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On the Interaction between Manganese Cation (Mn^{2+}) and the Nucleic Acid Bases (T, U, C, A, G) in the Gas Phase

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ABSTRACT: The coordination modes, the equilibrium geometrical structures, and the gas-phase metal ion affinity for the Mn^{2+} metal cation interacting with uracil, thymine, cytosine, adenine, and guanine were determined considering different low energy tautomers for the free nucleic acid bases and by using the density functional theory. For uracil and thymine, the mono-coordinated complexes coming from the metalation of the oxo tautomers are not minima, whereas the manganese ion forms stable compounds with high energy tautomers for which the bi-coordination is possible. Also for cytosine, adenine, and guanine the bi-coordination is the favored binding mode. Despite the cytosine and guanine free bases have different tautomers lying in a very narrow range of energy, the stabilities of the corresponding metalated complexes differ significantly. A reverse situation occurs for uracil and thymine for which we obtain manganese complexes of comparable stability, while the tautomeric forms of the isolated free bases are well separated in energy. Int J Quantum Chem 90: 903–909, 2002

Key words: metal ion affinity; nucleic acid bases; density functional theory; manganese ion

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Introduction

The interaction of metal cations with DNA and RNA is of primary interest in chemistry and in biology [1, 2]. Since the interaction is meanly electrostatic in nature, the metal ions can interact both with the nucleic acid bases as well as with the phosphate and deoxyribose ring of the nucleic acids. The presence of the metal cations has a strong influence in the biochemical processes such as the stabilization of DNA helices or the inhibitory effects on the chain initiation process by RNA polymerase [3, 4]. In particular, manganese ion stimulates the primase activity [5] and influences the hammerheat ribozyme activity [6]. In recent years, researchers efforts were also devoted to the study of metal cation–nucleic acid interactions in solid, liquid, and gas phases [7–11]. Due to the complexity of the studied systems as well as to the environmental constraints, many questions about the elementary mechanisms that govern the formation of the metal ion–ligand complexes are still now unsolved. Recent advances in the experimental mass-spectroscopy methods have allowed study of these systems in the gas phase providing data free from the interference of solvent molecules or crystalline field. With the use of these techniques it was possible determine some important chemical properties of nucleic acid bases such as basicity, acidity, and metal ion affinity [9, 10, 12, 13]. At the same time, the improvement in the reliability of theoretical methods contributed further to highlight the physics of the metal ion–nucleic acid base interactions [10, 11]. The interaction of alkali metal ions with DNA and RNA bases was investigated extensively in the gas phase both at experimental [9, 10, 12] and theoretical [10, 11, 14] levels. On the contrary, to our knowledge, the study of the interaction of Mn^{2+} with the nucleic acid bases is a virgin field.

In a series of very recent papers, devoted to the study of metal ion complexes containing amino and nucleic acids [11, 14–16], we have proven that the methods based on the density functional theory are accurate enough to reproduce geometrical parameters and spectroscopic and energetic values with an error close to the uncertainty in the experimental measure (about 2–3 kcal/mol). By the comparison between the theoretical and experimentally known metal ion affinity (MIA) values, our previous work has demonstrated that often, in the case of cytosine and guanine, it is not correct to assign the experimental MIA values to the complexes formed by interaction of the cations with the most stable free bases isomers [10]. Thus in this study, several tautomers of nucleic acid free bases other than the most stable one were involved.

Finally, in order to ease the future and desirable experimental measurements for these systems, we have computed the entropic contributions giving, besides the enthalpy, also the free energy variation for the considered metalation processes.

Method and Computational Details

All the computations were carried out with the GAUSSIAN 94 code [17] by using the hybrid B3LYP exchange-correlation functional [18, 19].

Geometries were fully optimized first using the all-electron 6-31G** basis set. For each optimized stationary point, vibrational analysis was performed to determine its character (minimum or saddle point) and to evaluate the zero-point vibrational energy corrections, which we have then included in the computation of the relative (ΔE) energies and metal ion affinities. In order to increase the reliability of the energetic data, geometries were further optimized with the 6-311+G(2df, 2p) basis set [20].

