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Complexation of Al^{III} by Aromatic Amino Acids in the Gas Phase

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The coordination properties of three natural aromatic amino acids (AAAs)—phenylalanine (Phe), tyrosine (Tyr), and tryptophan (Trp)—to Al^{III} are studied in this work, devoting special attention to the role of the aromatic side chain. A comparison with aluminum(III)–alanine complexes is also presented. The polarizability arising from the ring has been seen to be a key factor in the stability of the complexes, with the order being Trp-Al^{III} > Tyr-Al^{III} > Phe-Al^{III}, starting from the most stable one. Cation–π interactions between the metal and the aromatic ring are present in the lowest energy conformers, especially for Trp, which seems to be very well suited for these kinds of interactions, occurring with both the six- and five-membered rings of the indole side chain. The most stable coordination mode for the three AAAs is found to be tricoordinated with the N and O of the backbone chain and the aromatic ring, as was found theoretically and experimentally for other metals.

1. Introduction

The noncovalent intermolecular forces are important contributors in the knowledge of the structural and reactivity behavior in biological systems.[1,2]

They are usually much weaker than covalent bonds, and therefore they provide peptides and proteins the flexibility to vary their structure and function with changes in the local environment.[3] The complex three-dimensional structures that biological macromolecules assume are determined by a delicate balance of weak noncovalent interactions, which determine the structure and influence the function of the biological system.[4]

Cation−π interactions belong to the noncovalent binding forces that involve cations and π systems. The literature offers numerous studies referring to cation−π interactions that underline the importance of these forces in the stabilization of protein geometry.[2,5] They are also responsible for the function and selectivity in variable ion channels[6−8] or in biological recognition processes.[9,10] Several studies have investigated the nature of cation−π interactions, which are dominated by electrostatic[11−13] and cation-induced[14] polarization terms, which would correlate with the magnitude of the quadrupole moment of the aromatic ring and the molecular polarizability of the aromatic compounds, respectively.[15−17]

The aromatic amino acids (AAAs)—phenylalanine (Phe), tyrosine (Tyr), and tryptophan (Trp)—account for 8.4% of the amino acids in proteins,[18] and it is known that 26% of all Trp residues are involved in energetically significant

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(1) Wilson, M.; Pohorille, A. *J. Am. Chem. Soc.* **1996**, *118*, 6580.
(2) Ma, J.; Dougherty, D. *Chem. Rev.* **1997**, *97*, 1303.
(3) Ruan, C.; Rodgers, M. *J. Am. Chem. Soc.* **2004**, *126*, 14600.
(4) Ruan, C.; Yang, Z.; Hallowita, N.; Rodgers, M. *J. Phys. Chem. A* **2005**, *109*, 11539.
(5) Gokel, G.; DeWall, S.; Meadows, E. *Eur. J. Org. Chem.* **2000**, *17*, 2967.
(6) Kumpf, R. G.; Dougherty, D. A. *Science* **1993**, *261*, 1708.
(7) Zhong, W.; Gallivan, J.; Zhang, Y.; Li, L.; Lester, H.; Dougherty, D. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12088.
(8) Donini, O.; Weaver, D. *J. Comput. Chem.* **1998**, *19*, 1515.
(9) Cabarcos, O.; Weinheimer, C.; Lisy, J. M. *J. Chem. Phys.* **1999**, *110*, 8429.
(10) Wall, S. D.; Meadows, E.; Barbour, L.; Gokel, G. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 6271.
(11) Gallivan, J.; Dougherty, D. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 9459.
(12) Mecozzi, S.; West, A.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10566.
(13) Dougherty, D. A. *Science* **1996**, *271*, 163.
(14) Cubero, E.; Luque, F. J.; Orozco, M. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 5976.
(15) Garau, C.; Frontera, A.; Quinonero, D.; Ballester, P.; Costa, A.; Deya, P. *J. Phys. Chem. A* **2004**, *108*, 9423.
(16) Garau, C.; Frontera, A.; Quinonero, D.; Ballester, P.; Costa, A.; Deya, P. *Chem. Phys. Lett.* **2004**, *392*, 85.
(17) Garau, C.; Frontera, A.; Quinonero, D.; Ballester, P.; Costa, A.; Deya, P. *Chem. Phys. Lett.* **2004**, *399*, 220.
(18) Meadows, E.; Wall, S. D.; Barbour, L. J.; Gokel, G. W. *J. Am. Chem. Soc.* **2001**, *123*, 3092.

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cation−π interactions.[11] Protein Data Bank research has revealed the cation−π interaction to be widespread, also in the interiors of proteins.[11,19]

In order to understand such cation−π interactions in peptides and proteins, several small cation−π systems have been studied, both experimentally and theoretically, in the literature. Most of them are devoted to the interactions of cations with AAAs, especially the alkali Na^+, K^+, and Li^+ metal ions.[3,12,20−27] Other cations such as Cu^+, Cu^{2+},[28] Ag^+,[29,30] Ca^{2+}, Mg^{2+}, NH_4^+, NMe_4^+,[23] Rb^+, Cs^+,[24] and Zn^+ [29] were also studied. This work examines the interaction of an Al^{III} ion with the three AAAs (Phe, Tyr, and Trp), which, to the best of our knowledge, have not been studied yet.

