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环境化学研究中的质谱方法

余明月，魏奶杰，严晓文，陈 石，陈建彬，杨利民，王秋泉
（厦门大学化学化工学院化学系，谱学分析与仪器教育部重点实验室，福建 厦门 361005）

摘要：研究环境化学及与其相关的生命科学，对了解环境污染和生命物种的暴露程度，以及由此引发的健康问题非常必要。这一过程中，质谱是不可或缺的强有力工具。本文简要介绍了基于质谱的相关方法在环境化学研究中的应用。概括地强调了电感耦合等离子体质谱（ICP-MS）、电子捕获负化学源质谱（ECNI-MS）、电喷雾离子化质谱（ESI-MS）、基质辅助激光解吸电离质谱（MALDI-MS）以及高分辨串联质谱（HR-MS）、非变性质谱（nMS）和质谱成像（MSI）技术对环境和生命介质中污染物的分析鉴定，及其对正常生命过程的扰动机制研究所发挥的作用；并展望了质谱技术在环境化学中的发展趋势，指出了反应蛋白组学的发展和具有污染物分子及其代谢产物的反应性官能团分子标尺的设计，深化对污染物分子及其代谢产物与关键生物分子相互作用的理解，加深对环境污染健康效应的认识。

关键词：质谱；环境污染；健康；分析鉴定；分子机制
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Mass Spectrometry for Environmental Chemistry Research

YU Ming-yue, WEI Nai-jie, YAN Xiao-wen, CHEN Shi,
CHEN Jian-bin, YANG Li-min, WANG Qiu-quan
(*Department of Chemistry & the MOE Key Laboratory of Spectrochemical Analysis and Instrumentation, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen* 361005, *China*)

Abstract: Studies of environmental chemistry and its related life science are essential to understand the exposure of environmental pollution to living species and the resulted health problems. During this process, mass spectrometry is an indispensably powerful tool thanks to its qualitative and quantitative abilities and remarkable mass resolution. In this review, the state-of-the art mass spectrometric methods were introduced, including inductively coupled plasma mass spectrometry (ICP-MS), electron capture negative ionization mass spectrometry (ECNI-MS), electrospray ionization mass spectrometry (ESI-MS), matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS), high-resolution tandem mass spectrometry (HR-MS) and native mass spectrometry (nMS) as well as mass spectrometry imaging (MSI), which have been applied in environmental chemistry and the related life science research, with an emphasis on their role in the determination, characterization, discovery and biological impacts research of environmental pollutants in the environmental media, and the related metabolites during

本文共同第一作者余明月，魏奶杰；通信作者王秋泉，严晓文

life process. Furthermore, the trend of MS methods from fundamental to applied perspectives was outlooked, in order to solve the emerging issues, such as the ambiguous interaction mechanisms of the environmental pollutants and/or their metabolites with biomolecules. It is very much expected that novel MS-based strategy like reactive proteomics approach together with the design of new molecular ruler will help to solve the "mystery" of the environmental pollutants and/or their biological metabolites impacted on a normal physiological process, deepening our understanding on the influence of environmental pollution on health.

Key words: mass spectrometry; environmental pollution; health; analytical characterization; molecular mechanism

如今，人们清醒地意识到与社会经济迅猛发展相伴而来的环境污染和随之产生的健康问题[1-2]，由此深入开展了这些问题所触发的环境化学及与其相关的生命科学研究[3-4]。为了探索环境污染与健康的关系，开展环境化学研究，其前提和基础是了解污染物分子或它们的不同形态以及聚集体（颗粒污染物）的含量、分布和迁移转化的源汇归趋途径。针对包含生命体在内的复杂环境介质开展研究，了解其中生命物种的生存繁衍规律，特别是在环境污染暴露或胁迫下生命物种主动或被动地适应性改变行为，都需要分析化学的深度参与；此外，各种物理测量工具的研制和化学生物策略/方法的提出，极大地深化了人们对环境污染和生命健康关系的理解，促进科学理性地寻找经济发展与生命健康之间的平衡点，推动绿色经济的发展。质谱技术以分子离子的质荷比为检测对象，辅以不同离子源产生的特异性碎片离子，具有分子结构解析能力，在环境和生命科学研究中备受青睐。本文将示例性地介绍环境化学及与其相关的生命科学研究中的质谱方法，不求包罗万象，仅期管中窥豹。更为全面系统的介绍可参见环境质谱方法的系列综述[5-14]。

