The Lithium Cation Binding Energies of Gaseous Amino Acids

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Received: September 20, 2002; In Final Form: November 26, 2002

The lithium cation binding energies of 15 of the common amino acids were determined via the kinetic method in a quadrupole ion trap mass spectrometer. Values were obtained in two ways. First, a ladder of relative lithium cation binding energies was developed from pairwise comparisons of the amino acids. Second, values were determined by comparison to a pair of simple reference compounds, dimethoxyethane and diethoxyethane. The values from the two approaches are in good accord. The scale from glycine to glutamic acid spans a range from 41.6 to 52.9 kcal/mol. The present values for lithium cations have been compared to those obtained by others previously for sodium, copper, and silver cations. These comparisons suggest that the alkali metals have exalted binding energies for amino acids with side chains that include oxygen-bearing functional groups (i.e., alcohols and carboxylic acids) whereas the transition metals have enhanced binding energies for amino acids with side chains that include sulfur-bearing or aromatic functional groups. This analysis is in accord with the principles of hard−soft acid/base behavior.

Introduction

Mass spectrometry has proven to be an excellent tool for determining the thermodynamic properties of a wide range of species, and with the advent of new ionization techniques such as electrospray (ESI) and matrix-assisted laser desorption (MALDI), it has been possible to study materials of low volatility including many molecules of biological interest. Cation affinity is a fundamental property and provides important insight into the gas phase ion chemistry of a substrate. In addition, gas phase properties such as cation affinities in many situations can aid in our understanding of condensed phase phenomena. This is particularly true for peptide/protein systems where folding can lead to encapsulated pockets within the molecules that are characterized by low dielectrics and often catalytic activity. In a recent paper, we reported the proton, lithium cation, and sodium cation binding energies of a series N-glycylated and N-acetylated amino acids.[1] In the present study, we extend that work to include the lithium binding energies of 15 bare amino acids. There have been reports of the lithium cation affinities of a few amino acids and Bojesen and co-workers[2,3] have presented a ranked list of the lithium affinities of all the common amino acids; however, a comprehensive, quantitative study has not been reported in the literature. Recently, Talley et al.[4] have compared the lithium affinities of amino acids to their methyl ester derivatives. Aside from lithium, studies have been completed on the sodium,[3,5−7] copper(I),[8,9] and silver(I)[10] cation affinities of amino acids. In addition, there have been several quantitative studies of the proton affinities of the amino acids and the subject has been reviewed by Harrison.[11]

Given their low volatility, it is very difficult to use equilibrium methods to determine the cation affinities of amino acids and other biologically relevant molecules. Instead, most groups have turned to kinetic approaches. To obtain absolute binding energies, threshold dissociation measurements have been used in some cases.[12] With a reasonable model of the dissociation transition state, it is possible to extract sometimes highly accurate binding energies with this approach. Alternatively, relative binding energies can be obtained using the Cooks' kinetic method.[13−16] This approach has been widely used in recent years and has successfully determined binding energies in a wide range of systems. The application of the Cooks kinetic approach to metal ion binding energies involves the formation of a ternary complex ($A_1M^+A_2$) between the cation and the two amino acids whose binding energies are to be compared (A_1 and A_2). Collision-induced dissociation (CID) of the complex leads to the loss of one amino acid. Since either amino acid can be lost, the product ratio potentially gives a measure of the relative amino acid binding affinity. If one assumes that the stabilities of the dissociation transition states are directly related to the stabilities of the dissociation products (i.e., "late" transition state), then the ratio of dissociation rates (k_1/k_2) is approximately equivalent to the equilibrium constant of eq 3. Of course, the ratio of k_1/k_2 is equal to the ratio of ion intensities $I(A_1M^+)/I(A_2M^+)$ because the dissociation is irreversible under the reaction conditions.

$$A_1M^+A_2 \xrightarrow{k_1} A_1M^+ + A_2 \quad (1)$$

$$\xrightarrow{k_2} A_2M^+ + A_1 \quad (2)$$

$$A_2M^+ + A_1 \overset{K}{\rightleftharpoons} A_1M^+ + A_2 \quad (3)$$

$$A_1M^+ + \xrightarrow{\Delta G_M(1)} M^+ + A_1 \quad (4)$$

$$A_2M^+ + \xrightarrow{\Delta G_M(2)} M^+ + A_2 \quad (5)$$

The observed intensities can be converted to pseudo-thermodynamic values in the following way:

$$I(A_1M^+)/I(A_2M^+) = k_1/k_2 \approx K \quad (6)$$

$$-RT_{\text{eff}} \ln K = \Delta G_M(1) - \Delta G_M(2) \quad (7)$$

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10.1021/jp022112d CCC: $25.00
Published on Web 01/08/2003

