# Comparison between Protonation, Lithiation, and Argentination of 5-Oxazolones: A Study of a Key Intermediate in Gas-Phase Peptide Sequencing

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# Comparison between Protonation, Lithiation, and Argentination of 5-Oxazolones: A Study of a Key Intermediate in Gas-Phase Peptide Sequencing

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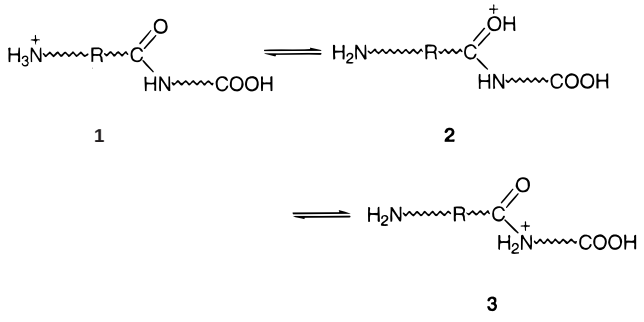
Molecular orbital calculations at B3LYP/6-31++G(d,p) are reported for bases 2-(aminomethyl)-5-oxazolone, 2-(aminomethyl)-4-methyl-5-oxazolone, 2-phenyl-5-oxazolone, and 2-phenyl-4 methyl-5-oxazolone and for the cations formed by protonation of these bases on their imino nitrogens. Structures and relative energies for isomers generated by protonation at each of the four heteroatoms of 2-(aminomethyl)-5-oxazolone are reported. Lithium and silver cations both add to 2-(aminomethyl)-5-oxazolone, but unlike the proton, they bind with two heteroatoms simultaneously. For both the lithiated and argentinated 2-(aminomethyl)-5-oxazolone cations the lowest energy isomers have the metal coordinated with the two nitrogen atoms. Proton affinities of these bases are in the range 217.0−221 kcal mol$^{-1}$, with the methyl group at $C_4$ increasing the proton affinity by ∼3 kcal mol$^{-1}$. Single-point calculations were performed at MP4(fc)/6-311++G(2df,p)//B3LYP/6-31++G(d,p) for 2-(aminomethyl)-5-oxazolone, diketopiperazine, glycine, and alanine and their conjugate acids. The proton affinities from this level of theory are lower by as much as 2.7 kcal mol$^{-1}$ than those calculated at B3LYP/6-31++G(d,p). Enthalpies of formation calculated at B3LYP/6-31++G(d,p) from isodesmic reactions for glycine, alanine, and their conjugate acids are all within 1 kcal mol$^{-1}$ of the experimental values, but those calculated at MP4 deviate by as much as 4.8 kcal mol$^{-1}$. Enthalpies of formation from atomization reactions at the MP4 level are in larger disagreement with experimental values.

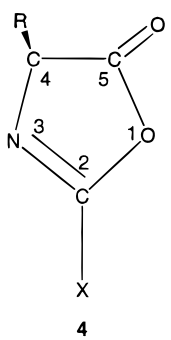
## Introduction

The predominant mechanism for fragmentation of a collisionally activated protonated peptide in the gas phase under laboratory energies <100 eV is through cleavage of a C−N bond adjacent to the charge site.[1−9] In peptides that do not have a basic side chain, the terminal amino group has the highest proton affinity (structure **1**), followed by the carbonyl oxygen

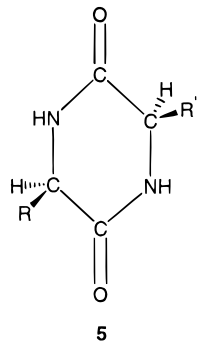


**1** **2** **3**

atoms of the amide groups (structure **2**). Protonation at these two sites, however, does not permit facile cleavage of the amide bond; for this to occur protonation must be on the nitrogen of the amide bond (structure **3**).[1,10−12] Heterolytic fission of the C−N bond of **3** should initially result in an acylium ion,[9,13] but there is considerable evidence, supported by theory, that these ions are not formed in the fragmentation.[11,14−18] Rather the N-protonated amide is subject to internal nucleophilic attack on the carbon atom of the amide group by either the carbonyl oxygen or the nitrogen atom of the amino group on the adjacent amino acid residue, thereby displacing the C-terminal amino acid or peptide. If attack is by the oxygen then the ion formed is a protonated 2-substituted-5-oxazolone. Subsequent proton transfer to the peptide may occur as both the oxazolone and the peptide have similar proton affinities.[19] In the usual nomenclature used in peptide analysis, the oxazolone is referred to as a $b_n$ ion;[20] the $b_2$ ion formed from a tripeptide has structure **4**, where X = CHR′$NH_2$, with a proton added to one of the nitrogen atoms.



**4**



**5**

If the terminal amino group were to attack the carbonyl carbon, then the resulting ion would be an N-protonated diketopiperazine (**5** with a proton added to one of the nitrogens) and, as proton transfer from this cation to the amino group of the C-terminal peptide is exothermic, then the protonated peptide, the y ion, would be formed.[14,19] Alternatively, the protonated diketopiperazine could be formed by rearrangement of the protonated 5-oxazolone.[19] In the product ion spectra of protonated tripeptides, e.g., glycinylglycinylglycine (GGG) and glycinylglycinylalanine (GGA) the intensities

