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How does a small peptide choose how to bind a metal ion? IRMPD and computational survey of CS versus Iminol binding preferences

Robert C. Dunbar[a,*], Giel Berden[b], Jos Oomens[b,c]

[a] Chemistry Department, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106, United States
[b] Radboud University Nijmegen, Institute for Molecules and Materials, FELIX Facility, Toernooiveld 7, 6525ED Nijmegen, The Netherlands
[c] University of Amsterdam, Science Park 904, 1098XH Amsterdam, The Netherlands

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ABSTRACT

Binding to proteins and peptides in condensed phases, it is normal for alkali and alkaline earth metal ions to interact preferentially with Lewis-basic oxygen, nitrogen and similar open chelation points, while late transition metals like cobalt, nickel and copper characteristically deprotonate and bind to amide nitrogens along the peptide chain. Parallel to these contrasting condensed-phase binding-mode alternatives, metal ions in the gas phase can form complexes with small peptides in several complexation modes, among them the charge-solvated (CS) and the Iminol patterns. Reported here is a computational study of the factors determining the choice between these patterns in the gas phase for model ligands, dialanine and trialanine, also including illustrative experimental spectroscopic results for $Ag^+(Ala)_3$ using the infrared multiple photon dissociation (IRMPD) technique (which has also provided previous experimental results for many of the ions studied here). Across a survey of 29 metal ions in normal oxidation states (+1, +2 and +3), unexpectedly strong correlations are found (for each charge state) between the preference for CS versus Iminol binding and the overall binding energies of the ions. Ions of +1 charge invariably prefer CS binding, while those with higher charge exhibit variable preferences. Within a given charge state, Iminol binding is more favorable, and overall binding is stronger, for light metal ions and for metal ions ("transition metals") late in the periodic table. The tendency to go from CS to Iminol in the gas phase is generally parallel to the tendency to bind deprotonated amide nitrogens in condensed-phase, but with possible divergence between the differing environments at the point where the tendencies cross over near Mg(II). Hard/soft character of the metal ions correlates to some extent with the binding preferences, but this correlation shows numerous discrepancies. For "main-group" metal ions, electrostatic character of the binding is suggested by excellent scaling of binding energies with a scaling parameter q/R, while a contribution of enhanced binding in addition to the electrostatic binding energy is indicated for "transition" metals.

1. Introduction

Gas-phase ion chemistry study of metal–ion–peptide complexes can model and illuminate corresponding complexation in liquid or crystal. However, the large differences in solvation, polarization and related electrical forces between the bare gas-phase environment and the closely packed surroundings of the condensed-phase complex induce crucial variations in the conformations of the most favored structures. For example, the preference for ionized (zwitterionic) acidic and basic end groups in aqueous solution is in striking contrast with the general preference for canonical structures in gas phase [1–6]. Recently a notable parallel between the gas phase and condensed phases has been recognized in the choice between metal ion complexation via *charge solvation* by ligand carbonyl groups (and other Lewis-basic chelation points) and deprotonation of skeletal amide nitrogen atoms with formation of *metal–nitrogen bonds* at the resulting anionic nitrogen sites [7].

Incorporation of metal ions into peptide and protein molecules characteristically involves chelation of the metal ion at several Lewis-basic sites drawn both from the amide linkages and the amino acid side chains. In the extensive literature of gas-phase metal-ion binding to mono-amino acids, a question drawing much attention has been the transition from charge-solvated binding to the formation of zwitterionic ground states [1,2,8–10]. For complexation with small gas-phase peptides, this question has not been as interesting, since zwitterion binding is generally not preferred on account of the larger number of basic charge-solvating

* Corresponding author. Tel.: +1 216 368 3712; fax: +1 216 368 3006.
E-mail addresses: rcd@po.cwru.edu, rcd@case.edu (R.C. Dunbar), joso@science.ru.nl (J. Oomens).

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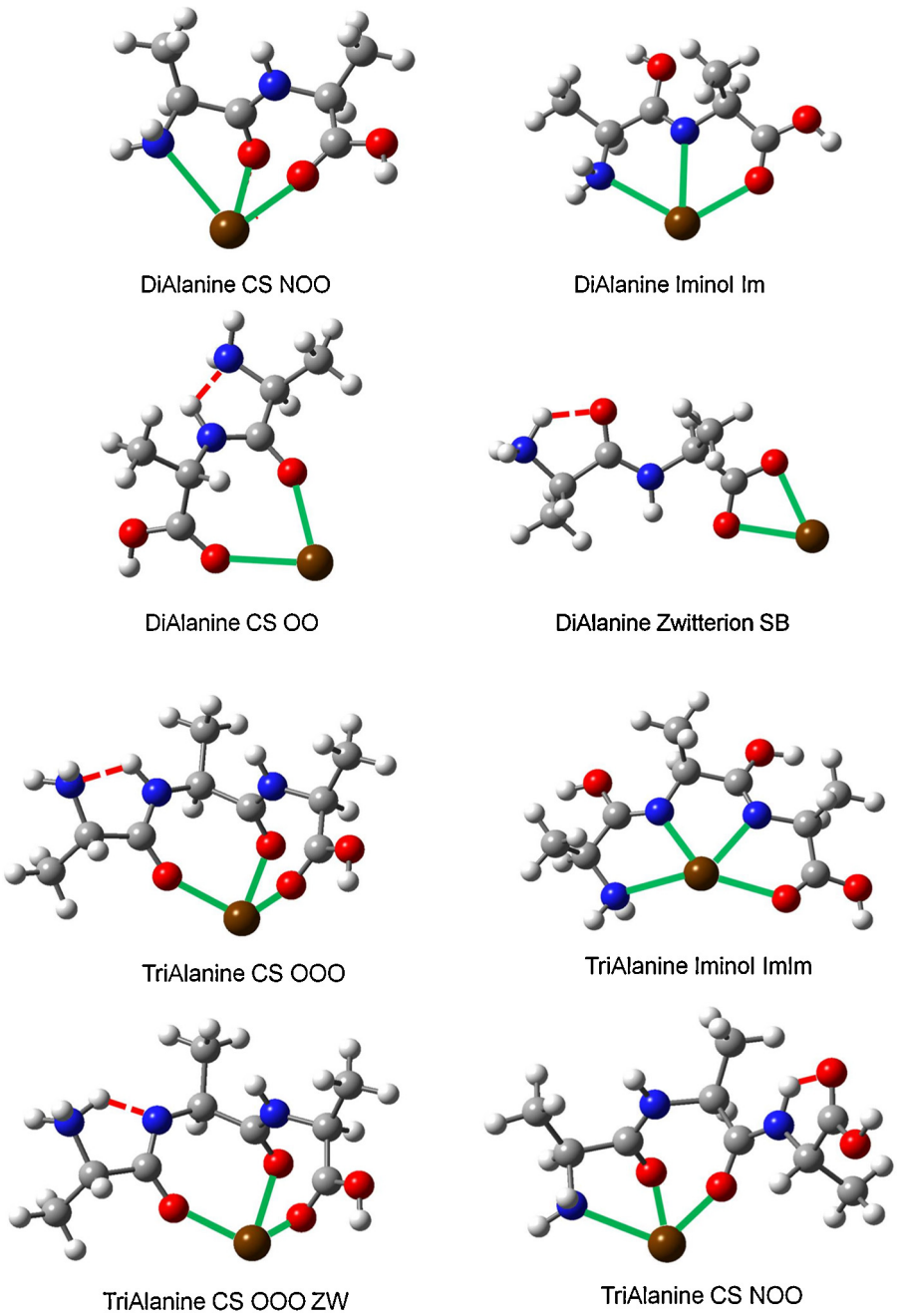