TABLE 1: Data Used for Assigning Anchor Points and Standard Values for the Lithium Cation Binding Energy Scale

anchor compound	reference base	ref ΔG_{Li} (kcal/mol)[a]	$\ln(k_2/k_1)$	ΔG_{Li} (kcal/mol)	ave ΔG_{Li} (kcal/mol)	lit. ΔG_{Li} (kcal/mol)[b]
Gly(Li^+)	$HCON(CH_3)_2$	41.5	−1.25	42.3	42.1	42.5
	$CH_3C(O)NHCH_3$	41.5	−0.79	42.0		
	$CH_3C(O)N(CH_3)_2$	42.8	0.98	42.1		
DEE(Li^+)	DME	44.9	−3.32	47.2		

[a] Reference 19. [b] Value derived from data in ref 3 for Gly relative to dimethylformamide and Taft's value for the lithium binding energy of dimethylformamide (ref 19).

where $\Delta G_M(1)$ and $\Delta G_M(2)$ are the binding free energies for A_1 and A_2, respectively, and T_{eff} is the effective temperature of the system during the dissociation process. In quadrupole ion traps, it has been observed that T_{eff} is usually slightly above ambient temperature.[1,17] Values of T_{eff} can be approximated in a number of ways and in the present study we have relied on a previously determined value from a related system.[18] In our quadrupole ion trap we presently cannot alter the dissociation temperature in a systematic manner so it is not possible to partition the energetics into enthalpic and entropic contributions. Although it has been assumed in many cases that ΔS is approximately zero for equilibria such as eq 3, this is not a reliable assumption in amino acids and peptides where variable coordination schemes with the charge carrier are possible. Consequently, the data will be reported in terms of free energies (i.e., ion binding energies) at 373 K.

In developing a scale, two other issues must be addressed. First, one can measure the binding energies of all of the amino acids against a single reference compound or one can make measurements between many pairs of compounds and then combine the data to create a scale (i.e., ladder). The former approach has the advantage that it maximizes the probability of a uniform cancellation of errors across the whole series (i.e., all comparisons are to the same species); however, in some cases, it requires measurements involving compounds with large differences in their ion binding energies (i.e., roughly one-half the energy range of the scale). In these situations, the signal for the cation bound to the weaker ligand can be very small and the ratio of intensities is difficult to measure accurately. The pairwise approach has the advantage that it relies on measurements between compounds of fairly similar binding energies (i.e., near neighbors on the scale); however, the measurements are codependent and an error on one part of the scale is propagated to all the species farther along the scale. In the present study, we have used both approaches. This was done to maximize our ability to identify breakdowns in the kinetic method. The amino acids with the strongest binding (e.g., arginine) were not included in this study because it was not possible to investigate them by multiple approaches (the gap to the reference compounds was too large). The two approaches, ladder and single reference, rely on somewhat different sets of approximations, so perfect correspondence is not anticipated; however, reasonably similar values should be obtained. If not, it is likely that some factor is invalidating the assumptions built into the kinetic method. Second, to convert the relative values to absolute values, a ladder scale must be anchored to a species whose ion binding energy is already known. As in our previous work, we have chosen the simplest species in the series, glycine, as our anchor point.[1] It is a logical choice because it has been the most widely studied of the amino acids and there are both experimental and theoretical data on its binding to lithium cations.

Experimental Methods

All measurements were made in a Finnigan-LCQ quadrupole ion-trap mass spectrometer operating with a background helium pressures of 1.75×10^{-3} Torr. All reagents were obtained from commercial sources and used without further purification. Typical operating conditions involved an ESI voltage from 3.5 to 4.5 kV, an analyte flow rate from 3 to 8 μL/min, and a heated capillary temperature from 150 to 200 °C. The amino acids were dissolved in H_2O/CH_3OH mixtures ($10^{-4}-10^{-5}$ M) and a small amount of the appropriate metal halide was added to the solution. The dimer ions were isolated in the ion trap using the LCQ advanced scan software and were subjected to CID by an activation voltage of about 0.5 V for 10 ms. Each measurement of product ion signals was the result of averaging of about 200−300 scans. A greater number of scans (several thousand) were used in cases were product ions had low intensities. The experimental uncertainty in the product intensity ratios was estimated to be ±12% on the basis of their reproducibility. Given the uncertainties in the absolute binding energies of the anchor points and the necessary assumptions of the kinetic method, the present values are assigned absolute uncertainties of ±3 kcal/mol. Relative uncertainties within the scale should be smaller, particularly between species with similar binding energies.