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**TABLE 1: Bond Lengths[a] in 2-X-5-oxazolones[b]**

| | $O_1$—$C_2$ | $C_2$—$N_3$ | $N_3$—$C_4$ | $C_4$—$C_5$ | $C_5$—$O_1$ | C═O | $C_4$—R | $C_2$—X |
|---|---|---|---|---|---|---|---|---|
| | | | | 5-Oxazolones | | | | |
| **4a**, R = H, X = $CH_2NH_2$ | 1.393 | 1.274 | 1.460 | 1.523 | 1.396 | 1.198 | 1.096 | 1.506 |
| **4b**, R = $CH_3$, X = $CH_2NH_2$ | 1.394 | 1.273 | 1.466 | 1.529 | 1.394 | 1.199 | 1.533 | 1.506 |
| **4c**, R = H, X = $C_6H_5$ | 1.396 | 1.279 | 1.456 | 1.522 | 1.391 | 1.199 | 1.096 | 1.466 |
| **4d**, R = $CH_3$, X = $C_6H_5$ | 1.396 | 1.279 | 1.461 | 1.528 | 1.396 | 1.200 | 1.534 | 1.467 |
| | | | | Protonated 5-Oxazolones | | | | |
| **6a**, R = H, X = $CH_2NH_2$ | 1.313 | 1.305 | 1.458 | 1.523 | 1.480 | 1.174 | 1.095 | 1.501 |
| **6b**, R = $CH_3$, X = $CH_2NH_2$ | 1.315 | 1.303 | 1.469 | 1.528 | 1.476 | 1.176 | 1.534 | 1.501 |
| **6c**, R = H, X = $C_6H_5$ | 1.331 | 1.327 | 1.458 | 1.519 | 1.448 | 1.179 | 1.174 | 1.436 |
| **6d**, R = $CH_3$, X = $C_6H_5$ | 1.332 | 1.324 | 1.469 | 1.523 | 1.445 | 1.180 | 1.533 | 1.438 |

[a] Bond lengths are in angstroms. [b] For numbering system see structure **4** in the text.

of both the $b_2$ and $y_1$ ions are abundant. Furthermore, the $a_2$ ion, an immonium ion, is also typically intense. This product ion is believed to form via elimination of carbon monoxide from the $b_2$ ion.[11,14,16]

The collision-induced fragmentations of peptides in the presence of $Li^+$, $Na^+$, and $Ag^+$ ions have been investigated extensively.[21−28] These metalated peptides produce similar fragmentation patterns, although the relative abundances of the different product ions vary with the metal. Tripeptides are the smallest peptides that can fragment to form an oxazolone or a diketopiperazine. Here we use molecular orbital theory to examine the protonated and metalated oxazolones derived from the computationally least-expensive tripeptides, GGG and GAG, and in the case of GGG, we have also examined the protonated and argentinated diketopiperazine. In particular, we were interested in the sites of protonation and metalation of the oxazolones and also in the relative proton affinities of an oxazolone and its isomeric diketopiperazine. One of the difficulties in establishing the identity of the $b_2$ ions in peptide fragmentation stems from the unavailability of 2-(aminomethyl)-5-oxazolones. To show that the protonated oxazolone is indeed the intermediate, 2-phenyl-5-oxazolone, a stable precursor, was synthesized and shown to have an identical mass spectrum to the ion derived from an N-terminal benzoylated peptide.[11,16]

There have been previous theoretical studies of the 5-oxazolones produced in the fragmentation of protonated peptides.[11,16−18] Here we use higher levels of theory to examine the susceptibility to protonation of the different heteroatoms of 5-oxazolones that have either an aminomethyl or phenyl substituent at $C_2$ and have either two hydrogens or one hydrogen and one methyl group at $C_4$. We also report structures and energetics for 2-(aminomethyl)-5-oxazolone ligated with lithium and silver ions (separately) and consider attachment at all the different basic sites.

## Computational Methods

All molecular orbital calculations were performed using Gaussian 98.[29] Structure optimizations were carried out using the density functional theory (DFT) hybrid method at the B3LYP level.[30−33] The 6-31++G(d,p) basis set[34−37] was used for structure optimizations on all protonated and lithiated ions and the DZVP basis set[38] on the argentinated ions. All critical points were characterized by harmonic frequency calculations.[39]

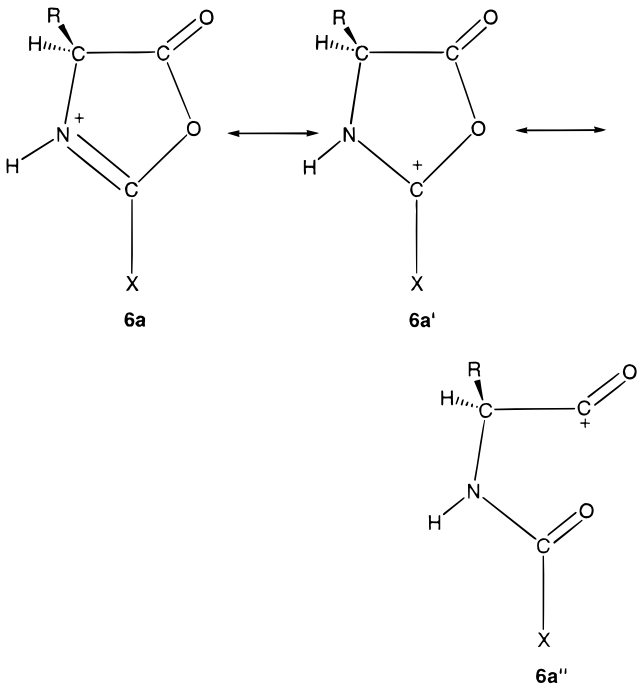
## Experimental Section

Cooks' kinetic method[40] with Fenselau's correction[41] was employed for estimating the proton affinities of 2,5-diketopiperazine and 2-phenyl-4-methyl-5-oxazolone on a triple quadrupole mass spectrometer (PE-SCIEX API 3000 prototype). Measurements were performed under constant center-of-mass energies ($E_{cm}$) at several $E_{cm}$ values; for 2,5-diketopiperazine, $E_{cm}$ = 1.0, 1.5, 2.0, and 2.5 eV, whereas for 2-phenyl-4-methyl-5-oxazolone, $E_{cm}$ = 0.90, 0.95, 1.00, and 1.05 eV.[42] Reference bases were cycloheptanone, cyclooctanone, *p*-tolualdehyde, 5-nonanone, cyclopropylethanone, and acetophenone for 2,5-diketopiperazine and 1-propanamine, 1-butanamine, 2-methyl-1-propanamine, 1-hexanamine, and 1-octanamine for 2-phenyl-4-methyl-5-oxazolone.

## Results and Discussion

**A. Structures of Protonated 2-Substituted-5-Oxazolones.** Some structural details of the 2-substituted-5-oxazolones and their imino-nitrogen protonated isomers are given in Table 1.

