” chemistry principles is often important. Techniques which meet these requirements, along with an ability to be coupled with in situ derivatization and successfully applied for amine compounds are HF-LPME and SDME. However, it need to be mentioned that optimization of sample preparation will involve the chemistry of the sample matrix.

In the case of the highly sensitive and selective detection of amine-derivatives, nitrogen-selective detection, electron capture detection, nitrosamine-specific detection and mass

spectrometry areexcellent choices in gas chromatography techniques, while fluorescence detection, UV-VIS and mass spectrometry are important in liquid chromatography.

While the utilization of derivatization techniques in amine determination by chromatographic methods is clear with applications in many areas, few applications in environmental analysis are available. Moreover, due to the variety of sample matrices, increasing demands on the quality of the results obtained, and requirements for environmental methodologies it is necessary to carry out further studies and develop new or modified analytical procedures. This review gives the reader a detailed overview of the current situation with respect to chemical derivatization of amines and provides an information base for future developments in the area.

Table 7. Methodologies of amine compound determination in various matrices using appropriate modes of derivatization and sample preparation

Type of material object	Analyte	Derivatization mode	Derivatization reagent	Technique of sample preparation	Type of fiber	Extraction time [min]	Analytical technique	LODs/LOQ	Ref
Water	DMA	*Pre-column; on-fiber*	FMOC/OPA-NAC	DI-SPME	CW-TR, 50 µm	15	HPLC-fluorescence detector	0.3/1.0 µg/mL	93
	MA	*Pre-column; on-fiber*	FMOC	DI-SPME	CW-TR, 50 µm	15	HPLC-fluorescence detector	0.75/2.5 µg/ml	108
	DMA, MA, TMA	*Pre-column; on-fiber*	FMOC	DI-SPME	CW-TR, 50 µm	10 (DMA, MA), 30 (TMA)	HPLC-fluorescence detector	5-250/ 20-1000 ng/mL	172
	anatoxin-a	*Pre-column; on-fiber*	FNBD	SPME	CW-TR	30	HPLC-fluorescence detector	20 ng/mL/-	173
	BA, EA, DMA, HeA, MA, PeA, PrA	*In situ*	SIBA	HS-SPME	PPMS, 70 µm	60	GC-FID	0.13–7.2 nmol/l/-	174
	Amitriptyline	*In situ*	MTBSTFA	SBSE	PDMS (stir: 10 × 0.5 mm)	30	GC-EI-QMS	31 ng/L	175
Sewage sludge	AA, BA, CA, EA, HA, IAA, IBA, IPA, MA, PeA	*Pre-column; off-line*	PFBA	PHWE-HS-SPME	PA, 85 µm	15	GC-IT-EI-MS-MS	9–135/ 50–450 µg/kg	94
Biological samples	AMA, MDA, NEP	*Pre-column; off-line*	OPA-NAC	DI-SPME	CW-TR, 50 µm	5-30	HPLC-fluorescence detector	0.25/0.75-1.0 (µg/mL)	176
	KET, MAMP, MDMA	*In situ; off-line*	HC	SPME	PDMS, 100 µm	20	GC-QMS	0.05-0.1/ 0.1-0.5 mg/mL	177
	AMA, FFA, MAMP	*In-port*	HFBA	HS-SPME	PDMS, 100 µm	15	GC-EI-MS	5-10/- ng/g	178
	FLU	*In situ; off-line*	ECF	SBSE	PDMS, 24 µm	15	GC-EI-MS	0.46/ 1.37 pg/mg	179
	Nicotine	*Pre-column; off-line*	ECF	HSSE	PDMS, 25 µm	60	GC-EI-MS	-	180
	COC	*In situ; off-line*	AAA	SBSE	PDMS, 25 µm	60	GC-EI-MS	-	181

