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Chiral Recognition and Determination of Enantiomeric Excess by Mass Spectrometry: A Review

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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.

Keywords: mass spectrometry, chiral recognition, enantiomeric excess (ee), ion mobility

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 observed in MS was in good agreement with that obtained using high performance liquid chromatography (HPLC) [26-32]. As listed in Table 1, various ionization techniques, including CI, FAB, MALDI and ESI, have been

successfully implemented in this method. The chiral recognition of this method can be achieved indirectly through two successive measurements or directly through only one measurement as discussed below.

2.1 Chiral recognition

2.1.1 Indirect method based on two measurements

This chiral recognition method was developed in the early stage of chiral mass spectrometry based on the fact that two diastereomers have the same mass and cannot be differentiated in one MS spectrum. It was first employed in CI [33-38], and later applied widely in other ionization techniques such as FAB [39-47] and ESI [27, 47-55]. According to the study by Liang et al. [47], for the chiral recognition between dimethyldiketopyridino-18-crown-6 and α-(1-naphthyl)ethyl ammonium, FAB gave more stable results, but with a smaller degree of enantioselectivity, than ESI. The investigation by Lu and Guo [53] revealed that the nozzle potential of ESI and the type of acids used for pH adjustment could have significant effects on the chiral recognition of borneol with zinc(II) and l-tryptophan, e.g., chiral discrimination with acetic acid or propanoic acid but not with hydrochloric acid or formic acid. To compensate the signal variations during the two measurements, an internal standard, which is usually the isotopically-labeled analyte or a molecule with a structure similar to the anlayte [54-56], was added for the two measurements. The relative peak intensity (RPI) [39, 41, 42], defined as the intensity ratio between the analyte complex and internal standard complex, was used for comparison and characterization. The RPI ratio (RPI_R/RPI_S, where RPI_R is the RPI for the R-

analyte and RPI_S for the S-analyte) was used to indicate the enantioselectivity. For example, as shown in Fig. 1, d_5-L-Phe and 5-F-L-Trp were used as the internal standards for chiral analysis of Phe and Trp, respectively, and the two chiral discriminations could be obtained by comparing $[Cu(L\text{-}Phe\text{-}H)chiragen]^{+\cdot}/[Cu(d_5\text{-}L\text{-}Phe\text{-}H)chiragen]^{+\cdot}$ with $[Cu(D\text{-}Phe\text{-}H)chiragen]^{+\cdot}/[Cu(d_5\text{-}L\text{-}Phe\text{-}H)chiragen]^{+\cdot}$, and $[Cu(L\text{-}Trp\text{-}H)chiragen]^{+\cdot}/[Cu(5\text{-}F\text{-}L\text{-}Trp\text{-}H)chiragen]^{+\cdot}$ with $[Cu(D\text{-}Trp\text{-}H)chiragen]^{+\cdot}/[Cu(5\text{-}F\text{-}L\text{-}Trp\text{-}H)chiragen]^{+\cdot}$ [54]. In the chiral recognition involved in host-guest interaction and equilibrium, to improve enantioselectivity, RPI could be modified as the equilibrium constant for an assumed equilibrium, such as in equation 1 [44] and equation 2 [45], where H_{ref} is the reference host, H_{chir} is the target chiral host, G_{ref} is the internal standard and G_{chir} is the analyte.

$$H_{chir}H^+ + H_{ref}G_{chir}^+ \rightleftharpoons H_{chir}G_{chir}^+ + H_{ref}H^+ \quad (1)$$

$$H_{chir}G_{ref}^+ + H_{ref}G_{chir}^+ \rightleftharpoons H_{chir}G_{chir}^+ + H_{ref}G_{ref}^+ \quad (2)$$

In the absence of any internal standard, it is feasible to normalize diastereomer intensity to other ion intensity as RPI. Schug et al. [27] successfully implemented the intensity ratio of $[selector+analyte+Na]^+$ to $([selector+H]^+ + [selector+analyte+Na]^+)$ as RPI to screen the enantioselectivity of a series of cinchona alkaloids, and the intensity of $[selector+analyte+H]^+$ relative to $([selector+H]^+ + [2selector+H]^+)$ was used as RPI to screen the enantioselectivity of cinchona alkaloids by Czerwenka et al. [26]. The intensity ratios of $[selector+analyte+H]^+$ to $[selector+H]^+$ and $[selector+analyte+H]^+$ to $[analyte+H]^+$ were also used as RPIs in the chiral recognition studies by Cheng et al. [51] and Wu et al. [46], respectively. In a study by Bobbitt

et al. [57], the degree of complex formation, assessed as the sum of intensities of all observed ionic complex forms divided by the sum of the intensities of all ion forms, was used to investigate the stereoselective interaction between alkylsulfonate-modified cinchona alkaloid and alanine–alanine dipeptide enantiomers. Additionally, the ratio of dissociation constant, which could be measured by using ESI-MS titration, could also be applied for chiral recognition [21, 58-60].

Comparison of the chiral discrimination results revealed that the preference of heterochiral (the analyte and the selector of different configurations) or homochiral (the analyte and the selector of the same configurations) complex formation depended on the analyte and selector. For example, the relative intensities of heterochiral complexes were higher than those of homochiral complexes in the chiral analyses of amino acids and α-hydroxy acids with 2-methyl-1-butanol as the chiral selector [33], secondary alcohols with diacetoxysuccinic/dibenzoyloxysuccinic anhydride as the chiral selectors [40], as well as alkylammonium ion with diketopyridino-18-crown-6 as the chiral selector [47]; while the opposite results were reported in the chiral analyses of secondary alcohols and amino acids with phenylbutyric anhydride/mandelic acid/methylbutonic acid/α-phenylethylamine as the chiral selectors [35], cyclic α-amino acids with mandelic acid/camphanic acid/α-phenylethylamine as the chiral selectors [36], and phenylethylamine with phorsaeure-(1,1'-binaphthyl-2,2'-diylester) as the chiral selector [46].

2.1.2 Direct method based on one measurement

2.1.2.1 Enantiomer-labeled method

To eliminate the need to make two successive measurements for comparison and the need to select suitable internal standards, a direct and simple enantiomer-labeled method was developed by Sawada et al. in 1994 [61], allowing direct chiral recognition by the peak intensity ratio of two mass-shifted diastereomers in one MS spectrum. In the enantiomer-labeled host method, one enantiomer of host molecule (H, selector) was isotopically labeled with deuterium, and an equimolar mixture of H_R (R-host without isotopic labeling) and $H_{S\text{-}dn}$ (S-host with n atoms deuterium-labeled) was complexed with the guest prior to MS analysis, while in the enantiomer-labeled guest method, one enantiomer of guest molecule (G, analyte) was isotopically labeled with deuterium, and an equimolar mixture of G_R (R-guest without isotopic labeling) and $G_{S\text{-}dn}$ (S-guest with n atoms deuterium-labeled) was complexed with the host prior to MS analysis (see Fig. 2) [62]. After MS analysis, two mass-shifted H-G diastereomers would simultaneously appear in a single-stage MS spectrum, where the peak intensity ratio of two diastereomers (I_R/I_S), termed by Sawada et al. as the IRIS value [63], would reflect the enantioselectivity. As can be seen in Fig. 3(b), the intensity ratio between [(S)-1+L-AlaOMe+H]$^+$ and [(S)-1+D-AlaOMe-d_3+H]$^+$ (0.61) reflected the chiral recognition ability of (S)-1 towards AlaOMe·HCl [64]. The more different was the IRIS value from unity, the higher degree of chiral recognition could be achieved. Such enantiomer-labeled method was applicable not only to protonated complexes but also to metal bound complexes [65, 66], and the enantioselectivity of cinchonane-type chiral selector towards *N*-(3,5-dinitrobenzoyl)leucine

(DNB-Leu) was found to increase with the increase of Li^+ concentration [66]. It should be noted that control experiments to investigate the effect of isotopic labeling must be performed prior to the determination of enantioselectivity based on the intensity ratios, since isotope effect of deuterium has been observed in MS analysis of the binding between tert-butylcarbamoyl-quinine/quinidine and isotopomeric quasienantiomers of DNB-Leu [67].

In the enantiomer-labeled guest method, amino acid esters were often used as guests [61, 64, 68-83] since isotopic labeling could be easily achieved through the esterification between amino acid and deuterated alcohol; while crown ether [61, 63, 64, 68, 70, 72, 78, 80, 81, 84], carbohydrate and its derivatives, including both cyclic oligosaccharides [69, 75, 79, 85] and acyclic saccharides [73, 74, 76, 77, 82, 86, 87], were the most commonly investigated hosts. For the chiral recognition of acyclic saccharides, an induced-fitting mechanism, that is the conformation of acyclic saccharide changing from a linear to a pseudo-ring structure during the chiral recognition process, was proposed [74, 76, 77]. The enantiomer-labeled guest method has been successfully applied for high-throughput screening of enantioselective catalysts in combinatorial chemistry [88] and screening of chiral selectors for chromatographic applications [75].

For the enantiomer-labeled host method, it was often used to determine ee of samples (see below for details) [65, 66, 89-91]. According to the cross-chiral relationship [62], for the same host and guest, the IRIS value obtained from the enantiomer-labeled host method should be

equivalent to that obtained from the enantiomer-labeled guest method [62, 77]. It can be found from Table 1 that diketopyridino-18-crown-6 was better than crown ether for chiral differentiation of alkylammonium ions, probably due to the presence of favorable π-π stacking between pyridino moiety of diketopyridino-18-crown-6 and the guest; while methylated β-CD was better than α/β/γ-CD for chiral differentiation of amino acids. In addition, cinchona alkaloid [66], trianglamine [92], resorcinarenes and glucosylthioureidocalixarenens [93, 94], and pseudopeptidic molecules [95] could also be used as hosts for chiral discrimination of dinitrobenzoyl-leucine, carboxylic acids, ammonium salts, amino acids, and dipeptide, respectively. Chiral recognition of leucine by enantiomer-labeled antimony tartrate was also reported [96]. More details about chiral recognition of metal tartrates can be found in a review by Wijeratne et al. [97].

2.1.2.2 Pseudo-enantiomer mass-tagged method

Following the enantiomer-labeled method, the pseudo-enantiomer mass-tagged method, which uses mass-shifted analogues rather than isotopically labeled enantiomers, was developed later. In this method, an equimolar mixture of pseudo-enantiomeric reagent, which is a mixture with each pseudo-enantiomer having opposite configuration and a slightly different mass due to different substituents remote to the chiral center [98], is used to form complexes with the analyte. The intensity ratio of two pseudo-enantiomeric selector-analyte complexes in one single-stage MS spectrum is used to measure the enantioselectivity. Since the first introduction of this method in 1999 by Guo et al. [98], there have been 9 pairs of pseudo-enantiomeric

selectors developed for chiral recognition, and their structures are summarized in Fig. 4. These pseudo-enantiomeric selectors were all based on the structure of pirkle-type chiral stationary phases (CSPs) with the enantioselectivity observed in MS comparable to that in HPLC. Among them, *N*-acylprolines (1a/1b) have been used to differentiate alcohols and amines in covalent complexes through acylation or esterization reaction [98, 99]; *N*-pivaloyl-*trans*-4-hydroxyproline-anilides (2a/2b), ester derivatives of *N*-pivaloyl-*trans*-4-hydroxyproline-3,5-dimethylanilide (3a/3b), and *N*-pivaloyl-proline-anilides (4a/4b) have been used to differentiate DNB-amino acids, and DNB-amino acids (5a/5b), amide derivatives of DNB-leucine (6a/6b and 8a/8b) and amide derivatives of DNB-phenylglycine (7a/7b) have been found to possess chiral recognition ability on a number of chiral analytes by Koscho's group [28-32]; and compounds (9a/9b), variants of Marfey's reagent N_{α}-(2,4-dinitro-5-fluorophenyl)-D-leucinamide and N_{α}-(2,4-dinitro-5-fluorophenyl)-L-valinamide, possess chiral recognition ability towards all 19 chiral proteinogenic amino acids [100]. Two mass-tagged enantiomeric substrates have also been used to screen chiral catalysts in asymmetric synthesis through monitoring the ESI-MS spectra of mass-tagged enantiomeric products or intermediates [101-108].

