Subsequently, a solution of **20** (0.300 g, 0.638 mmol) and $[Pd(PPh_3)_4]$ (0.055 g, 0.048 mmol) in THF (5 mL) was added to the organozinc intermediate by cannula. The mixture was heated at reflux for 20 h, cooled to room temperature, and placed in a freezer. The white precipitate was filtered, washed with cold THF, and dried. The precipitate was dissolved in dichloromethane and extracted vigorously with saturated aqueous EDTA and basified with saturated aqueous sodium bicarbonate. The organic layer was separated, dried over magnesium sulfate, filtered, and evaporated to afford a white crystalline solid (270 mg, 81 %), m.p. 130–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.05$ (d, $J = 2.0$ Hz, 1H), 9.04 (d, $J = 8.0$ Hz, 1H), 8.83 (d, $J = 8.5$ Hz, 1H), 8.53 (d, $J = 2.0$ Hz, 1H), 8.41 (d, $J = 8.5$ Hz, 1H), 8.06 (d, $J = 2.0$ Hz, 1H), 7.88 (d, $J = 9.0$ Hz, 1H), 7.81 (d, $J = 9.0$ Hz, 1H), 7.72 (dd, $J = 2.0$, 8.0 Hz, 1H), 6.74 (s, 2H), 6.70 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 2.07 (s, 6H), 2.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.85$, 158.67, 156.12, 154.37, 151.80, 149.63, 145.51, 144.67, 138.38, 137.83, 137.67, 136.89, 136.41, 135.84, 130.23, 130.01, 128.66, 128.49, 126.62, 122.41, 120.56, 112.88, 112.82, 55.23, 55.20, 21.43, 21.34; UV/Vis (CH_3CN): λ_{max} (ε) = 240 (6.3×10^4), 296 (4.3×10^4), 354 (8.7×10^3) nm; HR-MS: *m/z*: calcd for $C_{35}H_{31}N_3O_2$: 525.2416; found: 525.2407.

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Parallel Reactions for Enantiomeric Quantification of Peptides by Mass Spectrometry**

W. Andy Tao and R. Graham Cooks*

The accelerating trend towards the use of enantiomerically pure compounds as drugs has underscored the need for new methods of enantioselective synthesis and chiral analysis.[1] The capabilities of mass spectrometry for the rapid analysis of complex mixtures have encouraged its exploration for gas-phase chiral recognition.[2] This has been achieved by direct measurement of the relative abundance of two diastereomeric ions formed by complexing enantiomers and a chiral reference,[2d,g–i] ion–molecule reactions of diastereomeric adducts,[2c,e] or collisional dissociation of diastereomers.[2b] Quantitative analysis, especially when one enantiomer comprises only a few percent of a mixture, remains a challenge. Competitive reactions of two enantiomers toward a chiral reference are unavoidably influenced by the relative concentrations of the enantiomers, which affects the accuracy of the measurement of the enantiomeric excess (*ee*) unless the selectivity factor *s* (the ratio of competing rate constants) is

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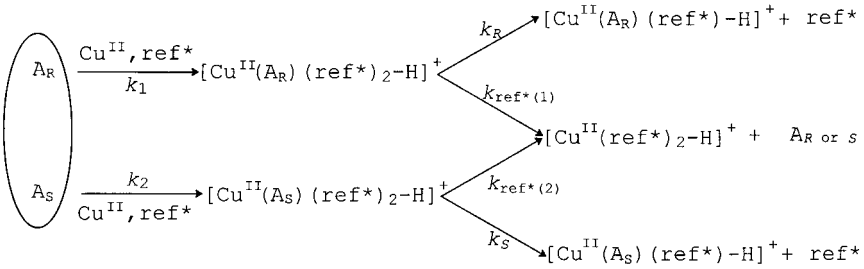
extremely large. Taking condensed-phase kinetic resolution as an example, *s* must be at least 200 for resolution at 96% *ee*, and 500 at 98% *ee*.[3] Such selectivities are currently beyond the reach of most condensed-phase reactions,[4] let alone gas-phase reactions, which usually display lower selectivities.[5]

We describe here a novel gas-phase method for rapid chiral quantification at low *ee* values by using a simple technique in which chiral analysis is performed on the basis of two parallel ion–molecule reactions followed by low-energy dissociations. High selectivity is not required to quantify enantiomers at low *ee* values. A solution containing two enantiomers (A_R and A_S) is transformed into gas-phase cluster ions $[Cu^{II}(A_R)(ref^*)_2 - H]^+$ and $[Cu^{II}(A_S)(ref^*)_2 - H]^+$ through electrospray ionization (ESI; Scheme 1). The experiments



