Silver Ion Binding Energies of Amino Acids: Use of Theory to Assess the Validity of Experimental Silver Ion Basicities Obtained from the Kinetic Method

Tamer Shoeib, K. W. Michael Siu, and Alan C. Hopkinson*

Department of Chemistry and Centre for Research in Mass Spectrometry, York University, Toronto, Ontario, Canada, M3J 1P3

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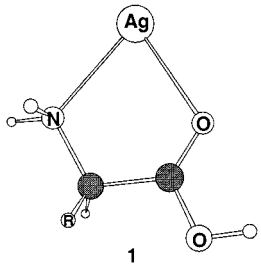
The complexes of silver ion, Ag^+, with the twenty naturally occurring amino acids have been calculated using hybrid density functional theory at the B3LYP/DZVP level. For all of these silver complexes, several possible structures were examined, but as there are remarkable similarities between all the structures at the global minima, only summarized data are reported. All of the complexes, except that with proline, are solvated ions. Amino acids containing only hydrocarbon side chains are bidentate, coordinating through the amino and carbonyl groups and the remaining amino acids (with the exception of proline) are tricoordinate with the same two interactions as in the simpler amino acids and an additional interaction through the side chain. The proline complex contains zwitterionic proline with the Ag^+ ion attached to the carboxylate anion. Enthalpies (at 298 K) for dissociation of Ag^+ from the complexes range from 49.3 kcal mol^{-1} for glycine to 80.4 kcal mol^{-1} for arginine. Free energies for these reactions are in the range of 40.7 kcal mol^{-1} for glycine to 70.3 kcal mol^{-1} for arginine. Comparison of the calculated free energies (relative to that of glycine) with those measured by the kinetic method shows good agreement, with the largest discrepancy being 3.9 kcal mol^{-1} for aspartic acid. There are some systematic trends with theory giving lower values than experiment for amino acids containing aromatic groups in the side chains (phenylalanine, tryptophan, and tyrosine) and higher values for the four amino acids with carbonyl groups in their side chains (aspartic acid, asparagine, glutamic acid, and glutamine).

Introduction

Metal complexes of peptides and proteins are important in biological systems.[1−4] Copper ions, both Cu^+ and Cu^{2+}, are important in biological processes.[5] Copper is present in several proteins and the interaction of Cu^+ with amino acids and with small peptides has recently been examined both theoretically and experimentally in the gas phase in attempts to understand Cu^+-protein interactions.[6−17] Ag^+ has the same outer electronic configuration as Cu^+ (d^{10}) and, while it does not appear to have a role in natural biological systems, it is used medicinally.[18−22]

Recently, peptide complexes of Ag^+ have been found to be useful in the sequencing of peptides.[23,24] This raised the question of how Ag^+ binds to peptides and stimulated us to examine the structure of Ag^+-glycine and Ag^+-oligoglycine complexes using theory.[17] In particular, we were interested in whether Ag^+ is attached to more than one basic site in the amino acid, i.e., whether it is dicoordinate in the case of amino acids with no basic substituent in the side chain (e.g., glycine, alanine, etc.). In such a combination, there are two likely structures. One is an η^2-N,O complex or charge-solvated ion in which Ag^+ coordinates with the carbonyl oxygen and with the nitrogen of the α-amino group (structure **1**). The other is an η^2-O,O−(CO_2^-) complex or salt bridge structure, in which Ag^+ is attached to the two oxygen atoms of the zwitterionic amino acid (structure **2**). In the case of glycine (R = H), **2** was calculated to be 4.5 kcal mol^{-1} above **1**.[17]

Ag^+ has been shown to be 4-coordinate in solution.[25−27] Theoretical studies of the coordination of Ag^+ by CH_3CN and by NH_3 have shown that addition of the first two ligand molecules have approximately the same exothermicities (around 38 kcal mol^{-1}), whereas the exothermicities of the next two additions are considerably lower (around 15 and 10 kcal mol^{-1}).[28,29] It therefore seems likely that amino acids that have basic groups in the side chain are likely to be 3-coordinate, providing that such structures do not introduce too much steric strain. Indeed molecular orbital calculations have shown Cu^+ to be 3-coordinate when complexed with serine and with cysteine.[13]



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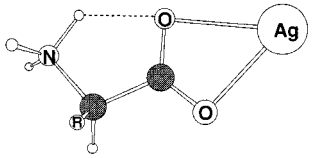

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The proton and metal cations are all strong Lewis acids that readily attach to bases and, in general, there are fair to good correlations between metal ion affinities and proton affinities of the same bases.[16,30−32] Proton affinities are larger in magnitude (ranging from 210 to 250 kcal mol^{-1} for amino acids) than metal ion affinities (Na^+ affinities were found to be in the range 40−52 kcal mol^{-1} for several amino acids).[31,33−36] Prior to 1999, there were several experimental values for the proton affinities of nineteen of the naturally occurring amino acids.[37−41] The exception was that for arginine, the most basic amino acid, for which it is difficult to find compounds of known proton affinities and of similar basicity that could be used in bracketing

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or kinetic method experiments. However, the experimental proton affinities for the amino acids, measured both by the equilibrium method and by the kinetic method showed considerable ranges of values for each individual amino acid. In a landmark paper, Maksic and Kovacevic reported a systematic study of the proton affinities of all twenty naturally occurring amino acids calculated at MP2(fc)/6-311+G(d,p)//HF/6-31G(d), a level of theory at which the accuracy is estimated to be ± 3 kcal mol^{-1}.[42] In general, they found reasonably good agreement between their theoretical proton affinities and data provided by the kinetic method. Two notable exceptions, however, were glutamine and lysine. For both amino acids, the theoretical values are considerably higher (by >10 kcal mol^{-1}) than those obtained from the kinetic method, and this was attributed to the existence of strong internal hydrogen bonding in the isolated protonated base (from NH_3^+ to the amide oxygen in glutamine, and from the terminal NH_3^+ group to the α-amino group in lysine).