	SCE, MSCE, SME, SEE,SDG	*Pre-column*	Acetic acid,	SBSE	PSP-TiO_2 organic–inorganic hybrid SBSE	15	HPLC-(PN)-ICP-QMS	50.2–185.5/-ng/l	182
Air	TMA	*Pre column; on-fiber*	FMOC	DI-SPME	CW-TR, 50 µm	15	HPLC-fluorescence detector	12/20 mg/m^3	95
Food samples	CE, HiA, SP, SPr, TA	*Post-column; on-line*	OPA	Extraction with perchloric acid	-	20	UHPLC-fluorescence detector	< 0.2 mg/L	106
	CE, HiA, PEA, PU, TA, TR	*Post-column; on-line*	OPA	Extraction with perchloric acid	-	20	IP-HPLC-fluorescence detector	-	155
	MEL	*In-port*	BSTFA	HFSE	zirconia sol	30	GC-EI-QMS	0.001 mg/ml	104
Alcoholic beverages, wine	CE, EA, HiA, MA, MB, PEA, PU, TA	*On-column*	OPA	SPE with SAX and C18 cartridges	-	-	HPLC-fluorescence detector	100-300 µg/l/0.5 mg/l	183
	AG, CE, CR, DA, HiA, OC, PEA, PU, SE, SP, SPr, TA	*Post-column; on-line*	OPA+ MCE	-	-	-	IP-HPLC-fluorescence detector	0.03-0.06 mg/l	156
	AG, CE, HiA, PEA, PU, SP, TA	*Post-column*	OPA+ MCE	-	-	-	HPLC-fluorescence detector	-	184
Vegatables	AG, CE, HiA, PEA, PU, SP, TA	*Post-column*	OPA+ MCE	-	-	-	HPLC-fluorescence detector	-	184
	SCE, MSCE, SME, SEE,SDG	*Pre-column*	Acetic acid	SBSE	PSP-TiO_2 organic–inorganic hybrid SBSE	15	HPLC-(PN)-ICP-QMS	50.2–185.5/-ng/l	182
Polymeric cationic surfactants	DMA	*Pre-column; on-line; in-tube*	FMOC	DI-SPME	70 cm GC TRB-5 capillary column (0.32 mm i.d., 3 µm of coating thickness 95 % PDMS-5 % PDPS)	5	HPLC-DAD	50/200 ng/mL	167
Watewater	AMA, MAMP, MDMA, MDA	*In situ*	IBCF	SPME	PDMS-DVB, 65 µm	40	GC-EI-QMS	0.4 to 2 ng /L/-	185
Pharmaceutical compounds	AMA, MAMP, MDA, MDMA, MDEA	*Pre-column; on-fiber*	HFBA/HFBCl	HS-SPME	PDMS, 100 µm	30	GC-SIS-MS	0.016-0.193/ 0.052-0.641 ng/ml	186

AA, amylamine; AAA, acetic acid anhydride; AG, agmatine; AMA, amphetamine; BA, n-butylamine; BSTFA, bis(trimethyl)silyltrifluoroacetamide; CA, cyclohexylamine; CE, cadaverine; COC, cocaine; CR, creatinine; CW-TR, carbowax-templated resin; DA, dopamine; DMA, dimethylamine; DVB, divinylbenzene; EA, ethylamine; ECF,

ethyl chloroformate; FFA, fenfluramine; FLU, fluoxetine; FMOC, 9-fluorenylmethyl chloroformate; FNBD, 4-fluoro-7-nitro-2,1,3-benzoxadiazole; HA, n-heptylamine; HC, hexylchloroformate; HeA, n-hexylamine; HFBA, heptafluorobutyric anhydride; HFBCl, heptafluorobutyric chloride; HFSE, hollow fiber sorptive microextraction; HiA, histamine; IAA, isoamylamine; IBA, isobutylamine; IBCF, iso-butyl chloroformate; IP, ion-pair; IPA, isopropylamine; KET, ketamine; MA, methylamine; MB, 3-methylbutylamine; MDA, 3,4-methylenedioxyamphetamine; MDEA, 3,4-methylendioxyethylamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; MAMP, methamphetamine; MCE, 2-mercaptoethanol; MEL, melamine; MSCE, methylseleno-cysteine; MTBSTFA, N-(tertbutyldimethylsilyl)-N-methyltrifluoroacetamide; NEP, norephedrine; OC, octopamine, OPA-NAC, o-phthalaldialdehyde and N-acethyl-l-cysteine; PA, polyacrylate; PeA, n-pentylamine; PDMS, polydimethylsiloxane; PDPS, diphenylpolysiloxane; PEA, 2-phenylethylamine; PFBA, pentafluorobenzaldehyde; PHWE, pressurised hot water extraction; PN, pneumatic nebulization; PPMS, polyphenylmethylsiloxane; PrA, n-propylamine; PU, putrescine; SAX, strong anion-exchanger; SCE, selenocystine; SDG, selenodiglutathione; SE, serotonin; SEE, selenoethionine; SIBA, N-succinimidyl benzoate; SIS, select-ion storage; SME, selenomethionine; SP, spermidine; SPr, spermine; TA, tyramine; TMA, trimethylamine; TR, tryptamine; QMS, quadrupole mass spectrometer