1　环境介质和生命体中污染物的质谱分析鉴定

追求分析方法的灵敏度和选择性（分辨率）是分析化学的永恒主题，以期在环境化学和生命科学研究中获取全面准确的信息。在质谱分析中，与这2个指标最密切的仪器部件是离子源和质量分析器。针对不同的目标污染物选择合适的离子源尤为关键。例如，当检测以金属或类金属元素为核心的无机污染物时，电感耦合等离子体（inductively coupled plasma, ICP）是目前广为认可的"硬电离"离子源[15]，它可以断裂绝大多数原子之间的化学键，使几乎所有分子都转变成"原子离子"，便于获取核心金属或类金属元素的总量信息；为获取无机污染物的化学形态信息，如色谱等必要的形态分离工具常与ICP-MS联合使用[16-18]，示于图1；当需要进一步了解它们的未知形态组成和结构时，"软电离"离子源，如基质辅助激光解吸离子源（matrix-assisted laser desorption/ionization, MALDI）[19]和电喷雾离子源（electrospray ionization, ESI）[20]可以同时产生分子离子和碎片离子，有助于鉴定未知形态[21-23]，示于图2。除此之外，针对含有强吸电子原子（如卤素等）的有机污染物分子，电子捕获负离子源（electron capture negative ionization, ECNI）或负化学离子源因产生卤素负离子且呈现的同位素特征分布更合适而被普遍采用[24]；在发展大体积进样技术或具有更强吸电子能力的氟原子衍生策略基础上，不仅可以获得对卤素负离子检测时的超高灵敏度，而且使同时检测特征结构碎片离子成为可能，充分发挥了质谱的定性和定量分析能力[25-26]。同位素质谱[27]的应用使得人们对污染物来源和形成机制的理解越来越深入[28-30]。质谱成像（mass spectrometry imaging, MSI）技术[31]的发展为污染物的原位表征提供了强有力的工具，例如，污染物暴露下多细胞肿瘤球状体的代谢响应研究和颗粒污染物组成的表征等[32-34]。基于不同原理、种类繁多的离子源与各种质量分析器串联使用[35-36]，以及与多

