

## Threshold CID Investigation of Isomeric Cu(I) Azabox Complexes

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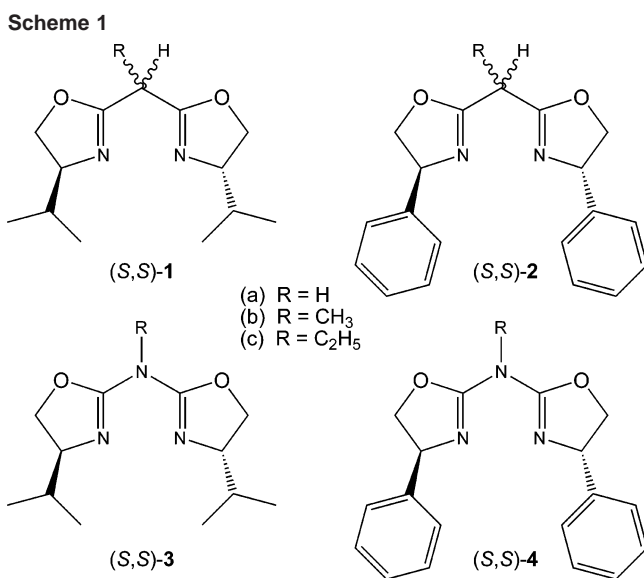
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An improved method for deconvoluting energy-resolved collision-induced dissociation cross sections yields ligand binding energies for organometallic complexes with substantially less prior information than before. Application to isomeric 2:1 complexes of azabox ligands with Cu(I) gives consistent results for the binding energies of the ligands to homo- and heterochiral complexes with pseudo-enantiomeric ligands for cases where previous deconvolution methods had failed to give satisfactory results.

## Introduction

The use of pseudo-enantiomers of chiral compounds to probe stereochemical effects has recently found new application in kinetic and thermochemical studies pertaining to asymmetric catalysis.<sup>1,2</sup> In particular, the classical kinetic approach by Kagan<sup>3</sup> to nonlinear effects in asymmetric catalysis requires, even for the simplest case, a knowledge of the relative thermodynamic stabilities of homochiral versus heterochiral 2:1 complexes of the chiral ligand to the catalytic metal center. In a recent publication,<sup>4</sup> we have applied gas-phase, tandem mass spectrometric methods to the extraction of the absolute ligand binding energies in 2:1 complexes of bis-oxazoline (box), **1–2**, and aza-bis-oxazoline (azabox), **3–4**, ligands with Cu(I), from which the requisite thermodynamic stabilities can be determined. Moreover, the comparison to DFT calculations indicated that the small energetic differences that would nevertheless exert a profound effect on stereoselectivity were not properly handled by the usual level of theory used in calculations on organometallic complexes of the typical size seen in homogeneous catalysis. Last, whereas the measurements for the reactions,  $L_2Cu^+ \rightarrow (L)Cu^+ + L$ , worked satisfactorily for ligands,  $L = \mathbf{1}, \mathbf{2}$ , and **3**, the experiment for the reaction,  $(\mathbf{4})_2Cu^+ \rightarrow (\mathbf{4})Cu^+ + \mathbf{4}$ , failed with the internal controls coming up grossly inconsistent. In the present report, the latter system,  $(\mathbf{4})_2Cu^+ \rightarrow (\mathbf{4})Cu^+ + \mathbf{4}$ , is reinvestigated using a newly developed deconvolution routine, L-CID, which produces consistent results, which, when compared to the previous findings,



underline the sensitivity of the relative stability of diastereomeric 2:1 complexes to small structural changes.

## Experimental Section

The preparation and treatment of samples was performed as has been described previously.<sup>4</sup> The preparation of the azabox ligand with larger labels is analogous to that for the previous ligands in our earlier work and is detailed in the Supporting Information. The 2:1 complexes were electrosprayed from CH<sub>2</sub>Cl<sub>2</sub> in a modified Finnigan MAT TSQ-700 tandem mass spectrometer. After thermalization of the ions to the 70 °C manifold temperature in a radio frequency 24-pole ion guide filled with 5–10 mTorr argon, a retarding potential could be applied as a control. The first derivative of the ion transmission curve, shown in Figure 1, along with a Gaussian fit, gives the kinetic energy distribution for the ions prior to collision-induced dissociation.