With the increasing demand for chiral analysis of a large number of samples, a high throughput screening system for chiral recognition has been developed by Schug and co-workers [58, 60, 109]. This system was based on dynamic titration using ESI-MS, where the dissociation constant was determined from the concentration dependence of complex formation. Another high-throughput system based on the pseudo-enantiomer mass-tagged method has also been

developed [110]. This system combined the ESI-MS analysis with a liquid-handling system and a comprehensive processing equipment, allowing ee determination of a large number of samples.

2.2 Determination of enantiomeric excess (ee)

Enantiomeric composition is commonly expressed as enantiomeric excess (ee), which reflects the degree to which a sample contains one enantiomer in greater amounts than the other [111]. It is defined as the absolute difference between the mole fraction of each enantiomer, that is ([R]-[S])/([R]+[S]), where [R] and [S] are the respective fractions of enantiomers in a mixture. It should be noted that such definition is very different from that for common chemical compositions. As shown in equation (3), the relationship between ee and [R]/[S], which usually corresponds to the intensity ratio of the two diastereomers in the spectra, is a reciprocal relationship.

$$ee = \frac{[R] - [S]}{[R] + [S]} = \frac{[R]/[S] - 1}{[R]/[S] + 1} = \frac{([R]/[S] + 1) - 2}{[R]/[S] + 1} = 1 - \frac{2}{[R]/[S] + 1} \quad (3)$$

For the indirect method based on two measurements, the relationship between RPI and ee (or mole fraction of one enantiomer of analyte) was reported to be linear in several previous publications [46, 47, 51, 54]. However, as discussed above, the relationship between RPI and

ee should not be directly linear, and a linear calibration curve for ee determination could be obtained after some mathematical transformation (see details in part 4.1.2).

For the enantiomer-labeled host method, except for the linear relationship between IRIS and ee obtained by data fitting [62, 89], intensity excess (Ie), defined as $(I_R-I_S)/(I_R+I_S)$, was introduced to allow a simple linear plot between intensity excess (Ie) and ee [65, 90, 91]. The ee of an unknown sample could be determined using equation (4), where Ie_{100} is the value of Ie for 100% ee analyte.

$$\% \text{ ee} = \frac{|\text{Ie}|}{|\text{Ie}_{100}|} \times 100 \tag{4}$$

A double labeling method, which involves mixing a pair of isotopically labeled host and optically pure isotopically labeled guest (R or S) with the guest analyte for the measurement, was developed to allow ee determination with only one single measurement [112].

For the pseudo-enantiomer mass-tagged method, the optical purity of a sample could be calculated using the following equation [98]:

$$\%\text{ee} = \left[\frac{(\text{y}-1)\cdot(\text{s}+1)}{(\text{y}+1)\cdot(\text{s}-1)} \right] \times 100 \tag{5}$$

where s is the ratio of fast and slow derivatization rate constants between the analyte and chiral selector, and y is the corrected intensity ratio determined from the observed intensity ratio and ionization correction factor (q). A calibration curve for equation (5) could be obtained with measurements of a racemic sample and a sample of known ee. This method has been

successfully used for the ee determination of amines and alcohols by using compounds (1a/1b) in Fig. 4 as the pseudo-enantiomeric selectors [98, 99]. By applying equation (5) to the enantiomer-labeled host method, since the value of s is constant and deuteration has no effect on the intensity of complex, i.e., q = 1, the linear relationship between ee and (y-1)/(y+1) (equals to the value of Ie) could be obtained [65, 90, 91].

Based on the linear relationship between mole fraction of one enantiomer and the complex intensity fraction (CIF, intensity of one selector-analyte complex divided by the sum of the intensities of both selector-analyte complexes), Zu et al. [30] proposed another calibration curve for the pseudo-enantiomer mass-tagged method, which is shown in the following equation:

$$\mathrm{CIF} = \left(\frac{\alpha - 1}{\alpha + 1}\right) X_R + \left(\frac{1}{\alpha + 1}\right) \tag{6}$$

where X_R is the mole fraction of R-analyte, and α is the enantioselectivity of MS, which is the same as the value s in equation (5). Equation (6) could be obtained from equation (5) by substituting s with α and y with CIF/(1-CIF), assuming that the four complexes (R-selector-R-analyte, R-selector-S-analyte, S-selector-R-analyte, S-selector-S-analyte) are of the same ionization efficiency. Equation (6) was used to obtain enantioselectivity α from the slope of the linear plot CIF versus X_R [31, 32].

It should be noted that the sample composition might influence the ionization correction factor due to the matrix effect. This problem was discussed in a study by Fraschetti et al [113].

Apart from the above two calibration curves (5) and (6), the linear relationships between the natural log of intensity ratio and ee [100], and the linear relationship between natural log of intensity ratio and mole fraction of one enantiomer of analyte [28, 29], were also reported. However, care should be taken when using these for chiral analysis since these relationships were built by fitting the experimental results without any theoretical deduction for confirmation.

3. Chiral recognition based on differences in thermodynamic or kinetic constants of gas phase ion-molecule reactions

3.1 Chiral recognition

This type of chiral analysis was implemented mainly by using mass spectrometers that could trap ions, including Fourier transform ion cyclotron resonance (FTICR) [114-145] and ion trap (IT) [124, 146] mass spectrometers. Triple quadrupole (QqQ) mass spectrometer was also used for this method by changing the voltage difference between the ion source and collision quadrupole [147]. Among them, FTICR-MS was most widely used due to its unique ability to passively trap ions for extended periods [148]. In fact, a comparison between FTICR-MS and IT-MS for investigating the guest exchange reaction of amino acids and β-cyclodextrin showed that the enantioselectivity obtained from FTICR-MS was better than that from IT-MS, probably due to the lower temperature of trapping cell in FTICR-MS [124].

This method was first used by Chu et al. in 1993 [114], when a significant chiral recognition of R- and S-α-(1-naphthyl)ethylammonium cation ($NapEtNH_3^+$) was observed based on

equilibrium constant of equilibrium (7), where $1_{R,R}$ and $1_{S,S}$ refer to two enantiomers of dimethyldiketopyridino-18-crown-6 and 18C6 refers to 18-crown-6. The equilibrium constant of equilibrium (8), which employed reference guest rather than reference host, could also be used to differentiate chirality of $NapEtNH_3^+$ [116].

$$[1_{S,S} + {}^{R/S}NapEtNH_3]^+ + 18C6 \rightleftharpoons 1_{S,S} + [18C6 + {}^{R/S}NapEtNH_3]^+ \quad (7)$$

$$[1_{R,R} + H + {}^{R/S}NapEtNH_2]^+ + \text{cyclohexylamine} \rightleftharpoons [1_{R,R} + H + \text{cyclohexylamine}]^+ + {}^{R/S}NapEtNH_2 \quad (8)$$

Since the equilibrium constant was directly related to free energy changes, the degree of chiral recognition could be readily quantified. This method is not limited to the host-guest system, and has also been used to assay the enantioselectiviy of Cu(I)-bis-oxazoline towards chiral alcohol, epoxides and ethers [146].

Recently, kinetic constant measurements have been more commonly used in the gas phase guest exchange reactions. Specifically, the ratio between k_L and k_D in equations (9) and (10) is employed to characterize enantioselectivity, where B is a foreign neutral reagent.

$$[H\text{-}G_D]^+ + B \rightleftharpoons [B\text{-}G_D]^+ + H \quad \text{(rate constant: } k_D\text{)} \quad (9)$$

$$[H\text{-}G_L]^+ + B \rightleftharpoons [B\text{-}G_L]^+ + H \quad \text{(rate constant: } k_L\text{)} \quad (10)$$

This methodology was developed based on the finding that the deprotonation reaction of cytochromes *c* with R-2-butylamine was much more significant than that with S-2-butylamine [115, 118]. In fact, the above guest exchange reaction was essentially a proton-transfer process mediated by a host molecule between G and B. Thus, a gaseous base alkylamine such as n-

propylamine, 2-butylamine, 1-amino-2-propanol was usually used as B. The MS spectrum acquired after the gas phase guest exchange reaction would show the signal of replaced diastereomeric ions $[B\text{-}G]^+$ and unreplaced diastereomeric ions $[H\text{-}G]^+$ with their relative intensities depending on the ee of the guest and the time of the exchange reaction. As illustrated in Figs. 5A & 5B [122], by plotting the natural log of I/I_0 (I: the intensity of $[H\text{-}G]^+$ at certain reaction time; I_0: the original intensity of $[H\text{-}G]^+$, i.e., the sum of intensity of $[B\text{-}G]^+$ and $[H\text{-}G]^+$) versus reaction time (t) for L-enantiomer and D-enantiomer of the guest, the reaction constants k_L and k_D could be obtained from the slope. It should be noted that a biexponential $\ln(I/I_0)$ versus t plot might be sometimes observed due to the presence of at least two different structures of diastereomeric ions. In this case, two constants (k_{fast} and k_{slow}) would be obtained and either k_{fast} or k_{slow} could be used to indicate enantioselectivity [129, 131-133, 137, 138, 143]. In addition, the diastereomeric ion $[H\text{-}G]^+$ is not limited to protonated dimers, protonated trimers could also be applicable in this method [136, 140, 145].

As shown in Table 1, measurement of kinetic constants for guest exchange reactions has been successfully applied in chiral analysis of amino acids, peptides, amino alcohols, amines, naphthol, and drugs, and commonly used hosts included crown ether [139], carbohydrate and its derivatives [117, 119-124, 126, 127, 131], tetra-amide macrocycle [130, 135, 140, 143, 145], and resorcinarene [125, 128, 129, 132-134, 136-138, 141, 142, 144], which possess the cavity to accommodate the guests [149]. The structural versatility resulted from the varied lateral chains and pendants allowed resorcinarene to be widely used [129, 136-138, 150]. According

to the results from Lebrilla's group [117, 119-121, 123, 131], chiral recognition of the amino acid guest with the cyclodextrin host through the guest exchange reaction could be derived from the cooperative interactions of several weak forces, such as dipole-dipole, hydrophobic, electrostatic interactions, van der Waals and hydrogen bonding, and the enantioselectivity was positively related to the size of the amino acid guest and the cavity size of the cyclodextrin host, i.e., increasing the size of amino acid could enhance enantioselectivity, while decreasing the size of cyclodextrin through derivatization could decrease the enantioselectivity. Additionally, the steric interaction between the neutral reagent and the host molecule was more important than the intrinsic basicity of the neutral reagent in the chiral recognition of the aforementioned guest exchange reaction.