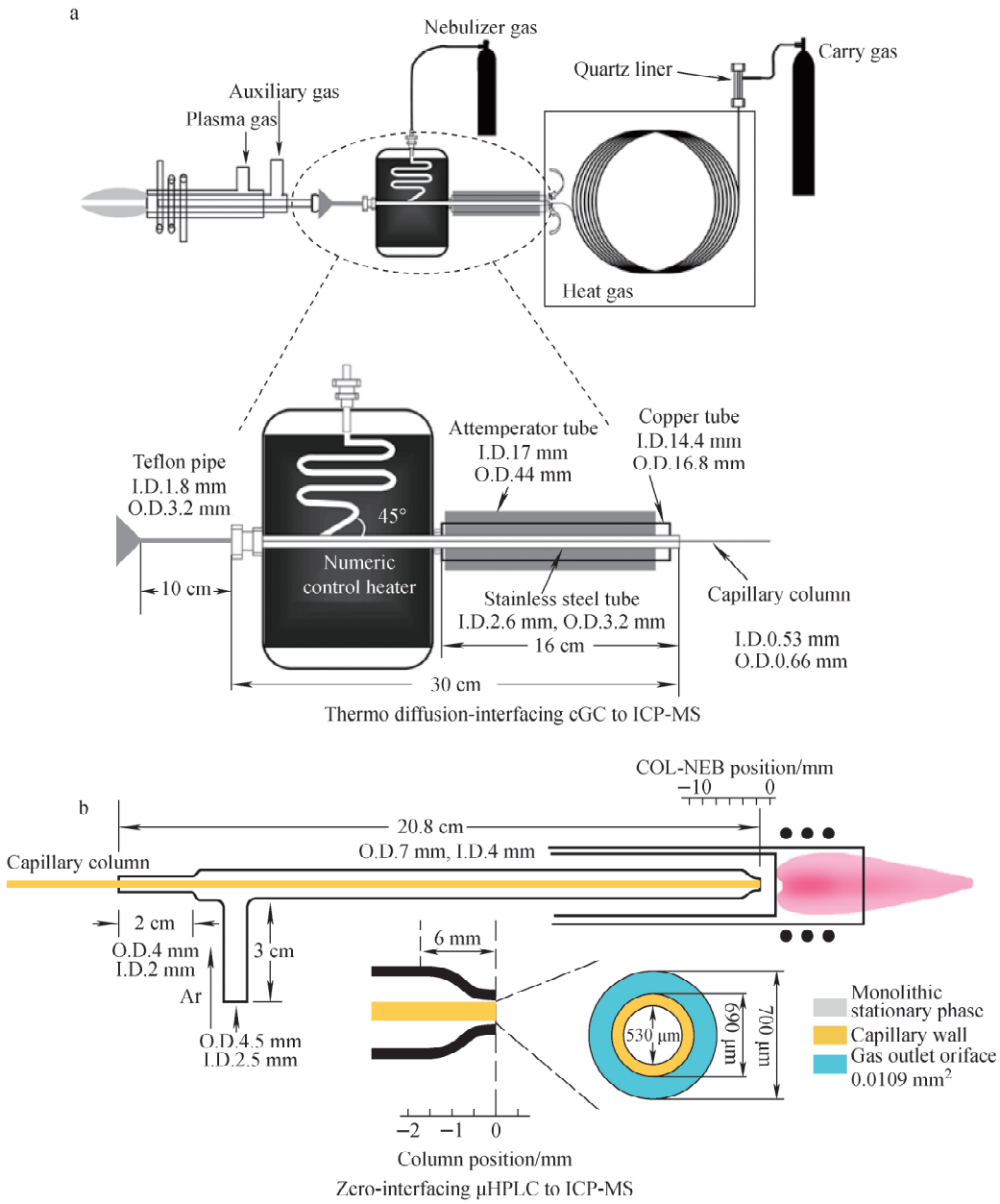


图 1 毛细管气相色谱与电感耦合等离子体质谱联用的热扩散接口(a)[16]和微径高效液相色谱与电感耦合等离子体质谱联用的零死体积接口(b)[18]

Fig. 1 Thermo diffusion-interfacing capillary gas chromatography (cGC) to ICP-MS (a)[16] and zero-interfacing microbore high performance liquid chromatography (μHPLC) to ICP-MS[18]

维色谱分离技术的联用[37]，都可以极大地提高质谱分析的灵敏度和分辨率，扩大和提升环境污染物检测的广度和深度。

除基于 Bottom-up 策略利用质谱直接检测环境介质中已知污染物外，通过分析环境中生命体中的污染物，不仅可以了解生命体受污染暴露的程度，也为研究环境污染的空间分布和历史演变趋势提供可能。例如，环境中生长的树木表皮因富含有机质且具有微孔结构是天然的污染物实时富集材料，使用质谱技术分析采自不同地理位置的树木表皮中持久性有机污染物(persistent organic pollutants, POPs)，可知大气污染状况的空间分布[38-39]；因某些树种的表皮在树木生长过程中可被包裹于树干中，大气污染状况便被实时记录下来，形成大气污染“时间隧道”[40]，依据树木年轮可以分辨其所记录