Previously, one of us has reported a ladder of Ag^+ basicities for amino acids using the kinetic method;[30] these underestimations of proton gas-phase basicities by the kinetic method caused us to question whether there may be similar discrepancies in the Ag^+ basicities. For that reason, here we have used molecular orbital theory to calculate absolute Ag^+ affinities and basicities for all twenty naturally occurring amino acids and compare the *differences* between them with the previously reported experimental values.[30]

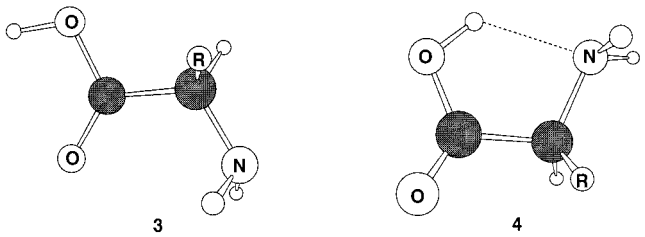
Methodology

All molecular orbital calculations were performed using Gaussian 98.[43] Structure optimizations were carried out using the Density Functional Theory (DFT) hybrid method at the B3LYP level.[44−47] The DZVP basis set [48,49] was used for structure optimization of all ions. This level of theory has been shown to give binding enthalpies for silver complexes of ammonia and acetonitrile that are within ± 3 kcal mol^{-1} of experimental values.[28,29] All critical points were characterized by harmonic frequency calculations and found to be at minima. Deficiencies in basis sets were corrected for Basis Set Superposition Errors (BSSE) by using the Counterpoise Method.[50−52]

Total energies, zero-point energies, thermal corrections and entropies are given in Supplemental Tables S1 and S2. Cartesian coordinates for structures with the lowest free energies for each amino acid and for each silver ion complex are given in Supplemental Table S3.

Results and Discussion

(a) Structural Details. *Neutral Amino Acids.* Most amino acids have a large number of conformations. These were examined carefully and, while there are individual subtleties in the compositions of the side chains, the structures at the global minima show remarkable similarities in the geometries of the $H_2NCHCOOH$ component that is common to all amino acids. The amino acids can be classified into two categories. The molecules in the first category, exemplified by glycine (R = H), for which there have been numerous and extensive studies,[13,33,34,53−59] have the proton of the carboxylic acid group between the two oxygen atoms and the amino group is staggered about the carbonyl group with the lone pair on N antiperiplanar to the carboxy group (structure **3**). The amino acids in this category mainly have nonpolar groups in their side chains e.g., glycine, alanine, valine and leucine. In addition, two molecules with polar side chains also adopt this conformation. These are methionine (side chain $CH_2CH_2SCH_3$) and proline, the only



naturally occurring amino acid that has a secondary amino group. In the case of the latter amino acid, the constraints of the five-membered ring in which the NH is incorporated prevents facile donation of the lone pair on the N to the proton of the COOH group. This makes formation of structure **4** less favorable for proline.

For the amino acids for which **3** is preferred the optimized bond lengths for the $H_2NCCOOH$ group generally vary by less than 0.004 Å. The C−N distance is an exception, being the smallest when R = H (1.455 Å) and increasing with the size f the R group. The largest value is for proline, although again it should be emphasized that this amino acid is the only one having a secondary α-amino group in a five-membered ring. The average parameters complete with maximum deviations are given in Figure 1.

The majority of amino acids adopt structure **4**. Here, the COH of the carboxylic acid group eclipses the CN bond, thereby permitting hydrogen bonding to the α-amino group. Again the structural parameters show little dependence on R. One amino acid with a hydrocarbon side chain, isoleucine, prefers this conformation. This is the bulkiest of the alkyl side chains. The parameter that is most sensitive to R is the length of the H-bond from OH to NH_2. This interaction is weak and hence the potential energy surface for stretching N····H is expected to be flat. The average N····H distance is 1.914 Å; the shortest distance (1.864 Å) is in glutamic acid and the longest (1.932 Å) is in aspartic acid.

Comparison of the "standard" structures in **3** and **4** (Figure 1) show that most of the bonds in the cyclic component of **4**, i.e., bonds C−N, C−C and O−H are longer by (0.013−0.016) Å in **3**; the exception is the C−OH distance which is 0.016 Å in **4**. By contrast, the C═O distance in **4** is almost the same as that in **3** (it is shorter by 0.002 Å)

The two most basic amino acids, lysine and arginine, are exceptions. For lysine, the structure at the global minimum has the hydrogen of the carboxylic acid group on the "outside" as in **4**, but it is hydrogen bonded to the amino group at the end of the side chain and not to the α-amino group. This hydrogen bond (1.833 Å) is shorter than all those in amino acids with structure **4**. This structure has an electronic energy that is 4.4 kcal mol^{-1} better than that of **4** (with R = $(CH_2)_2NH_2$). Previous calculations had concluded that lysine had an open structure with no hydrogen bonds.[60]

The structure of arginine in the gas phase has been the subject of considerable debate.[61−63] Two structures, one a neutral molecule with the carboxylic acid group in the same conformation as in **3** and with a hydrogen bond from the lone pair on the α-amino group to the secondary NH of the guanidinyl group, and the other a zwitterion in which the terminal guanidinyl group is protonated and the carboxylic group deprotonated, are very similar in energy.[63] At B3LYP/DZVP the neutral molecule has the better electronic energy (by 1.7 kcal mol^{-1}); this is reduced to a difference of 0.4 kcal mol^{-1} when zero-point energy is included and addition of thermal corrections results in the zwitterion having the better energy by 0.1 kcal mol^{-1}. The