Scheme 1.

are done by simply mixing the analyte with a copper salt ($CuCl_2$) and a chiral reference compound (ref*) in aqueous methanol. The relative abundances of $[Cu^{II}(A_R)(ref^*)_2 - H]^+$ and $[Cu^{II}(A_S)(ref^*)_2 - H]^+$ are found to reflect the enantiomeric composition of the analyte A in solution. Each cluster ion then undergoes competitive collision-induced dissociation (CID) in a quadrupole ion trap to form the dimeric complexes $[Cu^{II}(A)(ref^*) - H]^+$ and $[Cu^{II}(ref^*)_2 - H]^+$ by the loss of the neutral reference compound ref* and analyte A, respectively. Depending on the configuration of analyte A, the stabilities of the diastereomeric ions $[Cu^{II}(A)(ref^*) - H]^+$ can be different, which results in different abundances in the mass spectra relative to the abundance of $[Cu^{II}(ref^*)_2 - H]^+$. The independent dissociation steps provide a measure of chiral composition but there is no mutual influence on either the formation or the dissociation of the trimeric cluster ions $[Cu^{II}(A_R)(ref^*)_2 - H]^+$ and $[Cu^{II}(A_S)(ref^*)_2 - H]^+$ generated from the individual optical isomers. Therefore, the overall chiral analysis is simply a function of the initial concentrations of the two enantiomers. Analogies can be drawn between this approach and the condensed-phase "parallel kinetic resolution" experiment introduced recently by Vedejs and Chen.[6] The relative abundance ratio *R* [Eq. (1)] can be used to determine the enantiomeric composition of the analyte, provided a calibration curve is constructed.

$$R = \frac{[Cu^{II}(A)(ref^*) - H]^+}{[Cu^{II}(ref^*)_2 - H]^+} \quad (1)$$

We demonstrate the capability of this method with the quantification of several chiral peptides in this first report on chiral recognition and quantification of peptides using mass spectrometry. The copper(II) ion is selected as the central ion because of its ability to form polydentate complexes with amino acids or peptides, thus promoting chiral recognition according to the "three-point interaction" rule.[7] The degree of chiral discrimination is evaluated using the kinetic method,[8] through a measurement that depends on the difference in the free energy of activation for dissociation to generate the diastereomeric complexes ($[Cu^{II}(A_R)(ref^*) - H]^+$ and $[Cu^{II}(A_S)(ref^*) - H]^+$). The kinetic method can discriminate between processes with very small differences (approximately 1 kJ mol^{-1}) in the product ion energy. Competitive dissociation channels of a cluster ion with very small differences in free energy result in large changes in the respective rate constants, which are reflected in the abundances of the fragment ion.[8] This is a result of the logarithmic relationship between relative ion abundances and the free energy for dissociation that characterizes this method. A free-energy diagram for the dissociation of cluster ions $[Cu^{II}(A_R)(ref^*)_2 - H]^+$ and $[Cu^{II}(A_S)(ref^*)_2 - H]^+$ is shown in Figure 1. Note that the examination of trimeric cluster ions $[Cu^{II}(A_R)(ref^*)_2 - H]^+$ and $[Cu^{II}(A_S)(ref^*)_2 - H]^+$ (three chiral ligands in one complex, one mole of the analyte, and two moles of the reference compound) is required so that dissociation can yield the diastereomeric fragment ions $[Cu^{II}(A_R)(ref^*) - H]^+$ and

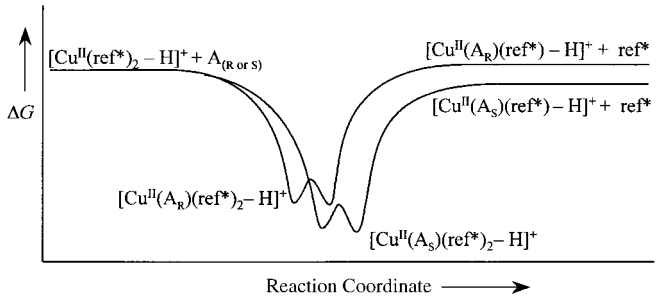


Figure 1. Free-energy diagram for the dissociation of cluster ions bound to copper(II) ions showing the competitive dissociations of two deprotonated trimeric cluster ions that differ in the chirality of one ligand. The two cluster ions yield identical products by one fragmentation route and diastereomeric product ions by a fragmentation process in which a competitive ligand is lost.