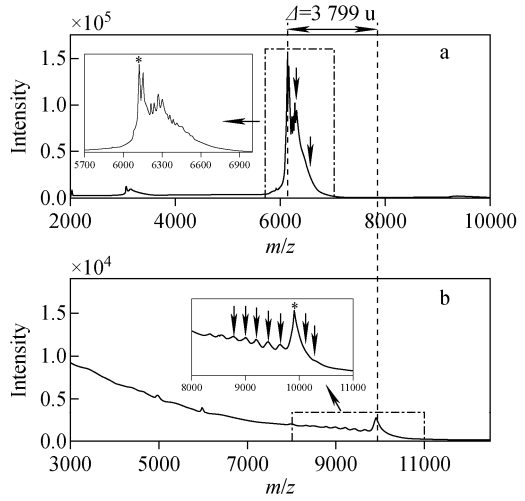


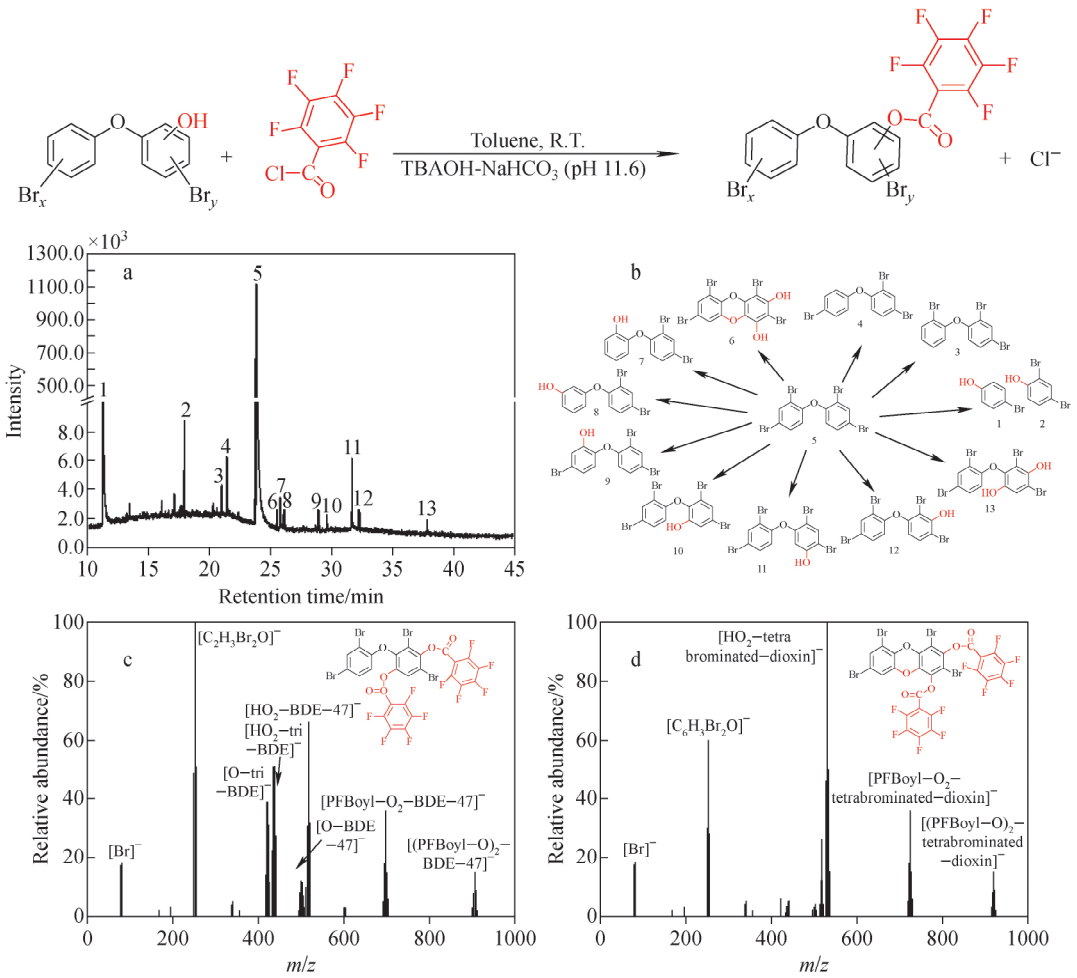
图 2　Zn_7 MT-2(a)和$(CH_3Hg)_x$-MT-2(b)($n_{CH_3Hg^+}/n_{MT\text{-}2}=20$ 时,$x=12\sim20$)的 MALDI-TOF-MS 图[22]

Fig. 2　MALDI-TOF-MS spectra of Zn_7 MT-2 (a) and $(CH_3Hg)_x$-MT-2 (x=12-20) (b) formed after the titration with CH_3Hg^+ at $n_{CH_3Hg^+}/n_{MT\text{-}2}=20$[22]

污染事件的时间。本课题组使用质谱技术分析树木"时间隧道"中 POPs 含量,获得了中国大陆东南地区 130 年跨越世纪的大气 POPs 污染历史演变数据[41-42]。另一方面,使用质谱技术分析不同人体样本(如血液、尿液和母乳等)中污染物及其代谢产物的含量是一种 Top-down 策略,可以客观地反映人类受环境污染的暴露程度[43-47],为鉴定污染物在体内的代谢途径和代谢产物提供了重要信息[26,48],示于图 3。鉴定新污染物和生命体内污染物的代谢产物通常以环境介质中测得的污染物为目标前体,从 Nontarget 策略[49-51]出发,利用高分辨质谱技术发现的新污染物极大地丰富了污染物外暴露和内暴露的内涵[26,52-60]。相比于 Bottom-up 策略直接获取环境介质和食物中污染物的外暴露信息,测量血液等生物样品中污染物的 Top-down 策略提供了更客观的内暴露信息;污染物代谢产物的质谱鉴定进一步弥补了仅以测得的外源污染物在生命体内的含量所造成的内暴露信息缺失。在与基因组学研究相结合的"暴露组学"层面上展开探索,对于更全面客观地评价环境污染暴露与生命健康的关系非常必要[61-62]。