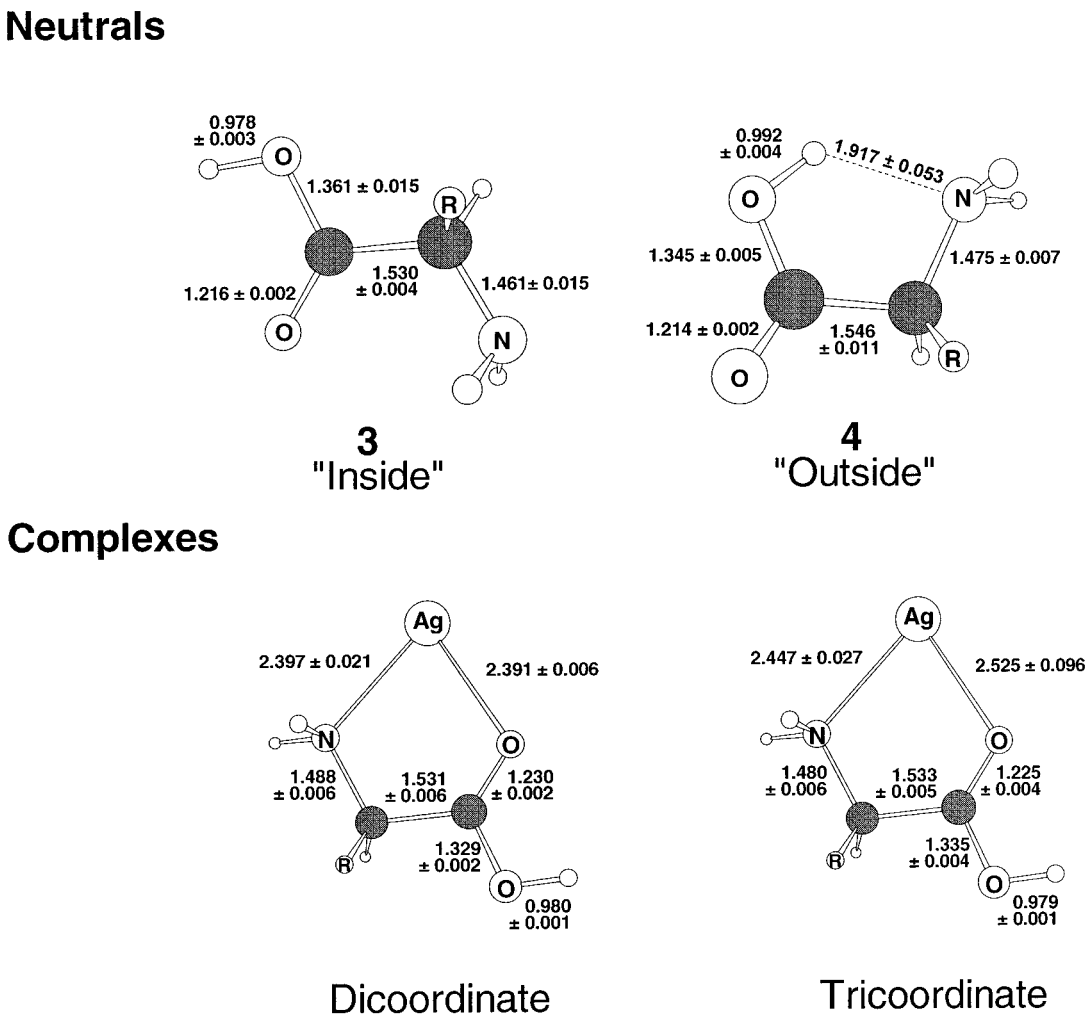


Figure 1. Average bond length and maximum deviation (in angstroms) of amino acids and their silver complexes as optimized at B3LYP/DZVP.

zwitterion is more constrained by having two intramolecular hydrogen bonds and hence, when entropy is included, then the neutral molecule is again favored and the free energy difference is 2.8 kcal mol^{-1}. Optimization at MP2(fc)/6-311++G(d,p) gave very similar results with the difference in electronic energies being 1.8 kcal mol^{-1}

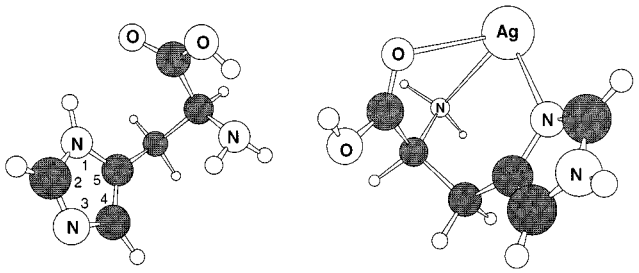
Complexes. (i) Dicoordinate. All the amino acids that have hydrogen or alkyl groups in their side chains form bidentate complexes with Ag^+; in these complexes the distances Ag−N and Ag−O in structure **1** are almost identical (both ∼2.39 Å) as in the analogous Cu^+-glycine complex (where the Cu−N and Cu−O distances are ∼2.05 Å.[64] Relative to the uncomplexed amino acids the bond lengths associated with the complexing atoms are increased, the C−N distance by 0.027 Å and the C═O by 0.014 Å. By contrast, the OH in the complex carries some of the positive charge and the C−OH distance is shorter by 0.032 Å than in the amino acids.

(ii) Tricoordinate. All the remaining amino acids, except proline, coordinate with Ag^+ through three sites. Two of these points of attachment are the NH_2 and carbonyl of the carboxyl group, as in the dicoordinate complexes. In these structures, the Ag−N is, on average, 0.050 Å longer than the (almost identical) Ag−N and Ag−O distances in the dicoordinate structures; in the tricoordinate complexes the Ag−O distances are considerably longer than Ag−N and are 0.134 Å, on average, longer than those in in the dicoordinate complexes. Comparison of the "average" structures in the two types of complexes (Figure 1) show the C−N and C═O distances to be slightly shorter in the tricoordinate structures, while the C−OH is slightly longer. All the distances in the tricoordinate complexes are closer to those in the uncomplexed amino acids; these geometric parameters indicate weaker binding with C═O and NH_2, presumably because of attachment through the third binding site.

In complexes involving the four amino acids that have the highest proton affinities (arginine, lysine, histidine, and glutamine),[42] the Ag-X distances are all shorter than the Ag−NH_2 and Ag−OC, distances, i.e., the bond with the side chain appears to be stronger than that with the functional groups common to all α-amino acids (see Figure 2 for bond lengths in these complexes). In three of these ligands, the coordination with the side chain is with a nitrogen atom, and in the fourth, glutamine, it is with the oxygen of an amide group, an arrangement which effectively transfers some of the charge on to the nitrogen of the amide. In the case of lysine, the terminal H_2C-NH_2 bond in the complexed amino acid is longer (by 0.015 Å) than that in the free amino acid, apparently reflecting the stronger Ag−N bond to the side chain.