Numerous experimental studies to date are devoted to the singly or doubly charged complexes, but very few gas-phase experiments on triply charged cation complexes emerge[31−37] because of the difficulties arising from the high third ionization energy (IE3) of the metals. Relevant to the present investigation is the recent research of Stace et al.[38] In this regard, computational chemistry tools can help in the study of the stability of highly charged complexes in the gas phase.[39]

Interest toward the biochemistry of aluminum derives from the toxicity of the metal,[40] related to several neurological diseases,[41] and which has been seen to interfere with different biochemical processes. Despite the research regarding the toxicity of the aluminum, its molecular basis is still largely unknown. Previous research has been done on the interactions of the aluminum in the protein environment, regarding its capability of binding metal sites in proteins,[42,43] and also on the interaction of the aluminum with the side chain of the AAA.[44] To determine how cation−π interactions can be influenced by the presence of other functional groups present in the side chain of peptides and proteins, these model studies have been extended to the entire group of AAAs.

2. Computational Details

This work appeals to the hybrid density functional theory (DFT), in particular the Becke hybrid exchange function (B3) together with the Lee−Yang−Parr (LYP). Previous extensive studies were carried out regarding different methods and DFTs, where B3LYP was seen to be a good compromise between accuracy and computational effort for these kinds of complexes.[45]

The formation energetics and structural and electronic parameters of the different conformations were evaluated and discussed. The possible complexes were selected by considering the different coordination modes of the metal ion on the most stable free conformer of every AAA. Particular interest was devoted to the interaction of Al^{III} with the π-electron cloud characterizing the side chain of these AAAs.

All of the calculations were performed with the *Gaussian03* code.[46] The B3LYP[47,48] hybrid exchange-correlation functional was employed in the determination of the optimized structures, binding energies, and vibrational frequencies for all Al-AAA complexes considered. Geometry optimization and vibrational frequency calculation were done using the standard all-electron 6-31+G(d,p) basis set for the Al ion and the compact effective-core potentials and shared-exponent basis set of Stevens, Basch, Krauss, and Jasien (SBKJ)[49] for C, N, O, and H atoms. This pseudopotentials/all-electron basis set combination for the ligand and the metal cation, respectively, was found by Garmer and Gresh,[50] Gresh et al.[51] and Gresh and Garmer[52] to represent a very well-balanced compromise between accuracy and computational efficiency. Subsequently, the accuracy of this combination was further assessed.[42,43,53,54] No