3.2 Determination of ee

For the chiral analysis based on the gas phase guest exchange reaction, a linear calibration curve could be obtained between ee (or mole fraction of analyte) and the intensity ratio I/I_0 [121, 122, 127], as shown in Fig. 5C. There was no doubt that the lower the enantioselectivity was, the larger the error for the ee measurements would become. Based on the calculation of rate constants k_L and k_D, equations (11) and (12) could be obtained, where b_L and b_D refer to the intercept in the plot of natural log of I/I_0 versus reaction time for L and D-analyte.

$$I([H_L\text{-}G]) = I_0([H_L\text{-}G])e^{-k_L t+b_L} \quad (11)$$

$$I([H_D\text{-}G]) = I_0([H_D\text{-}G])e^{-k_D t+b_D} \quad (12)$$

Then, for an enantiomer mixture with ee as the enantiomeric excess of the L-enantiomer, one can write (13):

$$\frac{I}{I_0}=\frac{I([H_L\text{-}G])+I([H_D\text{-}G])}{I_0([H_L\text{-}G])+I_0([H_D\text{-}G])}=\frac{1+ee}{2}e^{-k_Lt+b_L}+\frac{1-ee}{2}e^{-k_Dt+b_D}=\frac{e^{-k_Lt+b_L}+e^{-k_Dt+b_D}}{2}+(\frac{e^{-k_Lt+b_L}-e^{-k_Dt+b_D}}{2})ee \quad (13)$$

Thus, the linear relationship between ee and intensity ratio I/I_0 was obtained. Since ee is linearly proportional to the mole fraction of one enantiomer, the linear relationship between mole fraction of one enantiomer and intensity ratio I/I_0 could also be obtained [123].

4. Chiral recognition based on differences in dissociation of diastereomers

This method is based on MS/MS experiments, with the complex ions incorporating chiral selector and analyte selected to undergo collision induced dissociation (CID). The intensity ratio of product ion to precursor ion or the intensity ratio of two branching products ions can be used to implement chiral analysis.

4.1 Enantioselectivity based on differences in the intensity ratio of product ion to precursor ion

4.1.1 Chiral recognition

In this method, the stability difference between two diastereomeric complex ions, as determined by their differences in the relative intensities of product ion to precursor ion, is used to evaluate chiral recognition, with the chiral recognition ratio (CR) described as $([\text{product ion}]/[\text{precursor ion}])_{hetero}/([\text{product ion}]/[\text{precursor ion}])_{homo}$, where hetero and homo indicate

opposite and the same configuration of the incorporating analyte and selector, respectively [151-154]. For example, for the studies with protonated trimers as the precursor ions and protonated dimers as the product ions [151, 152], CR was expressed as:

$$CR_{chiral} = \frac{\left(\left[XYH^+\right]/\left[XY_2H^+\right]\right)_{hetero}}{\left(\left[XYH^+\right]/\left[XY_2H^+\right]\right)_{homo}} = \frac{\left(\left[XYH^+\right]/\left[XY_2H^+\right]\right)_{LD} + \left(\left[XYH^+\right]/\left[XY_2H^+\right]\right)_{DL}}{\left(\left[XYH^+\right]/\left[XY_2H^+\right]\right)_{LL} + \left(\left[XYH^+\right]/\left[XY_2H^+\right]\right)_{DD}} \quad (14)$$

where X is the analyte and Y is the chiral selector. The more different is CR from unity, the larger enantioselectivity would be obtained.

As can be seen in Table 1, the CR method has been successfully applied in the chiral recognition of amino acids [151-158], drugs (atenolol, DOPA, valacyclovir, tamsulosin and zolmitriptan) [159], peptides [160], hydroxyl esters [161], dialkyl tartrates [162, 163], alcohols [164, 165] and naphthol [166] by choosing appropriate chiral selectors such as amino acids [163], modified amino acids [151, 152], melamine derivative [154], tri-/tetra-nucleotides [155, 156, 159], cinchona alkaloid derivative [160], crown ether [157], alcohols [161] and cyclodextrin [165, 166], with ESI as the ionization technique. ESI-MS/MS has been shown to allow CR measurements insensitive to the changes in the solvent or concentration conditions and chiral recognition as well as ee determination of analytes in mixtures without the need of prior separation [152, 153]. For the studies with nucleotides as the chiral selectors, the negative ion mode was used, and better enantioselectivity was obtained for aromatic and acidic amino acids than for other amino acids, which might be related to the interactions of the aromatic ring and carboxylic group of the amino acids with nucleotides [155]; in addition, DNA triplet GCA and tetranucleotides GCAA showed D-selectivity while tetranucleotides GGCA showed L-

selectivity for the studied amino acids, probably due to the thermodynamically or kinetically controlled formation of the complexes [155, 156]. In the CR method, the protonated dimers and trimers were the most commonly used precursor ions for the chiral analysis of amino acids [151, 152, 154, 158], while the loss of analyte from precursor diastereomeric complex ion was the most commonly used product ion due to its higher intensity [154-156, 159]. The metal bound dimers or trimers were also employed in some cases when no chiral recognition was observed in the protonated complexes, since metal binding could increase the energy difference between the diastereomeric complex pair [157, 160, 162, 163].

In a study by Lu and Guo [53] using FTICR-MS for chiral recognition of bornel with tryptophan and Zn^{2+}, a new approach was developed for determination of chiral discrimination. Ion *m/z* 421 of complex ion $[Zn^{2+}$+borneol+tryptophan-H$]^+$ was selected for MS/MS with the high resolution equipment, and the intensity ratio of the resulting *m/z* 421 to its isotopic form *m/z* 423 allowed chiral differentiation of borneol. The same chiral selectivity was obtained with this new approach as using the intensity ratio of product ion to precursor ion.

4.1.2 Determination of ee

The ee determination by the CR method was first developed by Yao et al. [153] in 2000 with the following dissociations:

$$X_D Y_2 H^+ \rightarrow X_D Y H^+ \quad \text{(rate constant: } k_D\text{)} \tag{15}$$

$$X_L Y_2 H^+ \rightarrow X_L Y H^+ \quad \text{(rate constant: } k_L\text{)} \tag{16}$$

According to Yao et al., the reciprocal relationship between the relative ion abundances ratio (r, also the observed dissociation efficiency) and ee could be obtained with equation (17) based on equation (3) and the fact that the sum of product and precursor ion intensities for each enantiomer was proportional to the original concentration (assuming proportional constant as *k*).

$$r = a + \frac{b}{c + ee} \tag{17}$$

where a, b, and c are constants with a = $[kk_L(1+k_D)(1+k_L)-k_D]/[k(1+k_D)(1+k_L)-1]$, b = $200k(1+k_D)(1+k_L)(k_D-k_L)/[k(1+k_D)(1+k_L)-1]^2$, and c = $100[k(1+k_D)(1+k_L)+1][k(1+k_D)(1+k_L)-1]$. When ee is much smaller than c, then equation (17) can be simplified to (18), in which r is linearly proportional to ee.

$$r = a + \frac{b}{c + ee} = \frac{ac + a \cdot ee + b}{c + ee} \approx a + \frac{b}{c} + \frac{a}{c} ee \tag{18}$$

This explains why in some cases a linear relationship between r and ee could be obtained by data fitting. By plotting the data from the aforementioned study [46], Yao et al. found that a better correlation coefficient was obtained with equation (17) than with equation (18), demonstrating that the relationship between RPI and ee ought to be nonlinear.

Assuming r_0 is the value of r for racemic mixture of analyte, i.e., $r_0 = a + b/c$, then equation (19) can be obtained from equation (17):

$$\frac{1}{r\text{-}r_0} = -\frac{c}{b} - \frac{c^2}{b} \times \frac{1}{ee} \tag{19}$$

Thus, a linear calibration curve could be obtained by plotting $1/(r-r_0)$ versus 1/ee, as illustrated in Fig. 6. This methodology has been successfully applied in the ee determination of amino acids with measurement errors of no more than 2% [153].

4.2 Enantioselectivity based on differences in relative ratio of two branching product ions

4.2.1 Chiral recognition

This method, also called kinetic method (KM), was first introduced by Cooks et al. [167] in 1994, and was first applied in chiral analysis in 1997 [168]. Chiral discrimination was achieved based on the competitive fragmentation kinetics of diastereomeric ions, and more details of this method can be found in a review by Kumar et al. [169]. The metal bound trimeric ions $[M^{II}XY_2\text{-}H]^+$ [170-193] or $[M^{I}XY_2]^+$ [130, 168, 194-196] (M^{II}, divalent metal ion, such as Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, Fe^{2+}, Ca^{2+}; M^{I}, alkaline metal ion such as Li^+, Na^+, K^+ or proton; X, chiral analyte; Y, chiral selector) were commonly used as diastereomeric ions for dissociation study in this method. Taking diastereomeric ion $[M^{II}XY_2\text{-}H]^+$ as an example, the chiral recognition process of the enantiomers via KM is shown in Fig. 7, where the intensity ratios of the product dimeric ions of the two enantiomers are compared, as given by equation (20), to indicate the chiral discrimination (r_{chiral}).

$$r_{chiral} = \frac{r_D}{r_L} = \frac{[M^{II}X_DY-H]^+ / [M^{II}Y_2-H]^+}{[M^{II}X_LY-H]^+ / [M^{II}Y_2-H]^+} \quad (20)$$

As shown in Fig. 8, dissociation of Ni^{2+} bound trimetric ions produced dimeric product ions in different ratios for (R,R)- or (S,S)-cyclopentane β-amino acid with L-Phe as the chiral selector. The ratio of $[Ni^{2+}(L\text{-Phe})(1R,2R)\text{-}H]^+$ to $[Ni^{2+}(L\text{-Phe})_2\text{-}H]^+$ ($R_{R,R}$) was 8.82, while the ratio of

$[Ni^{2+}(L\text{-}Phe)(1S,2S)\text{-}H]^+$ to $[Ni^{2+}(L\text{-}Phe)_2\text{-}H]^+$ ($R_{S,S}$) was 12.55, indicating an enantioselectivity of 0.70 [189].

Various ionization techniques, mainly ESI [170-208] and also nanoESI [209], DESI [210, 211], sonic spray ionization (SSI) [202], MALDI [187] and FAB [168], have been applied in KM for chiral recognition of various analytes, such as amino acids [170, 171, 176, 185, 204], hydrdoxy acids [172, 180], phosphoserine [194], peptides [173], chiral drugs [174, 175, 177, 186, 191, 196, 211], and sugars [178, 206, 207]. Among these ionization techniques, ESI has been most commonly used due to its stability of signals as well as wide availability and applicability. Other ionization techniques have been applied in some cases. Compared with ESI, nanoESI was shown to allow better chiral recognition of ephedrine in real samples (drug formulation Mucoseptonex E) [209]; SSI was reported to allow chiral quantification of sugars with similar accuracies [202]; MALDI is of higher throughput and gave lower but acceptable correlation coefficient values in the chiral quantification of phthaloylglutamic acid and its dimethyl ester [187]. DESI was successfully applied in chiral analysis of drugs in blood samples or commercial pharmaceutical Mucoseptonexo E, without sample preparation, suggesting a promising tool for chiral analysis of drugs in real samples [210, 211].

The chiral selectors and metal ions used in these studies are summarized in Table 1. Amino acids and modified amino acids were the commonly used chiral selectors, among which aromatic amino acids and iodinated amino acids showed improved enantioselectivity for chiral

analysis of amino acids, drugs and alcohols [183, 185, 191, 193, 204]. It was proposed that the π-π stacking interaction and the charge transfer interaction might play an important role in the stereospecificity [171]. Since the charge transfer interaction would be interrupted when the analyte and the chiral selector were of the same configuration, the heterochiral dimer complexes were more stable than homochiral dimer complexes in most cases [171, 174-177, 181-183, 185, 187, 193, 194, 197, 204]. The choice of metal ions was found to be dependent on the analytes and chiral selectors. Cu^{2+} was the optimal choice in some cases [204, 205], but it was not so good as Ni^{2+} when *N*-acetyl-amino acids were chosen as the chiral selector [175, 180], suggesting the favorable effect of Cu^{2+} coordination by NH_2 group.