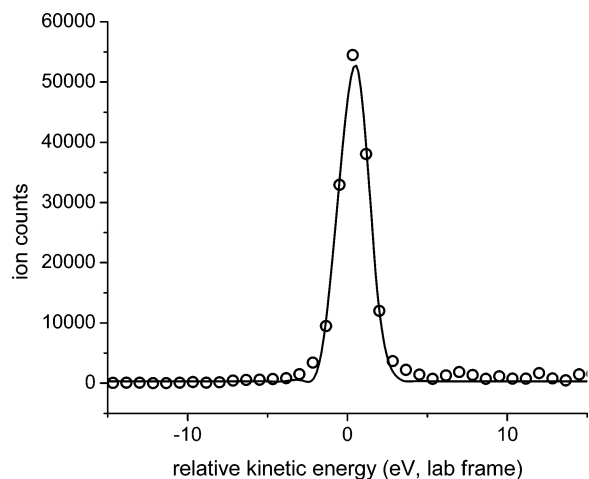
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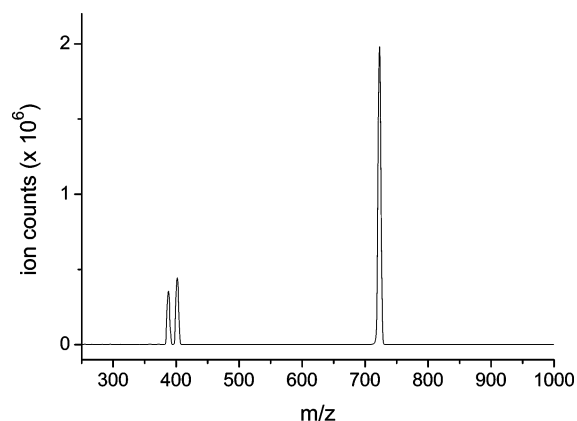
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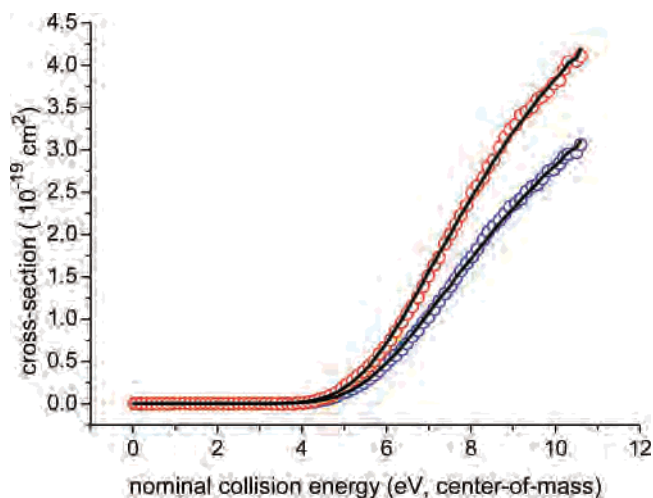
**Figure 1.** Kinetic energy distribution in the laboratory frame of the electrosprayed  $(L)_2Cu^+$  ions after thermalization in the rf 24-pole ion guide. From a fit to a Gaussian, the distribution has a FWHM of approximately 1.90 eV (lab frame).



**Figure 2.** Daughter mass spectrum taken by collision-induced dissociation of  $(S,S-4b)(R,R-4c)Cu^+$ ,  $m/z = 719$ , producing  $(S,S-4b)Cu^+$  and  $(R,R-4c)Cu^+$ , at  $m/z = 384$  and 398. There are no other daughter ions produced in the energy range employed in the threshold CID study.