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(19) Minoux, H.; Chipot, C. *J. Am. Chem. Soc.* **1999**, *121*, 10366.
(20) Hu, J.; Barbour, L.; Gokel, G. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5121.
(21) Siu, F.; Ma, N.; Tsang, C. *Chem.*−*Eur. J.* **2004**, *10*, 1966.
(22) Siu, F.; Ma, N.; Tsang, C. *J. Am. Chem. Soc.* **2001**, *123*, 3397.
(23) Moision, R.; Armentrout, P. *Phys. Chem. Chem. Phys.* **2004**, *6*, 2588.
(24) Polfer, N.; Oomens, J.; Dunbar, R. *Phys. Chem. Chem. Phys.* **2006**, *8*, 2744.
(25) Gapeev, A.; Dunbar, R. *J. Am. Chem. Soc.* **2001**, *123*, 8360.
(26) Ryzhov, V.; Dunbar, R. C.; Cerda, B.; Wesdemiotis, C. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 1037.
(27) Dunbar, R. *J. Phys. Chem. A* **2000**, *104*, 8067.
(28) Rimola, A.; Rodriguez-Santiago, L.; Sodupe, M. *J. Chem. Phys. B* **2006**, *110*, 24189.
(29) Polfer, N. C.; Oomens, J.; Moore, D. T.; Helden, G.; Meijer, G.; Dunbar, R. *J. Am. Chem. Soc.* **2006**, *128*, 517.
(30) Shoeib, T.; Cunje, A.; Hopkinson, A. C.; Siu, K. M. *J. Am. Soc. Mass Spectrom.* **2002**, *13*, 408.
(31) Blades, A. T.; Jayaweera, P.; Ikonomou, M. G.; Kebarle, P. *Int. J. Mass Spectrom.* **1990**, *101*, 325.
(32) Walker, N.; Wright, R. R.; Stace, A. J.; Woodward, C. *Int. J. Mass Spectrom.* **1999**, *188*, 113.
(33) Shvartsburg, A. *J. Am. Chem. Soc.* **2002**, *124*, 7910.
(34) Shvartsburg, A. *J. Am. Chem. Soc.* **2002**, *124*, 12343.
(35) Shvartsburg, A. *Chem. Phys. Lett.* **2002**, *360*, 479.
(36) Shvartsburg, A. A.; Jones, R. *J. Am. Soc. Mass Spectrom.* **2004**, *15*, 406.
(37) Cheng, Z.; Siu, K.; Guevremont, R.; Berman, S. *Org. Mass Spectrom.* **1992**, *27*, 1370.
(38) Puskar, L.; Tomlins, K.; Duncombe, B.; Cox, H.; Stace, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 7559.
(39) Mazzuca, D.; Russo, N.; Toscano, M.; Grand, A. *J. Phys. Chem. B* **2006**, *110*, 8815.
(40) Williams, R. *Coord. Chem. Rev.* **2002**, *228*, 93.
(41) Yokel, R. *Neurotoxicology* **2000**, *21*, 813.
(42) Mercero, J. M.; Matxain, J. M.; Rezabal, E.; Lopez, X.; Ugalde, J. M. *Int. J. Quantum Chem.* **2004**, *98*, 409.
(43) Rezabal, E.; Mercero, J. M.; Lopez, X.; Ugalde, J. M. *J. Inorg. Biochem.* **2006**, *100*, 374.
(44) Mercero, J. M.; Lopez, X.; Irigoras, A.; Fowler, J. E.; Ugalde, J. M. *J. Phys. Chem. A* **2001**, *105*, 1986.
(45) Rezabal, E.; Marino, T.; Mercero, J.; Russo, N.; Ugalde, J. **2007**, submitted for publication.
(46) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.
(47) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(48) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(49) Stevens, W. J.; Krauss, M.; Basch, H.; Jasien, P. G. *Can. J. Chem.* **1992**, *70*, 612.
(50) Garmer, D. R.; Gresh, N. *J. Am. Chem. Soc.* **1994**, *116*, 3556.
(51) Gresh, N.; Stevens, W. J.; Krauss, M. *J. Comput. Chem.* **1995**, *16*, 843.
(52) Gresh, N.; Garmer, D. R. *J. Comput. Chem.* **1996**, *17*, 1481.
(53) Mercero, J. M.; Mujika, J. I.; Matxain, J. M.; Lopez, X.; Ugalde, J. M. *Chem. Phys.* **2003**, *295*, 175.
(54) San Sebastian, E.; Mercero, J. M.; Roland, H.; Stote, A. D.; Cossío, F. P.; Lopez, X. *J. Am. Chem. Soc.* **2006**, *128*, 3554.

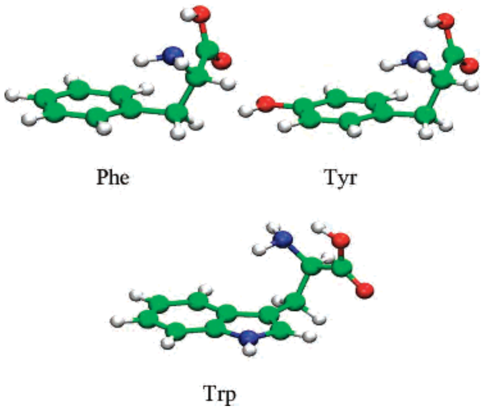

Figure 1. Most stable conformers of the three AAAs. C, H, N, and O atoms are presented in green, white, blue, and red, respectively.

imaginary frequencies were found for any of the complexes presented in this study. Single-point calculations with the 6-311++G-(2df,2p) basis set were carried out to improve the binding energies of the species considered.

The basis set superposition error was calculated and found to be very small (between 0.5 and 1.1 kcal/mol); thus, the correction was seen to be smaller than the intrinsic error of the method and has not been included in the results.

The affinity of the metal for the AAA will be studied, which is defined as the enthalpy change (ΔH) of the following process:

$$\mathrm{Al}^{3+} + \mathrm{AAA} \rightarrow (\mathrm{Al\text{-}AAA})^{3+} \qquad (1)$$

Natural bond orbital (NBO) analysis[49] was performed on all of the minima of considered species.

3. Results

3.1. Neutral AAAs. The most stable conformer of the neutral AAA was used in each case to compute the metal affinity. This structure, depicted in Figure 1, regarded additional stabilization gained through a hydrogen bond between the hydroxyl H atom and the amino N atom, as well as through interaction of one of the amino H atoms with the aromatic ring, as has been widely reported in the literature[3,24,25,28,29] and also confirmed by us.

3.2. Phe and Tyr. Different potential binding sites (electron-rich sites) for the Al^{III} ion on the free AAA were considered: the N and O atoms and the aromatic ring, considering both the mono- and bidentate coordination with the backbone of the AAA.