*(a) 2-(Aminomethyl)-5-oxazolone, **4a**.* Protonated 2-(aminomethyl)-5-oxazolone (**6a** with R = H and X = $CH_2NH_2$) is the $b_2$ ion formed in the collision-induced dissociation of protonated




GGG. Comparison of the structure of this cation with that of its conjugate base (**4** with R = H and X = $CH_2NH_2$) shows that protonation has a profound effect on the geometry of the ring.

In the neutral 2-(aminomethyl)-5-oxazolone molecule, **4a**, the bond angles in the planar five-membered ring are all in the range 105.1−106.3°, with the exception of angle NCO, which is 117.1°; i.e., the constraints imposed by the ring have resulted

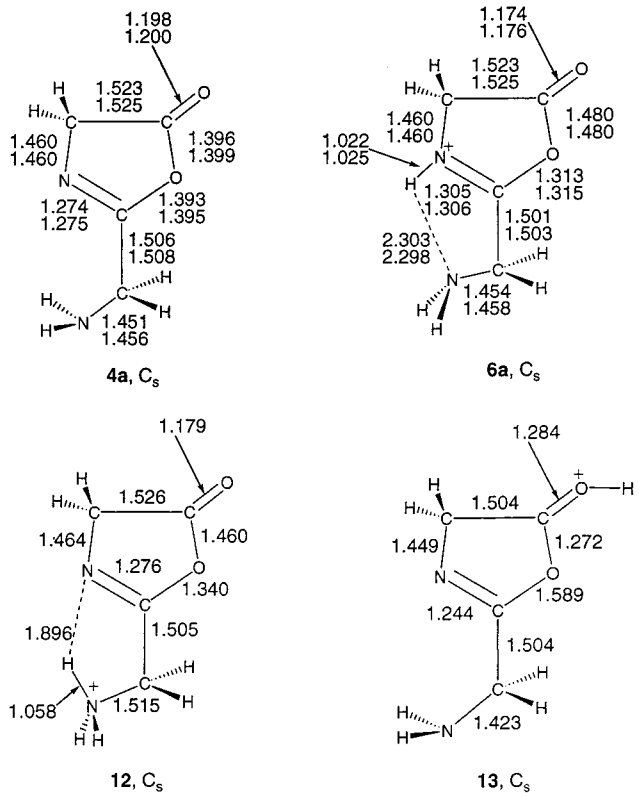



**Figure 1.** Structures of 2-(aminomethyl)-5-oxazolone and isomers of protonated 2-(aminomethyl)-5-oxazolone as optimized at B3LYP/6-31++G(d,p), showing only bond distances between heavy atoms. Where there are two sets of parameters, the upper ones are at B3LYP/6-31++G(d,p) and the lower ones at B3LYP/DZVP. Bond lengths are in ångstroms, and the bond angle is in degrees.

in these angles being smaller than the ideal values, and the deviation is particularly large at the carbonyl carbon. The bond distances within the ring are close to those in acyclic molecules, except for those associated with the oxygen. The two C−O distances in all the 2-substituted-5-oxazolones are almost identical at a distance of ∼1.395 Å, perhaps consistent with the fact that the oxygen is attached to two trivalent carbon atoms (Figure 1). These are intermediate between the bond lengths in an acyclic ester; for example, the experimental values in methyl formate are 1.334 Å for the HCO−$OCH_3$ bond and 1.437 Å for the HCOO−$CH_3$ bond.[43] The C═N distance of 1.274 Å in the ring is almost identical with the bond in methylenimine (1.273 Å).[43] The nitrogen atom of the aminomethyl side chain is coplanar with the five-membered ring and is cis to the C═N bond. The amino hydrogens adopt a staggered conformation about the C═N bond with the lone pair on the nitrogen atom oriented away from the double bond.

The most basic site on molecule **4** is the imino nitrogen. The energetics of electrophilic addition at other potential sites will be discussed in section B. The structure of protonated 2-(aminomethyl)-5-oxazolone, ion **6a**, has the conformation of the amino group in the side-chain rotated 180° about the $CH_2NH_2$ bond relative to that in the unprotonated base (Figure 1). In this conformation the amino protons eclipse the protons of the adjacent $CH_2$ group, but this energetically unfavorable arrangement is offset by a favorable interaction between the lone pair on the amino nitrogen and the proton that has been added to the imino nitrogen. Other geometric features, the $NH_2$....HN distance of 2.303 Å, the N−H distance of 1.022 Å, and the H−N═C angle of 119°, however, all indicate that there is minimal interaction between the lone pair and the protonated imine.

The most dramatic structural changes upon protonation of 2-(aminomethyl)-5-oxazolone, **4a** (**4** with X = $CH_2NH_2$ and R = H), are in the bond distances around the oxygen atom in the ring. The $C_5$—O distance in **6a** is 1.480 Å, compared with 1.396 Å in **4a** and the O−$C_2$ distance is 1.313 Å compared with 1.393 Å. Furthermore, the C═N bond in **6a** is 1.305 Å compared with 1.274 Å in **4a** and the C═O distance of 1.174 Å is shorter than that in **4a** (1.198 Å). These changes indicate that imino-protonation of the oxazolone ring greatly weakens the $C_5$—O bond and that resonance structure **6a″** is a significant contributor to this ion. Structure **6a″** is, of course, the elusive acylium ion that would be expected to lose carbon monoxide to form the immonium ion, $a_2$.