2　环境污染对生命过程的影响

环境污染对生命过程的影响主要体现在污染物对生命正常生理通路的干扰[63-64],这些干扰本质上触发了特定基因发生变化(突变或修饰),进而使其表达的生物分子丰度产生改变。蛋白质是维系正常生命活动的执行者,是环境污染对生命健康影响研究的焦点。MALDI 和 ESI 离子源因能产生带单电荷或多电荷的离子,配以高分辨串联质量分析器更适合分析生物大分子,相应的蛋白质组学研究技术和方法[65-69]被应用于发现在污染物胁迫下蛋白质的差异化表达[70-87]。大量差异化表达蛋白质的发现为理解环境污染对生命过程的影响提供了有价值的信息,引导研究进一步聚焦到这些差异化表达蛋白所发挥作用的生理通路上,探索引发这些变化的原因。另一方面,研究污染物分子及其代谢产物与这些关键蛋白质分子的相互作用,为理解环境污染对生命过程的影响提供了直接证据。非变性质谱(native mass spectrometry, nMS)是研究分子间非共价相互作用的方法[88]。活性蛋白质和污染物小分子配体通过非共价结合形成复合物,在电喷雾过程中被转化为气态,完整复合物离子得以检测。例如,在研究 15 种全氟烷基化合物(perfluoroalkyl substance, PFAS)与碳酸酐酶(hCA)非共价相互作用时,nMS 检测到至少 8 种 PFASs 可以抑制 4 种 hCA 同工酶(Ⅰ、Ⅱ、Ⅸ和Ⅻ)中的1 种,抑制常数达亚微摩尔水平[89]。污染物配体与蛋白质结合有可能改变蛋白质的折叠构象,从而改变目标蛋白质的热稳定性,与配体络合通常使目标蛋白更稳定、更耐热而诱导沉淀。应用高分辨质谱技术,基于这种热位移的检测方法被用于快速筛选全氟辛烷磺酸(perfluorooctanesulfonic acid, PFOS)在蛋白组中的靶蛋白[90]。此外,研究[91-95]发现,污染物还可以以共价方式与蛋白质结合形成蛋白质加合物。例如,利用液相色谱-质谱(LC-MS)法证明了 PFAS、双酚 A(bisphenol A)、三氯生(triclosan)以及消毒副产物单卤代乙酸(monohaloacetic acid)和单卤代乙酰胺(monohaloacetamide)可以与蛋白质反应性巯基发生共价反应。尽管如此,在细胞或活体中污染物分子及其代谢产物与蛋白质分子间的范德华弱相互作用或成键作



注：a. BDE-47 在大鼠肝微粒体中代谢产物；b. BDE-47 的代谢途径；c. BDE-47 代谢产物 di-OH-BDE-47 的 ECNI-MS 图；d. di-OH-tetrabrominated dioxin 的 ECNI-MS 图

图 3 五氟苯甲酰氯衍生介导的 BDE-47 代谢产物的质谱鉴定[26]

Fig. 3 Mass spectrometry of BDE-47 metabolites mediated by derivatization of pentafluorobenzoyl chloride[26]

用尚有待进一步研究，以阐明污染物分子/代谢产物集群和蛋白质组间多靶点相互作用规律。

3 总结与展望

质谱作为强有力的定性和定量分析工具，无论在离子源和质量分析器的种类以及串联组合应用模式，还是相应的分析方法学方面，近年来都有长足的进步。质谱技术在环境污染物监测中扮演重要角色、发挥关键作用的同时，新污染物和生物代谢产物的发现扩大了“暴露组学”研究的范畴，极大地推动了“环境污染与人类健康”关系研究的不断深入。但是，目前我们尚未达到真正厘清“环境污染和人类健康”关系的目标，还需要进一步在分子层面上研究宏观现象背后的支撑机制[96-97]，认清环境污染物及其代谢产物多靶标、多靶点与生物分子相互作用的特性。对这一特性更深入的了解，迫使我们在组学水平上开展研究，了解生物小分子、基因和蛋白质活性结构域和位点易与哪些功能基团的污染物相互作用，了解它们之间相互作用的机制以及强弱程度等信息。基于活性的蛋白质组分析技术[98-101]已经应用于药物与生物分子的作用机制研究和有效药物筛选，我们可以设计具有典型疑似致病污染物分子官能团的“分子标尺”，发展基于质谱技术的污染物分子集群和蛋白质组间的“污染物反应蛋白质组学”研究方法，发现污染物与生物分子间的反应机制，了解它们之间的作用途径和强弱程度以及所产生的

生物学效应[102]。这样才能够在分子水平上真正理解“环境污染与人类健康”的关系,从源头上指导设计保持“功能”且对环境和健康友好的化学品,使社会经济实现绿色可持续发展。

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