The stable complexes found for both Phe and Tyr are presented in Figure 2, while the main geometrical features and metal affinities, in conjunction with the total natural charge of the metal for each structure, are collected in Table 1.

From a topological point of view, very similar complexes were found for both amino acids, in agreement with previous studies involving other metals,[3,27,28] which suggested that the hydroxyl substituent does not significantly influence the binding.

The interaction of the Al^{III} cation with Phe and Tyr gave rise to five- and six-charged solvated complexes, respectively (see cs complexes in Figure 2).

For both systems, the most stable conformer showed a tridentate coordination (see cs1 in Figure 2), formed by the carboxylate O atom, the amine N atom, and the π interaction with the ring, as was recently observed also for one- and two-charged cations.[3,21,27,28,55] Another tridentate form found for alkali metals in the literature,[21] where the metal binds the carboxyl and hydroxyl groups together with the aromatic ring, was not found for the aluminum. Siu et al.[21] did not find this structure either for the smallest alkali metal, which suggests that the structural strain might be too high in this conformer in the case of such small ions.

The structure corresponding to cs1, without cation−π interactions, named cs2 in Figure 2, lies energetically above the global minimum (see Table 1), confirming that, despite the geometric constraints due to the small size of the metal ion, the presence of the π interaction largely stabilizes the complex.[21]

Two other canonical structures, cs3 and cs4 in Figure 2, lacking the cation−π interactions, were also found. The former corresponds to the same coordination as cs2 but with a trans carboxylic group instead of a cis group; the latter is related to cs2 through a rotation around the C−C bond so that Al^{III} is bound to NH_2 and OH groups in cs4.

The destabilization of cs4 with respect to cs2 (around 15 kcal/mol) is probably due to the weaker Al−OH interaction compared to Al−O, as confirmed by the lengthening of the Al−OH bond (1.98 Å for Phe and 2.08 Å for Tyr), compared to Al−O (1.88 and 1.92 Å), while the Al−N distance remains similar (see Table 1). This suggests that the contribution of the Al^{III} interaction with the carbonyl O atom to the binding is higher than the interaction with the amino N atom.

The charged solvated conformation cs5, a bidentate O/ring structure, lies at 31.7 and 30.2 kcal/mol for Tyr and Phe, respectively. It is characterized by the hydrogen bond with the aluminum-bound O atom, which in turn enlarges the Al−O distance by 0.05 Å for both amino acids (see Table 1).

The complex named cs6 in Figure 2 was only found for Tyr and presents Al^{III} bound to the N atom and interacting with the ring. This conformer is related to the structure cs5 by the rotation of the C−C bond of the backbone; as expected, this presents a lower affinity for the aluminum than cs5 because the Al^{III}−N interaction is weaker than the Al^{III}−O interaction.

The metalation process of the two amino acids produced three Al^{III} salt bridge complexes for both Phe and Tyr (zw1−3 of Figure 2).

The tridentate binding type, involving both carboxylate O atoms of the backbone and the aromatic side chain, reported in the literature[21,27] for alkali-metal cations was not found in our study. Instead, an analogous conformer lacking the cation−π interaction was found (see zw3 in Figure 2), which points out that in this case the cation−π interaction does not compensate for the high structural constraints resulting from the tridentate type of binding.

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[55] Amunugama, R.; Rodgers, M. *Int. J. Mass Spectrom.* **2003**, *227*, 1.