Fig. 1. Low-energy conformations of the dialanine and trialanine complexes, showing the Ba^{2+} complexes for illustration. Green lines represent metal–ion interactions with Lewis-basic sites, and red dashed lines represent clearly defined hydrogen bonds. (See text for explanation of structure labels.) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

chelation points available in these systems. Of greater interest for such peptides has been the transition from charge-solvated metal-ion binding to binding via direct metal bonding to the amide nitrogen(s). This is parallel to the well studied condensed phase process of deprotonation of amide nitrogens with formation of metal–nitrogen bonds. The difference between gas phase and condensed phase lies in the displaced proton remaining in the system in the gas-phase case, migrating by Iminol tautomerization to the amide carbonyl and forming the Iminol tautomer (as shown in Fig. 1). Infrared spectroscopic observations in the fingerprint region have proven to be an effective probe of this aspect of conformational preferences in electrosprayed complexes [11]; infrared multiple photon dissociation (IRMPD) experiments [1,2] using the free electron laser at the Free Electron Laser for Infrared eXperiments (FELIX) have characterized the switch to the Iminol binding mode for a few complexes of Ni^{2+}, Co^{2+} and Mg^{2+} with di-, tri- and tetra-peptides [7,12]. Here we describe further study of this complexation question as a suitable tribute to Detlef Schröder's sustained and diverse interests in the conformations, properties and reactivity of metal–ion complexes, exploring a wide variety of metal ions and of mass spectrometric techniques, including infrared spectroscopic approaches (for example, [13–17]).

In solution, the deprotonated amide mode of binding to peptide chains was recognized already early on as a common theme in transition-metal binding, and has been extensively studied and reviewed [18–24]. This aspect of metal–peptide binding has been

of recent interest in view of suspicions that Cu(II) interaction with prion proteins is central to Alzheimers and other prion diseases [25,26].

It is of interest to make a broader survey of a wider variety of metal ions, in the non-perturbing environment of the gas phase, in order to map out the expectations of when the transition to Iminol binding can be anticipated. The present study undertakes this task, using the minimally complicated small peptides dialanine and trialanine as trial ligands. The study is tightly focused on the question of the relative favorability of CS versus Iminol binding to gas-phase di- and tri-peptides without active side chains. The choice of which metal ion species to include is somewhat arbitrary, but in general we have aimed to include normal oxidation states of metals of actual or possible interest in biological systems, along with some more exotic species that are of interest for comparisons. Some species (like Co(III)) that would have been interesting were found to be computationally too troublesome for convincing results, and were dropped. Ions of charge greater than +3 give unreasonable and uninterpretable results in gas-phase calculations, as well as being unlikely as stable gas-phase species. Even +3 species were found to be prone to complications like Coulomb explosion and skeletal rearrangements, and the results obtained and shown below for +3 ions are rather scattered and clearly inferior to the +1 and +2 data sets. The set of 29 species selected gives a sufficiently wide coverage of the periodic table for some interesting trends to be fleshed out.

Fig. 1 displays the principal conformations of interest here. The terminology of the conformations is intended to be self-evident. "CS" designates charge-solvated complexes with unrearranged amide linkages and the metal ion chelated by the indicated set of O and/or N atoms. "ZW" appended to CS labels indicates a complex having retention of the metal ion in the charge-solvated form, but having a zwitterion-type rearrangement of an amide proton as explained below. An "SB" label designates a salt bridge zwitterion with an $-NH_3^+$ group and with the metal ion bound to the ionic $-COO^-$ group of deprotonated carboxyl. "Iminol" designates the Iminol-rearranged tautomeric form, with the following "Im" or "ImIm" notation indicating respectively one or two metal bonds to Iminol-rearranged nitrogens.

The CS conformations generally follow the established observation that as many as possible of the available carbonyl oxygens tend to coordinate the metal [27–29], although it has been found, and is seen below, that the amino nitrogen may compete with oxygen (trialanine structure CS NOO) if compensating hydrogen bonding of a carbonyl is available. A contrast emerges between the present peptide complexes and the metal-ion complexes of the mono-amino acids, where it is frequently found that the best conformation is the salt-bridging zwitterion in which the terminal carboxyl proton moves to the amino nitrogen (SB). This latter pattern is only rarely found as the preferred conformation in the present survey, and is not discussed here. However, with the trialanine ligand, it is shown below that the CS OOO conformation frequently transfers an amide proton to the amino nitrogen giving structure CS OOO ZW (see Fig. 1).