In many cases, ion binding energies from the ladder method were determined on the basis of measurements with more than one combination of amino acids. For example, three measurements were used to link the lithium binding energies of Gly, Ala, and Val: Gly-Li^{+-}Ala ($\ln k_2/k_1 = 2.52$), Ala-Li^{+-}Val ($\ln k_2/k_1 = 1.98$), and Gly-Li^{+-}Val ($\ln k_2/k_1 = 4.28$). The first two provide the ladder from Gly to Val and the last one is redundant, but proivdes an indirect confirmation of the other two. In this case there is about a 5% discrepancy (0.1 kcal/mol) in the values from the two approaches. To develop the scale, all the measurements were combined and a least-squares fit was used to assign binding energies to the amino acids. In some cases, other product channels were observed such as ligand fragmentation (e.g., loss of H_2O, CO_2, etc.).

To complete the measurements against simple reference species, dimethoxyethane (DME) and diethoxyethane (DEE) were used. These were chosen because their lithium binding energies are similar to those of amino acids and the bidentate nature of these ligands will parallel the expected complexation patterns in amino acids. A lithium binding energy is known for DME,[19] but it was necessary to determine one for DEE. This was done with the kinetic method and the results are shown in Table 1. DEE naturally has a higher lithium binding energy than DME and is more suitable for comparisons with the amino acids, but values were also obtained for DME when possible. Near mass coincidences or exceptionally large CID branching ratios made it impossible to explore all of the DME/DEE amino acid combinations.

TABLE 2: Lithium Binding Energies from Ladder and Single-Reference Measurements[a]

compound	ladder	DME	DEE	ave
Glu	53.3		52.4	52.9
Trp	52.8		51.7	52.3
Asp	51.4		51.6	51.5
Met	50.3		50.4	50.4
Thr	50.1	49.7		49.9
Tyr	49.5	49.3	48.3	49.0
Phe	48.8	48.5	47.8	48.4
Ser	48.8	48.3	48.6	48.6
Pro	47.9	47.4	47.2	47.5
Ile	45.6	45.2	45.2	45.3
Cys	45.5		44.9	45.2
Leu	45.4	45.1	45.2	45.2
Val	45.1	44.8		45.0
Ala	43.8		42.5	43.2
Gly	42.1	41.2	41.5	41.6
ave dev[b]	0.3	−0.1	−0.1	
ave abs dev[b]	0.3	0.2	0.3	

[a] kcal/mol. Absolute uncertainties ± 3 kcal/mol, but relative uncertainties are smaller (±1.5 kcal/mol). [b] Mean deviation and mean absolute deviation from the average values given in the fifth column.

To convert the measured ratios to energies, an estimate of T_{eff} is needed. As stated earlier, quadrupole ion traps generally give T_{eff}'s that are slightly above ambient temperature. In our previous work, we have used values from 325 to 350 K depending on the system. T_{eff} can be estimated by forming cation bound complexes of a species with a series of compounds of known binding energy. In a plot of $\ln(k_2/k_1)$ vs the binding energies of the standards, the slope is $1/RT_{eff}$. As a part of this study, we determined T_{eff} for a few related systems in this way and found an average value of ~325 ± 30 K. The large variation in these values is partly a result of their high sensitivity to the relative binding energies of the standards. For example, a 10% difference in relative binding energies (e.g., 0.1 kcal/mol difference in bases whose binding energies differ by 1 kcal/mol) directly leads to a 10% variation in T_{eff} (e.g., a 30 K difference at ambient temperature). Given the uncertainties in T_{eff}, we have opted to use a value of 325 K for all the species in the study and incorporate this factor into our estimate of the absolute uncertainties in the measurements. In the text, values are listed at 373 K. This is a result of anchoring the scale to Taft's lithium binding energy values, which are at 373 K.[19] This accounts for the major entropic factor (i.e., the free energy of the free lithium cation) and it is reasonable to assume that errors introduced in the relative values, based on the difference between 373 K and T_{eff}, are small compared to other errors associated with the method.