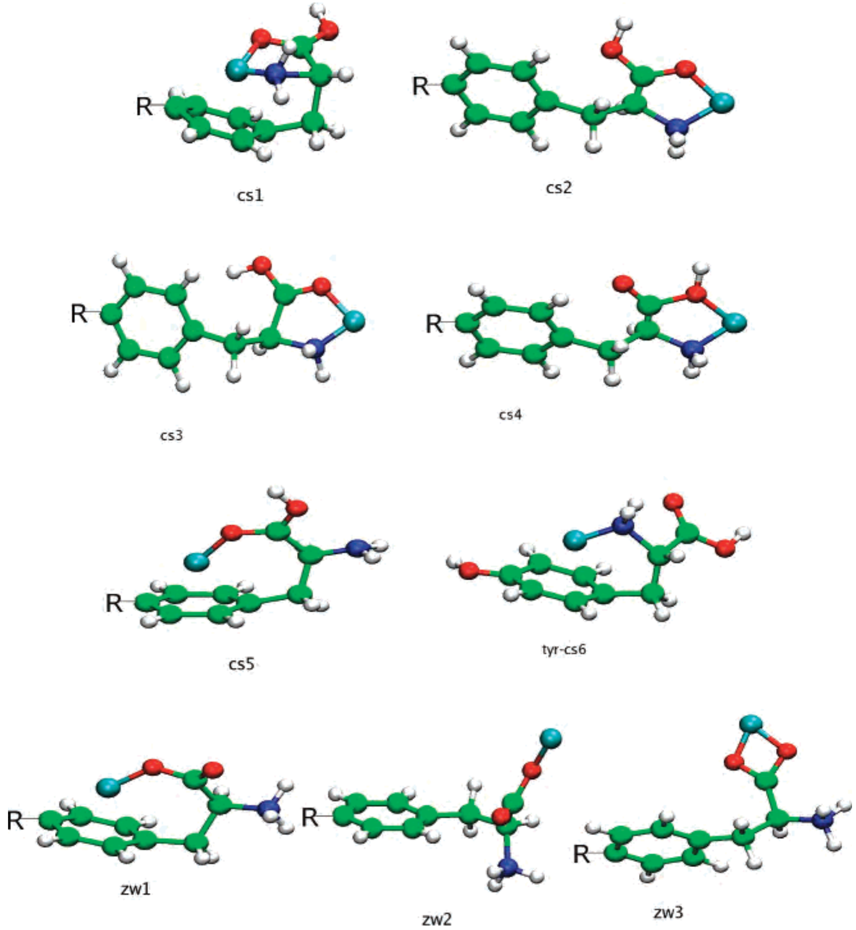

Figure 2. Phe- and Tyr-Al^{III} complexes. R stands for a H atom for Phe complexes and a hydroxyl group for Tyr complexes. C, H, N, O, and Al atoms are presented in green, white, blue, red, and cyan, respectively.

Table 1. Geometrical Features and Formation Reaction Enthalpies for Tyr-Al^{III} and Phe-Al^{III} (in Parentheses) Complexes[a]

	B3LYP					
Tyr (Phe)	ΔH	$\Delta\Delta H$	Q_{Al}	d_{Al-O}	$d_{Al-N/O}$	d_{Al-rc}
cs1	−565.6 (−555.2)	0.0 (0.0)	1.92 (1.98)	1.854 (1.859)	2.009 (1.985)	1.873 (1.919)
cs2	−554.5 (−525.7)	11.2 (29.5)	1.42 (1.57)	1.923 (1.881)	2.189(2.127)	
cs3	−542.7 (−515.1)	22.92 (40.1)	1.50 (1.66)	1.872 (1.835)	2.167 (2.103)	
cs4	−539.3 (−506.9)	26.3(48.3)	1.28(1.46)	2.082 (1.982)	2.238(2.142)	
cs5	−535.8 (−525.1)	29.8 (30.2)	1.98 (2.06)	1.736 (1.731)		1.787 (1.710)
cs6	−529.0	36.6	1.91		1.889	1.794
zw1	−561.5 (−550.6)	4.1 (4.6)	2.00 (2.07)	1.689 (1.683)		1.834 (1.714)
zw2	−550.7 (−521.2)	15.0 (33.9)	1.41 (1.52)	1.817 (1.797)		
zw3	−560.2 (−533.2)	6.2 (22.0)	1.43 (1.58)	2.099(2.032)	1.996 (1.967)	

[a] Absolute and relative formation reaction enthalpies (ΔH and $\Delta\Delta H$, respectively) are given in kcal/mol and the natural charge in Al^{III} (Q_{Al}) in e^-. Geometrical features are given in Å, and d_{Al-O} stands for the distance between the Al and O atoms, $d_{Al-N/O}$ denotes the distance between the metal and the other atom bound, either N or O, and d_{Al-rc} is the distance between the metal and the center of the ring.

The low-lying chelate conformation zw1 of Figure 2 shows the same coordination fashion as that in cs5, with the cation bound to a single carboxylate O atom and stabilized by a π interaction with the aromatic ring. Note that the charged solvated form, in this case, is remarkably less stable than the zwitterionic form (see Table 1). As compared to the most stable structure (cs1), the shorter Al−ring distance (1.71 vs 1.91 Å for Phe and 1.83 vs 1.87 Å for Tyr) indicates that it gains stability by a significant cation−π interaction, which compensates for the loss of the Al^{III}−N interaction, reaching a stability close to that of cs1 (see Table 1). In fact, NBO analysis indicates a stronger charge transfer from the π cloud of the ring to the Al^{III} ion in zw1 than in cs1.

Further evidence on the importance of cation−π interaction emerges through analysis of the only monodentate structure (zw2), whose ΔH value is considerably higher probably because of the lack of cation−π interaction.

The absolute and relative enthalpy values of the Al^{III} binding affinity of Phe and Tyr are presented in Table 1. For all of the studied coordination modes, Al^{III} presents a higher affinity for Tyr, as expected, because of its higher polarizability, which is a key factor in determining the strength of the binding in these systems.[3]

The stability of Tyr complexes as compared to Phe ones was more marked for structures without cation−π interaction (25−30 kcal/mol more stable for Tyr complexes) than for structures with cation−π interaction (10 kcal/mol), suggesting that the hydroxyl substituent plays a role in the overall polarizability of the amino acid rather than in the activation of the ring. Nevertheless, the NBO calculation reveals a higher charge transfer from the aromatic ring to the Al^{III} ion in Tyr.