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Notes

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ACKNOWLEDGEMENTS

The research is funded by the Polish Ministry of Science and Higher Education within the "Iuventus Plus" program in years 2015-2017, project no: IP2014 037573. The project is co-financed by the European Union within the European Social Fund – Human Capital Operational Programme (POKL04.03.00-00-238/12).

The authors are grateful to Mrs. Ailsa Morrison for assistance with proof reading and constructive comments.

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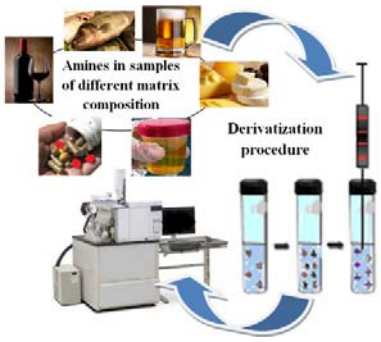
Table of contents graphic



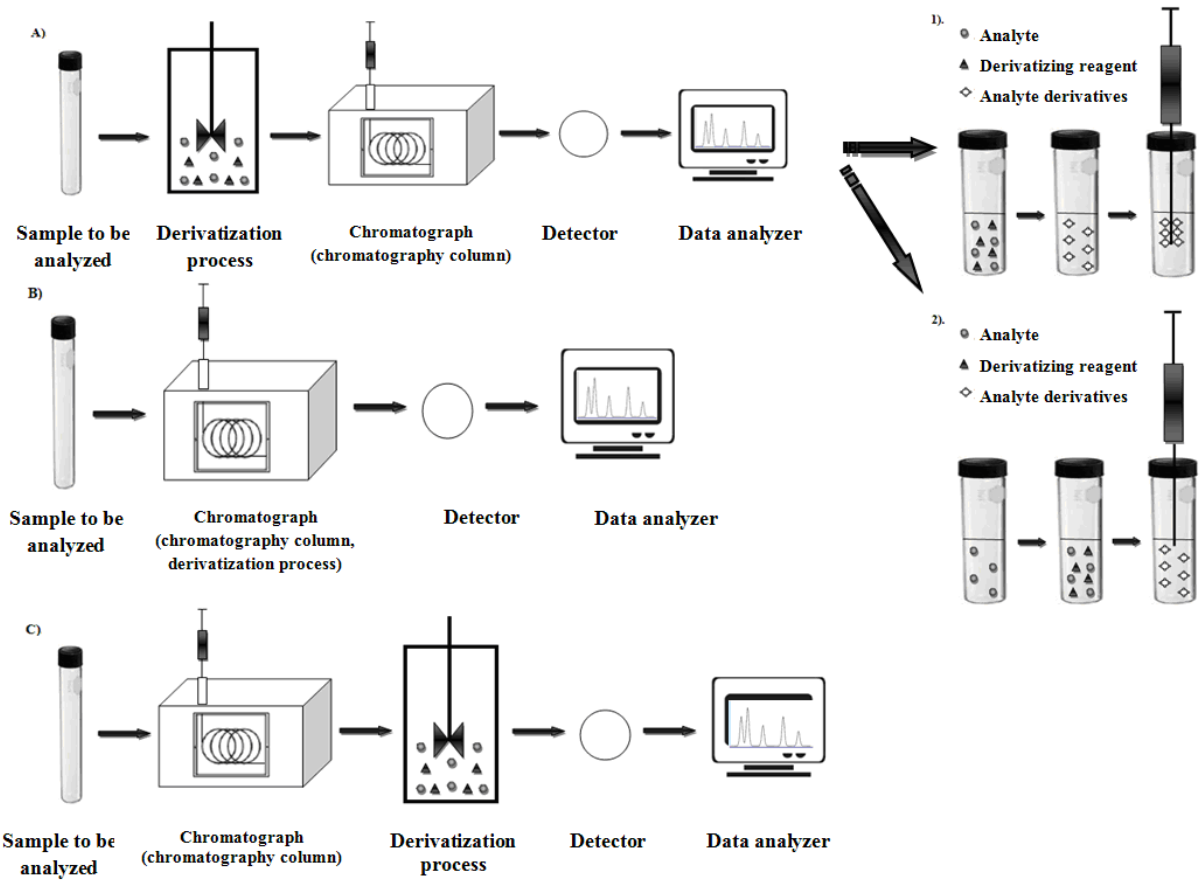


Figure 1. Schematic representation of analyte transformation method into derivatives depending on the process site[53]: A) *Pre-column* derivatization: 1) on SPME fiber; 2) directly in the sample taken or during sample-taking stage (*in situ*); B) In chromatograph dispenser chamber or on chromatographic column; C) *Post-column* derivatization.

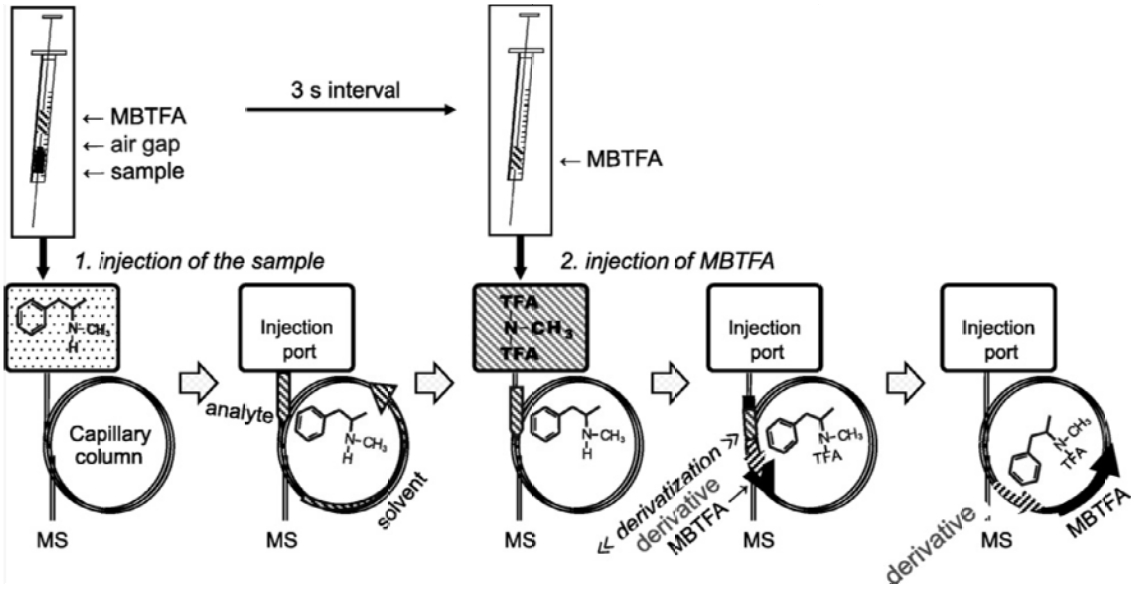


Figure 2. Mechanism of on-column trifluoroacetylation using the two-step injector and MBTFA (Reprinted with permission from ref 98. Copyright 2008 Elsevier.)

