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Derivatization for liquid chromatography-mass spectrometry

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ABSTRACT

Liquid chromatography-mass spectrometry (LC-MS) is one of the most prominent analytical techniques, due to its inherent selectivity and sensitivity. In LC-MS, chemical derivatizations are frequently used to enhance the MS ionization efficiency and selectivity, to facilitate structure elucidation, and to improve the chromatographic separation. In this review, we present an overview of derivatization-based LC-MS analysis. We summarize the reaction mechanisms of representative derivatization reagents and the selection strategy to guide and to stimulate future studies. Furthermore, we emphasize applications of derivatization in peptide and protein analysis, metabolite analysis, environmental analysis, pharmaceutical analysis, food-safety evaluation and MS imaging.

Contents

Abbreviations: AMPP,*N*-[4-(Aminomethyl)phenyl]pyridinium; APDS, 3-aminopyridyl-*N*-hydroxysuccinimidyl carbamate; BCEOC, 1,2-benzo-3,4- dihydrocarbazole-9-ethyl chloroformate; BPBA, 2-bromopyridine-5-boronic acid; BPB, ω-bromoacetonylpyridinium bromide; BPBr, *p*-bromophenacyl bromide; BQB, ω-bromoacetonylquinolinium bromide; BTA, 3-bromoactonyltrimethylammonium bromide; CID, Collision-induced dissociation; C_n-NA-NHS,*N*-hydroxysuccinimide ester of *N*-alkylnicotinic acid; DAABD-AB, 4-[2-(*N*,*N*-dimethylamino)ethylaminosulfonyl]-7-(2-aminobutylamino)-2,1,3-benzoxadiazole; DAABD-AP, 4-[2-(*N*,*N*-dimethylamino)ethylaminosulfonyl]-7-(2-aminopentylamino)-2,1,3-benzoxadiazole; DAABD-Cl, 4-(dimethylaminoethylaminosulfonyl)-7-chloro-2,1,3-benzoxadiazole; DAABD-MHz, 4-[2-(*N*,*N*-dimethylamino)ethylaminosulfonyl]-7-*N*-methylhydrazino-2,1,3-benzoxadiazole; DATAAN, Diacetyl-L-tartaric anhydride; DABS-Cl, Dabsyl chloride; DEEMM, Diethyl ethoxymethylenemalonate; D-FDLA, N^{α}- (5-fluoro-2,4-dinitrophenyl)-D-leucinamide; dimethyl CHD, 5,5′-dimethyl-1,3-cyclohexanedione; DMBA, 4-(dimethylamino)-benzoic acid; DMISC, 1,2-dimethylimidazole-4-sulfonyl chloride; DNPH, 2,4-dinitrophenylhydrazine; Dns-Cl, Dansyl chloride; Dns-Hz, Dansyl hydrazine; EDC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; ESI, electrospray ionization; FEM,*N*-(2-ferroceneethyl)maleimide; FMEA, Ferrocenecarboxylic acid-(2-maleimidoyl)ethylamide; FMOC-Cl, 9-fluorenylmethyl chloroformate; GITC, 2,3,4,6-tetra-*O*-acetyl-β-glucopyranosyl isothiocyanate; HFUA, Heptadecafluoroundecylamine; HMP, 2-hydrazino-1-methylpyridine; HTMOB, 4-hydrazino-*N*,*N*,*N*-trimethyl-4-oxobutanaminium iodide; IAM, Iodoacetamide; i-BuCF, Isobutyl chloroformate; iCAT, Isotope-coded affinity tag; IPCF, Isopropylchloroformate; iTRAQ, Isobaric tags for relative and absolute quantification; LC-MS, Liquid chromatography-mass spectrometry; L-FDAA, (1-fluoro-2,4-dinitrophenyl-5)-L-alanine amide; *m*-APBA,*m*-aminophenylboronic acid; MSI, Mass-spectrometry imaging; MSTFA, *N*-methyltrimethylsilyltrifluoroacetamide; NBD-F, 7-fluoro-4-nitrobenzoxadiazole; NQS, 1,2-naphthoquinone-4-sulfonate; *p*-BPB, 2-bromo-4′-bromoacetophenone; *p*-CPB, 2-bromo-4′-chloroacetophenone; PFBBr, Pentafluorobenzyl bromide; PMA, 1-pyrenemethylamine; PS, Pyridine-3-sulfonyl chloride; SBD-F, 7-fluorobenzo-2-oxa-1,3-diazole-4-sulfonate; SFP, Succinimidylferrocenyl propionate; SPA,*N*-succinimidyl-2(3-pyridyl)acetate; SPTPP, (5-nsuccinimidoxy-5-oxopentyl)triphenylphosphonium bromide; TAABD-Cl, 7-chloro-2,1,3-benzoxadiazole-4-sulfonylaminoethyltrimethylammonium chloride; TMPP-PrG, (4-hydrazino-4-oxobutyl) [tris (2,4,6-trimethoxyphenyl) phosphonium] bromide; TMPP-AcPFP, *S*-pentafluorophenyl tris(2,4,6-trimethoxyphenyl)phosphonium acetate bromide; 2NFP-APB, [3-(2-Nitro-4-trifluoromethylphenyl)aminophenyl]dihydroxyborane; 2-NPH, 2-nitrophenylhydrazine; 3-NPH, 3-nitrophenylhydrazine; 4-APC, 4-[2-(trimethylammonio)ethoxy]benzenaminium halide; 4-APEBA, 4-{2-[(4-bromophenethyl)dimethylammonio]ethoxy}benzenaminium dibromide.