Comparing the complexes containing cation−π interaction and those without, aluminum presents a higher natural charge in those structures containing the cation−π interaction. This arises from the electrostatic nature of the cation−π bond, which withdraws less charge than the covalent bonds.

Finally, regarding the geometry, Al−O and Al−N bond lengths in Tyr complexes are larger than those in Phe complexes (Table 1) in the complexes without cation−π interactions; instead, they are very similar for those with cation−π interaction. This suggests that, for the latter, the structure is very constrained, while for the former, the Al^{III} ion's lower charge in Tyr renders the bond longer.

In previous works, the interaction of Al^{III} with the aromatic rings was studied.[56] Stable aluminum(III)−benzene and aluminum(III)−phenol complexes were found, presenting cation−π interaction. In both cases, the distance between the metal and the ring center was seen to be 1.65 Å. However, for interaction with the whole AAA, the distance from the Al^{III} to the ring center is enlarged up to 1.87 Å for Tyr and 1.91 Å for Phe (see Table 1). This is due to the geometric constraint arising from the interaction of the metal with the other functional groups of the AAA. Anyway, the affinity of the metal for the functional groups stabilizes largely the complexes, overcoming the destabilization from the weaker cation−π interaction.

3.3. Trp. Cation−π interactions with both rings present in the Trp were tested for each different binding mode of the cation previously examined in the case of Phe and Tyr, giving rise to 11 different conformations, presented in Figure 3. The binding energies fall in a range of about 59 kcal/mol with respect to the lowest-energy structure (Trp-cs2 of Figure 3).

Three different stable structures similar to the cs1 conformer (see the previous section) were found. One of them (Trp-cs1) presents the cation−π interaction with the phenyl region of the indole π face; the other two, named Trp-cs2 and Trp-cs3, move off the metal to the edge of the six- and five-membered rings, respectively (see Figure 3). The NBO analysis of the systems provides some indication about the nature of the bond of the Al^{III} cation with the ring. Trp-cs1 is characterized by a charge transfer from the π orbitals of the six-membered ring C atoms, while in both the Trp-cs2 and Trp-cs3 complexes, the metal forms a covalent bond with a C atom. In the former, the C atom in the five-membered ring participates in the bond with a 3p orbital (88%) and a 3s orbital (12%) and the Al atom with an s orbital (80.4%) and a p orbital (19.3%); in the latter, the C atom participates with a p orbital (86%) and an s orbital (14%) and the metal with an s orbital (83%) and a p orbital (17%).

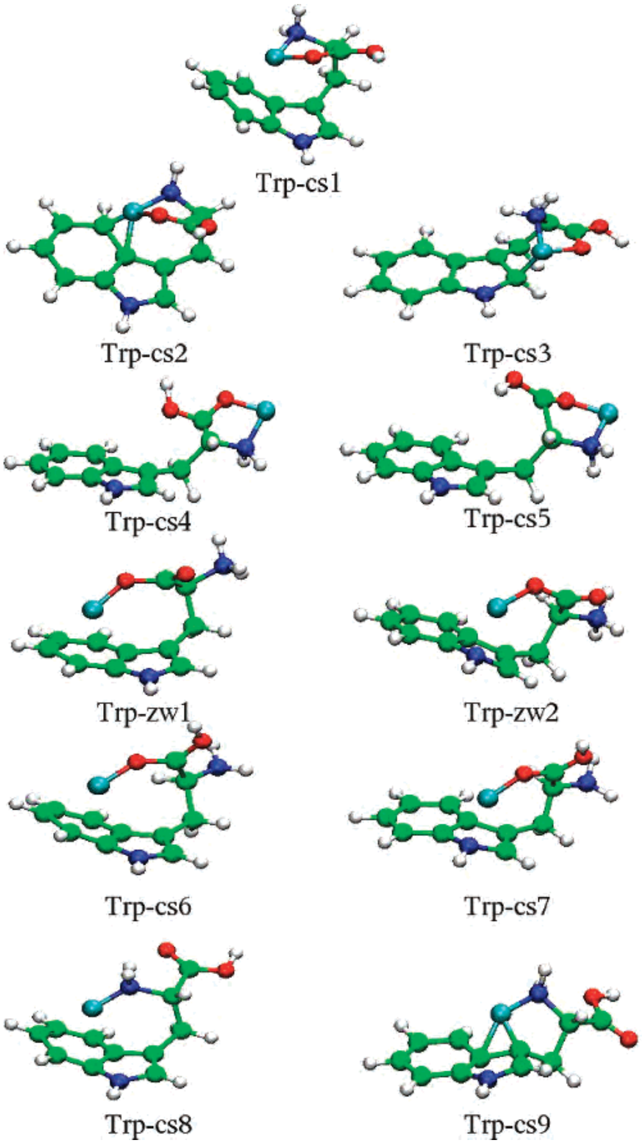

Figure 3. Trp-Al^{III} complexes. C, H, N, O, and Al atoms are presented in green, white, blue, red, and cyan, respectively.