The three amino acids that have aromatic groups in their side chains (phenylalanine, tyrosine, and tryptophan) have the Ag^+ situated almost directly above one of the carbon atoms. In both phenylalanine and tyrosine, it is above the carbon ortho to the CH_2 group of the side chain, whereas that in tryptophan/Ag^+ is above the carbon of the six-membered ring that is ortho to a carbon in the five-membered ring. Histidine is the other amino acid with an aromatic ring in the side chain. In uncomplexed histidine the NH group in the ring is adjacent to the side chain

(structure **5**), i.e., the hydrogen is on atom 1, whereas in the



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argentinated ion the hydrogen has migrated to the other N atom in the ring thereby permitting the first nitrogen to coordinate to silver (structure **6**).

Only one Ag^+-amino acid complex, that with proline, has the salt bridge structure **2** at the global minimum. This probably is a consequence of two features, the larger basicity of the secondary amine group and the constraints of the five-membered ring preventing the lone pair on the nitrogen from adopting the optimum orientation required to create a strongly bound bidentate complex. The charge solvated structure on this potential energy surface is at a minimum 2.2 kcal mol^{-1} higher than the salt bridge structure.[65] By contrast, the lowest energy Cu^+-proline complex does not have the salt bridge structure but prefers the more common arrangement, **1**, in which Cu^+ is coordinated to both the carbonyl oxygen and the amino group.[13b] This can be attributed to the inability of Cu^+ to coordinate strongly with *both* the oxygen atoms of the carboxylate anion, COO^-. [17]

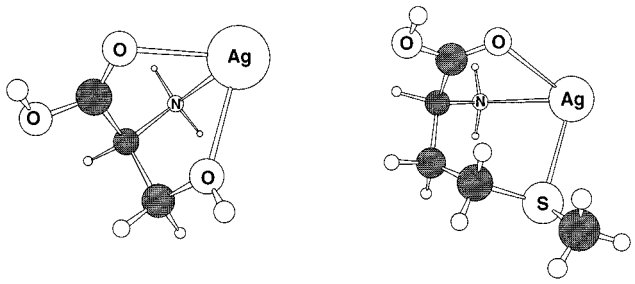
(b) Silver Ion Affinities. The silver ion affinity of an amino acid, M, at 298 K is defined as the enthalpy of the reaction in eq 1

$$Ag^+\text{-}M \rightarrow Ag^+ + M \qquad (1)$$

For glycine, theory at B3LYP/DZVP gives a Ag^+ affinity of 49.3 kcal mol^{-1}. This compares with a value of 64.3 kcal mol^{-1} for Cu^+ at 0 K.[13a]

In general, the Ag^+ affinity of an amino acid depends to a large extent on the interaction of the Ag^+ ion with the side chain. This interaction is dictated by two factors, the intrinsic Lewis acid strength of the substituent and the amount of steric strain introduced by forming the rings. Alkyl groups stabilize positive charges inductively and not by direct coordination. This results in small increases in Ag^+ affinities, with the stabilization increasing with the size of the alkyl group (Table 1). Isoleucine has the highest Ag^+ affinity (52.9 kcal mol^{-1}) of this group of dicoordinating amino acids, 3.6 kcal mol^{-1} higher than that of glycine.

Serine has a low Ag^+ affinity, probably due to the steric strain in the small rings in the complex (structure **7** has two 5- and one 6-membered rings). Threonine differs from serine by having a terminal methyl group rather than a hydrogen on the oxygen atom in the side chain and this increases the Ag^+ affinity by 2.1 kcal mol^{-1}. Replacing the oxygen in the side chain of serine by a sulfur atom results in cysteine; however, this amino acid also has a low Ag^+ affinity (56.1 kcal mol^{-1}) despite the high affinity of sulfur for metal ions. Two factors appear to be important, one is the ring strain resulting from the presence of two five-membered and one six-membered rings. The other comes from interaction between nonbonded hydrogen atoms. A close examination of the Ag^+-cysteine complex showed that, in the two lowest energy 3-coordinate structures, the hydrogen attached to the sulfur is almost eclipsing a hydrogen on the adjacent carbon. In the Ag^+-serine complex, this destabilizing feature is absent and may be part of the reason that the cysteine silver affinity is not considerably higher than that of serine. The importance of these two factors in the cysteine complex is illustrated by the much higher affinity of methionine (62.7 kcal mol^{-1}); the latter ligand has an extra CH_2 group in the side chain and this results in larger rings (structure **8** has five-, six-, and seven-membered rings) and allows for conformations in which there are no eclipsed hydrogen atoms. Another factor is that methionine has an additional terminal methyl group, but judging by the difference in the Ag^+ affinities of serine and threonine, this is not likely to make a significant difference.



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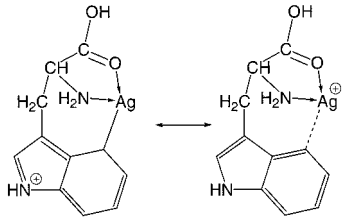
The Ag^+ affinities of phenylalanine and tyrosine differ by only 0.9 kcal mol^{-1}. The aromatic hydroxy group of tyrosine is two carbon atoms removed from the carbon to which the silver is coordinated, i.e., it is in the meta position and cannot therefore contribute effectively in stabilizing the positive charge. The opposite occurs in formation of the complex with tryptophan. Here, the Ag^+ interacts with the π-system of the six-membered ring and the shortest distance is to the ortho carbon as depicted in resonance structures **9a** and **9b,** which allows some of the positive charge to be delocalized onto the nitrogen in the ring. The Ag^+-C distance in the tryptophan complex is 2.52 Å (Figure 2), and is 0.1 Å shorter than the Ag^+-C distances in the phenylalanine and tyrosine adducts.



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Aspartic acid and glutamic acid both have carboxylic acid groups at the end of their side chains; the only difference between these molecules is that glutamic acid has an extra CH_2 group in its side chain. Both form tricoordinate complexes with Ag^+ and the slightly higher Ag^+ affinity of glutamic acid (57.4 compared with 55 kcal mol^{-1}) is attributed to the less-strained rings in the glutamic acid complex (five-, seven- and eight-membered rings compared with five-, six- and seven-membered rings).