$[Cu^{II}(A_S)(ref^*) - H]^+$, respectively. Under the circumstances just described, one can measure the selectivity to chiral recognition by a chiral selectivity factor R_{chiral}, which is the ratio of the individual ratios of fragment ion abundances when pure enantiomers (A_R and A_S) are applied [Eq. (2)].

$$R_{chiral} = R_R/R_S = \frac{k_R/k_{ref^*(1)}}{k_S/k_{ref^*(2)}} = \frac{[Cu^{II}(A_R)(ref^*) - H]^+/[Cu^{II}(ref^*)_2 - H]^+}{[Cu^{II}(A_S)(ref^*) - H]^+/[Cu^{II}(ref^*)_2 - H]^+} \quad (2)$$

In an initial diagnostic study of the formation of singly charged Cu^{II}-bound cluster ions we chose the complex $[Cu^{II}(Ala\text{-}L\text{-}Ala)_2(Phe) - H]^+$ (Phe is L- or D-phenylalanine) as the model ion. To facilitate data interpretation, deuterium-

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labeled L-phenylalanine was employed. (Note that only in this diagnostic study was isotopically labeled analyte used. The remaining experiments are performed without using isotopically labeled compounds, which is also one of the advantages of this chiral analysis method.) The relative abundance of $[Cu^{II}(A)(ref^*) - H]^+$ cluster ions in the mass spectrum depends on the configuration of A, for example, the ratio of relative abundance of $[Cu^{II}([D_5]$L-Phe)(Gly-L-Ala) $- H]^+$/ $[Cu^{II}$(L-Phe)(Gly-L-Ala) $- H]^+$ is approximately 1.8 when an equimolar mixture of D-Phe and $[D_5]$L-Phe is used in solution. Remarkably, the relative abundance of the cluster ions $[Cu^{II}([D_5]$L-Phe)(Gly-L-Ala)$_2 - H]^+$ and $[Cu^{II}$(D-Phe)(Gly-L-Ala)$_2 - H]^+$ varies linearly with the enantiomeric composition of phenylalanine in solution. Similar results were observed when L-tryptophan was employed as the chiral reference.[9] The abundance of the trimeric ions are reproducibly equal, while the relative abundance ratio of the dimeric ions varies with experimental conditions. The differential formation of dimeric ions may be the result of chiral discrimination, and indeed this experiment is the basis being used by several groups to conduct chiral studies using single-stage mass spectrometry. The present observation suggests that such effects arise from instrumental factors as well as the chemical effects of interest. In contrast, the use of branching ratios in a tandem mass spectrum is a more reliable and reproducible approach. The reason why the formation of cluster ions $[Cu^{II}(A_R)(ref^*)_2 - H]^+$ and $[Cu^{II}(A_S)(ref^*)_2 - H]^+$ is independent of stereochemistry is still under investigation.

Six dipeptides (Gly-Ala, Ala-Gly, Ala-Ala, Ala-Leu, Leu-Ala, and Ala-Phe) were selected for chiral analysis. The choice of appropriate chiral references was based in part on their abilities to produce large chiral interactions. Aromatic amino acids are favored since they are known to facilitate chiral distinction;[10] A second factor is structural similarity to the analyte, since this allows the ready formation of a complex. It also allows accurate measurements of relative abundance ratios, otherwise dissociation proceeds overwhelmingly to the more stable product. Typical tandem mass spectra showing the distinction of L-Ala-Gly and D-Ala-Gly using L-tryptophan are illustrated in Figure 2 and chiral recognition of all six dipeptides is summarized in Table 1. Repeat injections were found to give standard deviations of less than 3%. Chiral dipeptides Gly-Ala and Ala-Gly, each bearing one chiral center, are readily distinguished using L-tryptophan as the reference. The rest of the peptides have two chiral centers and are distinguished by R_{chiral} values of at least 1.4. Differentiation of regioisomers and diastereomers is also achieved using this method, but beyond the scope of this paper.