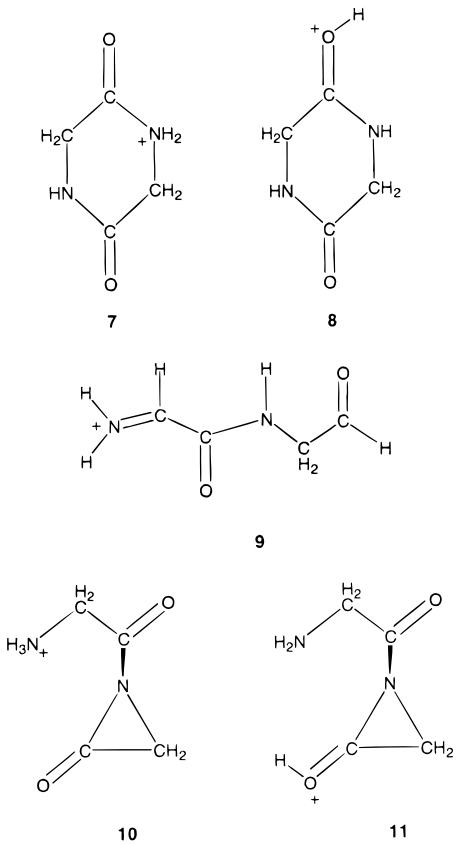
*(b) 2-(Aminomethyl)-4-methyl-5-oxazolone, **4b**.* Examination of the structural data in Table 1 shows that replacement of one of the hydrogens at $C_4$ by a methyl group, thereby creating **4b** and **6b**, has virtually no effect on the geometric parameters of the oxazolone ring. Also, the $C_4$−$CH_3$ distance in **6b** is insignificantly longer (by 0.001 Å) than that in the neutral compound, **4b**, indicating that the methyl substituent does not participate strongly in delocalizing the positive charge.

*(c) 2-Phenyl-5-oxazolones, **4c** and **4d**.* Replacement of the aminomethyl group by a phenyl group at the 2-position in the oxazolone ring has essentially no effect on the geometric parameters in the oxazolone ring; i.e., molecules **4a**, **4b**, **4c**, and **4d** all have almost identical geometries in the ring. The phenyl groups in **4c** and **4d** are coplanar with the oxazolone ring and the Ph−$C_2$ distance of 1.466 Å is indicative of some double bond character between the two rings. From a natural bond orbital (NBO) calculation[44] the phenyl group in **4c** is calculated to carry a positive charge of +0.055e.

Protonation on the imino nitrogen of **4c** produces **6c** and, unlike in the bases **4a** and **4c**, comparison between **6a** and **6c** shows there to be considerable difference in the oxazolone rings. Both **6a** and **6c** have longer C═N distances than in the bases, with the increases on protonation being 0.031 and 0.048 Å, respectively. This larger change in C═N in **6c** is accompanied by smaller changes in the C—O distances. The changes are in the same direction as in the protonation of **4a**, but $C_5$—O increases by only 0.057 Å (as opposed to an increase of 0.084 Å in forming **6a**) and O−$C_2$ decreases by 0.065 Å (as opposed to 0.080 Å). Ion **6c** then has less acylium-like character than ions **6a** and **6b**. In ion **6c** the $C_2$—phenyl bond is shorter than in **4c** and from the NBO analysis, which gave a charge of +0.258e on the phenyl group, ∼0.2 of the excess positive charge is located on the phenyl ring. The majority of this excess charge is on the para carbon and on one ortho carbon (the distant one); there are slight increases on the hydrogen atoms attached to these carbons also. By contrast, the charge on the ortho carbon adjacent to the protonated nitrogen has a slightly more negative charge in the cation. Approximately half the positive charge in the cation is located on the proton that has been added.

Substitution of a hydrogen atom at $C_4$ by a methyl group has very little effect on the structures of either the base or the conjugate acid; i.e., the structural parameters of **4c** and **6c** are almost identical to those of **4d** and **6d**, respectively.

*(d) Other Isomers on the $C_4H_7N_2O_2^+$ Surface.* Nucleophilic attack by the terminal amino nitrogen on the carbonyl carbon of the second amide linkage, which is protonated on its amide nitrogen, produces an N-protonated diketopiperazine, **7**, which then transfers a proton to the C-terminal amino acid to form




the $y_1$ ion. Alternatively, if protonation occurs on the amide nitrogen of the first amide linkage, it is believed that a nucleophilic attack can occur on the carbonyl carbon of this amide bond to form an N-protonated aziridinone **10**, which then transfers a proton to the C-terminal fragment to produce the $y_2$ ion.[15]

N-protonated aziridinone does not exist in isolation and immediately dissociates into CO and $H_2C{=}NH_2^+$.[45] It is, however, possible that N-protonated aziridinone can exist in a neutral-stabilized complex. Of more importance in the current context is the formation of N-protonated diketopiperazine, **7**, an ion whose formation could in principle be competitive with the formation of protonated 2-(aminomethyl)-5-oxazolone (**6a**).

We have optimized structures for the protonated diketopiperazines, along with those of isomers **9**−**11**. Isomers **10** and **11** could be formed by cyclization of the central amino acid in protonated GGG, although the instability of the intermediate ring N-protonated isomer toward loss of carbon monoxide is a problem. Ions of type **9**, derived from 5-oxazolones via the intermediacy of the acylium ion followed by a hydride shift, have been postulated as possible structures for the $b_2$ ion and we therefore include ion **9** for comparative purposes.[18] The total energies and relative energies of isomers **6**−**11** are given in Table 2. Isomers **6** and **8** have almost identical energies, with the relative energy of these ions depending on the level of theory. However, N-protonated diketopiperazine, **7**, is 14 kcal mol$^{-1}$ above **8** and it is important to realize that in the dissociation of N-protonated GGG it is the formation of this isomer that is in competition with formation of 2-(aminomethyl)-5-oxazolone, **6a**.

*(e) Proton Affinities.* The proton affinity of a base B is defined as being the exothermicity of the reaction given in eq 1.

