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Improvements in quantitative chiral determinations using the mass spectrometric kinetic method

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Abstract

A significant shortcoming of the kinetic method for determining chiral purity from the competitive dissociation of a metal complex chelated with a chiral analyte and chiral reference is that it does not give useful quantitative data for high purity chiral samples in comparison to the standard chiral chromatography techniques. To extend the range of applications of the kinetic method to high chiral purity samples, a "vernier" method is reported which gives more accurate quantitative data for samples covering a narrow range of chiral purity. This is demonstrated for the case of a model amino acid in which Ni^{II} is used as the metal cation, asparagine as the chiral reference, and the analyte is tryptophan. By selecting experimental conditions to give a measured peak abundance ratio near unity for the two competitive fragments (where abundance ratios are more accurately measured than at higher or lower values), samples of high (90–100%) chiral purity were more accurately assayed in the experiment using pure tryptophan. By switching the chirality of the reference compound, samples in the low (0–10%) chiral purity range could also be more precisely measured. The quantitative improvement in accuracy of the chiral measurement is shown by the average accuracy of 0.51% deviation (for the 90–100% chiral purity range of tryptophan using L-Asn as chiral reference) in comparison to the average deviation of 104.1% in the non-vernier region (the region that falls outside the high accuracy region of interest).

Keywords: Chiral analysis; Kinetic method; Tandem mass spectrometry; Cluster ions; Chiral chromatography

1. Introduction

Nature uses chirality to maximize specificity in chemical interactions. The observation of chirality in organic complexes was first announced by Louis Pasteur in 1861 to the Chemical Society of Paris in his famous lecture, *Molecular Asymmetry of Natural Organics* [1]. This was the first public description of the manual separation of right and left handed tartaric acid. Lord Kelvin later coined the term chirality and subsequently defined it as, "any geometrical figure or any group of points, is chiral and has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself", a definition that is still applicable [2]. Optical activity experiments, conducted by Jean Baptiste Biot, confirmed that tartaric acid, obtained from a recrystallization reaction, was in the racemic form when dissolved and analyzed in an optical polarizing apparatus [3].

Approximately 100 years after the discovery of chirality the importance of this breakthrough is more evident than ever. This finding has shaped and continues to shape the chemical and pharmaceutical industries [4,5], and one result is the importance of analytical methodologies to quantify the chiral purity (the percentage of one pure enantiomer over the total enantiomeric contribution) of natural and non-natural chiral compounds [6]. The exploitation of chirality in the pharmaceutical industry is based on high selectivity drug/target interactions that are often strongly influenced by stereospecificity [7,8]. Luckily, the analytical methods that measure chiral purity have advanced from the original optical experiments. Nuclear magnetic resonance spectroscopy (NMR) using chiral shift reagents [9], chiral chromatography [10], enzymatic techniques [11] and other newer techniques are commonly used for chiral analysis [8,12]. A relatively new analytical method of chiral analysis, mass spectrometry (MS), has sparked interest because of its speed, sensitivity, its ability to probe the analyte in a solvent free environment, and its tolerance to impurities [13–15].

Fales and Wright were the first to show chiral discrimination (of dialkyl tartarates) on the basis of different chemical ioniza-

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tion mass spectra [16], despite each enantiomer having the same mass/charge (m/z) ratio. After initial slow development, the last decade has seen a strong interest in improved MS methods for routine and reliable chiral identification and especially for chiral quantification, although the underlying understanding of stereospecific interactions in gaseous complexes is still being realized [12,17–20].

Current chiral MS identification methodologies can be grouped into two classes, depending on whether tandem MS or non-tandem MS methods are used. Non-tandem methods generally require isotopically labeled compounds (analyte or chiral reference) and the identification can involve but is not limited to [21–27] ion-inclusion complex formation, where the analyte of interest complexes with a labeled and an un-labeled chiral host compound [24,26,28–30]. The enantiomers produce different responses that are quantifiable as judged from the ion abundances. The quantitative limitations associated with non-tandem methods occur as a result of isotopic effects and/or differing ionization energies for diastereomers, often resulting in poor calibration data and poor quantitative accuracy [31].