CS predominance for the Na^+ complexes of di- and tri-peptides of Gly and Ala has been amply shown by the spectroscopy and computations of the Paris group [27,28]. Corresponding polyglycine and polyalanine peptides are expected to have similar complexation behavior in most circumstances, so both polyglycine and polyalanine studies can provide relevant examples of metal-ion complex conformations for binding to simple (i.e. without active side chains) peptides. As referenced below, all of the spectra of dialanine and trialanine metal ion complexes that have been acquired by the FELIX group have been published, with the exception of $Ag^+(Ala)_3$. Although the Iminol conformation of this last complex is definitely, and not surprisingly, less stable by a substantial margin than CS conformations, the spectrum is nevertheless exceptionally interesting because computation indicates nearly equal energies for the CS OOO and CS NOO conformations, and experiment is called on to resolve the nature of the favored conformation. Accordingly, its spectrum is shown here, and analyzed briefly.

2. Methods

2.1. Computation

All calculations were carried out using the Gaussian03 quantum chemical package [30]. Starting structures for the optimizations were assigned based on our previous experience with computational surveys of conformations giving low energies for a variety of metal ions complexed with di- and tri-peptides. The default computational level was the B3LYP density functional with the 6–31 + g(d,p) basis set. For metals starting with Rb, the SDD basis set with a relativistic effective core potential was used. For some of the transition metal complexes, additional full-optimization calculations were carried out using the MPW1PW91 functional. Use of this latter functional made little difference except in the case of Ni(II), for which the results from this functional are discussed below. In making comparisons of the energies of low-lying isomers, differences of less than 20 kJ mol^{-1} which were considered important for the present purposes were checked by full optimization with the larger 6–311 + g(d,p) basis. The two different basis sets usually gave difference values between isomers in agreement within a few kJ mol^{-1}, seldom disagreeing by as much as 5 kJ mol^{-1}, so the smaller basis set was considered to be large enough for reliable energy comparisons (to the extent of validity of B3LYP) within the present universe of complexes. Energies are taken as the 0 K enthalpy, without thermal or vibrational zero-point corrections. Binding energies were not corrected for basis set superposition error, which is typically not found to be large for B3LYP calculations at the level of precision needed in the present survey [31,32].

The Ag(I) complex was given special consideration, in light of the experimental result described below, showing a CS OOO conformation for $Ag^+(Ala)_3$ rather than the calculated CS NOO conformation (amino N bound to the metal), where the latter structure was favored by 12 kJ mol^{-1} at the B3LYP/6–31 + g(d,p) level and by 7 kJ mol^{-1} at the B3LYP/6–311 + g(d,p) level. Following the experience of the York group [33,34], we considered that the DZVP basis set might give more accurate energy results. (The computed infrared spectra are practically the same for all of these different basis sets.) As will be seen below, comparison using the latter basis set did indeed predict the correct (CS OOO) lowest-energy conformation, with the CS OOO conformation preferred by 6 kJ mol^{-1} compared with CS NOO, although these two conformations are not predicted to be very far apart by any of these calculations. This last value will be used in the following discussion.

Calculations were carried out at the LISA Linux cluster of the SARA Supercomputer center in Amsterdam. For comparison of DFT spectra to IRMPD spectra, the computed frequencies were scaled by a factor of 0.976, which is known to be adequate at the current level of theory [35]. Computed spectra were convoluted with a 20 cm^{-1} or 30 cm^{-1} FWHM Gaussian lineshape function for comparison to experimental IR spectra.

2.2. IRMPD experimental

IR spectra of the gaseous metal ion–dipeptide complexes were recorded employing a Fourier-transform ion cyclotron resonance mass spectrometer (FT-ICR MS) coupled to the Free Electron Laser for Infrared eXperiments (FELIX), as has been detailed elsewhere [2,12,36]. Metal–ion–peptide complexes were generated

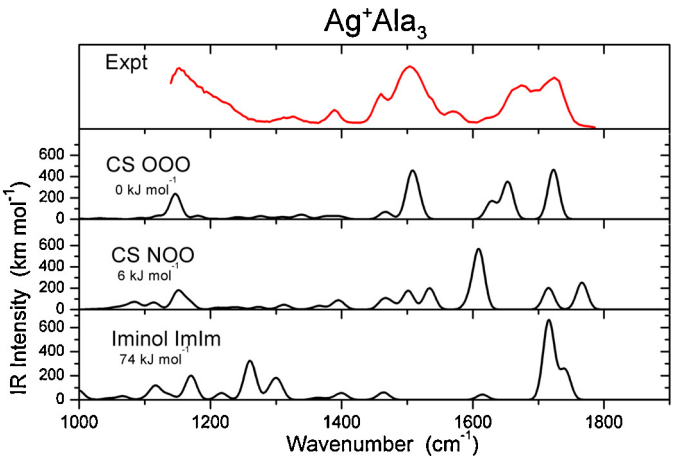

Fig. 2. Experimental IRMPD spectrum of $Ag^+(Ala)_3$ (top, red) and the calculated spectra of the three indicated conformations. The relative energies shown are from the calculations using the DZVP basis, as discussed in the text. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

by electrospray ionization (ESI, Waters Z-Spray) from a solution containing the peptide and metal salt in acetonitrile/H_2O (~4:1). Target ions were trapped and mass-selected in the FT-ICR cell and were irradiated with the wavelength-tunable infrared light from FELIX. Plotting the sum of all dissociation channels ratioed to the total ion count as a function of laser frequency, an infrared action spectrum was generated, and interpreted as a surrogate for the linear IR spectrum of the complex. DFT-computed linear IR spectra of candidate ion structures were compared with the observed spectra, where the calculated relative energetics provided additional guidance, to assign conformational and tautomeric structures.