$$BH^+ \rightarrow B + H^+ \qquad (1)$$

Molecules containing nitrogen atoms generally have high proton affinities, with the prototypical amine, ammonia, having a proton affinity of 204 kcal mol$^{-1}$.[46] The proton affinities of the four oxazolones, **4a**−**4d**, all fall in a very narrow range (Table 3). At B3LYP/6-31++G(d,p) 2-(aminomethyl)-5-oxazolone, **4a**, and 2-phenyl-5-oxazolone, **4c**, are calculated to have proton affinities of 217.4 and 217.8 kcal mol$^{-1}$, respectively, and in each case the introduction of a methyl group at $C_4$ increases the proton affinity by approximately 3 kcal mol$^{-1}$. For 2-phenyl-5-oxazolone, **4c**, 2-phenyl-4-methyl-5-oxazolone, **4d**, the O-protonated form of diketopiperazine, **5**, glycine, and alanine,[46] there is excellent agreement with the experimental values. The experimental proton affinities of 2-phenyl-4-methyl-5-oxazolone, **4d**, have never been reported and were specifically measured in this study. In a recent publication, we showed that the kinetic method with Fenselau correction is effective for estimating the proton affinity of an unknown base that binds differently (dicoordinating) from a series of reference bases that bind very similarly among themselves (monocoordinating), when data are collected under a series of different collision energy conditions.[42] We expect both 2-phenyl-4-methyl-5-oxazolone and diketopiperazine would bind the proton diffrently from the amines, ketones, and aldehydes used as reference bases in this study; the differences, however, are unlikely to be as drastic as that in the earlier study.[42] We are, therfore, expecting that our experimental values to have an accuracy comparable to that of the previous study (average deviation ± 1.0 kcal mol$^{-1}$).[42] Comparing the proton affinity of diketopiperazine, **5**, (cyclic GG) with those of cyclic AA (207.9 kcal mol$^{-1}$) and cyclic LG (209.9 kcal mol$^{-1}$),[19] it is apparent that there is good agreement. For oxazolones, substituting a methyl group for a hydrogen (replacing a glycyl with an alanyl residue) increases the proton affinity by approximately 3 kcal mol$^{-1}$. The difference of 207.9 − 201.1 = 6.8 kcal mol$^{-1}$ in the proton affinities of cyclic AA and cyclic GG is consistent with this trend.

Protonation of 5-oxazolone occurs preferentially at the imino nitrogen and the proton affinities for oxazolones **4a**−**4d** are all ∼13−16 kcal mol$^{-1}$ higher than that of methylenimine (203.8 kcal mol$^{-1}$).[46] This is attributable to the extensive structural

**TABLE 2: Energies[a] of $C_4H_7N_2O_2^+$ Isomers**

| molecule | B3LYP/ 6-31++G(d,p)[b] | ZPE[c] | MP4SDTQ(fc)/ 6-311++G(2df,p)[d] |
|---|---|---|---|
| **6** | −416.36765 (0) | 76.0 | −415.67444 (0) |
| **7** | −416.34850 (12.7) | 76.9 | |
| **8** | −416.37070 (−1.3) | 76.7 | −415.67353 (1.2) |
| **9** | −416.34794 (11.8) | 74.9 | |
| **10** | −416.30906 (30.0) | 75.8 | |
| **11** | −416.27402 (58.8) | 74.1 | |

[a] Total energies are in hartrees. [b] Numbers in parentheses are energies relative to **6** (in kcal mol$^{-1}$). These include zero-point energies and thermal corrections. [c] Zero-point energies in kcal mol$^{-1}$. [d] Single-point calculations using geometry optimized at B3LYP/6-31++G(d,p).

**TABLE 3: Proton Affinities[(a)]**

| molecule | B3LYP/ 6-31++G(d,p) | MP4[b] | exptl |
|---|---|---|---|
| 2-(aminomethyl)-5-oxazolone, **4a** | 217.4 | 214.7 | |
| 2-(aminomethyl)-4-methyl-5-oxazolone, **4b** | 220.4 | | |
| 2-phenyl-5-oxazolone, **4c** | 217.8 | | 216.7[c] |
| 2-phenyl-4-methyl-5-oxazolone, **4d** | 220.4 | | 220.7[d] |
| diketopiperazine, **5** | 199.9 | 198.4 | 201.5[d] |
| glycine | 212.1 | 212.0 | 211.9[e] |
| alanine | 216.2 | 214.8 | 215.5[e] |

[a] In kcal mol$^{-1}$. [b] At MP4SDTQ(fc)/6-311++G(2df,p)//B3LYP/6-31++G(d,p). [c] Reference 19. [d] This study. [e] Reference 46.

**TABLE 4: Enthalpies of Formation at 298 K[a]**

| molecule | calcd $\Delta H_f^0$ atomization | calcd $\Delta H_f^0$ isodesmic[b] | exptl |
|---|---|---|---|
| 2-(aminomethyl)-5-oxazolone, **4a** | −68.8 | −60.5 | |
| | | −68.3 | |
| diketopiperazine, **5** | −84.0 | −75.8 | |
| | | −79.1 | |
| glycine | −97.4 | −93.8 | −93.3 ± 1.1[c] |
| | | −94.7 | |
| alanine | −105.2 | −99.2 | −99.1 ± 1.0[c] |
| | | −103.9 | |

| ion | calcd $\Delta H_f^0$ atomization | calcd $\Delta H_f^0$ isodesmic[b] | exptl |
|---|---|---|---|
| N-protonated 2-(aminomethyl)-5-oxazolone, **6a** | 82.2 | 91.1 | |
| | | 83.7 | |
| O-protonated diketopiperazine, **8** | 83.3 | 88.2 | |
| | | 85.0 | |
| protonated glycine | 56.3 | 60.3 | 60.5[d] |
| | | 58.0 | |
| protonated alanine | 45.6 | 51.9 | 51.1[e] |
| | | 46.4 | |

[a] In kcal mol$^{-1}$. [b] Upper numbers are at B3LYP, lower numbers at MP4. [c] Reference 57. [d] From proton affinity of glycine. PA = 211.9 kcal mol$^{-1}$,[58] $\Delta H_f(H^+)_{298}$ = 365.7 kcal mol$^{-1}$.[59] [e] From proton affinity of alanine. PA = 215.5 kcal mol$^{-1}$,[58] $\Delta H_f(H^+)_{298}$ = 365.7 kcal mol$^{-1}$.[59]

rearrangement that occurs on protonation and to the extended charge delocalization. The proton affinities of glycine and alanine are also higher than that of methylamine (214.9 kcal mol$^{-1}$)[46] due to internal hydrogen bonding from the protonated amino group to the carbonyl oxygen of the carboxylic acid.

*(f) Enthalpies of Formation.* We have previously shown that ab initio molecular orbital calculations at MP4(fc)SDTQ/6-31++G(2df,p) can be used to calculate enthalpies of formation that are consistently within ±3 kcal mol$^{-1}$ of the experimental value. The procedure, using isogyric reactions and experimental enthalpies of formation of the atoms, has been described in detail elsewhere.[47−51] We have used this same method to give the enthalpies that are listed in Table 4 under the heading "atomization". Curiously, for both glycine and alanine and also for their conjugate acids the calculated enthalpies of formation are all lower by 4−6 kcal mol$^{-1}$.