As happened for Phe and Tyr, this tridentate coordination turns out to be the preferred coordination mode for Al^{III}, although this time the most stable binding mode (Trp-cs2) presents a covalent bond with the ring instead of a cation−π interaction. This is probably due to the marked loss of planarity of the indole ring in Trp-cs1 (see Table 2), which distorts the π cloud, leading to a weak cation−π interaction.

Related to these tridentate conformers, two structures, analogous to cs2 and cs3 in the previous section, named Trp-cs4 and Trp-cs5 in Figure 3, with similar binding modes but without cation−ring interaction were found. The first, which presented a hydrogen bond with the carbonyl O atom, is 12 kcal/mol more stable than the latter, without a hydrogen bond.

Binding modes analogous to those of cs5, cs6, and zw1 conformations in Figure 2 were found for Trp, the metal interacting with both six- and five-membered rings for each coordination type (see Trp-cs6, Trp-cs7, Trp-cs8, Trp-cs9, Trp-zw1, and Trp-zw2 in Figure 3). All of them presented a cation−π interaction with one of the rings, except Trp-cs9,

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(56) Mercero, J. M.; Lopez, X.; Matxain, J. M.; Fowler, J. E.; Ugalde, J. M. *Int. J. Quantum Chem.* **2002**, *90*, 859.

Table 2. Geometrical Features and Formation Reaction Enthalpies for Trp-Al^{III} Complexes[a]

Trp	B3LYP ΔH	$\Delta\Delta H$	Q_{Al}	d_{Al-O}	d_{Al-C}	d_{Al-N}	d_{Al-rc}	dihedral
Trp-cs1	−589.9	14.2	1.94	1.846		2.015	1.701	148.98
Trp-cs2	−604.1	0.0	2.06	1.821	1.976	1.970		179.49
Trp-cs3	−591.9	12.1	1.98	1.833	2.026	1.983		177.03
Trp-cs4	−584.8	19.3	1.23	2.000		2.303		176.95
Trp-cs5	−572.6	31.5	1.31	1.933		2.267		177.12
Trp-zw1	−586.4	17.7	2.06	1.692			1.659	158.5
Trp-zw2	−570.5	33.6	2.14	1.690			2.000	165.17
Trp-cs6	−556.9	47.1	2.04	1.737			1.611	155.9
Trp-cs7	−545.5	58.6	2.11	1.739			1.900	162.66
Trp-cs8	−549.7	54.4	1.95			1.903	1.626	147.69
Trp-cs9	−550.5	53.6	2.03		2.045	1.920		160.39

[a] Absolute and relative formation reaction enthalpies (ΔH and $\Delta\Delta H$, respectively) are given in kcal/mol and the natural charge in Al^{III} (Q_{Al}) in e$^-$. Geometrical features are given in Å, and d_{Al-O} stands for the distance between the Al and O Atoms, d_{Al-C} is for the distance between the metal and covalently bound C atom of the ring, d_{Al-N} denotes the distance between the metal and the N atom, and d_{Al-rc} is the distance between the metal and the center of the ring. The dihedral (in deg) stands for the angle between both rings of the indole.

Table 3. Geometrical Features and Formation Reaction Enthalpies for Ala-Al^{III} Complexes[a]

	ΔH	$\Delta\Delta H$	Q_{Al}	d_{Al-O}	$d_{Al-N/O}$
Ala-zw1	−445.89	0.0	2.37	1.84	1.82
Ala-cs1	−439.10	6.88	2.40	1.74	1.91
Ala-cs2	−433.58	12.40	2.42	1.72	1.91

[a] Absolute and relative formation reaction enthalpies (ΔH and $\Delta\Delta H$, respectively) are given in kcal/mol and the natural charge in Al^{III} (Q_{Al}) in e$^-$. Geometrical features are given in Å, and d_{Al-O} stands for the distance between the Al and O atoms, $d_{Al-N/O}$ denotes the distance between the metal and the other atom bound, either O or N.

where the Al atom forms a covalent bond with one of the C atoms of the five-membered ring. The metal contributes to this covalent bond with an s orbital (68%) and a p orbital (31%) and the C atom with a p orbital (89%) and an s orbital (10%).

As can be noted from Table 2, Trp presents an affinity for the Al^{III} cation higher than that presented by Tyr or Phe because of the higher polarizability of the amino acid.

The affinity of the Al^{III} ion for Trp is highly enhanced by the interaction of the metal with the aromatic ring; the vast majority of the low-energy conformers present an interaction of the metal with one of the rings, covalently or with a cation−π interaction.