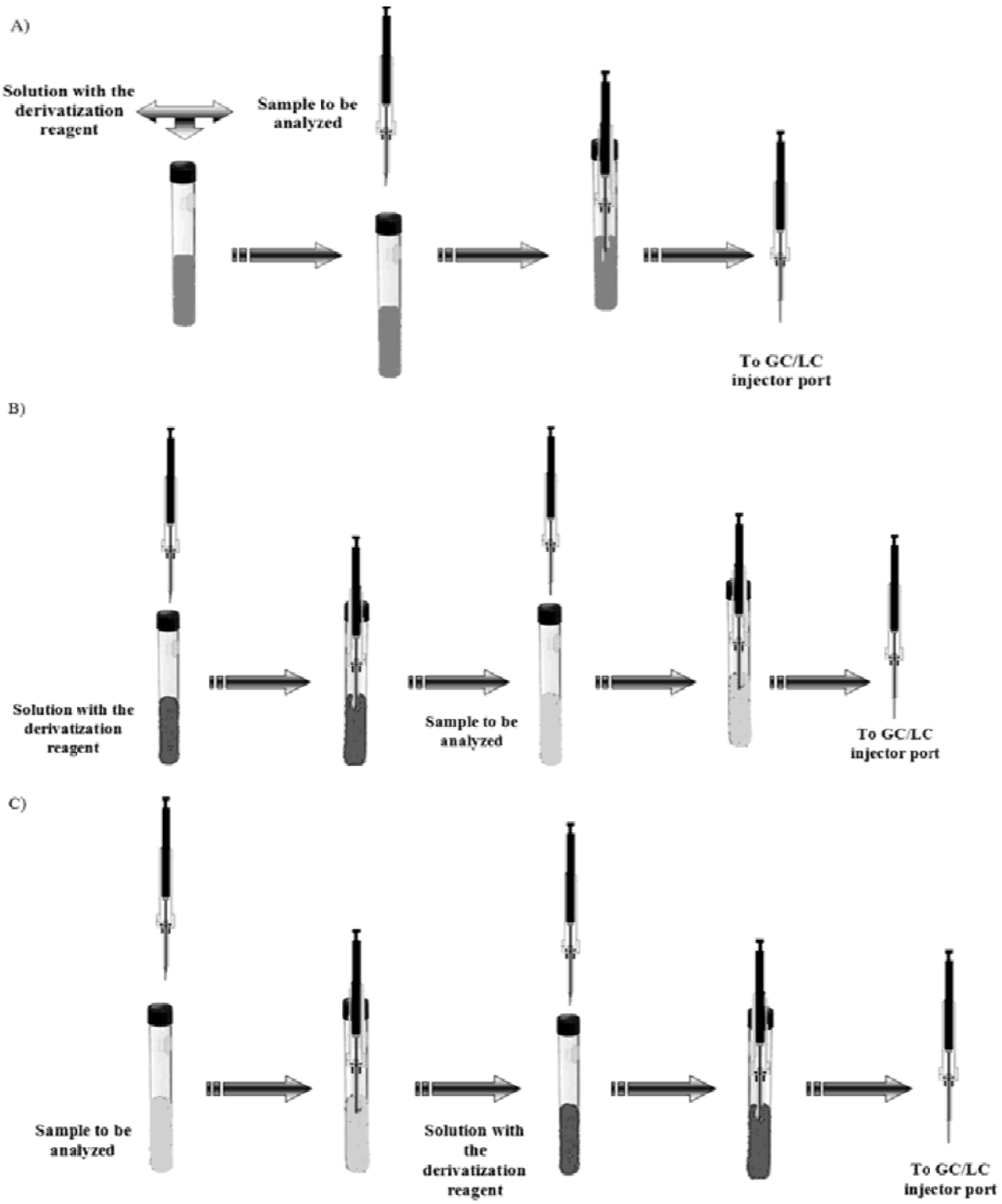


Figure 3. Schematic representation of SPME device with simultaneous analyte derivatization[118]: A) Analyte absorption with the use of an extraction fiber (SPME) after the chemical conversion process is carried out in the sample; B) Analyte sampled with the use of an SPME device, after derivatizing reagent adsorption on the extraction fiber; C) Extraction of analytes from the sample on the surface of the fiber before derivatization on the fiber.