Quantification was performed using the enantiomerically pure chiral reference and the analyte in various optical purities. Two representative systems with moderate chiral selectivity were selected: 1) Gly-Ala as the analyte and L-tryptophan as the reference and 2) Ala-Ala (a mixture of L-Ala-L-Ala and D-Ala-D-Ala) as the analyte and L-tryptophan as the reference. The ratio R of the two fragment ions was measured in a single tandem (MS/MS) spectrum as a function of the optical purity of the analyte. As illustrated in Figure 3, linear relationships of $\ln R$ versus *ee* values were obtained and

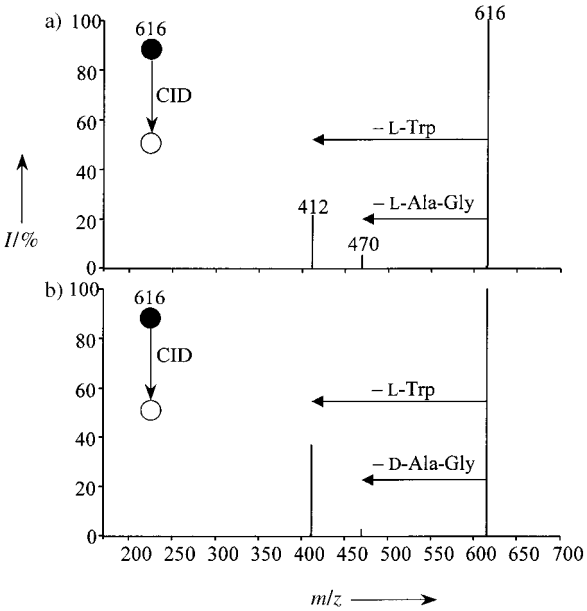

Figure 2. MS/MS product ion spectra of a) $[^{63}Cu^{II}$(L-Ala-Gly)(L-Trp)$_2 - H]^+$ (m/z 616); b) $[^{63}Cu^{II}$(D-Ala-Gly)(L-Trp)$_2 - H]^+$ (m/z 616). The CID activation level chosen (10.5%) corresponds to approximately 263 mV AC. I refers to the relative ion abundance. No other fragment ions of more than 1% relative abundance were observed.

Table 1. Chiral recognition of chiral peptides.[a]

A	Ref*[b]	$[Cu^{II}(ref^*)(A) - H]^+$/ $[Cu^{II}(ref^*)_2 - H]^+$	R_{chiral}
Gly-L-Ala	L-Trp	14.3	
Gly-D-Ala	L-Trp	6.10	0.427
L-Ala-Gly	L-Trp	4.51	
D-Ala-Gly	L-Trp	15.2	3.37
L-Ala-L-Ala	L-Trp	22.3	
D-Ala-D-Ala	L-Trp	33.4	1.50
D-Ala-L-Ala	L-Trp	73.00	
L-Ala-D-Ala	L-Trp	11.7	6.22
D-Ala-D-Leu	*N*-Me-L-Trp	13.2	
L-Ala-L-Leu	*N*-Me-L-Trp	9.50	1.39
D-Leu-D-Ala	*N*-Me-L-Trp	45.2	
L-Leu-L-Ala	*N*-Me-L-Trp	25.8	1.75
D-Ala-L-Phe	L-Phe-L-Tyr	0.0331	
L-Ala-D-Phe	L-Phe-L-Tyr	0.104	3.14
L-Ala-L-Phe	L-Phe-L-Tyr	0.0658[c]	

[a] The CID activation level is optimized in each experiment and then kept constant for the measurements of enantiomers. [b] See text for the criterion on the selection of the reference compound (ref*). [c] The value is not applied to the measurement of chiral selectivity since L-Ala-L-Phe is the epimer of D-Ala-L-Phe or L-Ala-D-Phe.

they showed correlation coefficients (r^2) of 0.9920 for the quantification of Gly-Ala and 0.9936 for the quantification of Ala-Ala enantiomeric mixtures. Note that the linear correlation between the logarithm of the fragment ion abundance ratio and the enantiomeric excess is intrinsic to the kinetic method. According to the kinetic method, $\ln R$ is linearly proportional to $\Delta(\Delta G)$ [Eq. (3)],

$$\ln R = \frac{\Delta(\Delta G)}{RT_{eff}} \quad (3)$$

where R in the denominator is the gas constant, T_{eff} is the effective temperature of the activated trimeric cluster ion, and