In addition, in the case of chiral analysis of phosphoserine with phospho-threonine/aminoethyl-phosphonic acid as the chiral selectors, the enantioselectivity for QqQ and FTICR was reported to be the same, indicating the negligible effect of instrument in chiral analysis by the KM method [194]. The KM method has also been applied for chiral recognition of analytes in mixtures [181].

To increase the flexibility in optimizing the interactions that allow chiral discrimination, a novel variant of kinetic method was introduced by Wu et al. [198] in 2003. In this new method, a fixed (nondissociating) ligand was employed to simplify the kinetics study. With the use of complex $[M^{II}XYL\text{-}H]^+$ (L, the fixed ligand) and the competitive fragmentation of $[M^{II}XYL\text{-}$

$H]^+$ to loss of X or loss of Y, the enantiomer discrimination ($r(fixed)_{chiral}$) could be given as (21):

$$r(\text{fixed})_{\text{chiral}} = \frac{r_D}{r_L} = \frac{[M^{II} X_D L - H]^+ / [M^{II} YL - H]^+}{[M^{II} X_L L - H]^+ / [M^{II} YL - H]^+} \quad (21)$$

By using the peptide or 1,10-phen as the fixed ligand, the chiral recognition of DOPA was achieved by Wu et al. [199] and Lee et al. [205]. Chiral recognition of monosaccharide with mononucleotides as the fixed ligand and amino acid as the chiral selector was also reported [206]. More recently, the fixed ligand kinetic method with a combination of two fixed ligands was employed for chiral and isomeric differentiation of 12 diastereomeric and enantiomeric pentose isomers [207].

As discussed in some literatures [171, 179, 191, 203], the two anticipated product ions could not always be observed, i.e., in some cases, only one product ion was present in the MS/MS spectra. Thus, the KM method could not be always applicable, as compared with the CR method. However, it was believed that the chiral discrimination obtained by the KM method was less subject to internal energy effects and thus might be more structurally diagnostic [171]. In addition, according to the study by Cooks et al. [167], the use of chiral selectors with a size and functionality similar to those of the analytes could minimize the entropy effects on fragmentation of the complex ions, and facilitate formation of the complex and allow accurate measurements of relative intensity ratios since the dissociation proceeding overwhelmingly to form the more stable product ion could be avoided.

4.2.2 Determination of ee

In the KM method, ee determination is based on the logarithmic relationship between the relative ion abundance (r) and ee, resulting from the logarithmic relationship between relative ion abundance and energy change, as shown in equation (22) [171], where *R* is the gas constant,

$$\ln r = \frac{\Delta(\Delta G)}{RT_{eff}} \tag{22}$$

T_{eff} is the effective temperature of the activated complex and $\Delta(\Delta G)$ is the free energy difference between two competitive fragmentation ways. A linear relationship between natural logarithm of relative ion abundance and ee could be further obtained, as shown in equation (23),

$$\ln r = \left[\frac{\ln r_D + \ln r_L}{2}\right] + \left[\frac{\ln r_D - \ln r_L}{2}\right] ee \tag{23}$$

where r_D and r_L are the relative ion abundances for the D- and L-enantiomers, respectively. This quantitative method is called single ratio (SR) method. Quantitative chiral analysis with the fixed ligand method is mainly based on the SR method [186, 198, 205].

The SR method is not applicable when only one pure enantiomer of the analyte is available, which is the case for some drugs derived from natural products. A modified version of the SR method, i.e., quotient ratio (QR) method, was then developed by Tao et al. [197] in 2002 to overcome this drawback. In the QR method, the complex $[M^{II}X_2Y\text{-}H]^+$, rather than $[M^{II}XY_2\text{-}H]^+$, was selected to undergo CID experiments, and two enantiomerically pure chiral selectors Y_D and Y_L were employed to conduct two separate and consecutive experiments. As shown in

equation (24), rr, the ratio of the two branching ratio, was used for comparison, and the ratio of the rr values obtained with two enantiomers was used to indicate enantioselectivity.

$$rr = \frac{[M^{II}XY_D - H]^+ / [M^{II}X_2 - H]^+}{[M^{II}XY_L - H]^+ / [M^{II}X_2 - H]^+} \quad (24)$$

$$\ln rr = \left[\frac{\ln rr_D - \ln rr_L}{2}\right] ee \quad (25)$$

For the same chiral system, rr was found to equal to the square of r [197]. As shown in equation (25), where rr_D and rr_L are constants that correspond to rr values of D- and L-enantiomers of the analyte, ln rr is directly proportional to ee. A calibration curve between ln rr and ee can then be constructed with the origin and only one single enantionmeric analyte or one sample of known ee. This methodology has been successfully applied in the quantitative chiral analysis of amino acids and DOPA with both traditional KM method [197] and the fixed ligand method [199].

It should be noted that, the following assumptions have been considered necessary when employing the KM method [19]: (1) the complex must be weakly bound; (2) there should be no more competing dissociation channels, that is, only the ion $[M^{II}XY\text{-}H]^+$ and $[M^{II}Y_2\text{-}H]^+$ should be present in MS/MS spectra except for the precursor ion; (3) the reverse activation barrier should be zero; and (4) the diastereomeric ions that undergo dissociation can be characterized by an effective temperature (T_{eff}). For assumption (2), if there are additional product ions from the fragmentation of $[M^{II}XY\text{-}H]^+$ or $[M^{II}Y_2\text{-}H]^+$, the intensities of the

additional product ions can be added to the intensity of $[M^{II}XY\text{-}H]^+$ or $[M^{II}Y_2\text{-}H]^+$ so as to get the branching ratio [192, 208].

In a study by Kong [212], in addition to the two aforementioned product ions, a new product ion $[Cu^+(Pro)_2]^+$ was also observed in the on-resonance collisionally activated dissociation mass spectra of complex ions $[Cu^{2+}(Pro)_2A\text{-}H]^+$ (A, amino acid analyte) obtained using a FTICR mass spectrometer, and chiral differentiation of leucine could be achieved by comparing the intensity ratios of $[Cu^+(Pro)_2]^+$ and $[Cu^{2+}(Pro)A\text{-}H]^+$ between the two enantiomers. In another study by Wang et al. [213], analytes, e.g., amino acids, amino alcohols and amines, formed covalent complexes with L-1-(phenylsulfonyl)pyrrolidine-carbonyl chloride, and the ratio of two product ions in the MS/MS spectra of complex ions allowed chiral recognition and ee determination of the analytes. Application of the technique in biological samples, e.g., determination of the ee value of Pro in dog plasma, was investigated in this study. The branching ratio of other products ions was also be used to indicate chiral discrimination of secondary alcohols [214]. More recently, comparison of the intensity ratios of two product ions has also been used to study the enantioselective photolysis of tryptophan enantiomers complexed with serine, crown ether, sodium mediated serine, and L-alanine peptides [215-219], and the enantioselective photolysis of monosaccharides enantiomers complexed with L-tryptophan [220].

5. Chiral recognition by ion mobility mass spectrometry (IM-MS)

5.1 Chiral recognition

This method was developed based on the use of ion mobility mass spectrometry (IM-MS), which possesses the ability to separate ions through their difference in mobility. Ion mobility is related to the mass (m), charge (z), and collision cross section (CCS) of the ion, where CCS reflects the shape and size of the ion in the gas phase. Chiral recognition by IM-MS is based on the CCS difference between diastereomers consisting of enantiomer analyte and chiral selector [221-223] or the CCS difference between enantiomers in the presence of chiral modifier in the drift gas [224]. So far, three IM-MS techniques have been applied for chiral recognition, namely drift tube ion mobility mass spectrometry (DTIM-MS) [224], field asymmetric waveform ion mobility mass spectrometry (FAIM-MS) [221, 222], and travelling wave ion mobility mass spectrometry (TWIM-MS) [223].

In 2006, by introducing a chiral modifier S-(+)-2-butanol in the drift gas, Dwivedi et al. [224] first reported the use of DTIM-MS for enantiomeric separation of drugs, amino acids and carbohydrates, including atenolol, serine, methionine, threonine, methyl α-glucopyranoside, glucose, penicillamine, valinol, phenylalanine, and tryptophan. It was proposed that the stereospecific interaction with the chiral gas led to the different mobility of the enantiomers. Despite the higher ion mobility resolution of DTIM-MS than FAIM-MS and TWIM-MS [225] as well as the easy availability of CCS due to its linear relationship with drift time in DTIM-MS, no further application of DTIM-MS in chiral recognition has been reported since.

The chiral separation in FAIM-MS was first demonstrated with D- and L-lactic acid by forming complexes with L-tryptophan [226]. Following that, six pairs of amino acid enantiomers and terbutaline enantiomers have been successfully separated in FAIM-MS as metal bound trimeric complexes $[M(Ref)_2A\text{-}H]^+$, where M is a divalent metal ion, Ref is the reference amino acid that acts as the chiral selector, and A is the analyte [221, 222].

TWIM-MS was also applied in chiral recognition by Domalain et al. [223] although TWIM-MS typically has lower ion mobility resolution than DTIM-MS and FAIM-MS in the currently available commercial IM-MS instruments [225]. In this study, enantiomers of aromatic amino acids (phenylalanine, tryptophan and tyrosine) could be differentiated through complexes $[Cu^{2+}(Pro)_2A\text{-}H]^+$ (A, analyte). Better chiral separation of enantiomers was achieved for tyrosine and tryptophan than for phenylanaline (see Fig. 9 for the spectral results for phenylalanine and tryptophan). Preliminary quantum chemical calculations on the copper trimers suggested the crucial role of the intramolecular bonds between ligands in the CCS difference. In TWIM-MS, the CCS of an ion could be derived from the drift time through power function relationship [227].

5.2 Determination of ee

With the separation of two enantiomers in an IM-MS spectrum, the peak area ratio of the two enantiomers is proportional to the original concentration ratio of the two enantiomers. Thus,

the reciprocal relationship between peak area ratio and ee could be obtained based on equation (3). For the chiral analysis using FAIM-MS by Mie et al. [221, 222], when one enantiomer was in large excess (＞95%), a linear relationship was obtained between the intensity ratio of the two signals measured at two separated compensation voltages and mole fraction of the enantiomer in much less excess. This may be considered as a simplified treatment of the hyperbolic curve, as shown in equation (18). For the chiral analysis using TWIM-MS by Domalain et al. [223], through direct data fitting, linear curves were obtained by plotting the drift time of the unseparated enantiomers versus mole fraction of one enantiomer (Fig. 9B), or plotting log of peak area ratio of the two separated enantiomers versus mole fraction of one enantiomer (Fig. 9D).

6. Conclusions and prospects

Different MS methods, including single-stage MS, MS/MS and IM-MS, have been used for chiral analysis. Compared to single-stage MS, MS/MS is now more commonly used in chiral analysis since the intensity ratios obtained with MS/MS spectra are more reliable and reproducible than those with single-stage MS spectra [173]. Moreover, MS/MS analysis is independent of analyte concentration while single-stage MS analysis is typically related to the analyte concentration [152, 171]. However, single-stage MS is preferred for investigation of solution-based chiral recognition mechanism since enantioselective binding and solvent/solution influence could be preserved and measured in single-stage MS, while these information could be lost in MS/MS experiments [59]. For the recently developed IM-MS, its

applications in chiral analysis are still very limited. Improvement in instrument resolution to allow differentiation of diastereomers with small CCS difference is needed to expand IM-MS for chiral analysis.