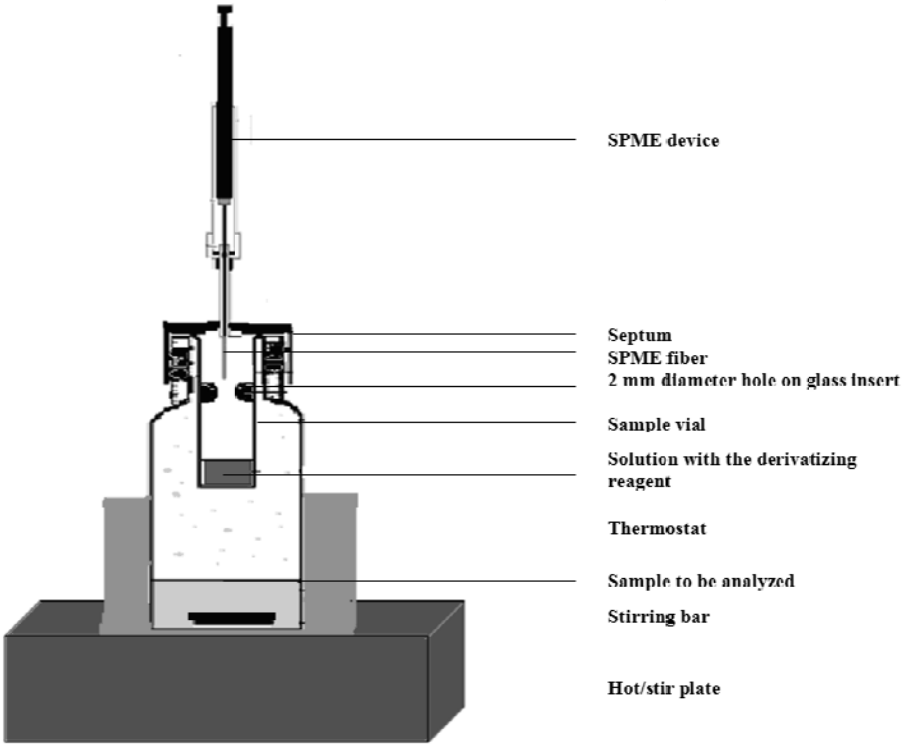


Figure 4. Schematic representation of analyte sampling stage from HS-SPME with simultaneous derivatization. (Reprinted with permission from ref 118. Copyright 2004 John Wiley and Sons.)

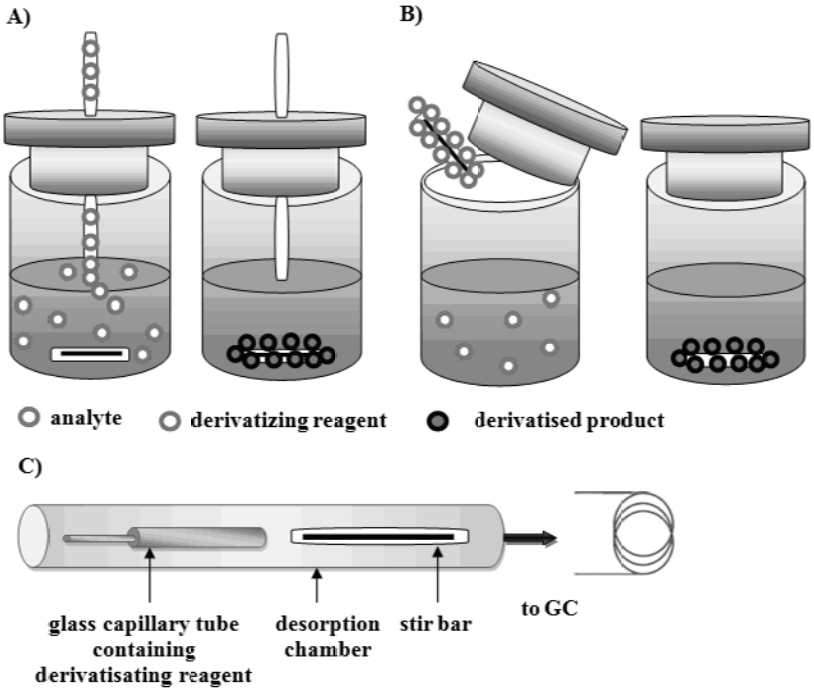


Figure 5. Schematic representation of different derivatization modes using SBSE: A) *in situ*; B) *on-stir-bar* with the derivatization reagent preloaded before exposure to the sample; C) *in-tube* derivatization. Reprinted with permission from ref 125. Copyright 2008 Elsevier.)