3. Results

3.1. Spectroscopy of $Ag^+(Ala)_3$

Fig. 2 displays the IRMPD spectrum of the trialanine/silver(I) complex, along with computed spectra for the two lowest-energy CS structures (CS OOO and CS NOO) and the Iminol ImIm complex. The CS OOO structure provides a very acceptable match between the major predicted absorption bands and the observed spectrum in the fingerprint region. The carboxyl carbonyl stretching band near 1715 cm^{-1} and the Amide II peak near 1500 cm^{-1} are well matched, while the Amide I peak seen at about 1670 cm^{-1} is predicted about 20 cm^{-1} too low, which is not an unacceptable degree of error. The predicted spectra for the alternative possibilities, CS NOO and Iminol ImIm, are in poor agreement with the observed spectrum. The spectroscopic conclusion is thus strong that the CS OOO conformation dominates this ion population.

3.2. Ground states of the complexes

The principal computed relative energies from the survey are tabulated in Tables 1 and 2. For a small fraction of the complexes studied here, a zwitterion salt-bridge (SB) complex having a proton transferred from the carboxyl group to the terminal amino group was found to be competitive, or even favored, versus CS isomers. This is not surprising for the Ba^{2+} complex, since experience with its complexes with monomeric amino acids has shown that the zwitterion is typically the ground state for those complexes [37–39], in contrast to most other alkali and alkaline earth metal-ion complexes of the same ligands. It is thus not unexpected that the zwitterion is competitive with CS structures for the dipeptide in this case. SB zwitterionic structures were also competitive for the group 3 triply charged complexes of scandium(III) and lanthanum(III). In the present analysis, however, the SB structures were ignored and these exceptional complexes were subjected to the same assessment as the rest of the data set, addressing in particular the question of whether the lowest-energy CS conformation is favored over the Iminol conformation or not.

Other aberrations of the triply charged complexes were cases where the apparent DFT ground state formed a covalent bond between the metal and a skeletal carbon. These conformations were also ignored, but if formation of such triply charged peptide complexes ever becomes experimentally feasible, extreme rearrangements like these will be of interest.

Uniquely among the diverse metal ions in the present data set, several dialanine complexes with alkali cations have a two-coordinate charge-solvated structure CS OO as their ground state, rather than the usual ground-state CS NOO structure. Microsolvation of the metal ion by only two Lewis-basic sites instead of three definitely involves a substantial energetic sacrifice, but this is compensated for by the presence of a strong hydrogen bond between the free NH_2 group and the proton on the amide nitrogen. The

Table 1
M^{n+}AlaAla. Energies of selected isomers, relative to the most stable CS or Iminol isomer, which is assigned as 0 kJ mol^{-1}. Binding energies to neutral ligand are defined as the energy to detach the metal ion from the most stable complex. All values in kJ mol^{-1}. Last column indicates the structure assigned based on the experimental spectrum in the given reference(s). Values for entries left blank were not calculated or available in the literature.

M^{n+}	CS NOO	CS OO[a]	Iminol	SB[b]	Binding	Spectrum
Li(I)	9	0	38		311	CS OO[c]
Na(I)	8	0	49		224	CS NOO or CS OO[d]
K(I)	12	0	72	58	161	CS OO[c,e,f]
Rb(I)	13	0	78		135	
Cs(I)	15	0	85		118	CS OO[f]
Mg(II)	0	74	0		905	
Ca(II)	0	36	40	20	603	CS NOO[c,e,f]
Sr(II)	0	25	46	10	563	CS NOO[c,e]
Ba(II)	0	17	53	0	484	CS NOO[c,e,f]
Sc(III)	0		26	−12	1877	
Y(III)	0		34	27	1471	
La(III)	0		48	−14	1269	
Mn(II)	10		0		924	
Fe(II)	19		0		1035	
Fe(III)	39		0		2413	
Co(II)	20		0		1097	
Ni(II)	35[g]		0[h]		1179	
Pd(II)	127		0		1436	
Pt(II)	157		0		1502	
Cu(I)	0	34	29		393	
Cu(II)	84	94	0		1296	
Ag(I)[i]	0	1[j]	32		282	
Ag(II)	58		0		1187	
Au(I)	0	36[j]	51		370	
Zn(II)	45	120	0	95	1135	
Cd(II)	28	89	0	31	907	
Hg(II)	31		0		996	
Al(III)	68		0	185	2406	
Ga(III)	96		0		2525	

[a] CS OO conformation with amino nitrogen hydrogen-bonded to amide proton.
[b] Salt bridge zwitterion with $-NH_3$ group and metal ion bound to $-COO^-$ group.
[c] Ref. [40].
[d] Ref. [27]. Our calculation found CS NOO less stable than CS OO by 8 kJ mol^{-1}, while Ref [27] reported it to be more stable by 2 kJ mol^{-1} using a slightly different protocol. These structures cannot be distinguished with confidence based on the spectrum in the mid-infrared, and we will not decide between them.
[e] Ref. [41].
[f] Ref. [12].
[g] Triplet state. Singlet is higher than triplet by 80 kJ mol^{-1}.
[h] Singlet and triplet states are equally stable by B3LYP. Using MPW1PW91 the triplet was more stable than the singlet by 18 kJ mol^{-1}.
[i] B3LYP/DZVP.
[j] CS NO with amide proton hydrogen-bonded to carboxyl carbonyl.

Table 2
$M^{n+}(Ala)_3$. Energies of selected isomers, relative to the most stable isomer, which is assigned as 0 kJ mol^{-1}. Binding energies to the neutral ligand are defined as the energy to detach the metal ion from the most stable complex. All values in kJ mol^{-1}. Last column indicates the structure assigned based on the experimental spectrum in the given reference(s). Values for entries left blank were not calculated or available in the literature.