Tandem methods have advantages of rapid implementation and applicability to impure samples including mixtures, and they generally employ ion selection followed by dissociation of the mass-selected precursor ion. The precursor ion can undergo ion/molecule (I/M) reactions with a chiral host compound [32,33] or undergo collision induced dissociation (CID) reactions involving competitive loss of a reference and the analyte compound [34–39]. In both cases reactions occur to a different extent for each enantiomer. Quantitative limitations associated with the tandem MS methods are the difficulty in reproducibly measuring product ion peaks from the I/M or CID reactions, resulting in limited precision and/or accuracy as compared to the more commonly used chiral chromatography techniques, especially high-performance liquid chromatography [6]. Both types of MS methods, tandem and non-tandem, represent novel approaches for chiral identification and despite the above caveats, the kinetic method formalism [40,41] for chiral MS, a tandem MS method used to infer relative thermochemical information, has become a popular, reliable, and easily employed method.

Amongst other advantages, the kinetic method has proven to be useful as a high throughput chiral analysis technique [42]. In addition to the diversity of compounds that have been chirally analyzed [35], this method has been optimized to such an extent that any chiral compound has the potential to be identified [43,44]. Moreover, this method is applicable to analytes present in complex matrices, since the ion selection which proceeds CID separates the analyte of interest. When using the kinetic method, where a comparison of the ratio of peak abundances for pure enantiomers dictates the degree of chiral selectivity available for a particular system, reliable quantitative data below 5% and above 95% chiral purity are hard to obtain because of the difficulty of accurately measuring a ratio of peak heights in a mass spectrum for the pure enantiomers when the two peaks being compared differ in intensity by a factor of two or more orders of magnitude [45,46]. To extend the range of applications of the kinetic method, a "vernier" method has been investigated, where quantitative improvements result by selecting experimental conditions that place the most accurately measured fragment ion ratio (1:1), in the range of chiral purity of interest. This is demonstrated here by measuring 0–10% and 90–100% chiral purity of D-Trp quality control (QC) samples with high accuracy and precision. The work presented here is an attempt to address the quantitative limitation, when using high purity chiral samples, commonly seen with MS methods that use the kinetic method formalism for chiral quantification.

2. Experimental

Experiments employed a triple quadrupole mass spectrometer (Finnigan TSQ 7000) equipped with an electrospray ionization (ESI) source and operated in the positive ion mode under the following instrument conditions: spray voltage, 5.00 kV; capillary voltage, 20 V; source temperature, 160 °C; manifold temperature, 70 °C; sheath gas flow, 50 (L h^{-1}); and auxiliary gas flow, 10 (L h^{-1}). For MS/MS data collection, argon was used as the collision gas with a collision gas pressure of 2.4 mTorr and a laboratory collision energy of 10 eV. Quantitative MS/MS data were collected using single reaction monitoring (SRM) scans with the following precursor to product ion transitions m/z 525 → m/z 393 and m/z 525 → m/z 321. The SRM scan time was set to 0.8 s with a scan width of 10 units.

Stock solutions of $NiCl_2$ (M^{II}, metal cation), D and L-asparagine (ref*, reference compound) and D and L-tryptophan (A, analyte compound) were prepared at a concentration of 3 mM and diluted in a 75/25 methanol/water solvent mixture. Standards were prepared gravimetrically in a 1:1:1 (M^{II}:ref*:A) mixture that produced D-Trp standards of 0, 20, 25, 50, 75, 80, and 100% chiral purity. These standards were used to create a calibration plot. Low level (0–10% D-Trp) QC samples were prepared by volumetrically diluting the 20% D-Trp standard with L-Trp to make %chiral purity QC samples of 2.00, 2.12, 2.18, 3.00, 3.75, 5.40, 7.70, and 10.17% D-Trp. High level (90–100% D-Trp) QC samples were prepared by volumetric additions of D-Trp to the 80% D-Trp standard to make %chiral purity QC samples of 90.77, 93.66, 96.84, 97.02, 97.31, 97.83, 97.88, and 98.00% D-Trp.