Each 2:1 complex was mass-selected in turn and then subjected to collision-induced dissociation with xenon in an octopole ion guide.

The collision-induced dissociation cross section was recorded as a function of the nominal ion kinetic energy in the laboratory frame of reference. The measurement was repeated three times for each of five pressures of xenon in the octopole. The averaged cross section at each pressure was then extrapolated to zero pressure and plotted against nominal collision energy in the center-of-mass frame of reference. Taking into account the kinetic energy distribution, the internal energy content, and the contribution due to thermal motion of the target xenon atoms, the activation energies for the ligand dissociation were deconvoluted using the new L-CID program.<sup>5</sup> With the assumption, normally valid for ion–molecule reactions, that there is no reverse barrier for the ligand dissociation reaction, the extracted activation energy can be equated with the ligand binding energy. A comparison deconvolution with the *CRUNCH-D1* program from Armentrout and co-workers<sup>6</sup> was done for  $(S,S-4b)_2Cu^+$ , which has exactly 87 atoms, the maximum size for which *CRUNCH* is dimensioned.



**Figure 3.** Threshold CID curves for the dissociation of  $(S,S-4b)(R,R-4c)Cu^+$ ,  $m/z = 719$ , to  $(S,S-4b)Cu^+$ ,  $m/z = 384$  (blue), and  $(R,R-4c)Cu^+$ ,  $m/z = 398$  (red). L-CID fits are shown using the two (competing) channel model with loose transition states.

## Results

A representative daughter mass spectrum, showing the collision-induced dissociation (CID) of  $(S,S-4b)(R,R-4c)Cu^+$ , is given in Figure 2. It is important that the CID proceeds predominantly to no more than two competing product channels and that the rise of daughter ions as well as the decline of the parent ion intensity is measured as a function of collision energy.

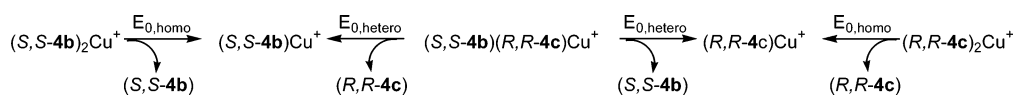
This latter condition is needed for the cross-section calculation, and, furthermore, allows the user to exclude artifacts due to nonchemically relevant ion-loss processes. Extrapolation of the threshold CID curves at five different pressures to the zero-pressure limit produces curves, such as the ones shown in Figure 3, which are depicted with the L-CID fit. In the case of Figure 3, a two-channel fit was done. The comparable curves for  $(S,S-4b)_2Cu^+$  and  $(R,R-4c)_2Cu^+$  were fit as single-channel dissociations.

It is important to notice that the heterochiral 2:1 complex  $(S,S-4b)(R,R-4c)Cu^+$  can lose either of the ligands with the same  $E_{0,hetero}$  in the limit that the remote label is indeed innocuous. Nevertheless, the two threshold CID curves in Figure 3 are not co-incident, despite their coming from two dissociations of the same parent with what should be very similar activation energies. While L-CID does not constrain  $E_0$  for the two channels to be identical, or even similar, a two-channel fit uses a common effective frequency, which means that the difference between the two competing transition states is manifested by slightly different  $\alpha'$  parameters, which correspond physically to transition states of slightly different looseness.<sup>5</sup> The comparable data for complexes  $(S,S-4b)_2Cu^+$  and  $(R,R-4c)_2Cu^+$  are given in the Supporting Information. One can compare the fits to those by *CRUNCH* in the previous publication.<sup>4</sup> It is first of all evident that the improved treatment of the threshold function for CID produces an L-CID fit, which is satisfactory for the entire region from the onset of the dissociation up to and including the energy at which the cross-section plateaus. In

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(6) *CRUNCH*, version D1, was kindly provided as an executable by Prof. P. Armentrout.