M^{n+}	CS OOO	CS OOO ZW	ImIm	SB[a]	Binding	Spectrum
Li(I)	0	[b]	102		363	CS OOO[c]
Na(I)	0		122		268	CS OOO[d]
K(I)	0		151		199	CS OOO[c,e]
Rb(I)	0		153		165	
Cs(I)	0	[b]	157	11	144	CS OOO[c]
Mg(II)	2	16	0	31	1050	
Ca(II)	0	33	80	42	790	CS OOO[c,e]
Sr(II)	0		103	26	682	CS OOO[c]
Ba(II)	0	36	118	25	594	CS OOO[c,f,e]
Sc(III)	56	0	78	45	2215	
Y(III)	41	0	79	34	1744	
La(III)	34	0	129	25	1540	
Mn(II)	8	20	0		1051	
Fe(II)	28	[b]	0		1183	
Fe(III)	82		0		2731	
Co(II)	51		0		1248	
Ni(II)	146[g] (T)	110 (T)	0[h] (S)		1385	ImIm[e]
Pd(II)	167	175	0		1611	
Pt(II)	234		0		1706	
Cu(I)	0	[b]	68		429	
Cu(II)	98	106	0		1453	
Ag(I)[i]	0	6[j]	74		285	CS OOO[k]
Ag(II)	14		0		1306	
Au(I)	0 (CSD)	17	90		407	
Zn(II)	57	62	0		1278	
Cd(II)	56	61	0	80	1031	
Hg(II)	52	56	0	94	1115	
Al(III)	160	91	0	134	2804	
Ga(III)	201	127	0		2900	

[a] Salt bridge zwitterion with $-NH_3^+$ group, and the metal ion bound to $-COO^-$ group.
[b] Spontaneously rearranges to CS OOO.
[c] Ref. [40].
[d] Ref. [27].
[e] Ref. [12].
[f] Ref.[41].
[g] Triplet (more stable than singlet by 27 kJ mol^{-1}).
[h] Singlet (more stable than triplet by 58 kJ mol^{-1}).
[i] B3LYP/DZVP.
[j] CS NOO.
[k] Fig. 2.

energetic gain from this H-bond was assessed for the five alkalis by comparing the strain energy of the bare CS OO dipeptide against the same bare CS OO dipeptide altered by having the terminal $-C(H)(CH_3)(NH_2)$ group rotated 120° to take the amino group out of contact with the amide proton. For the set of five alkali ion complex geometries, the hydrogen bond was found by this test to be worth about 37 kJ mol^{-1}. This is sufficient in the alkali ion cases to compensate for the loss of the nitrogen–metal bond in going from CS NOO to CS OO, although it does not compensate for the loss of the chelation site for any of the other metal ions.

As context for this hydrogen-bonding result, no literature comparison was found for the strengths of hydrogen bonds specifically like this one with an amide NH donor and an amino nitrogen acceptor. Our result of 37 kJ mol^{-1} for this hydrogen bond strength is of the same magnitude as estimates for related donor-acceptor pairs: amide NH donor and amide carbonyl oxygen acceptor (~25–35 kJ mol^{-1}) [42,43] or phenolic OH donor with a dimethylamino nitrogen acceptor (~35 kJ mol^{-1}) [44].

For Ni(II) with dialanine, the Iminol ground state was calculated to be equally stable in its singlet or triplet state, using B3LYP. The MPW1PW91 functional has been considered to give more reliable energy results than B3LYP for transition metals [45,46], so a variety of isomers of the dialanine and trialanine Ni(II) complexes were re-optimized using this alternative functional. In accord with the results reported for condensed-phase systems [23], we found that the ground state of the Ni(II)–dipeptide complex is the triplet Iminol (18 kJ mol^{-1} more stable than the singlet), while the ground state for the tripeptide is the singlet Iminol. The values used below for the Ni(II) complexes are those calculated at the MPW1PW91/6–31+G(d,p) level.

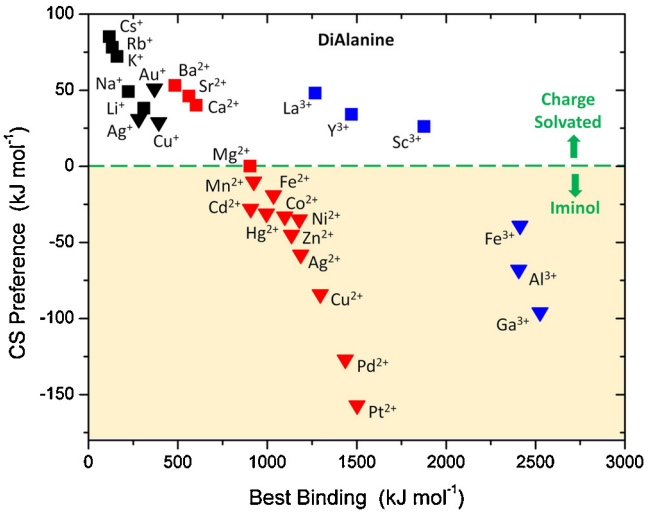

Fig. 3. Plot of the CS preference value (excess of the stabilization energy of the best CS structure over the Iminol structure) for complexes of dialanine with all ions studied. The points are coded as follows: Black is +1 charge, red is +2 charge and blue is +3 charge; (■) are "early" or "main-group" metal ions, (▼) are "late" or "transition" metal ions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

4.1. Predicted conformational preferences

We can note that for those complexes where the IRMPD spectra have been examined (as noted in the right-hand columns of the tables), the computed lowest energy conformation is always the one that is observed experimentally.

To sharpen the focus of the present study, these computed results have been reduced to a characteristic number, designated as the "CS preference," which is the difference between the energies of the most stable CS and Iminol structures found. In Figs. 3 and 4, these values are plotted for the two ligands versus the binding energy of the most stable complex (i.e. the energy required to remove the metal from the most favorable complex in each case). The signs are taken such that a positive CS preference value corresponds to an energy advantage in favor of CS versus Iminol. The points on the plots are coded to distinguish between the three different charge states (colors); and between the "early" metal ions lying in groups 1–4 and the "late" metal ions in groups 7–13. We will make a point of the distinction between metals early in the periodic table, also referred to as "main-group" metals, and those late in the periodic table, which we will also call "transition" metals.