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1. Introduction

Sensitive and selective methods for the determination of trace-level compounds in complex matrices are essential in many research fields. Due to its inherent sensitivity and selectivity, liquid chromatography-mass spectrometry (LC-MS) has become one of the most prominent analytical techniques. However, many compounds cannot be analyzed well by LC-MS, especially if they are difficult to ionize or to fragment, as that makes detection sensitivity extremely low [1].

Improvements in instrument design can increase the performance of LC-MS analysis. Performance can also be improved through a better sampling protocol or through better chromatographic performance. Chemical derivatization has proved to be a powerful strategy to improve the detection characteristics of compounds in LC-MS and a considerable number of derivatization reagents have been synthesized and derivatization methods have been established [2,3].

Chemical derivatization-based LC-MS has been developed from 1980s [4]. Since then, there has been a steady growth of derivatization-based LC-MS techniques, which provide a promising strategy that has solved many analytical problems [5]. Derivatization aims to modify the structure of the target compounds and, as a consequence, the chemical and physical properties. The advantages of integrating derivatization with LC-MS analysis include:

(1) improvement of selectivity and separation [6–9];
(2) enhancement of ionization efficiency [10–14];
(3) improvement of structural elucidation [15–18];
(4) removal of endogenous interference [19]; and,
(5) facilitation of isomer separation [20–22] (Fig. 1).

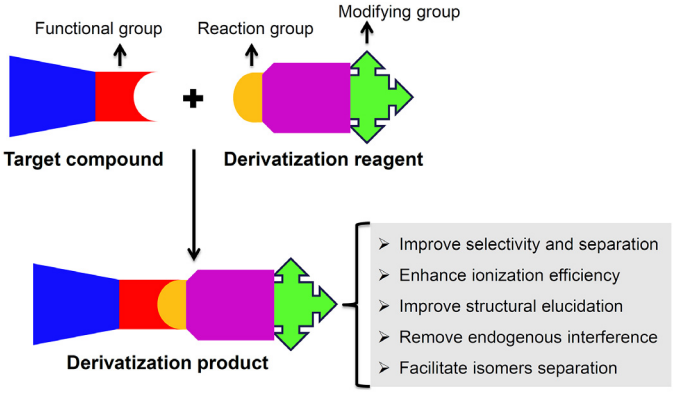

Fig. 1. General reaction mechanism between target compound and derivatization reagent and the advantages of derivatization-based LC-MS methods.

Derivatization reagents can react with target compounds that contain various functional groups, including carbonyl [23,24], hydroxyl [25,26], carboxyl [27,28], amine [29,30] and thiol [31,32]. Derivatization reagents can therefore be categorized into different groups based on the reactions with various functional groups of target compounds. Design and use of proper derivatization reagents to achieve fast, specific reactions are important for derivatization-based LC-MS analysis.

Due to rapid expansion of derivatization-based LC-MS studies, a summary of newly synthesized derivatization reagents and established reaction methods is valuable. Here, we provide a comprehensive review of derivatization-based LC-MS studies with the main focus being on the general principles of representative derivatization reagents. We discuss the relationships between the chemical structure of target compounds and derivatization reagents. We also describe different derivatization strategies combined with LC-MS (mainly for electrospray ionization-LC-MS) and their advancement, giving their advantages and prospects. In addition, we briefly summarize the applications of derivatization-based LC-MS, especially in peptide and protein analysis [33–36], metabolite analysis [37–39], environmental analysis [24,40,41], pharmaceutical analysis [42–47], food-safety evaluation [48–51] and MS imaging [52–54]. We hope that this review can guide and stimulate future studies on derivatization-based LC-MS analysis.

2. Selection strategy for derivatization reagents

Derivatization is a specific chemical reaction, and a reactive functional group in the target compound and the corresponding reaction group(s) of derivatization reagent are the prerequisites for derivatization. Many challenges of derivatization-based LC-MS still exist, including formation of by-products, non-quantitative reaction, requirement for harsh reaction conditions, long reaction time, and product degradation. For effective derivatization-based LC-MS analysis, the derivatization reaction should therefore be fast, efficient, and specific, and form relatively stable products.

The selection of derivatization reagent mainly depends on the reactive functional group of the target compound and the purpose of the research. Upon derivatization, the chemical and physical properties of the compound will change, so affecting compound stability, polarity, solubility, retention on LC, and ionization efficiency in MS [1,3]. In this respect, study of the chemical structure of target compounds will suggest the strategy to prepare appropriate derivatization reagents for any given research purpose.