Cation−π interaction with the six-membered ring is more favored than that with the five-membered one (see Table 3) because the electron density is fairly isotropic and greatest above the phenyl ring. In contrast, the electron density above the pyrrolyl ring is much less isotropic and somewhat reduced as a result of the presence of the N heteroatom.[4] In agreement with that, the metal−ring distance is about 0.3 Å shorter upon interaction with the phenyl ring (see Table 2), for the same coordination modes.

In fact, the charge transfer to the metal is higher upon interaction with the six-membered ring, which indicates that the phenyl ring can donate more charge to the metal and, because of the less constrained geometry achieved, the interaction is better.

Figure 4. Ala-Al^{III} complexes. C, H, N, O, and Al atoms are presented in green, white, blue, red, and cyan, respectively.

Regarding the interaction of Al^{III} with indole, it was not possible to find any stable aluminum(III)−indole complex with cation−π interaction;[56] instead, upon interaction with the whole Trp amino acid, the presence of other functional groups stabilizes several complexes presenting cation−π interaction with both rings. The unique stable aluminum(III)−indole conformation presented a metal interacting with the C atoms on the edge of the ring, as happens in the Trp-cs9 complex of the present paper. In this case, the bond length remains similar, 2.04 Å (see Table 2) vs 2.10 Å in the Trp-Al^{III} and aluminum(III)−indole, respectively.

3.4. Comparison with Alanine (Ala). The comparison of Ala with the AAAs has been taken as a useful indication of the extent of cation−π stabilization in the metal complexes. Only three stable structures were found for Ala, all bidentate-coordinated to the Al^{III} ion (see Figure 4). The metal bound to both carboxylate O atoms was found to be the most stable coordination mode (zw in Figure 4), regarding the zwitterionic form of the amino acid. The other two structures, derived from the charge solvation form of the amino acid, presented the metal ion bound to the carbonyl O atom and to the N atom, in the canonical form of the amino acid. The most stable form presents an intramolecular hydrogen bond between the hydroxyl H atom and the carbonyl O atom. Other bidentate and monodentate complexes found for alkali-metal ions[57] and Cu$^+$ and Cu^{2+}[58] could not be found in the present study.

The coordination modes described above were also found for the AAAs (zw3, cs2, and cs3 in Figure 2 and Trp-cs4 and Trp-cs5 in Figure 3), with the same stability order. The metal binding affinity for Ala obtained for the most favorable structure was −445.98 kcal/mol, around 100 kcal/mol above the corresponding Phe complexes, evidencing the binding enhancement arising from the higher polarizability of the AAAs.

The presence of the aromatic ring in the side chain of the amino acid also made it possible to stabilize coordination modes not found for Ala in the lowest-energy conformations, zw2 and cs4 in Figure 2, for Phe and Tyr. For Trp, these conformations were not found between the most stable ones.

The other stabilizing factor of the AAAs is the opportunity for the Al^{III} ion to interact with the π system of the ring, which has been seen to render the highest stability to the system.

Besides, the bond lengths undergo enlargement when an aromatic side chain is added and the charge on the metal is

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(57) Marino, T.; Russo, N.; Toscano, M. *Inorg. Chem.* **2001**, *40*, 6439.
(58) Marino, T.; Russo, N.; Toscano, M. *J. Mass Spectrom.* **2002**, *37*, 786.

lowered around one unit because of the higher charge transfer in the AAAs (see Tables 1 and 2). The increased distances suggest, on the one hand, that the lower charge of the metal in the AAA-Al^{III} complexes enlarges the interaction and, on the other hand, that the interactions between the metal and the individual binding sites are weaker in AAAs than in the cases of Ala and the aromatic ring[44] (geometric constraints in the AAA ligand do not allow the alkali-metal cation to optimally interact with each of these groups[3]). However, this weakening of the binding strength at individual coordination sites is compensated for by the increased coordination number of the cation, as was previously seen in the literature for other metals.[21]

4. Conclusions

The coordination properties of the three AAAs (Phe, Tyr, and Trp) to Al^{III} and the role of the aromatic side chain have been studied using computational methods. The relative stability of the complexes has been seen to be a balance between structural constraint, the coordination number of the metal and its affinity for the ligands. N−O−ring tridentate complexation of Al^{III} has been found to be the preferred mode, as is seen in the literature for other metals. The lowest-energy conformers presented cation−π interactions, characterized by a significant charge transfer from the π cloud of the ring to the metal, confirming the important role of the side chain upon complexation. Trp was seen to be especially well suited for cation−π interactions, as is also confirmed by experimental data.[11]

As compared to the interaction of Al^{III} with the side chain of the AAAs,[56] it has been seen that the functional groups of the amino acid backbone stabilize and promote the complexes presenting cation−π interaction between Al^{III} and the ring.

The high polarizability of the AAAs has an essential role in the metal affinity of the complexes: the higher the polarizability, the more stable the complex. Consequently, Trp-Al^{III} complexes present the highest stability in our study.

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