We can initially make several generalizations from the plots:

1 Singly charged complexes always favor CS.
2 Among doubly and triply charged complexes, "early" metal ions favor CS, while "late" metal ions favor Iminol (with Mg(II) and Mn(II) lying close to the boundary).
3 Within each charge-state, there is a remarkably good, nearly (but not quite) linear correlation between binding strengths and CS preference values. Stronger ion binding correlates strongly with

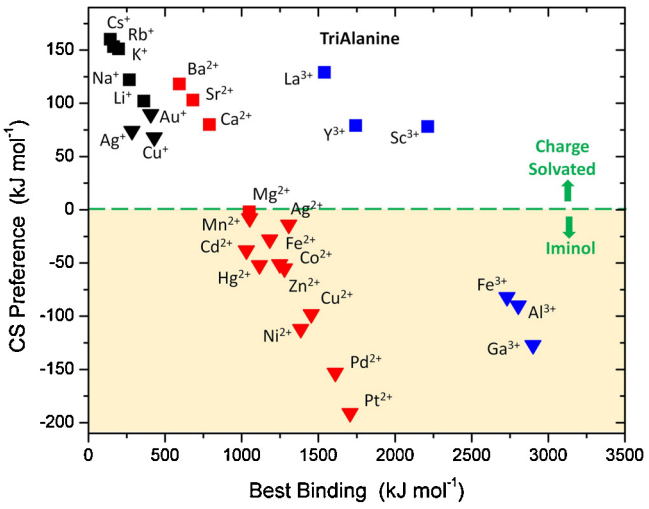

Fig. 4. Plot of the CS preference value (excess of the stabilization energy of the best CS structure over the Iminol structure) for complexes of trialanine with all ions studied. The points are coded as follows: Black is +1 charge, red is +2 charge and blue is +3 charge; (■) are "early" metal ions, (▼) are "late" metal ions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

greater preference for Iminol conformation. These correlations versus ion binding affinity are independent of whether the ion is "early" or "late".

4 Results for the dipeptide (Fig. 3) are nearly the same as for the tripeptide (Fig. 4).

Looking at the plots in more detail, there are some surprising and interesting trends. For ions within a given charge state group, the "late" ions have almost universally greater total binding strength as well as much greater Iminol preference than the "early" ions. On the other hand, increasing the charge of the metal ion while retaining the same character of "early" or "late" strongly enhances the overall binding, but need not have an effect on the CS preference. For instance, compare the series of dialanine complexes with Li(I), Ca(II) and Y(III), which have widely differing binding strengths but similar CS preferences. But conversely, passing from "early" to "late" while concurrently decreasing the charge can drastically increase the Iminol preference, while not changing the binding strength (compare Y(III) and Pd(II)). Other things being equal, heavier metals tend toward Iminol more strongly than lighter metals (compare the alkali metal series, for example). Thus it is seen that there are three independently variable dimensions affecting the CS preference values of the metal ions: (1) Charge state; (2) "Early" or "late"; (3) Size. It may also be suggestive in terms of differing bonding mechanisms that the "early" metal ions favoring CS have outer s and p electrons, whereas the "late" ones favoring Iminol (with the exception of Al^{3+}) have d electrons as their outer, exposed electrons, giving us the basis for our frequent designation of the former metals as "main-group", and the latter as "transition".

We can compare the propensities for metal ion binding to the amide nitrogen with corresponding trends observed in solution (for example, Refs. [22,23,47]), although the ionic equilibria in solution are complicated and pH sensitive, making quantitative conclusions rather hard to pin down. In solution, the tendency for depronation and metal binding of the peptide amide nitrogens by some of the most heavily studied ions follows the order [22]

$$Pd^{2+} > Cu^{2+} > Ni^{2+} > Co^{2+}$$

Tables 1 and 2 as well as Figs. 3 and 4 show that the calculated gas-phase preferences are in this same order for both dialanine and trialanine, except for the slight reversal of the Cu^{2+}/Ni^{2+} order with trialanine.

Table 3
Correlation of dialanine/metal–ion CS binding preference (listed in order of decreasing CS preference) versus assignments of hard or soft character of the metal ions.

Metal ion	Dialanine	Ahrland [48]	Pearson [49]	Klopman [51]
Cs(I)	CS	Hard	–	–
Rb(I)	CS	Hard	–	–
K(I)	CS	Hard	Hard	–
Na(I)	CS	Hard	Hard	Borderline
Au(I)	CS	Soft	Soft	Soft
Ba(II)	CS	Hard	–	Hard
Sr(II)	CS	Hard	Hard	Hard
Ca(II)	CS	Hard	Hard	Hard
La(III)	CS	Hard	Hard	Hard
Y(III)	CS	Hard	–	–
Li(I)	CS	Hard	Hard	Borderline
Ag(I)	CS	Soft	Soft	Soft
Cu(I)	CS	Soft	Soft	Soft
Sc(III)	CS	Hard	–	–
Mg(II)	Borderline	Hard	Hard	Hard
Mn(II)	Borderline	Borderline	Hard	
Fe(II)	Im	Borderline	Borderline	Borderline
Co(II)	Im	Borderline	Borderline	–
Cd(II)	Im	Soft	Soft	Soft
Ni(II)	Im	Borderline	Borderline	Borderline
Fe(III)	Im	Hard	Hard	Hard
Hg(II)	Im	Soft	Soft	Soft
Zn(II)	Im	Hard/borderline	Borderline	–
Ag(II)	Im	–	–	–
Al(III)	Im	Hard	Hard	Hard
Cu(II)	Im	Borderline	Borderline	Soft
Ga(III)	Im	Hard	Hard	Hard
Pd(II)	Im	Soft	Soft	–
Pt(II)	Im	Soft	Soft	–

4.2. *Nature of bonding and origin of the CS/Iminol preferences*

The empirical trends and robust observational conclusions described so far are suggestive of underlying regularities, but we are not confident yet of understanding these at a fundamental level. Questions to be addressed include: What is the nature of the binding interaction between metal ions and peptides, and does the nature of binding differ between CS and Iminol conformations, or between main-group and transition metals? Can we identify a specific aspect of the bonding which differs crucially between CS and Iminol to explain the regular preference trends displayed in Figs. 3 and 4? We present some further views of the data bearing on these questions, but it should be recognized that these reflections are tentative and speculative, and deeper understanding is still in the future.

