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Review

Chiral recognition and determination of enantiomeric excess by mass spectrometry: A review

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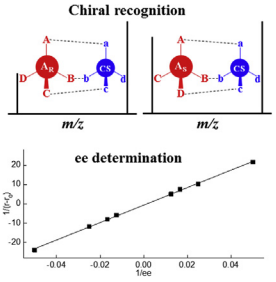
HIGHLIGHTS

- Both chiral recognition and determination of enantiomeric excess by mass spectrometry are systematically reviewed.
- Classification is based on the behavioral differences of diastereomers formed between chiral analytes and chiral selectors.
- Development of ion mobility mass spectrometry for chiral differentiation is covered.
- Various methods are highlighted and compared.

GRAPHICAL ABSTRACT



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ABSTRACT

Chiral analysis is of great importance to fundamental and applied research in chemical, biological and pharmaceutical sciences. Due to the superiority of mass spectrometry (MS) over other analytical methods in terms of speed, specificity and sensitivity, chiral analysis by MS has attracted much interest in recent years. Chiral analysis by MS typically involves introduction of a chiral selector to form diastereomers with analyte enantiomers, and comparison of the behaviors of diastereomers in MS. Chiral differentiation can be achieved by comparing the relative abundances of diastereomers, the thermodynamic or kinetic constants of ion-molecule reactions of diastereomers in the gas phase, the dissociation of diastereomers in MS/MS, or the mobility of diastereomers in ion mobility mass spectrometry. In this review, chiral recognition and determination of enantiomeric excess by these chiral MS methods were summarized, and the prospects of chiral analysis by MS were discussed.

Contents

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1. Introduction

Chirality plays an important role in chemical, biological and pharmaceutical sciences. Most organic compounds, including the biomolecular building blocks of life such as amino acids, sugars, proteins, nucleic acids and polysaccharides are chiral. Due to the intrinsic chiral environment of living systems, enantiomers often show different physiological behaviors or different pharmacological activities. For example, (8R,8′R,7′S)-lyoniresinol enantiomer is strongly bitter whereas (8S,8′S,7′R)-lyoniresinol is tasteless [1]; the S-enantiomers of 4-mercapto-2-hexanone and 4-acetylthio-2-hexanone have more fruity and pleasant notes than the R-enantiomers [2]; R-thalidomide is a potent drug while S-thalidomide can cause adverse effects [3]. Enantiomeric drugs have been increasingly developed for the pharmaceutical markets due to their superiority in potency and safety. According to statistics for 2013, nine of the top ten best-selling pharmaceuticals are enantiomer-based drugs [4]. Therefore, chiral recognition and quantitative determination of individual enantiomers are essential for the discovery and quality control of drugs [5]. Moreover, chiral analysis is crucial for asymmetric synthesis and natural product chemistry, and for understanding the evolutionary process of life [6].

Chiral analysis generally includes qualitative analysis, i.e., recognition of chirality of analyte molecules, and quantitative analysis, i.e., determination of the enantiomeric composition, which is usually described in terms of enantiomeric excess (ee). Chiral analysis can be performed using various approaches [7–11], including X-ray crystallography, vibrational optical activity (VOA), optical rotary dispersion (ORD), circular dichrosim (CD), nuclear magnetic resonance (NMR), and a series of chromatographic methods, such as liquid chromatography (LC), gas chromatography (GC), capillary electrophoresis (CE) and supercritical fluid chromatography (SFC). Among these methods, chromatographic methods, which typically involve the use of columns with chiral stationary phases, are more popularly used for chiral analysis.

Mass spectrometry (MS) is a commonly used analytical tool with significant advantages in terms of speed, specificity and sensitivity. Since enantiomers usually show the same mass spectra, MS had been considered as a “chiral-blind” technique until the first observation of chirality effect in chemical ionization mass spectrometry (CI-MS) in 1977 [12]. Since then, with the development of various ionization methods, including fast atom bombardment (FAB), electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI), MS has been playing an increasingly important role in chiral analysis on its own without the need of coupling with chiral chromatographic techniques. FAB, ESI and MALDI are much softer than CI for ionization of analytes [13–15]. Particularly, ESI is the softest ionization technique that much facilitates detection of intact chiral analytes, chiral selectors and their complexes, and has been commonly used in chiral mass spectrometry.

Like other methods for chiral recognition, chiral recognition by MS is achieved in a chiral environment. In fact, chiral recognition by MS generally depends on the introduction of a chiral selector, which could react with enantiomers of chiral analytes to form diastereomers. Based on the behavioral differences of diastereomers, methodologies of chiral recognition by MS could be divided into four types: (1) chiral recognition based on differences in relative abundances of diastereomers; (2) chiral recognition based on differences in thermodynamic or kinetic constants of ion-molecule reactions in the gas phase; (3) chiral recognition based on differences in dissociation of diastereomers; and (4) chiral recognition based on mobility differences in ion mobility mass spectrometry (IM-MS). As summarized in Table 1, MS has been widely used for chiral analysis, although most of the studies were mainly based on pure chiral compounds. In this paper, the above methodologies are reviewed and commented. Although several reviews on chiral analysis by mass spectrometry have been published [5,16–25], there is not yet any systematic summary on the qualitative and quantitative strategies of different chiral mass spectrometric methods, which will be presented in this review.

2. Chiral recognition based on differences in relative abundances of diastereomers

This method is based on comparison of relative abundances of diastereomers in single-stage mass spectra. The differences in the relative abundances of diastereomers may be due to the differences in the affinity or reactivity of the chiral selector towards enantiomers in solution phase. Studies showed that such enantioselectivity