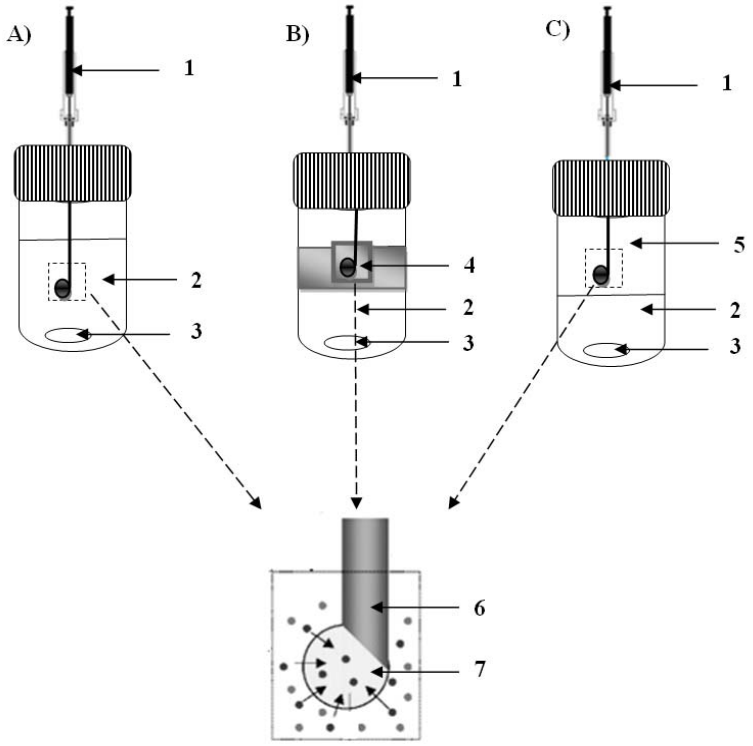


Figure 6. Single drop microextraction[128]: A) direct immersion SDME (two-phase); B) direct immersion SDME (three-phase); C) headspace SDME. 1 Syringe; 2 Aqueous sample; 3 Stir bar; 4 Organic solvent layer; 5 Headspace; 6 Needle; 7 Solvent drop.

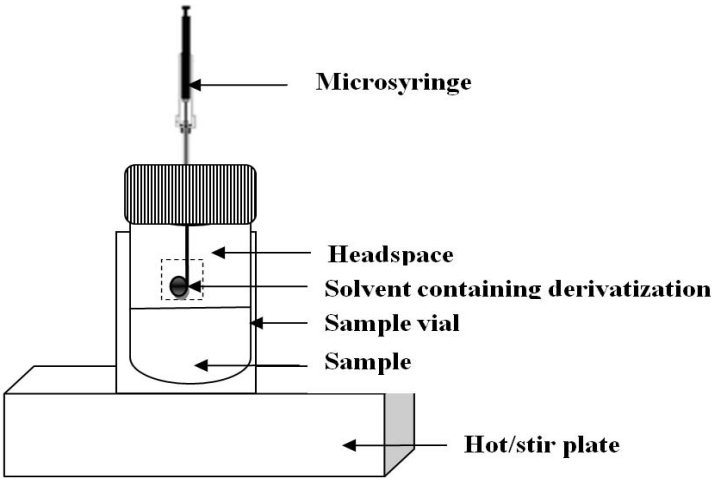


Figure 7. Schematic representation of analyte sampling stage from HS-SDME with simultaneous droplet derivatization[128].