4.2.1. *Correlation with hard/soft character*

A commonly invoked basis for two-way partitioning of metal ion behavior is the hard/soft acid distinction popularized by Pearson, and used with many variations by many authors. Table 3 correlates the CS/Iminol behavior described here for our dialanine data set with several assigments of metal-ion hardness/softness. The metal ions are ordered according to their CS preference character. Three hard/soft assignments are given in the last three columns of the table: These are the early classification of Ahrland et al. [48] into metal ions of classes A and B (and borderline) where A is equivalent to "hard" and B to "soft; the classification adopted by Pearson [49], which is essentially adopted in many more recent studies and texts [50]; and the theoretically-derived classification developed by Klopman [51]. The table shows a general tendency for the hard metal ions to favor CS conformations in our results, and the soft metal ions to favor Iminol conformations. However, there are

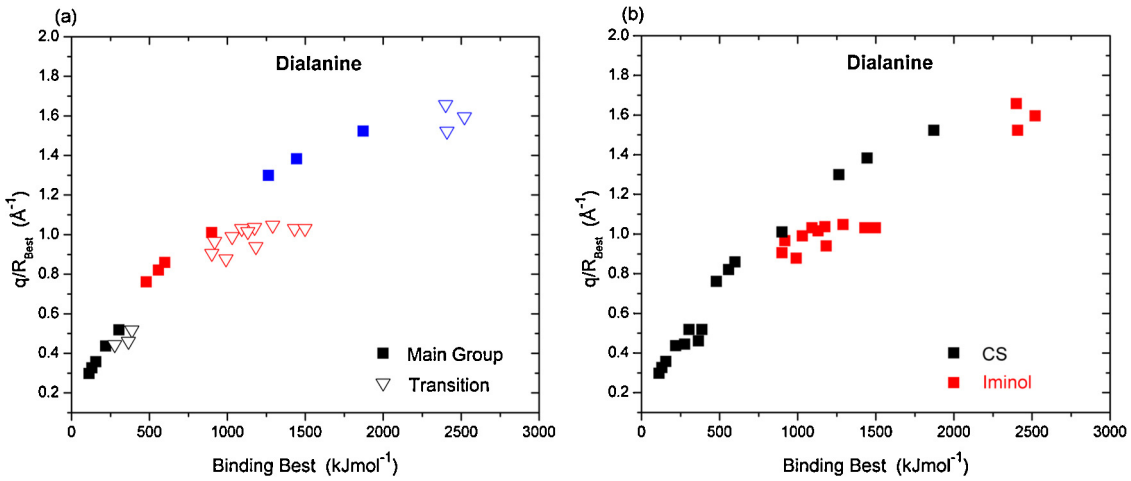

Fig. 5. (a) Binding energy to dialanine in the CS conformation versus the electrostatic scaling parameter q/R_{CS}. Black symbols are +1, red symbols are +2, and blue symbols are +3. (b) Replot of the same data with points labeled with black for metals favoring CS and red for those favoring Iminol. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

numerous discrepancies (7 wrong, and 4 indeterminate, out of 29) with some hard ions giving Iminol binding, as well as some soft ions giving CS binding. It appears that the hard/soft classification is a rough, unreliable and inaccurate basis for correlating the binding behavior studied here.

4.2.2. Correlations of bond lengths

The strength of metal binding (and by extension the CS preference) is highly correlated with the length of the bonds between metal and Lewis-basic chelation sites, in keeping with the usual bond-length–bond-strength relationship. In considering CS complex conformations, we will use the length of the carboxy carbonyl metal-to-oxygen bond length (R_{CS}) as a uniform measure of the effective CS chelation size of the metal ion. (The other metal-to-atom bond lengths to amide carbonyl and amino nitrogen closely follow R_{CS}). Similarly for Iminol structures, the length of the metal-to-amide-nitrogen bond (R_{Im}) will serve as a uniform measure of the effective Iminol chelation size of the metal ion. These bond lengths are shown in Table S1.

The first point is that R_{CS} and R_{Im} are well correlated with each other, as demonstrated for dialanine in Fig. S1 (Supplementary material) which displays the bond-length data tabulated in Table S1. The linearity of this plot is good. The slope deviates a bit from unity, such that the largest metals (notably the alkali metal ions) tend to have longer bonds in the Iminol, possibly because there is additional steric strain in the more crowded Iminol binding site. Assuming that bond lengths and bond strengths vary together, this deviation from unit slope in Fig. S1 is simply another way of showing, just as do Figs. 3 and 4, that the weakly binding metal ions (long bonds) favor CS, while the strongly binding metals (short bonds) favor Iminol. This point of view is even more clearly displayed in Fig. S2, plotting the Iminol binding energy against the CS binding energy, and showing the slight deviation from unit slope that underlies the preferences displayed by Figs. 3 and 4. It is notable that the span of CS/Iminol preferences is much smaller (basically tens of kJ mol^{-1}) than the span of bond strengths across this data set (hundreds and thousands of kJ mol^{-1}).

The fact that the length of the metal–oxygen bond to a CS chelated atom and the length of the metal–nitrogen bond to the deprotonated Iminol nitrogen are almost co-varying across this wide range of metal ions suggests that there is nothing special about the metal–deprotonated-nitrogen bond compared with the metal–ion pair interactions with the carbonyl oxygens and the amino nitrogen.