## Scheme 2



**Table 1.** Ligand Binding Energies Extracted from Threshold CID Curves by L-CID<sup>a</sup>

complex	cleaved ligand	$E_0$ (loose TS) (eV)	$E_0$ (tight TS)d(eV)
$(R,R\text{-4c})_2\text{Cu}^+$	$(R,R)\text{-4c}$	$2.00 \pm 0.04$	1.40
$(S,S\text{-4b})(R,R\text{-4c})\text{Cu}^+$	$(R,R)\text{-4c}$	$2.15 \pm 0.03$	1.53
$(S,S\text{-4b})(R,R\text{-4c})\text{Cu}^+$	$(S,S)\text{-4b}$	$2.12 \pm 0.05$	1.48
$(S,S\text{-4b})_2\text{Cu}^+$	$(S,S)\text{-4b}$	$2.00 \pm 0.05$	1.40

<sup>a</sup>The standard deviations for the loose transition state contain the reproducibility of the data sets for three different measurements together with the uncertainty of the fit of L-CID with a genetic algorithm for each data set.

*CRUNCH*, one typically scales the parameter  $\sigma_0$  to produce a satisfactory fit only for the region around the onset of CID. At higher energies, the *CRUNCH* fit can deviate markedly from the experimental curve. The origins of the difference have been discussed previously.<sup>5</sup> Table 1 summarizes the parameters taken from L-CID fits, with uncertainties computed by repeated applications of the genetic algorithm under conditions that the convergence criterion is set to the statistical indistinguishability of the fits.

One should note that, of the complexes investigated here, one is still small enough for a *CRUNCH* fit. Careful application of *CRUNCH* to the T-CID of  $(S,S\text{-4b})_2\text{Cu}^+$  yields a value of  $E_0 = 2.16 \pm 0.05$  eV. Given that the uncertainty bounds in the *CRUNCH* fit only account for the degree of reproducibility of the fit, the agreement between the two methods, and the agreement with our previously reported measurement on the same system,<sup>77</sup> is satisfactory. For the interpretation of small differences in binding energies in the range of  $\sim 0.1$  eV, or equivalently, about 2 kcal/mol, one should therefore exercise caution in comparing absolute values extracted with L-CID to those extracted with *CRUNCH*. The practical advantage for L-CID, aside from having no constraints on size, is that L-CID did not require a prior quantum chemical calculation of frequencies. Whereas previous work, as well as an examination of the particular reaction, indicates that the ligand dissociation needs to be treated as a reaction with a loose transition state, Table 1 also lists the extracted binding energies for the hypothetical case of a tight transition state. The  $E_0$  values for the tight transition state have the same relative ordering, but are simply displaced by about 0.6 eV relative to those for the loose transition state.

## Discussion

Dissociation of diastereomeric ionic clusters as a means for the determination of stereochemical effects on stability

(7) The present dataset for L-CID differs from that required for *CRUNCH* in that L-CID requires the simultaneous measurement of the peak intensities for both the parent and the daughter ion. *CRUNCH* requires only the latter measurement. As long as there are no other processes depleting parent ion intensity, the two methods should be equivalent, although we do find that total integrated ion intensity can decline at very high collision energies.