Asparagine and glutamine are formed by converting the terminal carboxylic acid groups of aspartic and glutamic acids into amides. The higher basicity of the amide group relative to that of the carboxylic acid group results in higher Ag^+ affinities. Asparagine has an affinity of 60.0 kcal mol^{-1}, 4.4 kcal mol^{-1} higher than that of aspartic acid. Glutamine has an affinity of 63.2 kcal mol^{-1}, 5.8 kcal mol^{-1} higher than that of glutamic acid. The difference in Ag^+ affinities of asparagine and

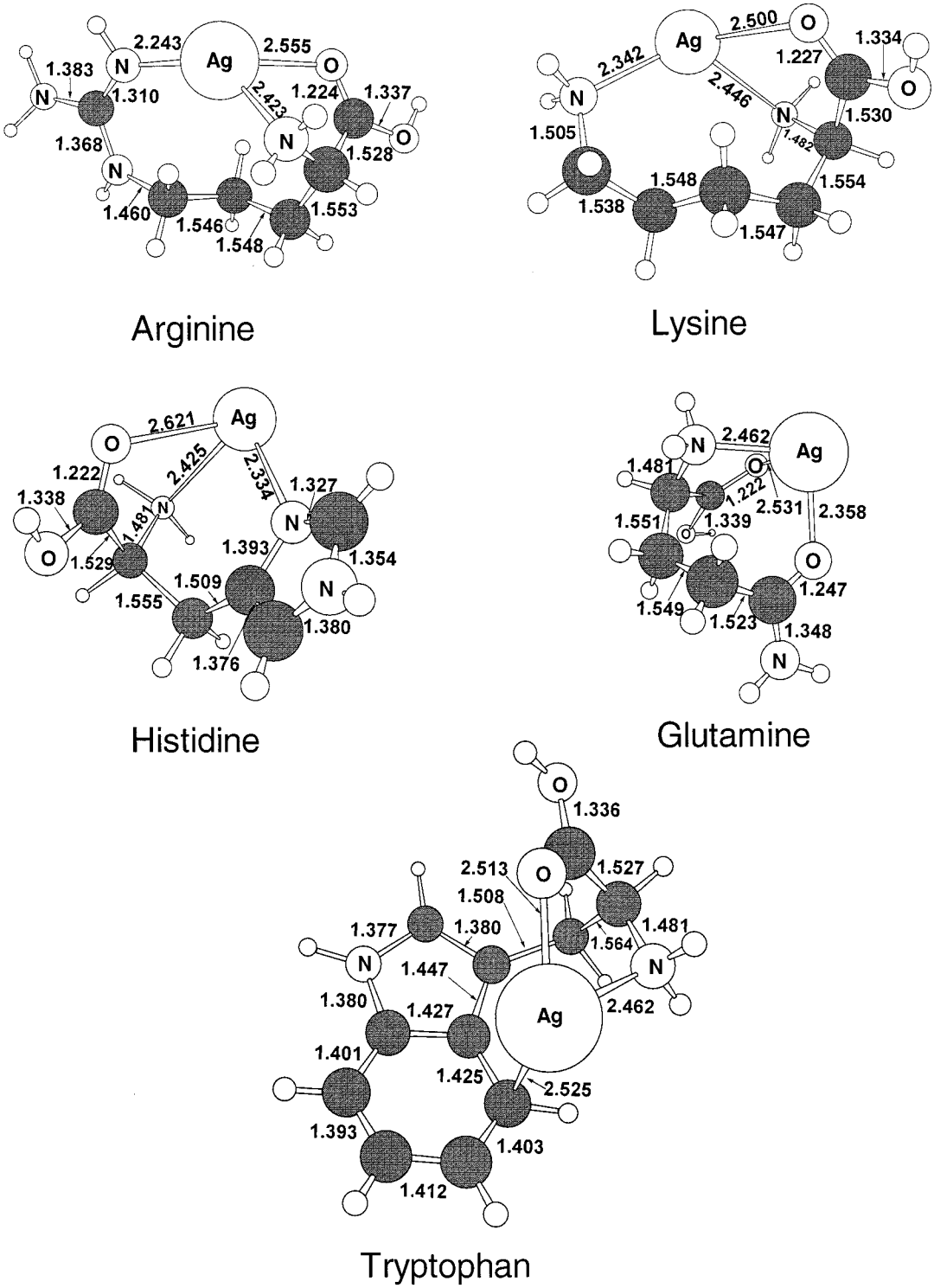


Figure 2. Structural parameters (in angstroms) for silver complexes of arginine, lysine, histidine, glutamine and tryptophan as optimized at B3LYP/DZVP.

glutamine (3.2 kcal mol^{-1}) is again attributed to the less-strained rings in the glutamine complex.

Two of the most basic amino acids, histidine, and lysine, also have some of the larger Ag^+ affinities. In both of these complexes the shortest, and presumably strongest, coordination bond is with a nitrogen in the side chain. Despite the presence of this strong third interaction in the Ag^+ complexes of these amino acids, the entropies for complex formation are relatively small. $T\Delta S$ terms are 8.4 and 8.6 kcal mol^{-1} for histidine and lysine respectively, and these compare with a value of 8.6 kcal mol^{-1} for prototypical dicoordinate complex, glycine. For lysine the entropy change is also in marked contrast with the larger value reported for formation of the Cu^+-lysine complex.[68]

The calculated small $T\Delta S$ terms for formation of the Ag^+-lysine complex is attributed to the lowest energy conformer of neutral lysine in which there is a hydrogen bond between the amino group at the end of the side chain and the carboxylic acid group. Using the second best optimized structure for lysine (2.0 kcal mol^{-1} higher in free energy), one in which the terminal NH_2 group is distant from the carboxylic acid group and the

TABLE 1: Enthalpies and Free Energies in (kcal mol^{-1}) for Ag^+ Addition to α Amino Acids