Results and Discussion

Lithium Cation Binding Energies. The anchor for the lithium ladder scale was determined by using the kinetic method to link glycine to molecules with known lithium affinities, dimethylformamide, methylacetamide, and dimethylacetamide.[19] Good agreement is observed between the three measurements (±0.2 kcal/mol) and a value of 42.1 ± 2.0 kcal/mol is obtained when they are combined and the uncertainties in the reference compounds are included (Table 1). This value is in reasonable accord with the work of Bojesen et al. whose data suggest a lithium binding energy of 42.5 kcal/mol on the basis of a measurement relative to dimethylformamide.[3] As noted above, multiple measurements against a pair of reference compounds, DME and DEE, were used in conjunction with the ladder approach. The results are presented in Table 2 for all the approaches. In general, there is good correspondence in the values with average deviations from the mean on the order of 0.3 kcal/mol. The overall trend is for higher values to be obtained in the ladder measurements and they are on average about 0.5 kcal/mol higher than those obtained with DME/DEE. This is evident with glycine, the reference point for the ladder. Because the lithium cation binding affinities for DME and the amides used to establish the binding energy of glycine came from the same literature source,[19] the origin of this shift is unclear. Nonetheless, the values are in reasonable accord given the various assumptions and uncertainties involved in the methods. In the text, the average values from the methods are used on the basis of the assumption that they offer the most balanced cancellation of errors.

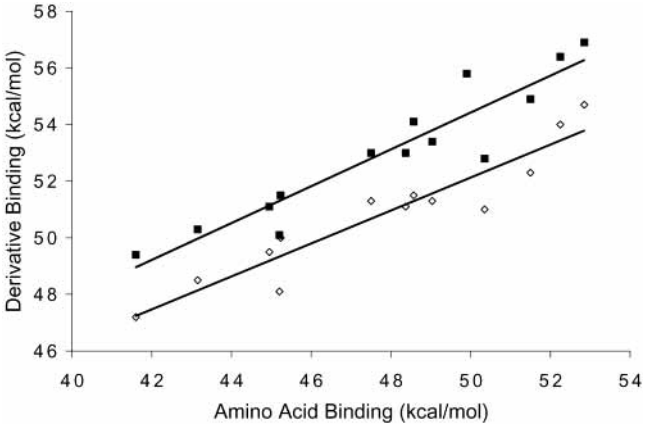


Figure 1. Comparison of the lithium cation binding of bare amino acids with their N-acetylated (open diamonds) and N-glycylated (filled squares) derivatives.

As we had noted in our earlier work with N-acetylated and N-glycylated amino acids,[1] the metal cation affinity increases as polarizable and metal-coordinating groups are introduced into the side chains. For example, glutamic acid, tryptophan, and aspartic acid have the highest lithium cation binding energies on our scale and all of these amino acids have a good metal coordinating group in the side-chain. Conversely, glycine and alanine lack coordinating groups in the side chain and exhibit the lowest lithium cation binding energies. A comparison of the data for the bare amino acids with those for the N-acetylated and N-glycylated derivatives is shown in Figure 1. Although there are not good linear correlations between the affinities of the amino acids and their derivatives, it is clear that similar factors are affecting them. It is interesting to note that for the simplest amino acids (e.g., glycine and alanine), the N-acetylation or N-glycylation has a very large effect on the lithium binding energies (5−7 kcal/mol). This must be primarily a result of the greater inherent metal ion affinity of the amide functional group.[19] The advantage of the N-acetylation or N-glycylation drops off to as little as 2−3 kcal/mol as the side chains of the amino acids incorporate more powerful coordinating groups that can offset the inherently high metal cation affinity of amides.