3. Results and discussion

The kinetic method, used as the basis for the present quantitative chiral purity analysis methodology, is a relative method used to infer thermochemical information [40,41]. Criteria for successful application of the kinetic method include formation of gas-phase clusters followed by their competitive dissociations in a two pathway reaction that involves the competitive loss of the chiral analyte and chiral reference, respectively. Chiral purity is inferred from the relationship between the fragment ion abundance ratio and the free energy change, as shown in Eq. (1), where $\Delta(\Delta G)$ is the change in gas phase basicity for the two dissociation pathways which result from stereochemical differences, **R** is the universal gas constant and T_{eff} is the effective temperature (the empirical parameter that relates a very specific weighted average of mean internal energies to the population of

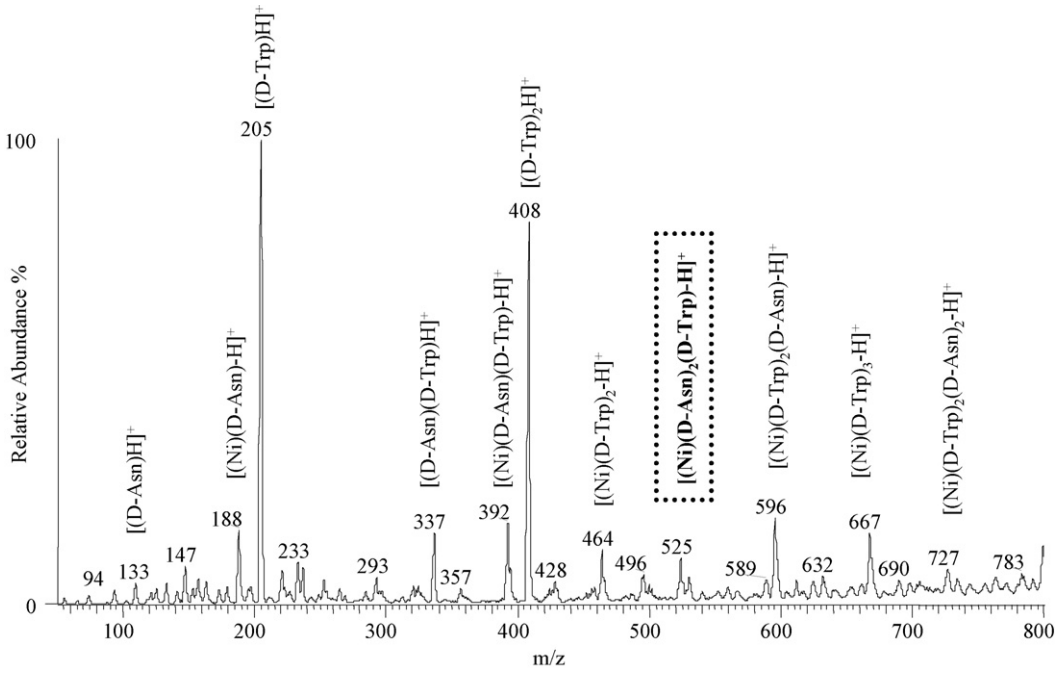

Fig. 1. ESI mass spectrum of a 1:1:1 mixture of $NiCl_2$, D-Trp, and D-Asn dissolved in 75/25 methanol/water. The trimeric cluster ion of interest is at *m/z* 525.

isolated fragment ions [47]). When applying the kinetic method to complex ions which can fragment by two competitive dissociation channels, where the branching ratio (R) for ions containing D (or L) versus the corresponding isomer, viz. the ratio of the two fragment ion abundance branching ratios, is logarithmically related to the chiral purity of the analyzed mixture.

$$\ln R = \frac{[(M^{II})(A)(ref^*) - H]^+}{[(M^{II})(ref^*)_2 - H]^+} = \frac{\Delta(\Delta G)}{\mathbf{R}T_{eff}} \quad (1)$$

The singly charged trimeric cluster ion ([(Ni)(D-Asn)$_2$(D-Trp)-H]$^+$) was formed by ESI, the mass spectrum being shown in Fig. 1. The cluster ion of interest was mass selected and dissociated in an MS/MS experiment to form competitively the dimeric products, [(Ni)(D-Trp)(D-Asn)-H]$^+$ and [(Ni)(D-Asn)$_2$-H]$^+$, by loss of the neutral analyte and reference, respectively, Fig. 2. The difference in free energy ($\Delta(\Delta G)$) for the reaction which involves loss of either the analyte or the reference molecule from the cluster is associated with a characteristic fragment ion branching ratio. More specifically, fragment ion abundances are dependant on the chirality of the analyte. Thus, chiral purity can be indirectly evaluated from the ratio of peak heights of the fragment ions in the tandem mass spectrum. It has been shown elsewhere that Eq. (1) implies that a linear relationship should