Although MS has been demonstrated as a powerful and promising tool for chiral recognition and ee determination, some issues in this field need to be addressed. For example, further clarification is needed for quantitative relationships in ee determination, since different strategies of constructing calibration curves are present and some of them were just obtained from fitting experimental data without mathematical derivations. Moreover, further investigation and comparison of different chiral MS methods will enable us to choose the appropriate MS methods and selectors for chiral analysis, and get more insight about the mechanism and fundamental of chiral recognition. The capability of IM-MS in measuring the size of diastereomeric complexes might provide a new strategy for investigation of recognition mechanism. Combination of mass spectrometry with other technologies, such as infrared multiple photon dissociation spectroscopy [228-230], resonance-enhanced multiphoton ionization spectroscopy [231, 232] and circular dichroism [233, 234], provided new approaches for chiral analysis and could be further explored. Furthermore, so far, most chiral MS studies have been based on pure model chiral compounds. Extending chiral MS techniques to solve real-life problems, particularly for chiral analysis of complex samples, should be pursued, and development of versatile and highly selective chiral selectors is highly recommended.

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Table 1. Summary of chiral recognitions by mass spectrometry

Analyte	Chiral selector	Ionization mode	Method[a]	Enantioselectivity	Reference
alkylammonium ions	modified β-mannofuranoside/crown ether	FAB	IDM	0.9~1.6	[39, 41]
	diketopyridino-18-crown-6	FAB/ESI	IDM	0.12~3.3	[44, 47]
		ESI	IMR	0.23~4	[114, 116]
	crown ether	FAB	DM	0.37~2	[62, 89]
	saccharide derivative	FAB	DM	1.5	[90]
natural amino acids (Ala, Arg, Asn, Asp, Cys, Glu, Gln, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val)	2-methyl-1-butanol	CI	IDM	1.4~3.11	[33]
	mandelic acid/methylbutonic acid/α-phenylethylamine	CI	IDM	0~6.47	[35]
	α/β-cyclodextrin (CD)	ESI	IDM	1~2	[51]
	Cu + bipyridine derivative	ESI	IDM	1.1~2	[54]
	antimony-tartrate	ESI	IDM	1.16-1.77	[55]
	α/β/γ-CD	MALDI	DM	0.73~0.9	[85]
	glucosylthioureidocalixarene	ESI	DM	0.61-2.56	[94]
	β-CD/2,3,6-tri-O-methyl-β-CD	ESI	IMR	0.56~5.3	[117, 120, 131]
	permethylated β-CD/maltoheptaose	ESI	IMR	0.4~4.9	[119, 121, 124]
	resorcinarene	ESI	IMR	0.49~1.64	[128, 129, 132, 133, 144]
	tetra-amide macrocycles	ESI	IMR	0.45~1.5	[135, 140, 143]
	N-tert-butoxycarbonyl-Phe/-Pro/-O-benzylserine	ESI	CR	0.494~4.316	[151, 152]
	melamine derivatives	ESI	CR	0.51~1.76	[154]
	DNA triplet GCA	ESI	CR	1.1~6.4	[155]
	DNA tetranucleotides	ESI	CR	0.25~3.1	[156]
	camphor	ESI	CR	1.18	[158]
	crown ether	ESI	CR	unshown	[157]
	amino acid	ESI	KM-SR	0.645~1.233	[168]

	Cu + amino acid	ESI	KM-SR	0.47~11	[170, 171, 181]
	Ni + amino acid	ESI	KM-SR	0.73~7.86	[176]
	Cu/Ni + F/Cl/Br/I-substituted Phe/Tyr	ESI	KM-SR	1.4~15.8	[185, 204]
	Cu/Zn + amino acid	ESI	KM-QR	0.109~15.4	[197]
	Cu + amino acid + Ala-Ala	ESI	KM-QR	0.0813~0.398	[199]
	2-butanol	ESI	IM-MS	[b]	[224]
	Mg/Cu/Ni/Zn + amino acid	ESI	IM-MS	[b]	[221, 223]
non-natural amino acids (homoserine, allo-threonine, allo-isoleucine, *cis*-4-hydroxyproline, phosphoserine)	permethylated β-CD	ESI	IMR	1.4~22	[126]
	resorcinarene	ESI	IMR	0.4~1.22	[133]
	(1-aminoethyl)phosphonic acid/phosphothreonine	ESI	KM-SR	0.65~0.88	[194]
DNB-amino acid	cinchona alkaloids	ESI	IDM	1.1~17	[27]
		ESI	DM	3~25	[66]
amino acid esters	crown ether	ESI	DM	0.61~1.64	[64, 80]
	resorcinarene	ESI	IMR	0.51~0.84	[133, 144]
	tetra-amide macrocycles	ESI	IMR	0.14~1.47	[135, 143]
		ESI	KM-SR	0.8~5	[135]
amino acid ester hydrochlorides	crown ether	FAB	IDM	1.6	[42]
		FAB	DM	0.5~1.9	[61, 63, 91]
	monosaccharides	FAB	IDM	~0.7	[71]
	linear/cyclic oligosaccharides	FAB	DM	0.14~3.72	[73-77, 79, 82]
β-amino acids	crown ether	ESI	IMR	0.5~1.84	[139]
	Cu/Ni + amino acid	ESI	KM-SR	0.5~2.68	[188, 189]
amino alcohols	resorcinarene	ESI	IMR	0.47~3.94	[141, 144]
	Cu/Ni + Phe/Tyr/I-substituted Phe or Tyr	ESI	KM-SR	1.11~2.36	[193]
	2-butanol	ESI	IM-MS	[b]	[224]

dialkyl tartrates		Li+threhydrobenzoin (THB)	FAB	CR	2~3	[162]
		Zn+tryptophan	ESI	CR	0~1.98	[163]
α-hydroxy acids		2-methyl-1-butanol	CI	IDM	> 9	[33]
		Co + amino acid	ESI	KM-SR	0.67~1.43	[172]
		Cu/Co/Zn/Ni + acetyl amino acid	ESI	KM-SR	0.65~7.32	[180]
hydroxyl esters		(2S,3S)-butanediol	NICI	CR	0.7/2	[161]
monosaccharides		Cu/Zn/Co/Ni + modified amino acid	ESI	KM-SR	0.26~1.68	[178]
		2-butanol	ESI	IM-MS	[b]	[224]
peptides		permethylated β-cyclodextrin/maltoheptaose	ESI	IMR	0.3~7.24	[127]
		resorcinarene	ESI	IMR	0.1~4.7	[138]
		tert-butylcarbamoylquinine	ESI	CR	0.87~1.23	[160]
		Cu + amino acid/dipeptide	ESI	KM-SR	0.427~6.22	[173]
primary and secondary amines		phorsaeure-(1,1'-binaphthyl-2,2'-diylester)	FAB	IDM	0.23	[46]
		tetra-amide macrocycles	ESI	IMR	0.62~0.87	[130]
			ESI	KM-SR	~4	[130]
secondary alcohols		2-phenylbutyric anhydride	CI	IDM	0~25	[35]
		diacetoxysuccinic/dibenzoyloxysuccinic anhydride	FAB	IDM	0.03 ~ >10	[40]
		Ni + BINOLato	ESI	KM	0.86~1.44	[214]
naphthol		heptakis-(2,6-di-O-methyl)-β-CD	ESI	CR	2.64	[166]
		tetra-amide macrocycles	ESI	IMR	0.7	[143]
Drugs	amphetamine	permethylated β-cyclodextrin/maltoheptaose	ESI	IMR	0.9~1.46	[122]
	atenolol	Cu + abrine	ESI	KM-SR	1.74	[174]
		Cu + iodo-Phe/diiodo-Tyr	ESI	CR	0.33/0.36	[191]
		2-butanol	ESI	IM-MS	[b]	[224]
	DOPA	permethylated β-cyclodextrin/maltoheptaose	ESI	IMR	0.93~4.98	[122]
		resorcinarene	ESI	IMR	0.69~2.68	[128, 129, 133]
		Cu + Tyr	ESI	KM-SR	5.52	[174]

	Cu + amino acid + Ala-Ala	ESI	KM-QR	0.0581~0.463	[199]
	Cu/Mn/Fe + amino acid + 1,10-phen	ESI	KM-SR	0.36~3	[205]
	Cu + iodo-Phe/diiodo-Tyr	ESI	KM-SR	11.2/12.75	[191]
ephedrine	permethylated β-cyclodextrin/maltoheptaose	ESI	IMR	0.78~0.83	[122]
	Cu + Trp	ESI	KM-SR	3.4	[174]
Flindokalner	Li + 5-fluorodeoxyuridine	ESI	KM-SR	1.75~1.95	[196]
2'-Fluoro-5-methyl-β-arabinofuranosyluracil	Cu/Co/Zn/Ni + Acetyl-Phe/Acetyl-Pro/thymidine/Ile	ESI	KM-SR	0.81~3.15	[175]
ibuprofen	Cu/Co/Zn + monosaccharide	ESI	KM-SR	0.75~1.07	[182]
isoproterenol	Cu + abrine	ESI	KM-SR	1.54	[174]
	Cu + iodo-Phe/diiodo-Tyr	ESI	KM-SR	1.34/1.19	[191]
norepinephrine	Cu + Phe	ESI	KM-SR	1.24	[174]
penicillamine	permethylated β-cyclodextrin/maltoheptaose	ESI	IMR	1.85~6.18	[122]
	2-butanol	ESI	IM-MS	[b]	[224]
pramipexole	Cu + iodo-Phe/diiodo-Tyr	ESI	CR	1.12/1.18	[191]
pregabalin	Cu + iodo-Phe/diiodo-Tyr	ESI	KM-SR	0.8/0.68	[191]
propranolol	Cu + His	ESI	KM-SR	0.43	[174]
	Cu + iodo-Phe/diiodo-Tyr	ESI	CR	0.54/0.49	[191]
pseudoephedrine	Cu + Trp	ESI	KM-SR	2.05	[174]
tamslosin	Cu + iodo-Phe/diiodo-Tyr	ESI	CR	0.88/0.77	[191]
tenofovir	Cu + iodo-Phe/diiodo-Tyr	ESI	CR	1.28/2.05	[191]
terbutaline	Cu/Mg + amino acid	ESI	IM-MS	[b]	[222]
thalidomide	Cu/Co/Zn/Ni + α-hydroxy acids/monosaccharide	ESI	KM-SR	0.17~1.34	[177]
thyroxine (T4)	Cu/Mn/Ga/Ni/Zn + amino acid + dipeptide	ESI	KM-SR	0.46~3.03	[186]
tropine	α/β/γ-CD	ESI	CR	1.17~2.40	[165]

	valacyclovir	Cu + iodo-Phe/diiodo-Tyr	ESI	CR	1.2/1.44	[191]
	zolmitriptan	Cu + iodo-Phe/diiodo-Tyr	ESI	CR	0.8/0.27	[191]

[a] IDM/DM refers to indirect/direct method of chiral recognition based on difference in relative abundances of diastereomers; IMR refers to chiral recognition based on differences in thermodynamic or kinetic constants of gas phase ion-molecule reaction; CR refers to chiral recognition based on differences in the intensity ratio of product ion to precursor ion; KM-SR/KM-QR refers to single ratio/quotient ratio method of chiral recognition based on difference in relative ratio of two branching product ions; IM-MS refers to the chiral recognition by ion mobility mass spectrometry.

[b] Different from that for other MS methods, the enantioselectivity described in IM-MS method is based on the enaniomeric or diastereomeric separation in the IM-MS spectra (see the context).