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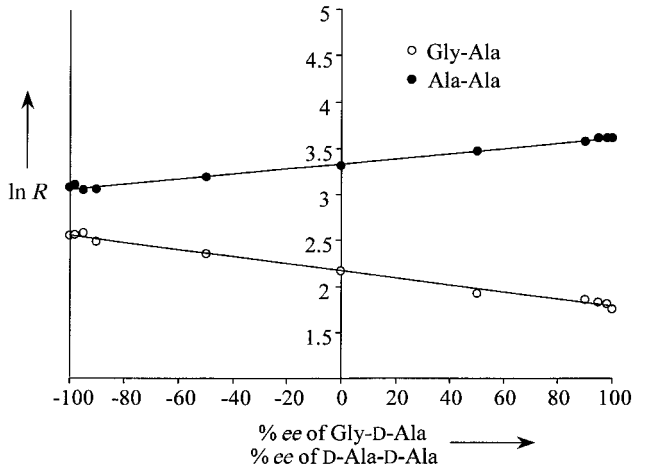

Figure 3. Calibration curves for chiral analysis of Gly-Ala (enantiomeric mixture of Gly-D-Ala and Gly-L-Ala) and Ala-Ala (enantiomeric mixture of D-Ala-D-Ala and L-Ala-L-Ala) using L-Trp as the chiral reference.

$\Delta(\Delta G)$ is defined as the difference in free energies for Equation (4).

$$[Cu^{II}(ref^*)_2 - H]^+ + A \longrightarrow [Cu^{II}(ref^*)(A) - H]^+ + ref^* \quad (4)$$

The quantity $\Delta(\Delta G)$ is linearly proportional to the enantiomeric excess of the analyte A, therefore $\ln R$ changes linearly with *ee*. A derivation based on the bond energy instead of free-energy formalism is given elsewhere.[10] Calibration can be performed with an experimentally established semi-log plot using only a racemic sample and a sample of known enantiomeric excess for each analyte (a two-point calibration). Quantitative chiral analysis is then carried out by measuring the ratio of two fragment ions in a single spectrum in just a minute. For example, Gly-Ala is analyzed to give an accuracy of 3.6% *ee* over the range 2–100% *ee*.[11]

The method for gas-phase chiral quantification reported here has several distinctive features: a) Since chiral selectivity in the gas phase is usually low, the proposed method using parallel reactions is especially attractive for gas-phase chiral quantification of samples with small *ee* values. b) The method does not rely on condensed-phase derivatization or chromatographic separation, and therefore may be particularly useful for cases in which chromatography and derivatization is ineffective or inconvenient. c) The analysis time is short and does not involve wet-lab steps or chromatographic process. d) The measurements are simple, rapid, and amenable to automation: they use standard ESI mass spectrometry and tandem mass spectrometry, and require very small amounts of sample for analysis. e) The present parallel reaction methodology is general and should be useful for quantification of other biologically important compounds, such as chiral drugs. The experiments are not restricted to copper(II) ions or any particular metal ion complexes, other chiral interactions such as host–guest interactions are possible. The approach used here therefore serves as a possible basis on which to build a general procedure for molecular recognition and chiral analysis in the gas phase.

Experimental Section

A commercial LCQ ion trap mass spectrometer (Finnigan, San Jose, CA), equipped with an ESI source was operated in the positive ion mode as follows: spray voltage: 5.00 kV; capillary voltage: 3 V; heated capillary temperature: 150 °C; tube lens offset voltage: 20 V; sheath gas (N_2) flow rate: 30 units (roughly 0.75 L min^{-1}). The spectra shown represent the average of about 50 scans, each requiring 200 ms. The sample was infused by a syringe pump at a flow rate of 1–3 μL min^{-1}. In the full scan MS^2 and MS^3 modes, the parent ion of interest was first isolated by applying an appropriate waveform across the endcap electrodes of the ion trap to resonantly eject all trapped ions, except those with the m/z ratio of interest. The isolated ions were then subjected to a supplementary AC signal to resonantly excite them and so cause CID. The Mathieu q_z values for resonance excitation and resonance ejection were 0.25 and 0.83, respectively. The ion excitation time for CID (values range from 0 to 100% relative collision energy corresponding to 0 to 2.5 V zero-to-peak resonant excitation potential) was 30 ms with the amplitude of the excitation AC being optimized in each experiment, but being kept constant for the measurements of *R* and *S* enantiomers.

Gas phase Cu^{II} complexes with dipeptides or amino acids were generated by electrospraying solutions containing a mixture of dipeptides and amino acids (100 μM each) and copper(II) chloride (25 μM) in water/methanol (50/50). Dipeptides and amino acids were purchased from Bachem (Torrance, CA) and Sigma (St. Louis, MO) and were used without further purification.

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