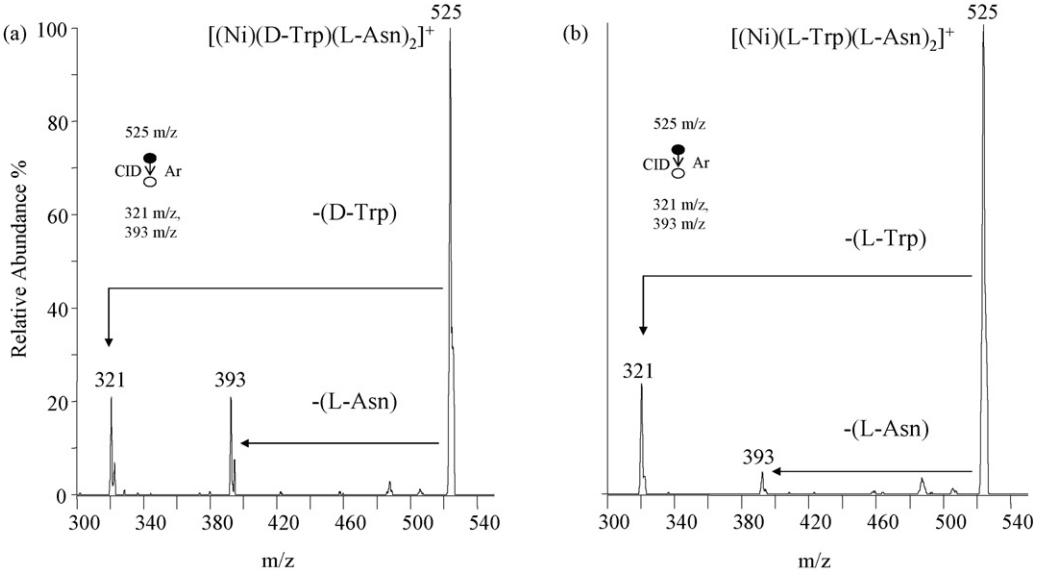

Fig. 2. Tandem (MS/MS) analysis of a mixture containing (a) D-Trp, $NiCl_2$, and L-Asn and (b) L-Trp, $NiCl_2$, and L-Asn. The MS/MS data were recorded using the fragment ion abundances, a collision energy of 10 eV and a collision gas pressure of 2.4 mTorr.

exist between the logarithmic ratio of fragment ion abundances and chiral purity, Eq. (2), where ee represents the enantiomeric excess [48]. With this relationship a calibration curve was constructed and a linear response was evaluated between the chiral purity of the analyzed mixture and fragment ion branching ratio.

$$\ln R = \frac{\Delta(\Delta G)_D + \Delta(\Delta G)_L}{2\mathbf{R}T_{eff}} + \frac{\Delta(\Delta G)_D - \Delta(\Delta G)_L}{2\mathbf{R}T_{eff}} \times ee \quad (2)$$

It has been demonstrated that there is an apparent trade off between large selectivity and accuracy for mixtures near the racemate [45]. The vernier concept described, is an exploitation of improved accuracy in a limited range as a result of small changes in the relative fragment abundances, requires a large R_{chiral} (Eq. (3)) and a ratio near unity for the fragment ion branching ratio in the case of one pure enantiomer. When these criteria are met, the method cannot produce data of high accuracy for samples in which the chiral purity is near that of the racemate, since large changes in the relative abundance are not as accurately measured.

$$R_{chiral} = \frac{[(M^{II})(A_L)(ref^*) - H]^+ / [(M^{II})(ref^*)_2 - H]^+}{[(M^{II})(A_D)(ref^*) - H]^+ / [(M^{II})(ref^*)_2 - H]^+} \quad (3)$$

The vernier concept was tested using a previously reported system that consisted of D-Trp using Ni^{II} as the metal cation and L-Asn as the reference compound [46]. The results from this previous study showed that the specified criteria for the vernier methodology were satisfied with this specific system, where the ratio for the pure enantiomer D-Trp was reported to be 1.10 and the R_{chiral} was 7.86. Improved performance in terms of accuracy was expected to be found at the extremes of chiral purity, especially in the important 90–100% chiral purity range. Results showed that the method was indeed found to give quantitative improvements in the aforementioned chiral purity region: linearity, accuracy, and precision were evaluated.

The linearity was evaluated by observing the fit between the standards and the calibration plot, where r^2 values obtained were, 0.9895, Fig. 3a. When data below the 90% D-Trp range was removed there was an additional improvement in the systems linearity as judged from the correlation coefficients obtained, 0.9959, inset of Fig. 3a. It was determined, based on an observation of peak heights, that the 90–100% chiral purity region could be used for improved quantitative identification of D-Trp.