4.2.3. Electrostatic binding of main-group metal ions

There is quite a good correlation of bond energies and bond lengths within each charge state (see Table S1 and Fig. S3) although some transition metal ions are outliers, and the different charge states have very different trends. A more revealing and suggestive way to plot the same data, shown in Fig. 5, can be based on a crude model of electrostatic interaction, having the character of interaction of a point charge on the metal ion interacting with fixed (negative) charge accumulations on the chelating atoms. This electrostatic energy of interaction ($V_{Coulomb}$) would be expected to follow to a first approximation the form of a Coulomb charge–charge potential

$$V_{Coulomb} \propto q/R$$

where q is the charge on the metal ion and R is the distance from the metal ion to the (assumed unvarying) effective charge at an atomic chelation site. This model is too crude to afford even an approximation to the actual binding energies, but we can try out its prediction that the binding energy will scale as q/R. Fig. 5(a) plots the data in this way for the dialanine case. As in Fig. 3, the binding energy for each metal ion is that for the best conformation (either CS or Iminol). The bond length parameter q/R_{Best} is taken from the corresponding bond length for that conformation and the ion charge q. Actually, it is found to be unimportant whether the plot is made for the best conformations, or for the CS conformations, or for the Iminol conformations. As is clearly seen from the alternative plots using all CS, or all Iminol, (shown as Figs. S4 and S5 in the Supplementary), the appearance and the essential features of the plot are virtually identical and indistinguishable for these different choices of data plotting.

The most striking and suggestive aspect of the Coulomb-based plot of Fig. 5(a) is that it places the main-group elements (filled square symbols) on an excellent smooth line encompassing all three charge states and a wide range of metal ion sizes. This smooth scaling of the main-group complexes according to the Coulomb-based interaction parameter q/R suggests that an electrostatic binding model for the main-group metals is a good first-order description. Also shown by the plot is that the transition elements (empty triangle symbols) are consistently below the trend line of the main-group metals, although these deviations vary substantially in magnitude. These deviations can be interpreted to say that a transition metal ion of the same size and charge will bind more strongly than a corresponding main-group metal ion. Thus we suggest that a dominant interaction underlying binding of the metal

ions with dialanine is a Coulomb electrostatic potential energy, and that in addition to this Coulomb interaction the transition metal ions have a variable additional interaction. We can speculate that the enhanced binding of the "transition" metal ions could arise by an enhanced interaction of the exposed d electrons of the transition metal ions with the chelating sites. Or it might be attributable more directly to their late position in the periodic table with concomitant contraction of the valence orbitals. The precise origin of this effect can be left as a question for future elucidation.

A different perspective on this plot is shown as Fig. 5(b), where the points have been re-labeled according to whether the complex prefers CS (black) or Iminol (red) binding. This view shows that it is the Iminol-binding ions that deviate from the Coulomb picture of binding, and reinforces the speculation that Iminol binding is promoted by an enhanced binding contribution from the valence d electrons of the "transition" metal ions. The singly-charged ions do not form Iminol complexes, which we would say reflects an insufficiently strong d-orbital contribution to tip the balance in favor of Iminol binding.

Another major term in the interaction potential between an ion and a ligand is the polarization potential, pictured in the simplest model as the force arising from the charge-induced-dipole interaction. In the simplest model, the polarization potential energy scales as [52]

$$V_{\text{Polarization}} \propto q^2/R^4.$$

We tested this alternative scaling prediction for our data set as shown in Fig. S6. Although the figure indicates that this polarization scaling is also somewhat successful in ordering the data, we see that this plot yields nowhere near the same smooth regularity for the main-group points, and seems much less satisfactory for sorting out the main-group elements than the plot of Fig. 5. We conclude from this failure, and from the excellent scaling shown in Fig. 5, that the Coulomb electrostatic component of binding is dominant at least for the main-group metals, and the polarization component of binding is less important in these complexes.

5. Conclusions

With the discovery that IRMPD spectroscopy is a widely applicable probe for conformational characterization of metal-ion peptide complexes of small peptides, it has become interesting to explore the transition from charge-solvated binding (CS) to binding involving a metal–amide-nitrogen bond (Iminol). A survey of almost thirty ions of interesting metals in normal oxidation states was undertaken to map out the energetic aspects of this choice of different binding modes using two uncomplicated peptide ligands. The experimental capabilities underlying our interest in this question have been illustrated with the example of the previously unpublished Ag^+ complex with trialanine, which clearly displays a CS mode of binding in the CS OOO conformation.

The computational energy survey quantifies the energetic preference for the best CS complex in each case, versus the Iminol conformation. The principal general features which emerge are:

- Singly-charged systems are always CS.
- Among doubly and triply charged systems, "late" or "transition" metal ions favor Iminol, while the "early" or "main-group" metal ions favor CS, with Mg(II) and Mn(II) being the cases most nearly approaching the cross-over values.
- There is an impressive extent of correlation between the CS preference energy values and the total binding energies of the best complexes. The correlation trend lines are strongly dependent on the charge states, but within a given charge state the correlation trends are independent of whether the metal is early or late in the periodic table or whether the ion is large or small.
- The results are very similar for the dipeptide ligand (dialanine) and the tripeptide (trialanine) notwithstanding the different numbers of Lewis-basic chelation points available in these different cases.
- The distinction of hard versus soft metal ions correlates to some degree with the CS/Iminol binding preferences, but this correlation has multiple discrepancies and does not seem helpful.
- Binding energies of the "main-group" metal ions scale smoothly with a Coulomb electrostatic scaling parameter q/R, while the "transition" metal ion binding energies deviate from this scaling by variable amounts in the direction of stronger chelation of the "transition" metal ions for a given size and charge of the metal ion. We conclude from this observation that a simple electrostatic binding model gives a good first-order description of the binding for the "early" or "main-group" metal ions, while additional contributions to the binding of the "late" or "transition" metal ions are important.

In summary, it is interesting and suggestive that a preference for Iminol complexation goes along with the properties of strong overall binding, an excess of binding energy beyond simple electrostatic binding, "transition" or "late" character of the metal ion, and exposed d electrons in the outermost occupied metal orbital.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijms.2013.07.017.

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