There have been previous reports, both experimental[2,3] and computational,[20−22] focused on the lithium cation binding of amino acids. In two studies, Bojesen and co-workers[2,3] have used the kinetic method to probe lithium binding. They have reported lithium affinity values for glycine, alanine, and valine as well as a ranked list of lithium affinities for the 20 common amino acids. Because we have reported binding free energies rather than affinities, it is easiest to make comparisons in terms of relative values. Since the simplest amino acids are not

expected to use their side chains for specific interactions with the metal, entropy effects should not be important in the comparisons. For this small set, there is reasonable correspondence between the values (kcal/mol):

Gly (0.0) < Ala (1.6) < Val (3.4) [present values]

Gly (0.0) < Ala (1.6) < Val (3.8) [Bojesen et al.][3]

There are several discrepancies in the order of lithium affinities from our study and the earlier one by Andersen and Bojesen,[2] but quantitatively, the differences are fairly small. The biggest differences occur toward the middle of the scales involving Met, Thr, Tyr, Ser, Phe, and Pro; however this whole set spans less than 3 kcal/mol on our scale and therefore all of the binding energies are fairly similar. As a result, the difference in order involves only a few tenths of a kcal/mol in many cases. Nonetheless, the differences are somewhat surprising because the experimental approaches are very similar. We studied some of the same lithium-bound dimer complexes, but found that different fragmentation pathways were preferred in some cases. The key difference in the methodology is that Bojesen and coworkers examined metastable decay spectra whereas our experiment involves multicollision CID in a quadrupole ion trap. One possible explanation for the variations in binding preferences is that the clusters involved in the metastable decay process are effectively "hotter" than those in the multi-collision CID and therefore the data were essentially obtained at different temperatures. Some support for this rationalization comes from the fact that in the metastable decay, some of the amino acids that are expected to chelate to the metal through their side chains (i.e., serine, threonine, methionine and cysteine) are ranked lower than in the CID experiments. Internal chelation of this type is entropically unfavorable and would reduce the relative binding energies of these amino acids at higher effective temperatures. Computationally, recent work at the B3LYP/6-311++G** level by Marino et al.[20] gives a lithium cation binding energy for alanine of 50.1 kcal/mol (298 K), a value which is much greater than ours or the one from Bojesen et al.[3] (even when the temperature difference is taken into account). Computed data from Jensen[21] for glycine also leads to a large overestimate of the lithium binding energy. However, Hoyau and Ohanessian[22] have incorporated a basis set superposition error (BSSE) correction in their calculations and computed a value that is much closer to the experimental ones for lithiated glycine.

Experimental data is also available for the binding of sodium cations to amino acids. The most comprehensive set of data was recently presented by Wesdemiotis on the basis of the kinetic method work and includes many of the common amino acids.[6,7] Since sodium is larger than lithium, smaller binding energies are expected, but because they are both alkali metals, similar trends should be observed in the binding of the amino acids. A plot of the relative lithium vs sodium cation binding energies is shown in Figure 2. A good correlation is observed in the data and as in our previous work with lithiated and sodiated dipeptides, a slope near unity (1.06) is found indicating that the side chains provide nearly equal stabilization to both lithium and sodium cations. This might not be expected because one would assume that lithium would interact more strongly with the side-chain functional groups, just as it has a higher overall affinity for the amino acids. However, the larger size of sodium might better accommodate multidentate chelation by the amino acids and therefore offset the advantage of the greater charge concentration in the lithium cation. Proline is an interesting case because there is evidence that its sodium salt involves a zwitterionic structure.[4,5] In Figure 2, it can be seen that proline is the only amino acid with an aliphatic side chain that falls significantly off the correlation line (i.e., gly, ala, leu, ile, and val are close to the line). The position of the data point (above the line) suggests that the zwitterionic form of the proline sodium complex is significantly more stable than the conventional one. This rationalization assumes that the lithium complex does not adopt a zwitterionic form or that the zwitterionic form is not significantly more stable than the conventional one (it also assumes that when expelled from a complex, the proline adopts a neutral, nonzwitterionic form because otherwise, dissociation would be less energetically favorable and a high binding energy would be suggested by the data). Recent theoretical and experimental work suggests that the lithium complex of proline does prefer a zwitterionic form.[4] At the MP2/6-311+G(2d,2p) level, Talley et al. found that the zwitterion is favored by about 3 kcal/mol.[4] To gain a more reliable measure of the stability of the zwitterionic form of lithiated proline, we have completed higher level calculations on the system.[23] For the conventional and zwitterionic forms of lithiated proline, all stable minima obtained in molecular mechanics calculations were optimized at the HF/6-31+G(d) level. These structures were used for single point calculations at the MP2/6-31+G(d,p) level. The best conventional and zwitterionic form at this level then was optimized at the MP2/6-31+G(d) level and single point calculations were completed on these structures at the CISD(T)/6-31+G(d,p) level (Figure 3). After including zero-point energy corrections (HF level scaled by 0.9135[24]), the zwitterion is favored by just 0.8 kcal/mol. This preference is much smaller than the one found for the sodium system and therefore, it is not surprising that the plot in Figure 2 points to an unusually high sodium affinity for proline relative to the lithium affinity. Our data however do not address the issue as to whether the proline is expelled from the complex in a zwitterionic or conventional form during CID.