Recently, there have been reports that enthalpies of formation and binding energies from G2 and G2(MP2) calculations on larger molecules show substantial deviations from experimental values and this has been attributed to accumulation of errors.[52−55] This problem can be partly alleviated by using bond separation reactions,[43] and more accurate enthalpies of formation can be calculated by using isodesmic or homodesmotic reactions.[54,55] Here we use isodesmic reactions at both B3LYP and MP4 to separate each pair of heavy atoms. For example the following balanced reaction is the equation used for glycine.

$$H_2NCH_2COOH + 3CH_4 \rightarrow H_3CNH_2 + H_3CCH_3 + H_2CO + H_3COH \quad (2)$$

For all the product molecules in eq 2 and for $CH_4$, experimental enthalpies of formation were taken from the compilation in ref 54. For other isodesmic reactions, the following enthalpies of formation (in kcal mol$^{-1}$) were used: $CH_3NH_3^+$, 145.3;[46] $CH_2OH^+$, 171.7;[46] $CH_2NH_2^+$, 178.1;[56] $CH_2NH$, 16.5.[56]

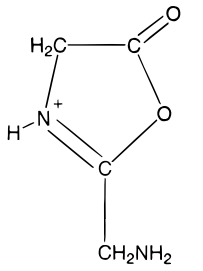
In the case of protonated 2-(aminomethyl)-5-oxazolone the positive charge is formally located on the imino nitrogen and separation of the heavy atoms in this ion requires formation of both protonated methylenimine and protonated methylamine.

**TABLE 5: Energies for Protonated and Metalated Ions[(a)]**

| molecule | B3LYP/6-31++G(d,p)[b] | ZPE | MP4[c] |
|---|---|---|---|
| Base | | | |
| 2-(aminomethyl)-5-oxazolone, **4a** | −416.01050 (−416.04255)[d] | 67.9 (68.2)[d] | −415.32155 |
| Protonated 2-(Aminomethyl)-5-oxazolone | | | |
| imino-protonated, **6a** | −416.36765 (0) (−416.39591)[d] | 76.0 (76.1)[d] | −415.67444 |
| amino-protonated **12** | −416.35991 (5.7) | 76.8 | |
| carbonyl-protonated **13** | −416.32212 (27.4) | 74.5 | |
| Lithiated 2-(Aminomethyl)-5-oxazolone[e] | | | |
| $Li^+$ coordinated by two N atoms **14a** | −423.39095 (0) (−423.42630)[d] | 70.3 (70.5)[d] | |
| $Li^+$ coordinated by $NH_2$ and O **15a** | −423.37748 (8.1) | 69.9 | |
| carbonyl-lithiated **16a** | −423.36435 (15.7) | 68.8 | |
| imino-lithiated **17** | −423.35340 (22.7) | 69.0 | |
| Argentinated 2-(Aminomethyl)-5-oxazolone[e] | | | |
| $Ag^+$ coordinated by two N atoms **14b** | −5615.32789[d] (0) | 69.6 | |
| $Ag^+$ coordinated by $NH_2$ and O **15b** | −5615.31295[d] (9.1) | 69.4 | |
| carbonyl-argentinated **16b** | −5615.29696[d] (18.5) | 68.4 | |

[a] Total electronic energies are in hartrees, relative energies and zero-point energies are in kcal mol$^{-1}$. [b] Numbers in parentheses are relative enthalpies at 298 K. [c] At MP4SDTQ(fc)/6-311++G(2df,p)//B3LYP/6-31++G(d,p). [d] At B3LYP/DZVP. [e] At B3LYP/6-31++G(d,p) the electronic energy of $Li^+$ is −7.28459 hartrees, and at B3LYP/DZVP the energy of $Ag^+$ is −5199.19815 hartrees.

Here the ammonium ion has to be added as one of the reactants (eq 3).




$$+ 6\,CH_4 + NH_4^+ + H_2O \rightarrow H_2CNH_2^+ + CH_3NH_2 + H_2CO + 2\,CH_3OH + 2\,CH_3CH_3 + CH_3NH_3^+ \quad (3)$$

The $\Delta H_f$ values computed using isodesmic reactions at B3LYP are in remarkably good agreement with experimental values (the largest deviation, that for protonated alanine, is 0.8 kcal mol$^{-1}$). Those for isodesmic reactions calculated at MP4 are intermediate between the $\Delta H_f$ values calculated at B3LYP and others calculated using the atomization method at MP4. From this very limited number of calculations, it appears that the B3LYP calculations using isodesmic reactions provide the most reliable enthalpies of formation.

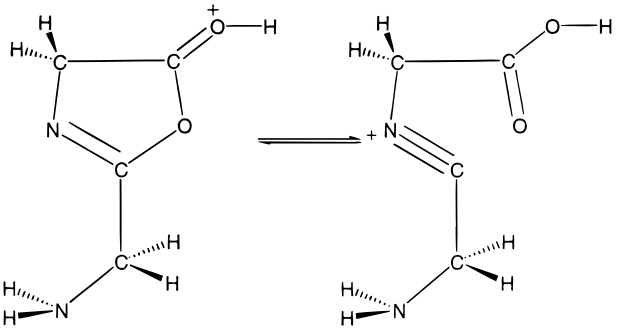
**B. Comparison of Protonation and Metalation of 5-Oxazolones.** The total energies and relative energies of several isomers of protonated, lithiated, and argentinated 2-(aminomethyl)-5-oxazolones are given in Table 5, and their structures are given in Figures 1−3. The base, **4a**, and the lowest energy isomers of the protonated and lithiated ions were optimized at both B3LYP/6-31++G(d,p) and B3LYP/DZVP and, in each case, the structures are almost identical. The remainder of the protonated and lithiated structures were optimized at B3LYP/6-31++G(d,p) and the argentinated ions were all optimized at B3LYP/DZVP.