α-amino acid	BSSE	$-\Delta H$ (298)	$-\Delta G$ (298)	$\Delta\Delta H$ (298) theory	$\Delta\Delta G$ (298) theory	$\Delta\Delta G$ exp	$\Delta\Delta H_{theory} - \Delta\Delta G_{exp}$	$\Delta(\Delta\Delta G)$ theory-exp
Glycine (G)	2.2	49.3	40.7	0.0	0.0	0.0	0.0	0.0
Alanine (A)	2.2	50.9	42.3	1.6	1.6	1.4 ± 0.0	0.2	0.2
Valine (V)	2.3	51.7	43.3	2.4	2.6	2.4 ± 0.2	0.0	0.2
Leucine (L)	2.3	52.5	44.4	3.2	3.7	2.5 ± 0.1	0.7	1.2
Isoleucine (I)	2.2	52.9	45.2	3.6	4.5	2.8 ± 0.0	0.8	1.7
Serine (S)	2.6	53.7	45.5	4.4	4.8	3.2 ± 0.4	1.2	1.6
Cysteine (C)	2.8	55.1	46.5	5.8	5.8	N/A	N/A	N/A
Aspartic acid (D)	2.6	55.6	47.6	6.3	6.9	3.0 ± 0.2	3.3	3.9
Threonine (T)	2.6	55.8	47.8	6.5	7.1	4.6 ± 0.1	1.9	2.5
Proline (P)	1.6	56.1	47.8	6.8	7.1	5.0 ± 0.1	1.8	2.1
Phenylalanine (F)	3.1	56.5	47.5	7.2	6.8	9.5 ± 0.3	−2.3	−2.7
Glutamic acid (E)	2.8	57.4	48.6	8.1	7.9	4.6 ± 0.1	3.5	3.3
Tyrosine (Y)	3.1	57.4	48.4	8.1	7.7	9.6 ± 0.1	−1.5	−1.9
Asparagine (N)	2.4	60.0	52.0	10.7	11.3	8.3 ± 0.3	2.4	3.0
Tryptophan (W)	3.3	62.2	53.0	12.9	12.3	14.5 ± 0.2	−1.6	−2.2
Methionine (M)	3.1	62.7	52.6	13.4	11.9	13.1 ± 0.1	−0.3	−1.2
Glutamine (Q)	2.8	63.2	54.0	13.9	13.3	10.7 ± 0.2	3.2	2.6
Histidine (H)	3.0	68.0	59.6	18.7	18.9	18.0 ± 1.0	0.7	0.9
Lysine (K)	3.9	71.0	62.4	21.7	21.6	19.8 ± 1.2	1.9	1.8
Arginine (R) neut	3.8	80.5	70.3	31.2	29.6	>26.8	N/A	N/A
Arginine (R) zwit	3.8	80.4	73.0	31.1	32.3	>26.8	N/A	N/A

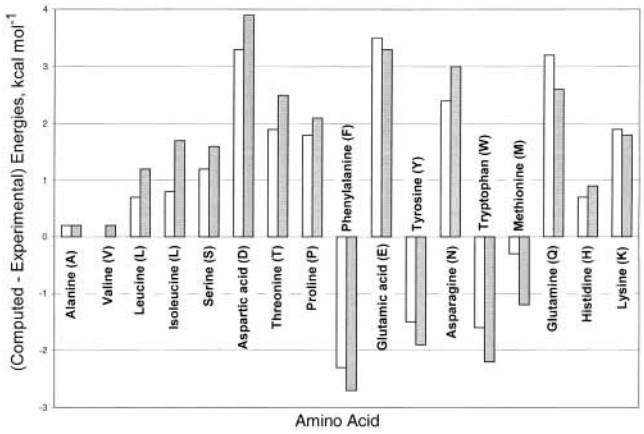


Figure 3. Plot of (computed − experimental) energies relative to those for glycine. Values given in white are $\Delta\Delta H$ and those in gray $\Delta\Delta G$. See Table for data.

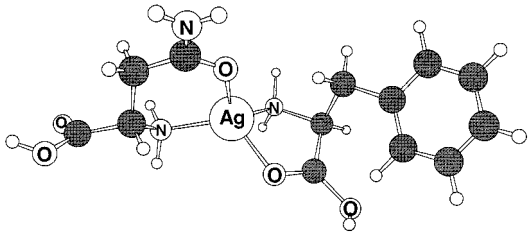
molecule is elongated, the $T\Delta S$ term for complex formation is 10.6 kcal mol^{-1}, a value larger than for the formation of any of the complexes listed in Table 1.

Arginine has the largest Ag^+ affinity; we report two values in Table 1, one for the uncomplexed arginine as a neutral molecule and the other as a zwitterion. The enthalpies for formation of Ag^+-arginine at 298 K are essentially the same regardless of which structure is used for arginine. However, the equilibrium involving the neutral form of arginine has the lower free energy.

(c) Comparison of Experimental and Theoretical Relative Ag^+ Affinities. Relative Ag^+ affinities obtained from kinetic method measurements are compared with those from theory in Table 1 and Figure 3. The theoretical values for both ΔH and ΔG were calculated at 298 K, and consequently the computed $\Delta\Delta H$ and $\Delta\Delta G$ values are at 298 K. The temperature, T_{eff}, at which the experimental $\Delta\Delta G$ values were recorded is unknown but, given that ΔS terms for addition of Ag^+ to amino acids are similar ($T\Delta S$ varies from 7.4 to 10.2 kcal mol^{-1} at 298 K, with the two extreme values resulting from formation of Ag^+-arginine, depending on whether the arginine molecule is in the zwitterionic or neutral form), the effect of temperature variations will have a small effect on the relative free energies.[30,36] Experimental Ag^+ basicities for two amino acids, cysteine and arginine, are not available for technical reasons. For the remainder, there is satisfactory agreement between the experimental and theoretical values. The best agreement is for amino acids that form dicoordinate complexes with Ag^+ (R = alkyl), and for the large majority of amino acids (fourteen in total) the difference between theory and experiment is within ± 2.8 kcal mol^{-1}. The three for which there are larger diffferences between theory and experiment are asparagine, glutamic, and aspartic acids, with the largest value being 3.9 kcal mol^{-1} for aspartic acid.

There are some obvious trends displayed in Figure 3. Three of the four compounds, phenylalanine, tyrosine, and tryptophan, for which theory gives lower relative free energies than experiment contain an aromatic group in the side chain. The compounds that deviate most markedly in the other direction, i.e., have theoretical values higher than experimental ones, are aspartic acid, asparagine, glutamic acid and glutamine. These are all structurally similar molecules in which there is either a carboxylic acid or an amide group in the side chain. In all of these molecules the carbonyl oxygen in the side chain coordinates to Ag^+.