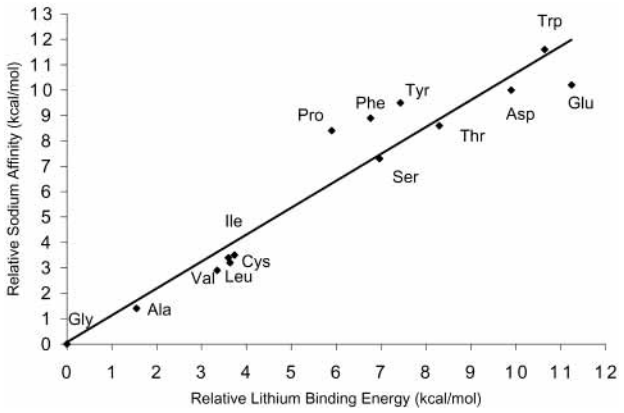


Figure 2. Comparison of lithium cation binding energies to sodium cation affinities.[6,7]

Comparisons to Other Cation Binding Affinities. An important goal of this work is to compare the binding of the amino acids to various cations to determine if there is inherent selectivity in their binding characteristics. In Figure 4, the lithium binding energies of the amino acids are compared to their gas-phase basicities.[11] At first glance, there appears to be only a rough correlation between the metal and proton binding energies, but when the comparison is limited to amino acids with simple alkyl groups in the side chain (large circles in Figure 4), a very good correlation is observed. The other amino acids lie above the correlation line indicating that their metal binding energies are unexpectedly high. In this analysis, it is assumed

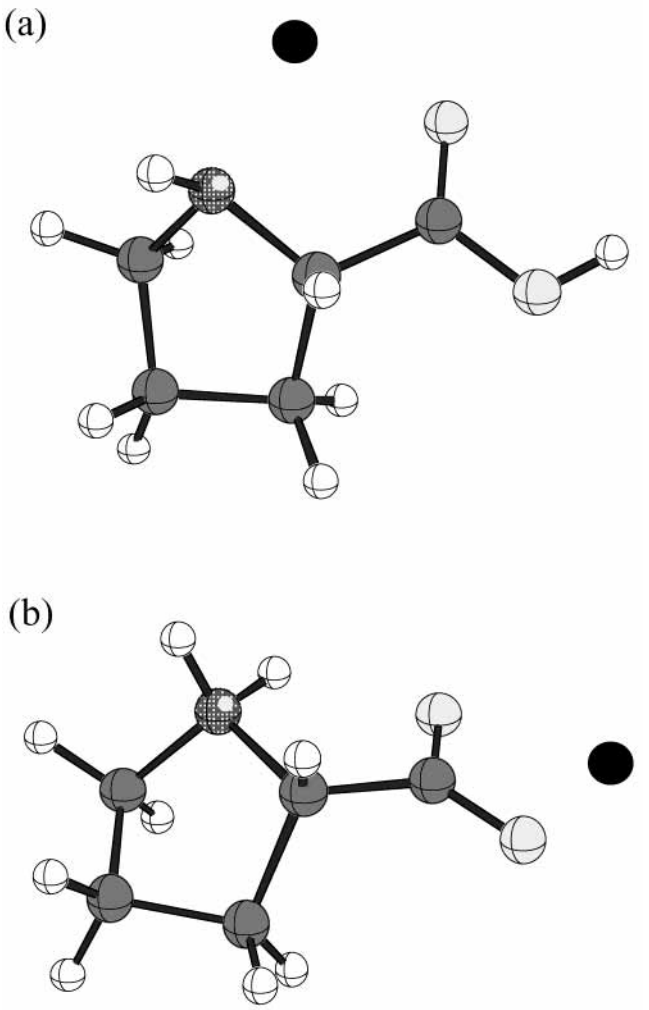


Figure 3. Optimized structures (MP2/6-31+G(d)) of best (a) conventional and (b) zwitterionic form of lithiated proline (carbon, dark gray; hydrogen, white; oxygen, light gray; nitrogen, patterned; lithium, black).