*(a) Alternative Sites of Protonation.* There are several potential sites for protonation of 2-(aminomethyl)-5-oxazolone. In

section A the profound effects of protonation at the preferred site, the imino nitrogen in the ring, on the geometric parameters in the ring were discussed. Here we examine the structural changes accompanying protonation at other sites (Figure 1).

The amino-protonated isomer **12**, has a proton of the $NH_3^+$ group in plane, cis to the imino nitrogen, and the distance from this hydrogen atom to the nitrogen atom in the ring is 1.896 Å, indicating the existence of a weak hydrogen bond. This isomer is 5.7 kcal $mol^{-1}$ higher in energy than the imino-protonated isomer, **6a**. Comparison of the structure of **12** with that of the base, **4a**, shows the two C−O distances in the ring to have undergone large changes on protonation. These geometric changes, a decrease in $C_2$−O and an increase in $C_5$−O, are slightly smaller but in the *same* direction as those resulting from protonation on the imino nitrogen.

Protonation on the carbonyl oxygen gives ion **13**, a cation that is energetically much less favorable than **6a** (by 27.7 kcal $mol^{-1}$). Relative to **4a**, **13** has slightly shorter $C_2$−N, N−$C_4$,



**13a** **13a'**

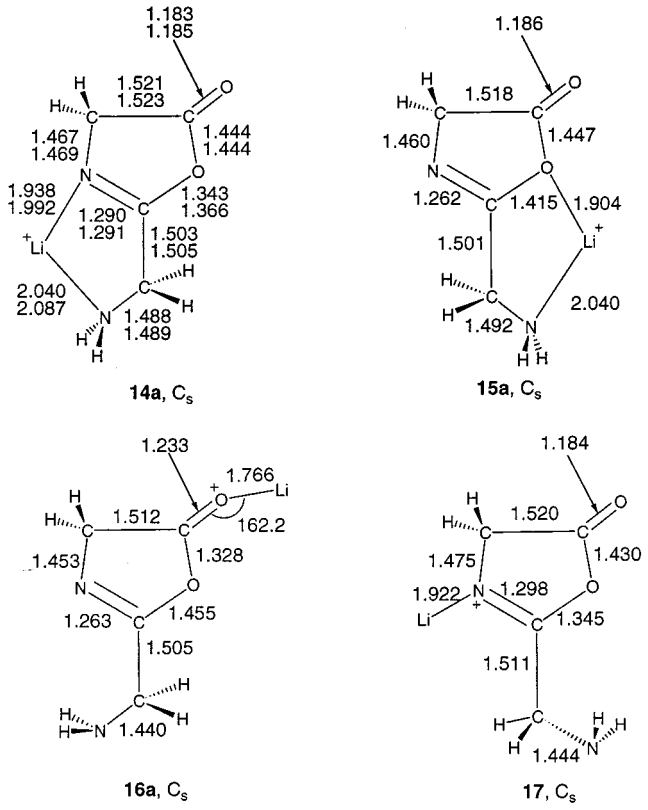
and $C_4$−$C_5$ distances, but again the largest changes are around the oxygen atom in the ring. Here the changes are in the *opposite* direction from when the proton is added to the nitrogen atoms. The O−$C_2$ distance in **13** is much longer (increased by 0.196 Å to 1.589 Å); this compares with a standard C−O single bond distance of ∼1.43 Å.[43] The $C_5$−O distance in **13** is 0.124 Å *shorter* than that in **4a**. These geometric parameters suggest that resonance structure **13a′**, an alkylated nitrile, is a significant contributor to the structure of **13a**.

*(b) Alternative Sites of Lithiation.* The lithium ion affinity of 2-(aminomethyl)-5-oxazolone as calculated at B3LYP/6-31++G-(d,p) is 58.7 kcal $mol^{-1}$ at 298 K.

Unlike the proton, lithium attaches to 2-(aminomethyl)-5-oxazolone, **4a**, in a bidentate fashion, and in the structure with the lowest energy **14a**, the O−$C_2$ is shorter (by 0.050 Å) and the $C_5$−O distance longer (by 0.048 Å) than in **4a** (Figure 2). These changes on lithiation are in the same direction but are only slightly more than half the magnitude of those resulting from protonation of the imino nitrogen. The N−Li distances of 1.938 Å (imino nitrogen) and 2.040 Å (amino nitrogen) are comparable with a distance of 1.963 Å in $CH_3NH_2Li^+$, as calculated at B3LYP/6-31++G(d,p).

Another bidentate structure in which the amino group is lithiated involves attachment to the oxygen atom in the ring (structure **15a**). This isomer lies 8.0 kcal $mol^{-1}$ above **14a**. In **15a** both the C−O distances in the ring are larger than in 2-(aminomethyl)-5-oxazolone and the C−$NH_2$ distance has increased by 0.041 Å as a result of lithiation.

The next highest energy isomer **16a**, has the carbonyl oxygen lithiated and is 15.7 kcal $mol^{-1}$ above **14a**. The difference between equivalent structures on the $C_4H_7N_2O_2^+$ surface, where



**14a**, $C_s$ **15a**, $C_s$ **16a**, $C_s$ **17**, $C_s$

**Figure 2.** Structures of isomers of lithiated 2-(aminomethyl)-5-oxazolone, showing only bond distances between heavy atoms. Where there are two sets of parameters, the upper ones are at B3LYP/6-31++G(d,p) and the lower ones at B3LYP/DZVP. Bond lengths are in ångstroms, and bond angles are in degrees.

H replaces Li, is 27.7 kcal $mol^{-1}$. The carbonyl lithiation enthalpy of 2-(aminomethyl)-5-oxazolone is 43.0 kcal $mol^{-1}$, and this compares with a value of 33.6 kcal $mol^{-1}$ for formaldehyde at the same level of theory. As in the case of protonation, lithiation results in a shortening of $C_5$−O and a lengthening of O−$C_2$, but lithiation produces much smaller structural changes.