Deviations between experimental and computed Ag^+ affinities, as displayed in Figure 3, can be examined in terms of a silver complex involving one amino acid containing an aromatic side chain and the other an amino acid with a carboxylic acid derivative in the side chain. For example, calculations based on equilibrium geometries give asparagine (N) to have a higher silver ion affinity than phenylalanine (F), whereas the kinetic method gives the opposite result. The schematic diagram in Figure 4 is consistent with these results for $[F-Ag-N]^+$. The adduct containing the two amino acids is probably 4-coordinate[29] and, based solely on the Ag^+ affinities of the different groups (in isolation),[66,67] structure **10** has the most plausible arrange-



10

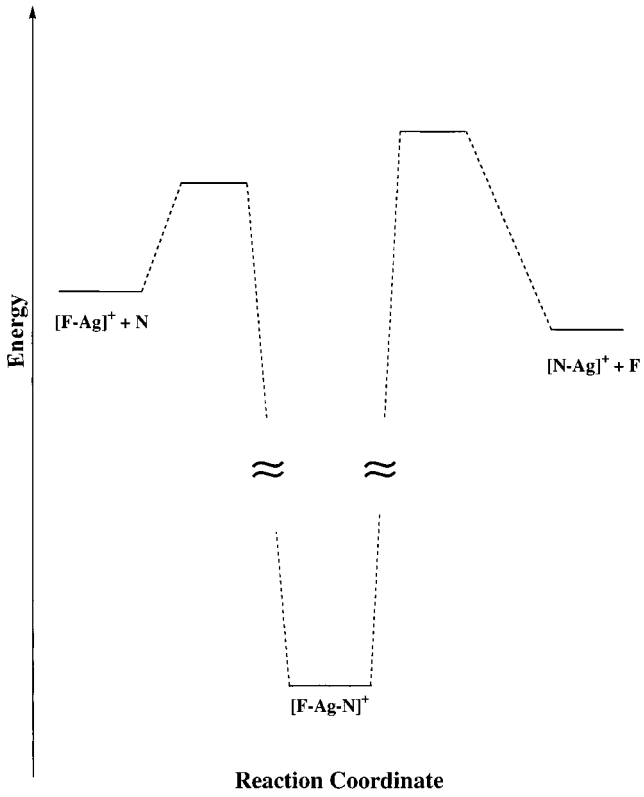


Figure 4. Schematic energy diagram for the fragmentation of complex $[F-Ag-N]^+$ that is consistent with the experimental and computational results.

ment. Dissociation of this complex into $[F-Ag]^+$ plus asparagine is favored experimentally and must have the lower barrier.[30] However, this combination is the less favored on the basis of calculated equilibrium structures; this then implies that there is a smaller reverse barrier for the dissociation into $[F-Ag]^+$ plus asparagine than into $[N-Ag]^+$ plus phenylalanine. Without a detailed study of the transition states for these two processes, a computationally very difficult task at this time, it is difficult to be more definitive. It should, however, be emphasized that that all differences between experimental and computed Ag^+ affinities are small and we conclude that the kinetic method, albeit inexact and nonrigorous, does appear to provide fairly satisfactory approximations of relative Ag^+ affinities of amino acid.