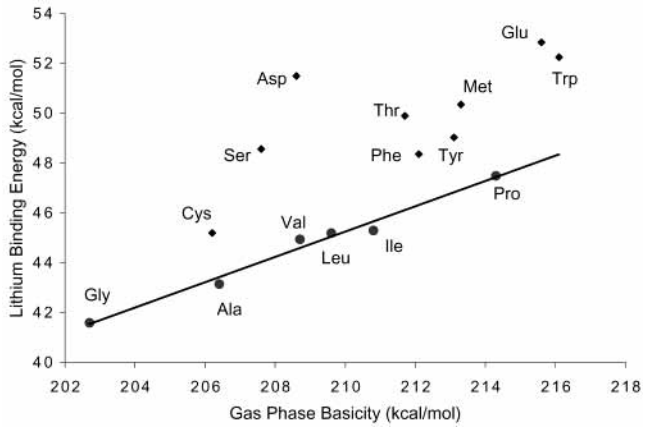


Figure 4. Comparison of the gas-phase basicity of amino acids with their lithium cation binding energies. Large filled circles represent amino acids used to generate correlation line. See text for details.

that the correlation line takes into account increases in binding related to the increasing polarizability of larger amino acids and other factors such as specific coordination to the side chain cause deviations from the line. Binding enhancements from polar side chains were seen in our earlier study of amino acid derivatives and are most apparent with lithium because the overall binding is tighter. The rationalization for this behavior is that the metals are better able to take advantage of coordination to the side

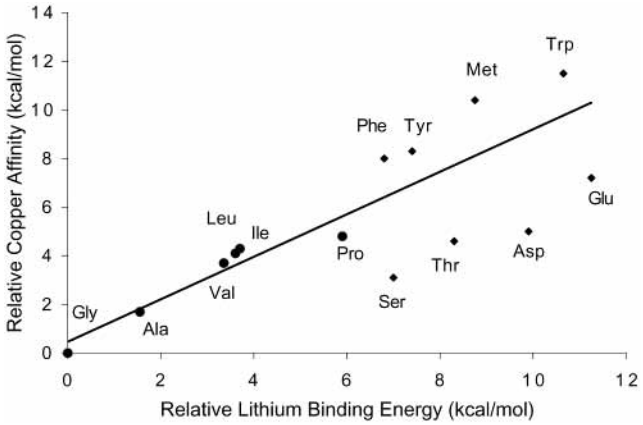
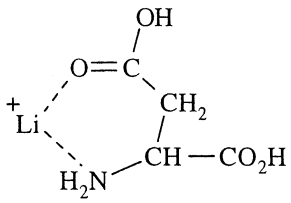


Figure 5. Comparison of the relative lithium cation binding energies of amino acids with their relative copper(I) cation affinities.[9] Large filled circles represent amino acids used to generate correlation line. See text for details.

chain functional groups than protons and therefore more readily adopt multidentate structures. As a result, metals can bind especially tight to amino acids that have heteroatoms such as oxygen and nitrogen in the side chain. Aspartic acid exhibits particularly strong binding with lithium (i.e., large deviation from the correlation line) and this is likely a result of the formation of a very stable, six-membered ring chelation structure involving the side chain carbonyl (interaction with the α-carbonyl is also likely). A less stable, seven-membered ring structure would result with glutamic acid.



A significant, but more modest, effect is seen when the side chain interaction involves an aromatic group rather than a heteroatom (i.e., phenylalanine). Finally, the sulfur in cysteine appears to be a more effective chelator in the bare amino acid than we had observed in the N-acetylated and N-glycylated amino acids. This may be related to the fact that the amino acid is less sterically crowded and contains fewer strong chelating groups than the derivatives and therefore sulfur chelation can be more competitive.

Recently, the relative metal binding energies of amino acids to copper and silver cations have been determined by Cerda et al.[8,9] and Lee et al.,[10] respectively, using the kinetic method. These transition metals offer a number of contrasts to an alkali metal cation like lithium. First, the transition metals are less electropositive so the role of covalent interactions with the ligand is much more important. Second, the alkali metals are examples of "hard" Lewis acids and copper and silver are considered to be "soft" Lewis acids.[25] Third, silver cations are considerably larger than the other cations. Given these differences, it would not be surprising if the transition metals displayed different preferences in their binding to the amino acid side chains. In Figure 5, the relative binding energies of the amino acids to copper and lithium cations are compared. Again, we have used the simple alkyl chain bearing amino acids to develop a correlation line (large circles). In this case, a good, but not excellent, correlation is seen with the major discrepancy involving proline. Nonetheless, the correlation line provides a