Finally, in an attempt to determine the amount of stabilization endowed upon the lithiated imine by interaction with the amino group, we decided to examine ion **17**, where the amino group is rotated away from the site of protonation. This isomer has a similar ring structure to **14a** but is 22.8 kcal $mol^{-1}$ higher in energy, giving it a binding enthalpy of 35.9 kcal $mol^{-1}$. In separate calculations at MP2(full)/6-311++G(d,p) the $Li^+$ affinities of $CH_3NH_2$ and of $CH_2NH$ were found to be 38.6 and 37.2 kcal $mol^{-1}$, respectively. Hence, in the absence of secondary interactions with another heteroatom the ability of the 5-oxazolone to delocalize the charge over the ring has little effect on the $Li^+$ affinity of the imino group in the ring. However, the binding resulting from interaction with the two nitrogens simultaneously is 17.1 kcal $mol^{-1}$ less than the sum of that with the two groups separately.

*(c) Alternative Sites of Argentination.* As with $Li^+$, silver ion preferentially binds with the two nitrogen atoms of 2-(aminomethyl)-5-oxazolone. The binding enthalpy as calculated at B3LYP/DZVP is 53.7 kcal $mol^{-1}$, i.e., slightly less than the binding enthalpy of $Li^+$. This compares with calculated values for these isolated functional groups of 40.6 kcal $mol^{-1}$ for $CH_2NH$ and 43.6 kcal $mol^{-1}$ for $CH_3NH_2$.

We examined three isomers, two in which the silver ion is bound to the amino group, structures **14b** and **15b**, and one in which it is attached to the carbonyl oxygen **16b**. The calculated

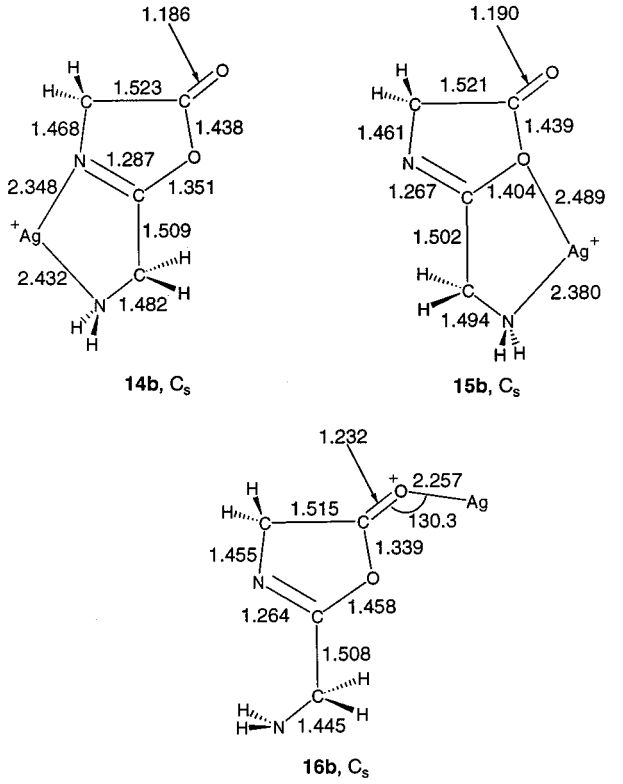



**Figure 3.** Structures of isomers of argentinated 2-(aminomethyl)-5-oxazolone, showing only distances between heavy atoms, as optimized at B3LYP/DZVP. Bond lengths are in ångstroms, and bond angles are in degrees.

binding enthalpy for attachment to the carbonyl oxygen, 35.2 kcal mol$^{-1}$, is larger than the binding enthalpy for argentination of formaldehyde (28.7 kcal mol$^{-1}$). The relative enthalpies of the three isomers are the same as for the corresponding isomers on the $C_4H_6N_2O_2Li^+$ potential energy surface and the energy differences are similar (Table 5).

A comparison of structures **14b**, **15b**, and **16b** with those of the lithiated analogues shows remarkable similarities in structural parameters with the obvious difference that Ag−ligand distances are longer than Li−ligand distances (Figures 2 and 3). Also, we were unable to locate a structure in which the silver is coordinated to only one nitrogen, as in **17** on the $C_4H_6N_2O_2Li^+$ potential energy surface. Two minor variations are worthy of note. In structure **15a** the Li−O distance is shorter than Li−N, whereas in **15b** the Ag−O distance is longer than the Ag−N, reflecting the preference of lithium for oxygen and that of silver for nitrogen. Also in the carbonyl metalated structures **16**, the metal−oxygen−carbon angle is much larger in the complex with lithium than in that with silver (162.2° compared with 130.5°).

*(d) Basis Set Superposition Errors (BSSE).* Basis set deficiencies from using only medium-sized basis sets result in a better description of a complex than of its dissociation products, the metal ion and the ligand. As a result, the enthalpies for the binding reactions are overestimated. This basis set superposition error (BSSE) can be remedied by performing calculations at the geometry of the complex on the dissociation products in which "ghost" functions from the other product of the dissociation are included.[60] At B3LYP/DZVP BSSE corrections (in kcal mol$^{-1}$) are for $CH_2NHAg^+$, 1.24; for $CH_3NH_2Ag^+$, 1.56; for $H_2COAg^+$, 1.29; and for 2-(aminomethyl)-5-oxazolone, **4a**, 2.36. These calculations establish that inclusion of BSSE corrections have only a minor effect in reducing binding enthalpies and will not change the relative energies discussed above.

## Conclusions

The preferred site for protonation of oxazolones is on the imino nitrogen and the proton affinities of the differently substituted structures examined here are ≈13 kcal mol$^{-1}$ greater than that of methylenimine. Furthermore, these proton affinities are largely independent of whether there is a phenyl or $CH_2NH_2$ substituent at the $C_2$-position on the ring, and also of whether there is H or $CH_3$ at the $C_4$-position. Protonation on the imino nitrogen results in large structural changes within the ring, the largest one being lengthening of the $C_5$−O distance, the bond that has to be broken if CO loss is to occur.

The lowest energy tautomers of protonated oxazolones are stabilized by hydrogen bonds, structures in which the proton is shared unsymmetrically between the two basic nitrogen sites. By contrast, cations in which either $Li^+$ and $Ag^+$ is coordinated to 2-(methylamino)-5-oxazolone, prefer dicoordination with the metal ion attached to both the amino group and either the imino nitrogen or the oxygen in the ring. The structural changes induced in the ring by adding a metal ion are similar to those produced on protonation; however, they are less dramatic.

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