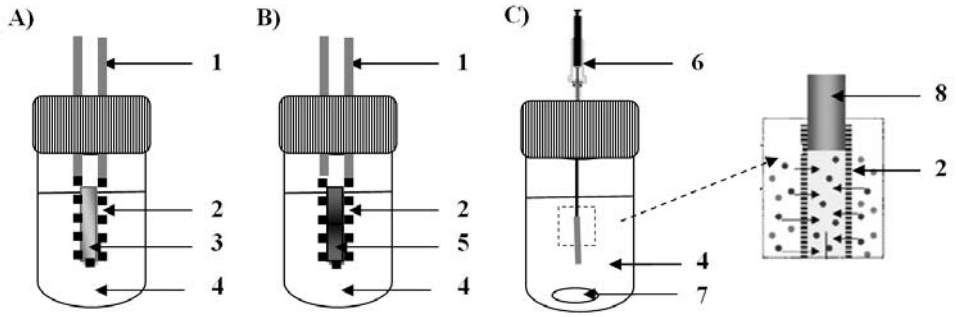


Figure 8. Hollow-fiber liquid phase microextraction coupled with *in situ* derivatization[128]: A) U-shaped HF-LPME (three-phase) and in situ derivatization; B) U-shaped HF-LPME (two-phase) coupled with in situ derivatization; C) rod-shaped HF-LPME (two-phase) coupled with in situ derivatization. 1 Guiding tube; 2 HF with organic phase; 3 Aqueous acceptor; 4 Aqueous sample with derivatizing reagent; 5 Organic acceptor; 6 Syringe; 7 Stir bar; 8 Needle.

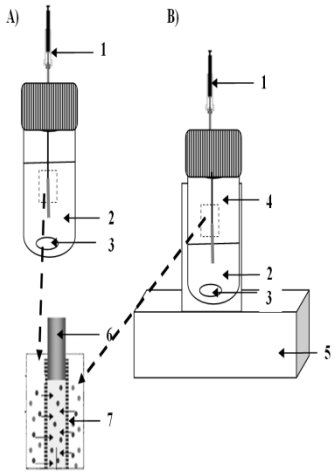


Figure 9. Schematic representation of HF-LPME using extraction medium contains both derivatizing reagent and organic solvent[128]: A) direct immersion; B) headspace of LPME. 1 Syringe; 2 Aqueous sample; 3 Stir bar; 4 Headspace; 5 Hot/Stir plate; 6 Needle; 7 HF with organic phase containing derivatizing reagent.

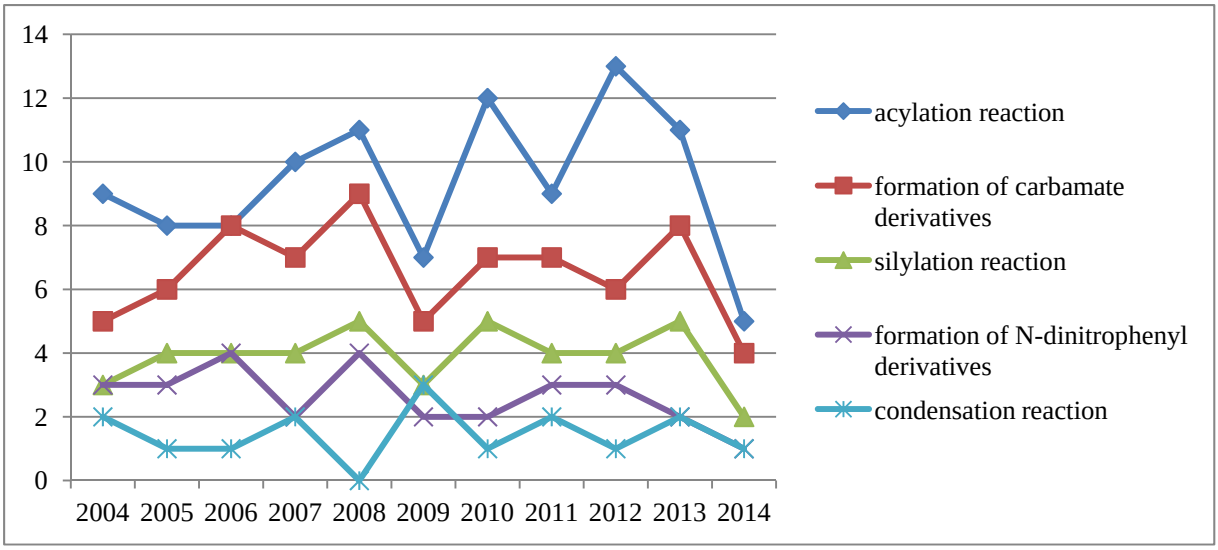


Figure 10. The number of publications concerning the application of GC technique and appropriate derivatization for amine compounds (calculated in Web of Science).