Figure captions

Fig. 1. ESI mass spectra of (A) [Cu(L-Phe-H)chiragen]$^{+\cdot}$ and (B) [Cu(D-Phe-H)chiragen]$^{+\cdot}$ in 100% CH_3OH with [Cu(d_5-L-Phe-H)chiragen]$^{+\cdot}$ as the internal standard complex, and ESI mass spectra of (C) [Cu(L-Trp-H)chiragen]$^{+\cdot}$ and (D) [Cu(D-Trp-H)chiragen]$^{+\cdot}$ in 100% CH_3OH with Cu(5-F-L-Trp-H)chiragen]$^{+\cdot}$ as the internal standard complex. Reprinted from ref. 52 with permission from John Wiley and Sons.

Fig. 2. Schematic depiction of the enantiomer-labeled host method (A) and enantiomer-labeled guest method (B). With the enantiomer labeling, two mass-shifted H-G diastereomers simultaneously appear in a single-stage MS spectrum, and the ratio of their peak intensities, termed as the IRIS value, reflects the enantioselectivity. The IRIS value closer to unity indicates smaller chiral discrimination.

Fig. 3. ESI-MS analysis of (a) (S)-[(2-Methoxyphenoxy)methyl]-15-crown-5 ((S)-1), D-AlaOMe·HCl and D-AlaOMe-d_3·HCl, and (b) (S)-1, L-AlaOMe·HCl and D-AlaOMe-d_3·HCl. Reprinted from ref. 58 with permission from Springer.

Fig. 4. Summary of the structures of pseudo-enantiomeric selectors developed for chiral recognition. 1a, *N*-benzoyl-(S)-proline, 1b, *N*-4-methylbenzoyl-(R)-proline; 2a, *N*-pivaloyl-*trans*-(2S, 4R)-4-hydroxyproline-3,5-dimethylanilide, 2b, *N*-pivaloyl-*trans*-(2R, 4S)-4-hydroxyproline-4-methylanilide; 3a/3b, ester derivatives of *N*-pivaloyl-*trans*-4-hydroxyproline-3,5-dimethylanilide; 4a, *N*-pivaloyl-(S)-proline-3,5-dimethylanilide, 4b, *N*-pivaloyl-(R)-proline-4-methylanilide; 5a/5b, *N*-(3,5-dinitrobenzoyl) amino acids (DNB-amino acids); 6a/6b and 8a/8b, amide derivatives of DNB-leucine; 7a/7b, amide

derivatives of DNB-phenylglycine; 9a, N_α-(2,4-dinitro-5-fluorophenyl)-D-leucinamide, 9b, N_α- (2,4-dinitro-5-fluorophenyl)-L-valinamide.

Fig. 5. ESI-FTICR mass spectra of a solution containing β-cyclodextrin and amphetamine (AMP) at various reaction times (the complex $[CD:AMP+H]^+$ was isolated and allowed to react with n-propylamine(NPA)) (A); rate plot of the reaction illustrated in A for both enantiomers (r^2=0.999, a, d-AMP, b, l-AMP) (B); and calibration curve for amphetamine (C) (I: intensity of $[CD:AMP+H]^+$; I_0: sum of the intensities of $[CD:NAP+H]^+$ and $[CD:AMP+H]^+$). Reprinted from ref. 114 with permission from American Chemical Society.

Fig. 6. ESI-MS/MS spectrum of protonated trimer from a mixture of His (L:D = 0.05:0.95) and D-*N*-tert-butoxycarbonyl-O-benzylserine (D-BBser) (A) and plot of $1/(r-r_0)$ as a function of 1/ee for L-His with D-BBSer as the chiral selector, where r_0=0.4590 (B). Reprinted from ref. 145 with permission from American Chemical Society.

Fig. 7. Schematic depiction of the chiral recognition via KM (X: chiral analyte; M: metal ion; Y: chiral selector; *k*: rate constant). The difference in intensity ratios of the product dimeric ions for two enaniomers of the analyte allows chiral recognition.

Fig. 8. CID spectra of trimeric Ni^{2+}-bound complexes: (a) trans-(1R,2R) and (b) trans-(1S,2S) enantiomers of cyclopentane β-amino acid. Reprinted from ref. 182 with permission from John Wiley and Sons.

Fig. 9. Drift time plot obtained for each proportion of the D- and L-Phe for the complex ion $[Cu^{II}+(^{D}Pro)_2+^{D/L}Phe-H]^+$(A); calibration curve between the mole fraction of L-Phe and drift time of

the complex ion $[Cu^{II}+(^{D}Pro)_2+^{D/L}Phe-H]^+$ (B); drift time plot obtained for each proportion of the D- and L-Trp for the complex ion $[Cu^{II}+(^{D}Pro)_2+^{D/L}Trp-H]^+$ (C); calibration curve between the mole fraction of L-Trp and log of peak ratio, where A(^{L}Trp) and A(^{D}Trp) are the areas of the peaks corresponding to complex ion containing L/D-Trp (D). Reprinted from ref. 210 with permission from The Royal Society of Chemistry.

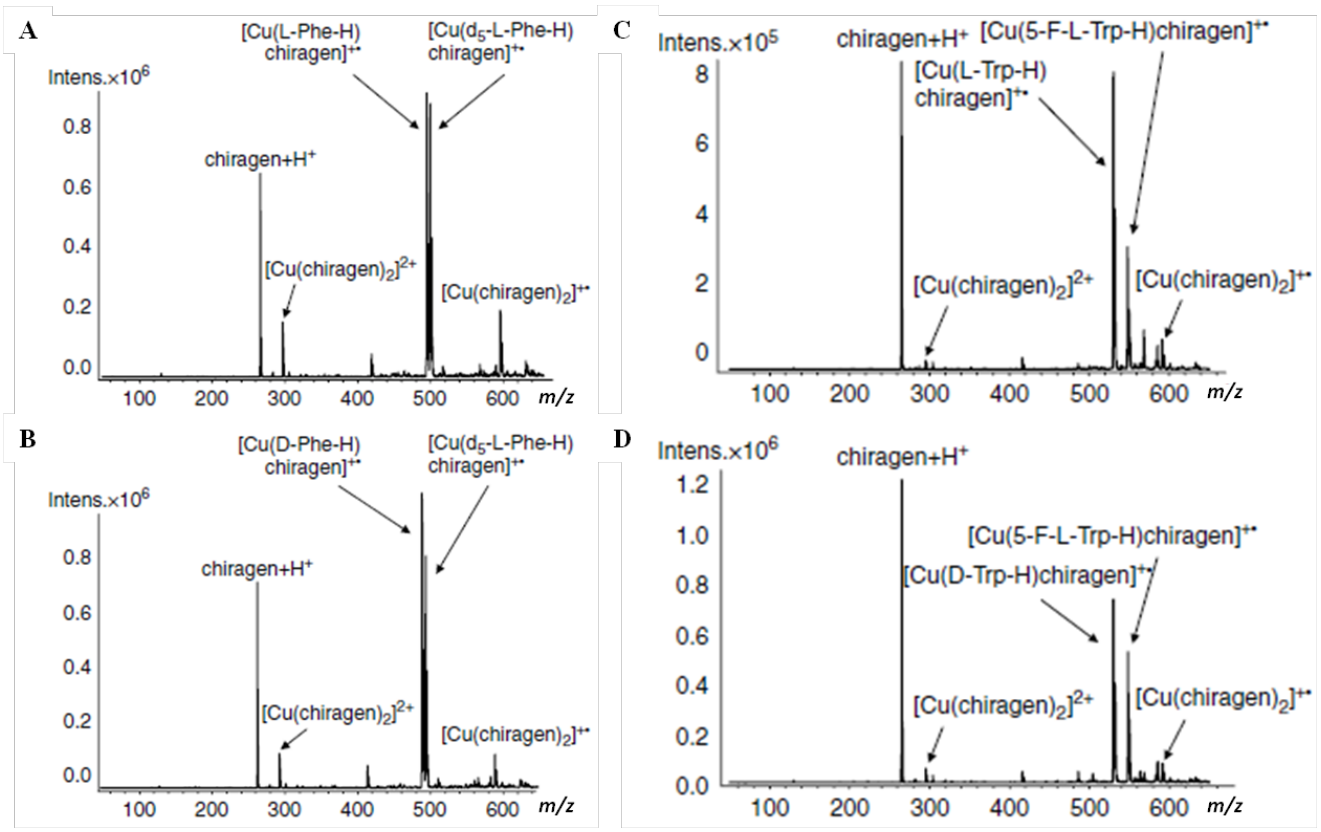
A
[Cu(L-Phe-H) chiragen]+•
[Cu(d5-L-Phe-H) chiragen]+•
Intens.×10^6
chiragen+H+
[Cu(chiragen)2]2+
[Cu(chiragen)2]+•
m/z
B
[Cu(D-Phe-H) chiragen]+•
[Cu(d5-L-Phe-H) chiragen]+•
Intens.×10^6
chiragen+H+
[Cu(chiragen)2]2+
[Cu(chiragen)2]+•
m/z
C
Intens.×10^5
chiragen+H+
[Cu(5-F-L-Trp-H)chiragen]+•
[Cu(L-Trp-H) chiragen]+•
[Cu(chiragen)2]2+
[Cu(chiragen)2]+•
m/z
D
Intens.×10^6
chiragen+H+
[Cu(5-F-L-Trp-H)chiragen]+•
[Cu(D-Trp-H)chiragen]+•
[Cu(chiragen)2]2+
[Cu(chiragen)2]+•
m/z

Fig. 1

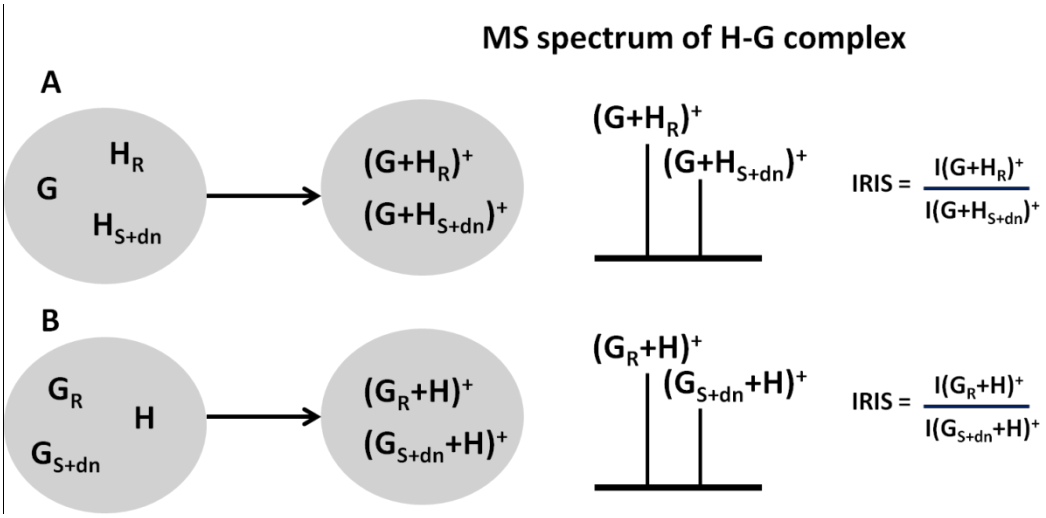
MS spectrum of H-G complex
A
G
H_R
H_{S+dn}
$(G+H_R)^+$
$(G+H_{S+dn})^+$
$(G+H_R)^+$
$(G+H_{S+dn})^+$
$IRIS = \frac{I(G+H_R)^+}{I(G+H_{S+dn})^+}$
B
G_R
G_{S+dn}
H
$(G_R+H)^+$
$(G_{S+dn}+H)^+$
$(G_R+H)^+$
$(G_{S+dn}+H)^+$
$IRIS = \frac{I(G_R+H)^+}{I(G_{S+dn}+H)^+}$