The precision was measured by triplicate injections of various QC samples. Measurements were made using three separate sample sets where three separate scans for each sample set were recorded. This totaled 180 average scans per QC sample at a scan rate of 0.8 s, where there was an average run time of 3 min per sample. An average %R.S.D. of 0.74% was obtained, Table 1. R.S.D.'s which fall outside the high accuracy range are also shown in Table 1 and results suggest that the precision is comparable throughout the entire calibration range, e.g., 0.72% R.S.D.

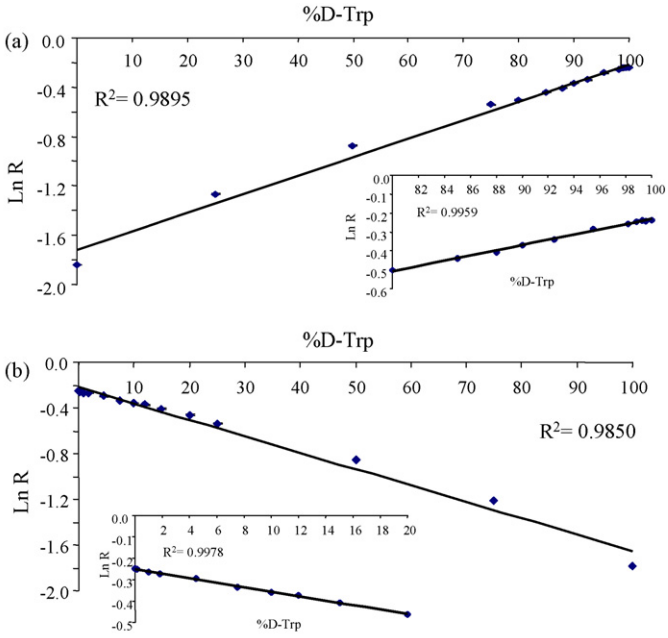

Fig. 3. Calibration plots were constructed using the following gravimetrically prepared standards—0, 20, 25, 50, 75, 80, and 100% D-Trp with the following references (a) L-Asn and (b) D-Asn. The insets show a blow up of the linear regions with QC sample data included on the calibration plots for the 80–100% D-Trp using L-Asn as the reference compound and the 0–10% D-Trp using D-Asn as the reference compound.

The accuracy for the system was judged by assessing the agreement between the actual chiral purity of D-Trp in the QC sample and the experimentally determined chiral purity of D-Trp in the same sample. By solving the least squares fit equation that was obtained from the constructed calibration plot for each unknown measurement, chiral purity of D-Trp was confirmed. Table 1 shows how accurate the method is at experimentally assessing the true %D-Trp chiral purity in the 90–100% D-Trp region, where an average %deviation of 0.51% was obtained in the vernier region. The non-vernier region (the region that falls outside the high accuracy region of interest) produced a %deviation of 104.1%.

By switching the chirality of the reference to D-Asn, the vernier region was inverted and quantitative improvements were extended to the 0–10% D-Trp chiral purity region, which can also be viewed as the 90–100% L-Trp region. The results showed quantitative improvements that are comparable to the L-Asn reference system, where the linearity, precision and accuracy were also evaluated. A correlation coefficient of 0.9850 was obtained for the 0–10% region and upon removing the data above 10% D-Trp there was a further improvement in the systems linearity, as judged from the correlation coefficient were a value of 0.9978 was obtained, Fig. 3b. The precision for this system was consistent throughout the entire calibration region, where the high precision region showed a %R.S.D. of 0.26% and a %R.S.D. of 0.65% for the non-vernier region, Table 2. Lastly, a %deviation of 5.68% was obtained in the vernier region and the non-vernier region showed a %deviation of 11.05%, Table 2. The data obtained in the vernier regions, 90–100% and 0–10% D-Trp, showed an overall improvement in the methods' linear-