have been reported and reviewed by Speranza and co-workers.<sup>8</sup> Relative stabilities were extracted from CID experiments using Cooks' kinetic method.<sup>9</sup> Seeking to avoid applying canonical rate theory, built into the Cooks' method via the effective temperature, to an experiment with micro-canonical excitation, and, furthermore, seeking to extract absolute ligand binding energies, we turned to the deconvolution of energy-resolved CID cross-section measurements, also called threshold CID experiments.<sup>10</sup> As Cooks had done for homo- and heterochiral complexes of isotopically labeled and unlabeled amino acids with Cu(II),<sup>11</sup> we constructed homo- and heterochiral 2:1 Cu(I) complexes,  $(\mathbf{4})_2\text{Cu}^+$ , with pseudo-enantiomeric  $\mathbf{4}$ , for which an innocuous label at a remote site must be introduced so that the pseudo-enantiomers, for example,  $(S,S)\text{-4a}$  and  $(R,R)\text{-4b}$ , have different masses. Given the assumption, not always proven, that the kinetic and thermodynamic behavior of the pseudo-enantiomers is in fact comparable to that of a pair of true enantiomers, the difference between the absolute ligand binding energies for the homo- and heterochiral 2:1 complexes gives the difference in thermodynamic stability needed to predict the sense and magnitude of a Kagan-type nonlinear effect for a 1:1 catalyst system in which the 2:1 complex serves as a reversibly formed reservoir species.<sup>3</sup> Absolute ligand binding energies for complexes with even a modicum of structural complexity are rare, despite the need for such data in constructing and validating mechanistic models. Threshold collision-induced dissociation experiments with electrosprayed complexes would appear to be a natural approach to the determination of ligand binding energies, but the procedure for deconvolution required prior quantum chemical calculations, which, for the coordinatively and electronically unsaturated organometallic species appearing in homogeneous catalysis, were disturbingly often themselves in need of validation against experiment. Nevertheless, threshold CID experiments on metal complexes have been

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reported by a few groups,<sup>12</sup> including the present one,<sup>13–16</sup> using the *CRUNCH* code from Armentrout and co-workers. In a recent publication, we applied threshold CID techniques to the determination of ligand binding energies in homo- and heterochiral 2:1 complexes of box and azabox ligands with Cu(I).<sup>4</sup> Internal control experiments validated the experimental approach for three of the four ligand families considered in the previous work. In the internal control using 2:1 complexes with pseudo-enantiomeric ligands, a particular heterochiral complex should show two different ligand losses with identical binding energies. Furthermore, the ligand binding energies for the two analogous homochiral complexes should agree with each other. Although the complexes with box ligands **1** and **2**, bearing isopropyl or phenyl substituents, as well as the isopropyl-substituted azabox complexes **3** met the criteria satisfactorily, the Cu(I) complex with phenyl-substituted azabox ligands failed the test for both homo- and heterochiral complexes. The latter complexes constituted an important test case for predictions of the relative stability for diastereomeric complexes, so a solution for the problem was needed.

The failure of the control experiments for (4)<sub>2</sub>Cu<sup>+</sup> could be attributed to structural (and then presumably energetic as well) distortions brought in by the substituents that were introduced to distinguish between pseudo-enantiomers, that is, the labels were not innocuous. The hydrogen versus CH<sub>3</sub>, rather than the better CH<sub>3</sub> versus C<sub>2</sub>H<sub>5</sub>, labels for that system were chosen, in turn, because *CRUNCH*, at least as it is presently available, cannot analyze data for ions with more than 87 atoms, which placed the complexes with **4c** out of reach. The ligands for 2:1 complexes in this study were chosen as the most-common ones in a privileged structure class, which appears repeatedly in asymmetric catalysis.<sup>17</sup> A smaller ligand certainly could have been used but only at the cost of applicability of the results to real systems of interest to solution-phase chemists. Aside from treating larger systems, and hence the more-optimal label scheme, the new analysis procedure, embodied in the program L-CID, removes a number of other limitations in *CRUNCH*, which become progressively more problematic as the complexes get larger. As has been discussed previously,<sup>5</sup> L-CID provides three major benefits: (i) A more realistic treatment of the electrostatic potential for the approach of the ion to the collision partner leads to a better, nonempirical threshold function, allowing the fitting of the cross section over the entire energy range rather than just the onset. (ii) Treatment of the kinetic shift with a new model for the density-of-states function eliminates the need for explicit entry of frequencies for the starting ion or the transition state without

loss of accuracy relative to direct state counts. (iii) Data fitting using Monte Carlo simulation and a genetic algorithm instead of the usual Marquardt–Levenburg least-squares routines not only produces an equivalent fit but also produces statistically relevant error bounds on the derived fit parameters.