Fig. 2

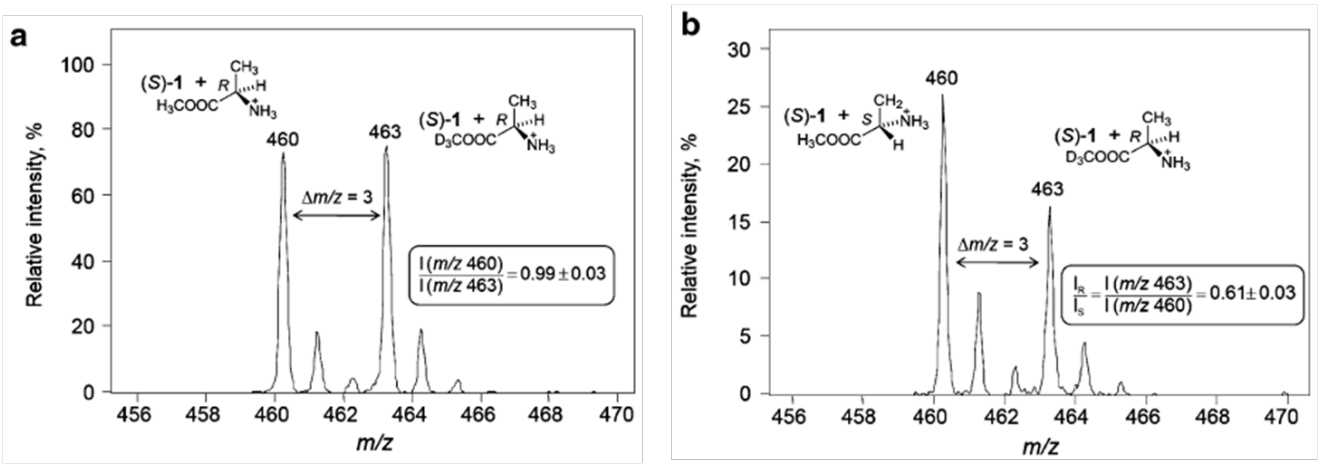
a
b
Relative intensity, %
m/z
460
463
Δm/z = 3
(S)-1 + R H3COOC CH3 NH3
(S)-1 + R D3COOC CH3 NH3
(S)-1 + S H3COOC CH2 NH3 H
I(m/z 460) / I(m/z 463) = 0.99 ± 0.03
I_R / I_S = I(m/z 463) / I(m/z 460) = 0.61 ± 0.03

Fig. 3

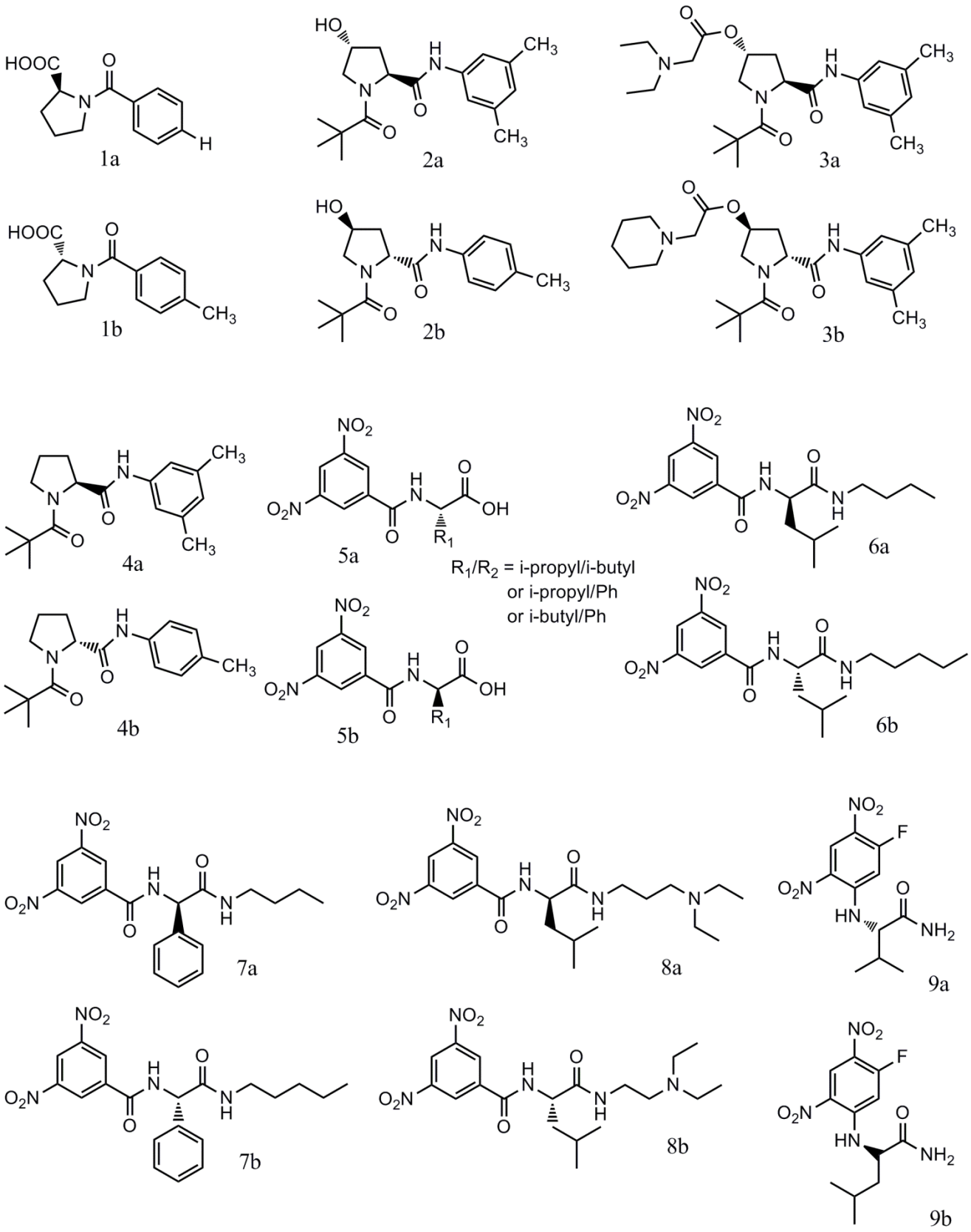
1a
2a
3a
1b
2b
3b
4a
5a
6a
4b
5b
6b
R1/R2 = i-propyl/i-butyl
or i-propyl/Ph
or i-butyl/Ph
7a
8a
9a
7b
8b
9b

Fig. 4

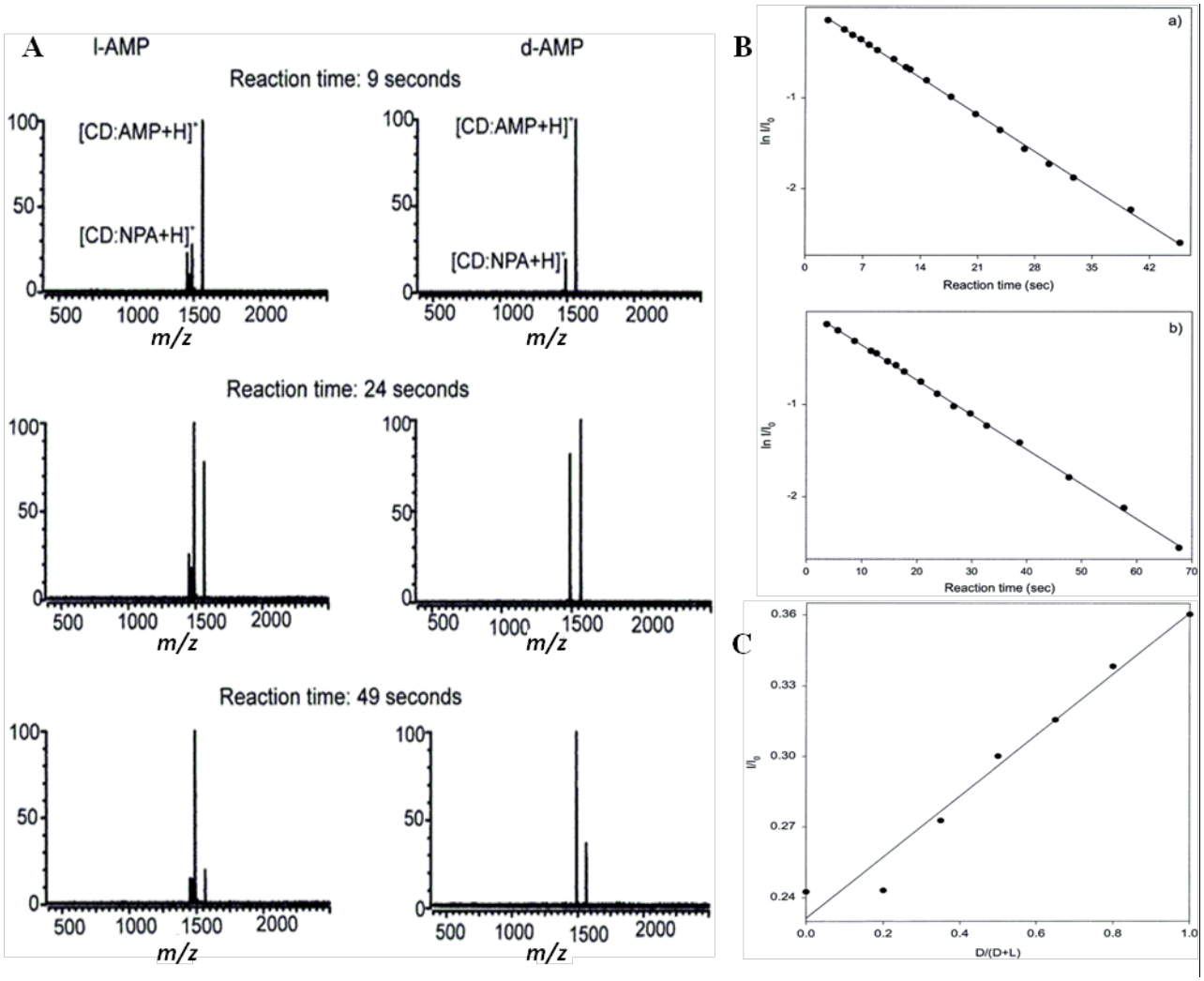
A
l-AMP
d-AMP
Reaction time: 9 seconds
[CD:AMP+H]+
[CD:NPA+H]+
Reaction time: 24 seconds
Reaction time: 49 seconds
m/z
B
a)
b)
ln I/I0
Reaction time (sec)
C
I/I0
D/(D+L)