Table 1
Measurement of %D-Trp in the 90–100% chiral purity range

Accuracy[a]			Precision[b]	
Actual[c]	Experimental[d]	%Deviation	S.D.	R.S.D.%
98.00	97.68	0.33	9.56E−03	1.23
97.88	97.23	0.67	7.47E−03	0.93
97.83	97.67	0.16	6.69E−03	0.83
97.31	96.59	0.74	6.44E−03	0.82
97.02	96.24	0.80	4.94E−03	0.63
96.84	96.19	0.67	4.53E−03	0.58
93.66	93.70	−0.04	2.45E−03	0.33
90.77	90.09	0.75	3.86E−03	0.54
74.04	77.31	−4.41	4.73E−03	0.81
50.00	56.04	12.07	2.69E−03	0.64
25.96	30.94	−19.17	1.64E−03	0.58
2.00	−5.61	380.57	1.34E−03	0.85
Average (90–100%)[e]	0.51	5.86E−03	0.74	
Average (0–75%)[f]	104.1	2.60E−03	0.72	

[a] QC samples were prepared using L-Asn as the reference compound.
[b] Experiments were repeated three times and the standard deviations (S.D.) and relative standard deviations (R.S.D.%) are reported.
[c] Actual chiral purity of the QC samples prepared in triplicate.
[d] Average experimental values obtained for three separate QC sample runs.
[e] Average values obtained are for the QC samples in the 90–100% D-Trp range.
[f] Average values obtained are for the standards in the 0–75% D-Trp range.

Table 2
Measurement of %D-Trp in the 0–10% chiral purity range

Accuracy[a]			Precision[b]	
Actual[c]	Experimental[d]	%Deviation	S.D.	R.S.D.%
2.00	2.06	2.95	2.13E−03	0.27
2.12	2.21	4.42	2.14E−03	0.28
2.18	2.52	15.74	2.28E−03	0.29
3.00	3.27	9.14	1.03E−03	0.13
3.75	3.81	1.65	2.95E−03	0.39
5.40	5.33	−1.41	2.56E−03	0.34
7.70	8.13	5.54	1.82E−03	0.26
10.17	9.70	−4.59	9.66E−04	0.14
25.96	22.12	−14.79	1.37E−03	0.23
50.00	44.06	−11.87	1.98E−03	0.46
74.04	69.03	−6.39	2.13E−03	0.72
98.00	108.90	11.13	2.01E−03	1.20
Average (0–10%)[e]	5.68	1.98E−03	0.26	
Average (25–100%)[f]	11.05	1.87E−03	0.65	

[a] QC samples were prepared using D-Asn as the reference compound.
[b] Experiments were repeated three times and the standard deviations (S.D.) and relative standard deviations (R.S.D.%) are reported.
[c] Actual chiral purity of the QC samples prepared in triplicate.
[d] Average experimental values obtained for three separate QC sample runs.
[e] Average values obtained are for the QC samples in the 0–10% D-Trp range.
[f] Average values obtained are for the standards in the 25–100% D-Trp range.

ity, precision and accuracy. Also, it was shown that the original hypothesis of deviation from the true value with mixtures close to the racemate is accurate [49–51].

4. Conclusion

Quantitative chiral analysis by MS using the kinetic method produces less accurate quantitative data for mixtures of high chiral purity when chiral selectivity (R_{chiral}) is large and when the system is chosen so that ion abundance ratios are most accurately measured for samples with chiral purity similar to the near racemic mixture. However, when the selectivity is large and when a ratio for one pure enantiomer is close to unity, improved quantitative chiral purity data are obtained for mixtures in the high chiral purity region of the calibration plot and not for the near racemic samples. When this region is moved along the calibration plot, viz. when the ref* is switched which results in an inversion in the calibration plot, improvements in quantitative data were obtained in the low chiral purity region as well, which is a test of the methods performance. The method showed quan-

titative improvements in these chiral purity percentages, where the average deviation from the correct result was 0.51% for the 90–100% L-Trp system using L-Asn as the reference compared to an average deviation of 5.68% for the 0–10% L-Trp system using the D-Asn as the reference compound and a deviation of 104.1% and 11.05% (for the 0–75% region using L-Asn as the reference and for the 25–100% region using D-Asn as the reference, respectively). These differences in accuracy correlate with expectations based on measuring the ratios of peaks of significantly different intensities.

The analytical techniques used to determine chiral purity are continuing to be improved and the potential of MS for understanding stereospecific chemical interactions is still being realized. Thus, the newly developed "vernier" methodology provides improved performance in quantitative chiral analysis in the important low (0–10%) and high (90–100%) chiral purity regions. This methodology has the potential to be extended to species of still higher chiral purity, where trace (chiral) measurements are needed.

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