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Supporting Information Available: Silver ion binding energies of amino acids (Supporting Tables 1−3). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Sauer, J. *Chem. Rev.* **1989**, *89*, 199.
(2) Bäckvall, J.-E.; Bökman, F.; Blomberg, M. R. A. *J. Am. Chem. Soc.* **1992**, *114*, 534.
(3) Dougherty, D. A. *Science* **1996**, *271*, 163.
(4) Silagyi, R. K.; Frenking, G. *Organometallics* **1997**, *16*, 4807.
(5) Lippard, S. J.; Berg, J. M. *Principles of Bioinorganic Chemistry*; University Science Books; Mill Valley, CA, 1994 and references therein.
(6) Grese, R. P.; Cerny, R. L.; Gross, M. L. *J. Am. Chem. Soc.* **1989**, *111*, 2835.
(7) Lausarot, P. M.*Org. Mass. Spectrom.* **1991**, *26*, 51.
(8) Nelson, R. W.; Hutchens, T. W. *Rapid Commun. Mass Spectrom.* **1992**, *6*, 4.
(9) Bouchonnet, S.; Hoppilliard, Y.; Ohanessian, G. *J. Mass Spectrom.* **1995**, *30*, 172.
(10) Karlin, K. D., Tyeklàr, Z., Eds. *Bioinorganic Chemistry of Copper;* Chapman and Hall, New York; 1993.
(11) Lei, P.; Amster, I. J. *J. Am. Soc. Mass Spec.* **1996**, *7*, 722.
(12) Lavanant, H.; Hoppilliard, Y. *J. Mass Spec.* **1997**, *32*, 1037.
(13) (a)Hoyau, S.; Ohanessian, G. *J. Am. Chem. Soc.* **1997**, *119*, 2016. (b) Hoyau, S.; Ohanessian, G. C. R. *Acad. Sci. Paris, t.1, Serie II* **1998**, 795.
(14) Wen, D.; Yalcin, T.; Harrison, A. G. *Rapid Comm. Mass Spec.* **1995**, *9*, 1155.
(15) Gatlin, C. L.; Turecek, F.; Vaisir, T. *J. Am. Chem. Soc.* **1995**, *117*, 3637.
(16) Cerda, B. A.; Wesdemiotis, C. *J. Am. Chem. Soc.* **1995**, *117*, 9734.
(17) Shoeib, T.; Rodriquez, C. F.; Siu, K. W. M.; Hopkinson, A. C. *Phys. Chem. Chem. Phys.* **2001**, *3*, 853.
(18) Petering, H. G. *Pharmacol. Ther. A* **1976**, *1*, 127.
(19) Grier, N. In *Silver and its Compounds in Disinfection, Sterilization and Preservation;* Block, S. S., Ed; Lea and Feibiger: Philadelphia, PA; 1983.
(20) Fox, C. L.; Modak, S. M. *Antimicrob. Agent Chemother.* **1974,** *5*, 582.
(21) Berners-Price, S. J.; Johnson, R. K.; Giovanella, A. J. *J. Inorg. Biochem.* **1988**, *33*, 285.
(22) Steininger, H.; Langer, E. *Dtsch. Med. Wochenschr.* **1990**, *115*, 657.
(23) Lee, V. W.-M.; Li, H.; Lau, T.-C.; Siu, K. W. M *J. Am. Chem. Soc.* **1998**, *120*, 7302.
(24) Chu, I. K.; Shoeib, T.; Guo, X.; Rodriquez, C. F.; Lau, T.-C.; Hopkinson A. C.; Siu, K. W. M. *J. Am. Soc. Mass Spectrom.* **2001**, *12*, 163.
(25) Bjerrum, J.*Acta Chem. Scand.* **1986**, *A40*, 392.
(26) Carlucci, L.; Ciani, G.; Proserpio, D. M.; Sironi, A. *J. Am. Chem. Soc.* **1995**, *117*, 4562.
(27) Tsutsui, Y.; Sugimoto, K.-I.; Wasada, H.; Inada, Y.; Funahashi, S. *J. Phys. Chem. A* **1997**, *101*, 2900.
(28) Shoeib, T.; El Aribi, H.; Siu, K. W. M.; Hopkinson, A. C. *J. Phys. Chem. A* **2001**, *105*, 710.
(29) Shoeib, T.; Milburn, R. K.; Koyanagi, G. K.; Lavrov, V. V.; Bohme, D. K.; Siu, K. W. M.; Hopkinson, A. C. *Int. J. Mass Spectrom.* **2000**, *201*, 87.
(30) Lee, V. W.-M.; Li, H.; Lau, T.-C.; Guevremont, R.; Siu, K. W. M *J. Am. Mass Spectrom.* **1998**, *9*, 760.
(31) Ryzhov, V.; Dunbar, R. C.; Cerda, B.; Wesdemiotis, C. *J. Am. Mass Spectrom.* **2000**, *11*, 1037.
(32) Shoeib, T.; Gorelsky, S.; Lever, A. B. P.; Siu, K. W. M.; Hopkinson, A. C. *Inorg. Chim. Acta* **2001**, *315*, 236.
(33) Jensen, F. *J. Am. Chem. Soc.* **1992**, *114*, 9533.
(34) Bouchonnet, S.; Hoppilliard, Y. *Org. Mass Spec.* **1992**, *27*, 71.
(35) Bojesen, G.; Breindahl, T.; Andersen, U. N. *Org. Mass Spec.* **1993**, *28*, 1448.
(36) Feng, W. Y.; Gronert, S.; Lebrilla, C. B. *J. Am. Chem. Soc.* **1999**, *121*, 1365.
(37) Bojesen, G.; Breindahl. T. *J. Chem. Soc., Perkin 2* **1994**, 1029.
(38) Gorman, G. S.; Speir, J. P.; Turner, C. A.; Amster, I. J. *J. Am. Chem. Soc.* **1992**, *114*, 3986.
(39) Campbell, S.; Beauchamp, J. L.; Rempe, M.; Lichtenberger, D. L. *Int. J. Mass Spectrom. Ion Proc.* **1992**, *117*, 83.
(40) Li, X.; Harrison, A. G. *Org. Mass Spectrom.* **1993**, *28*, 366.
(41) For an excellent review see Harrison, A. G. *Mass Spectrom. Rev.* **1997**, *16*, 201.
(42) Maksic, Z. B.; Kovacevic, B. *Chem. Phys. Lett.* **1999**, *307*, 497.
(43) Frisch, M. J.;. Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery Jr, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Rudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.5, Gaussian Inc., Pittsburgh, PA **1998**.
(44) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(45) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11 623.

(46) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(47) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett*. **1989**, *157*, 200.
(48) Godbout, N.; Salahub, D. R.; Andzelm, J.; Wimmer, E. *Can J. Chem.* **1992**, *70*, 560.
(49) Godbout, N. *Ensemble de Base pour la Théorie de la Fonctionnelle de la Densité-Structures Moléculaires Propriétés Mono-Électroniques et Modèles de Zéolites* Ph.D. Thesis, Université de Montréal, Montréal, Canada, 1996.
(50) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.
(51) Chalasinski, G.; Szczesniak, M. M. *Chem. Rev.* **1994**, *94*, 1723.
(52) van Duijneveldt, F. B.; van Duijneveldt-van de Rijdt; van Lenthe, J. H. *Chem. Rev.* **1994**, *94*, 1873.
(53) Jensen, J. H.; Gordon, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 7917.
(54) Yu, D.; Armstrong, D. A.; Rauk, A. *Can. J. Chem.* **1992**, *70*, 1762.
(55) Hu, C. H.; Shen, M.; Schaefer, H. F. *J. Am. Chem. Soc.* **1993**, *115*, 2923.
(56) Czaszar, A. G. *J. Am. Chem. Soc.* **1992**, *114*, 9568.
(57) Frey, R. F.; Coffin, J.; Newton, S. Q.; Ramek, M.; Cheng, V. K. W.; Momany, F. A. Schafer, L. *J. Am. Chem. Soc.* **1992**, *114*, 5369.
(58) Barone, V.; Adamo, C.; Lejl, F. *Chem. Phys.* **1995**, *102*, 364.
(59) Yu, D.; Rauk, A.; Armstrong, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 1789.
(60) Bliznyuk, A. A.; Schaefer, H. F., III.; Amster, I. J. *J. Am. Chem. Soc.* **1993**, *115*, 5149.
(61) Price, W. D.; Jockusch, R. A.; Williams, E. R. *J. Am. Chem. Soc.* **1997**, *19*, 11 988.
(62) Chapo, C. J.; Paul, J. B.; Provencal, R. A.; Roth, K.; Saykally, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 12 956.
(63) Maksić, Z. B.; Koracević, B. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2623.
(64) Bertrán, J.; Rodríguez-Santiago, L.; Sodupe, M. *J. Phys. Chem. B* **1999**, *103*, 2310.
(65) Shoeib, T.; Hopkinson, A. C.; Siu, K. W. M. *J. Phys. Chem. B* **2001**, *105*, 12 399.
(66) Ma, N. L.; Ng, K. M.; Tsang, C. W. *Chem. Phys. Lett.* **1997**, *277*, 306.
(67) Boutreau, L.; Leon, E.; Luna, A.; Toulhoat, P.; Tortajada, J. *Chem. Phys. Lett.* **2001**, *338*, 74.
(68) Cerda, B. A.; Wesdemiotis, C. *Int. J. Mass Spec.* **1999**, *185/186/187*, 107.