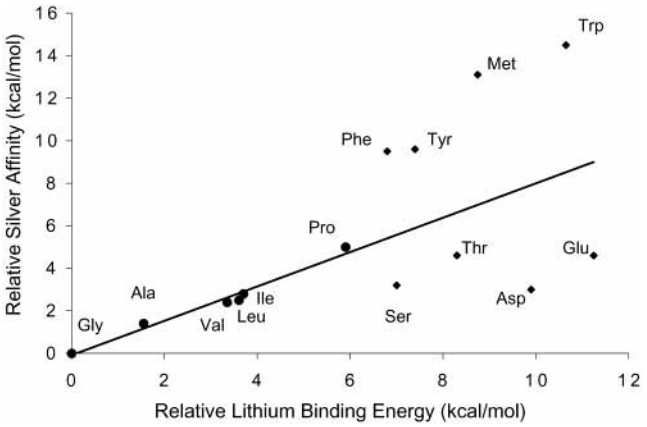


Figure 6. Comparison of the relative lithium cation binding energies of amino acids with their relative silver(I) cation affinities.[10] Large filled circles represent amino acids used to generate correlation line. See text for details.

good starting point for comparing the data. It can clearly be seen in the figure that the other amino acids separate into two groups, one above and one below the correlation line. The amino acids below the line have a relatively high affinity for lithium and share the common characteristic of having an oxygen in the side chain available for chelation to the metal cation. Those above the line have aromatic or sulfur containing groups in the side chain and appear to favor copper cations.

A similar approach can be used to contrast the bonding of lithium and silver to the amino acids (Figure 6). Using the correlation line for the alkyl amino acids, again the data neatly break up into two groups and qualitatively the plot looks much like that obtained in the copper comparison. The amino acids with oxygens in the side chain prefer lithium and those with aromatic or sulfur groups prefer silver. The preferences for silver binding to methionine and tryptophan are striking and indicate that their side chains have an unusually high affinity for silver cations.

Overall, these comparisons are in complete accord with the concept of hard/soft interactions.[25] It should be noted that Wesdemiotis and co-workers[7] have invoked similar arguments in comparing their sodium data with copper data, The "hard" alkali metal cations preferentially bind to the "hard" Lewis bases in the side chains. These would be the hydroxyl and carbonyl oxygens of serine, threonine, aspartic acid, and glutamic acid. The "soft" metal cations, copper and silver, prefer binding to the "softer", more diffuse functional groups in the side chains such as aromatic rings or sulfur atoms. In other studies with silver cations,[26] the application of the hard/soft interaction concept has been questioned, but the data in Figures 5 and 6 clearly validate it in the present system. This may be a result of the type of analysis that is being applied because it is very sensitive to subtle effects that might not be seen in a comparison of absolute binding energies. The application of hard/soft concepts to these systems provides a starting point for predicting the preferred locations for a metal in a peptide chain on the basis of the nature of the metal cation (i.e., "hard" vs "soft"). However, interactions in peptides are more complex and chelation is possible from several amino acids simultaneously. Nonetheless, the preferences in the amino acids provide a foundation for predicting metal locations in cationized peptides.

Conclusions

The lithium cation binding energies of 15 common amino acids have been determined in a quadrupole ion trap with the kinetic method and the results can be rationalized on the basis of the metal coordinating ability of the side chain functional groups. By comparison to the gas-phase basicities of these amino acids, it can be seen that oxygen-bearing functional groups in the side chain (i.e., alcohols and carboxylic acids) lead to exalted lithium cation binding energies. Smaller binding enhancements come with aromatic side chains. The trends in lithium binding mirror those seen in recent work with sodium, but are dramatically different than those observed in the copper(I) and silver(I) complexes of amino acids. Specifically, the transition metal cations appear to prefer sulfur-containing and aromatic side chains whereas lithium prefers oxygen-containing side chains. This observation is completely consistent with the concept of hard−soft acid/base interactions.

Acknowledgment. Support from the National Center for Research Resources (Research Infrastructure in Minority Institutions P20 RR11805) of the National Institutes of Health is gratefully acknowledged. We also thank Professor Chrys Wesdemiotis for generously providing a preprint of his group's work on sodium affinities.

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