As is evident in the results of the control experiments listed in Table 1, the larger labels do in fact eliminate the energetic, and presumably also structural, anomaly that impaired the previous data. Accordingly, the new fit results on the phenyl-substituted azabox complexes now clearly and unambiguously show that the ligand binding energy in the heterochiral 2:1 complex is larger than that in the homochiral analog, which is different from the case of the phenyl-substituted box complexes. Taking the present results together with those in the previous report,<sup>4</sup> one clearly sees that steric effects give the trend in ligand binding energy,  $E_{0,\text{hetero}} > E_{0,\text{homo}}$ , whereas  $\pi$ -stacking favors  $E_{0,\text{hetero}} < E_{0,\text{homo}}$  in the event that the substituents on the box or azabox ligand have  $\pi$ -systems. For the box and azabox ligands, **1** and **3**, with isopropyl substituents, there is only the steric contribution to the relative stability of the homo- and heterochiral diastereomers, so the observed ordering of  $E_{0,\text{hetero}} > E_{0,\text{homo}}$  is the expected one for both. For box ligand **2**, the structure permits  $\pi$ -stacking to an extent sufficient to invert the thermodynamic preference to  $E_{0,\text{hetero}} < E_{0,\text{homo}}$ . Importantly, nonbonded interactions, of which  $\pi$ -stacking is one example, are typically poorly treated in DFT calculations,<sup>18</sup> so theory provides only limited predictive ability. More concretely, DFT missed the inversion of the preference in the box case, as reported in the previous article.<sup>4</sup> On the other hand, extrapolation of the experimentally observed ordering of the phenyl-substituted box ligand case to the superficially similar complexes of the azabox ligand **4** would lead one to expect for the phenyl-substituted case the same  $E_{0,\text{hetero}} < E_{0,\text{homo}}$  ordering, which, however, is not borne out by experiment. We presume that the slightly different backbone in the azabox ligands leads to a geometry less favorable for a  $\pi$ -stacking interaction of sufficient magnitude to reverse the steric preference. In X-ray structures of related Zn(II) complexes,<sup>19</sup> as well as computed structures,<sup>4</sup> the box ligand is less nearly planar than a comparably substituted azabox ligand would be expected to be. One must conclude, given the failure of both DFT and argument by analogy, that the only reliable way to assess the sum of multiple, finely balanced interactions is direct experimental measurement of the binding energies for each case.

Methodologically, the extraction of the binding energies,  $E_0$ , from the threshold CID curves becomes, with L-CID, much more nearly a routine measurement for organometallic and coordination complexes with ~100 atoms or more. Because the structural diversity of these complicated systems is captured in a fit parameter, the effective frequency, one no longer needs to determine the structure and frequencies of the starting complex and transition state prior to deconvolution of the binding energy,  $E_0$ , from otherwise purely

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experimental data. Structural diversity introduced a lingering source of uncertainty in the results of fits with *CRUNCH*, as could be seen for dissociations of several classes of rhodium<sup>13</sup> or platinum<sup>15</sup> complexes in which the starting complex is formed in situ by gas-phase reactions, and for which there are multiple, energetically similar isomers for both the starting complex as well as the product of the collision-induced dissociation. Choosing a particular isomer in such a case makes the  $E_0$  derived with *CRUNCH* dependent on structures, which may prove incorrect upon later investigation. L-CID avoids this pitfall and hence should provide reliable thermochemical data even when structures are not known in advance.

### Conclusion

Application of a new deconvolution procedure for the determination of gas-phase ligand binding energies in transi-

tion-metal complexes to the stability of diastereomeric homo- and heterochiral 2:1 box and azabox complexes of Cu(I) reveals that the stability order depends sensitively on small structural differences. Given the previously demonstrated difficulty of reliable predictions by DFT theory, one would surmise that the direct experimental determination of the ligand binding energies would likely be a promising method for obtaining the thermochemical data needed to explain or predict Kagan-type nonlinear effects in asymmetric catalysis.

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**Supporting Information Available:** Reference mass spectra and full experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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