Fig. 5

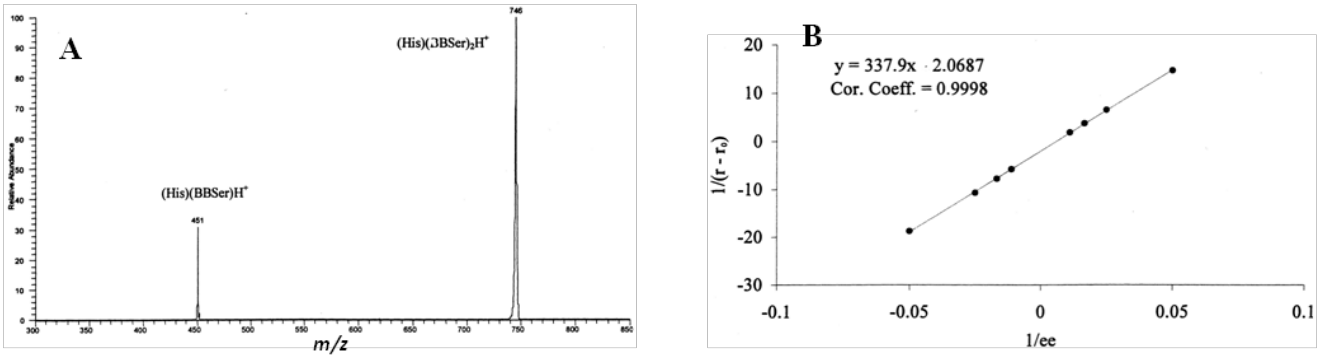
A
(His)(BBSer)H+
451
(His)(BBSer)2H+
746
m/z
B
y = 337.9x - 2.0687
Cor. Coeff. = 0.9998
1/(r - r0)
1/ee

Fig. 6

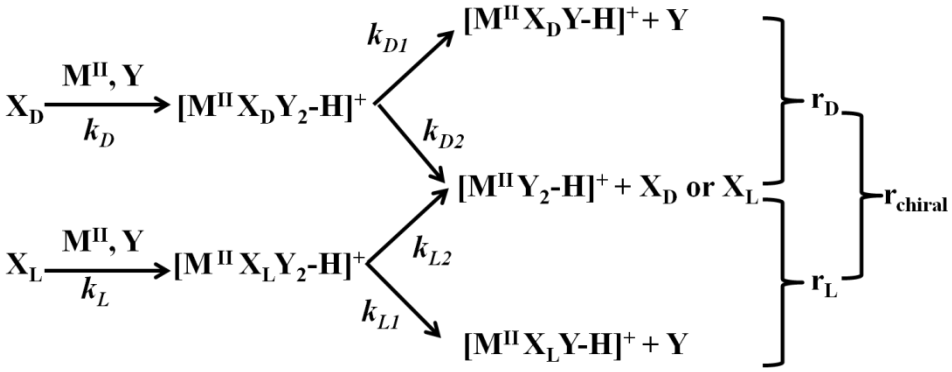
X_D
M^{II}, Y
k_D
$[M^{II}X_DY_2\text{-}H]^+$
k_{D1}
$[M^{II}X_DY\text{-}H]^+ + Y$
k_{D2}
$[M^{II}Y_2\text{-}H]^+ + X_D$ or X_L
X_L
M^{II}, Y
k_L
$[M^{II}X_LY_2\text{-}H]^+$
k_{L2}
k_{L1}
$[M^{II}X_LY\text{-}H]^+ + Y$
r_D
r_L
r_{chiral}

Fig. 7

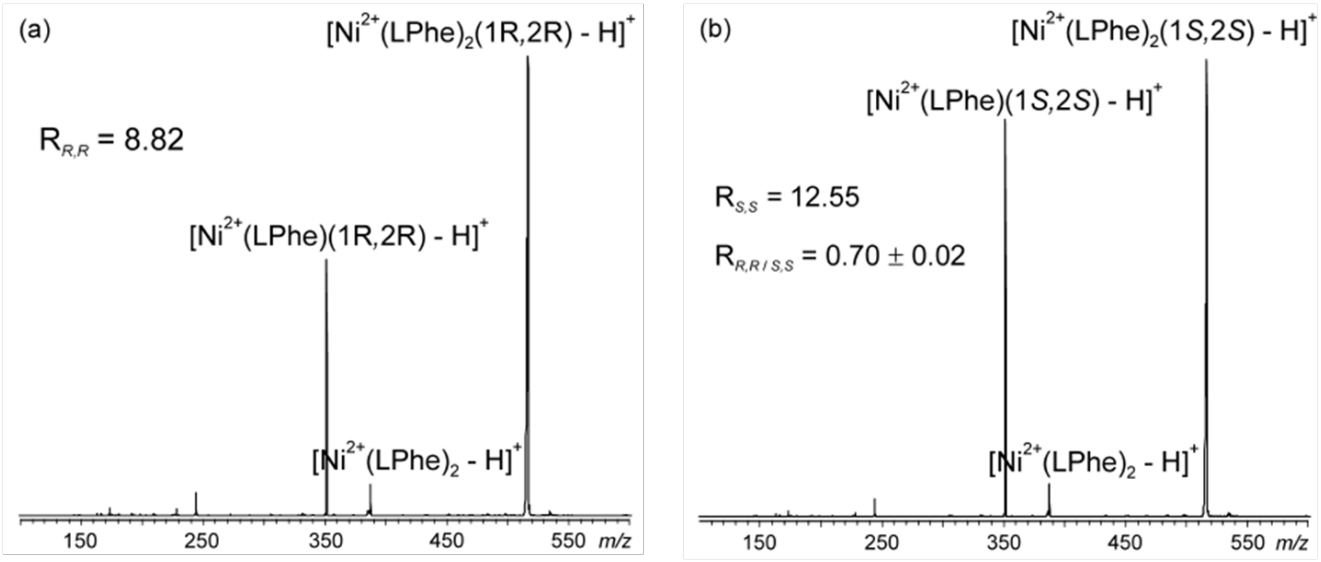
(a)
[Ni2+(LPhe)2(1R,2R) - H]+
RR,R = 8.82
[Ni2+(LPhe)(1R,2R) - H]+
[Ni2+(LPhe)2 - H]+
150
250
350
450
550 m/z
(b)
[Ni2+(LPhe)2(1S,2S) - H]+
[Ni2+(LPhe)(1S,2S) - H]+
RS,S = 12.55
RR,R / S,S = 0.70 ± 0.02
[Ni2+(LPhe)2 - H]+
150
250
350
450
550 m/z

Fig. 8

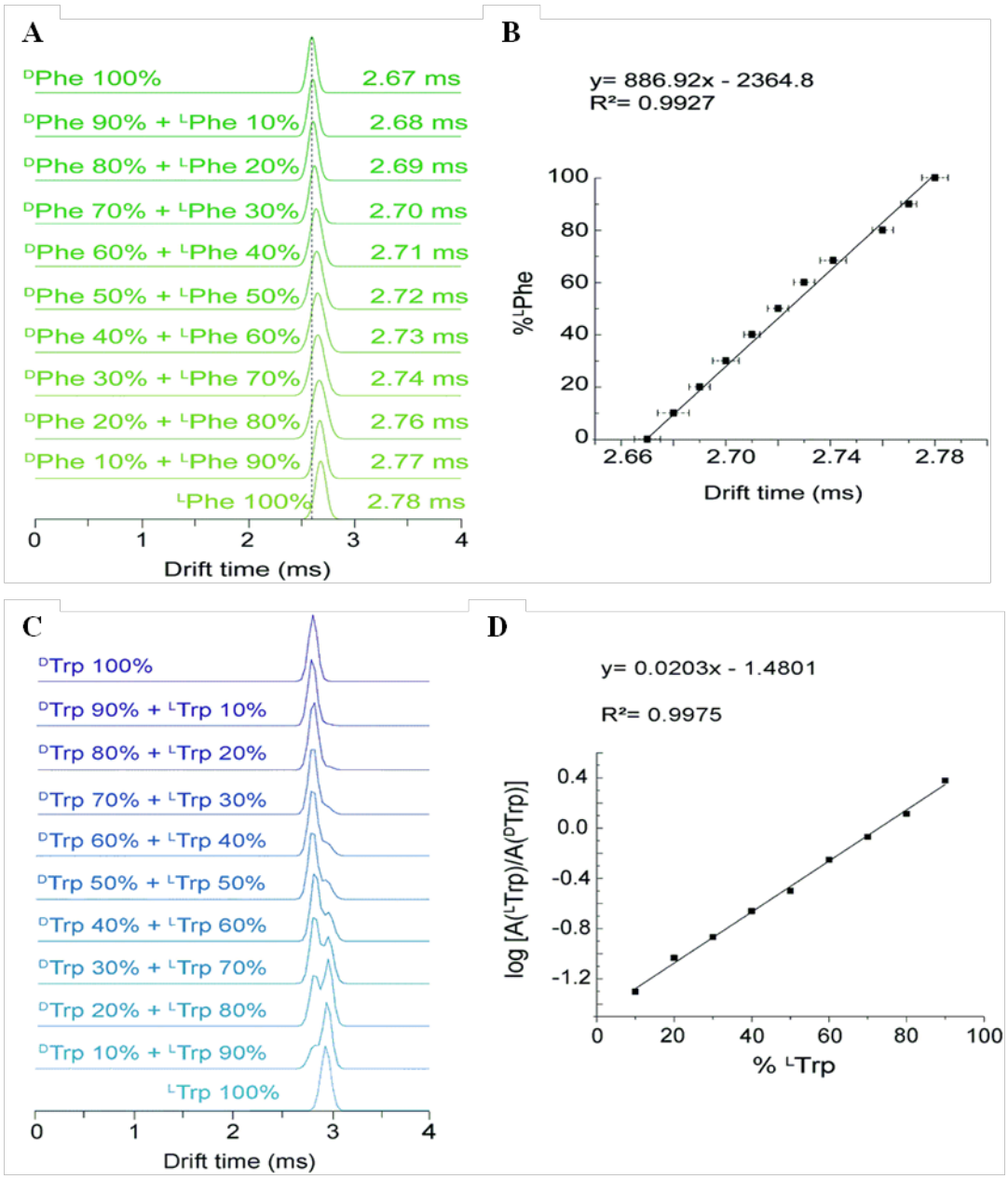
A
ᴰPhe 100%
2.67 ms
ᴰPhe 90% + ᴸPhe 10%
2.68 ms
ᴰPhe 80% + ᴸPhe 20%
2.69 ms
ᴰPhe 70% + ᴸPhe 30%
2.70 ms
ᴰPhe 60% + ᴸPhe 40%
2.71 ms
ᴰPhe 50% + ᴸPhe 50%
2.72 ms
ᴰPhe 40% + ᴸPhe 60%
2.73 ms
ᴰPhe 30% + ᴸPhe 70%
2.74 ms
ᴰPhe 20% + ᴸPhe 80%
2.76 ms
ᴰPhe 10% + ᴸPhe 90%
2.77 ms
ᴸPhe 100%
2.78 ms
0 1 2 3 4
Drift time (ms)
B
y= 886.92x - 2364.8
R²= 0.9927
%ᴸPhe
100 80 60 40 20 0
2.66 2.70 2.74 2.78
Drift time (ms)
C
ᴰTrp 100%
ᴰTrp 90% + ᴸTrp 10%
ᴰTrp 80% + ᴸTrp 20%
ᴰTrp 70% + ᴸTrp 30%
ᴰTrp 60% + ᴸTrp 40%
ᴰTrp 50% + ᴸTrp 50%
ᴰTrp 40% + ᴸTrp 60%
ᴰTrp 30% + ᴸTrp 70%
ᴰTrp 20% + ᴸTrp 80%
ᴰTrp 10% + ᴸTrp 90%
ᴸTrp 100%
0 1 2 3 4
Drift time (ms)
D
y= 0.0203x - 1.4801
R²= 0.9975
log [A(ᴸTrp)/A(ᴰTrp)]
0.4 0.0 -0.4 -0.8 -1.2
0 20 40 60 80 100
% ᴸTrp

Fig. 9