MIA was assumed as the negative of the enthalpy variation (ΔH) for the process

$$B + Mn^{2+} \rightarrow Mn^{2+}\text{–}B,$$

where B represents the particular DNA or RNA bases. In other words the MIA corresponds to the dissociation energy of the B–Mn^{2+} bond.

The variation in zero-point vibrational energies was considered in the calculations together with the thermochemical analysis at 298 K in order to obtain the entropic ($T\Delta S$) and the free energy (ΔG) variation for the considered process.

Results and Discussion

Because of the lack of experimental information on these systems, it would be useful to check the performance and the reliability of the chosen method and basis set in the MIA reproduction for charged complexes. In Table I, we have collected the available experimental and theoretical MIA values for a series of complexes, involving various metal cations, in which the coordination sites of the ligands are the same as those treated in this work. The

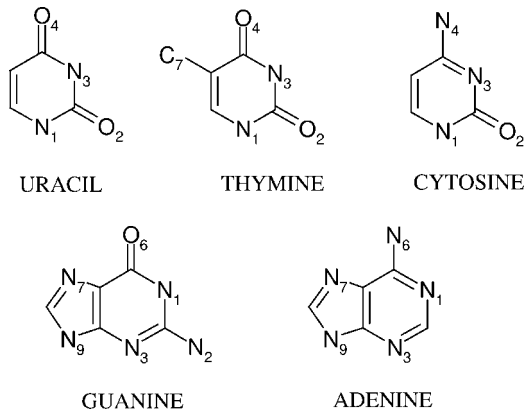
TABLE I
Computed (at 0 K) and experimental MIA (kcal/mol) for charged complexes.

System	Method	MIA
$Na^+(K^+)$–U	B3LYP/6-311+G(2*df*, 2*p*)[a]	34.1 (25.3)
	MP2[b]	32.1 (24.8)
	Exp.[c]	33.7 (24.1)
	Exp.[b]	32.2 (24.9)
$Na^+(K^+)$–T	B3LYP/6-311+G(2*df*, 2*p*)[a]	34.2 (25.0)
	MP2[b]	32.3 (24.7)
	Exp.[c]	34.4 (24.4)
	Exp.[b]	32.3 (24.7)
$Na^+(K^+)$–C	B3LYP/6-311+G(2*df*, 2*p*)[a]	42.2 (26.0)
	Exp.[c]	42.3 (26.3)
$Na^+(K^+)$–G	B3LYP/6-311+G(2*df*, 2*p*)[a]	44.9 (32.8)
	Exp.[c]	43.5 (28.0)
$Na^+(K^+)$–A	B3LYP/6-311+G(2*df*, 2*p*)[a]	29.7 (18.2)
	MP2[b]	30.7 (19.8)
	Exp.[c]	41.1 (25.3)
	Exp.[b]	33.4 (22.7)

[a] From Ref. [14].
[b] From Ref. [10].
[c] From Ref. [12].

table shows that the B3LYP exchange-correlation functional coupled with the 6-311+G(2*df*, 2*p*) basis set is able to give MIA values closest to the experimental and MP2 counterparts. The average error with respect to the experimental measurement of Cerda and Wesdemiotis [12] is less than 1.5 and 1.0 kcal/mol for sodium and potassium affinity, respectively. The maximum deviation occurs for adenine for which also the experimental measurements differ considerably from each other. The same agreement between density functional, MP2, and experimental MIA was found in the case of Li^+–nucleic acid base complexes [11] and in the metalation of glycine and alanine with different cations including lithium, sodium, potassium, and copper [15, 16]. On the basis of these results, we think that our prediction for the metal affinity of U, T, C, G, and A toward manganese cation can be treated with confidence.

Different binding sites, including mono-coordination on oxygen and nitrogen, bi-coordination on N, O and N, N (see Scheme 1), were considered for different low lying tautomers of nucleic acid bases. The possible out-of-plane interaction between the cation and the aromatic ring was also taken into account in the case of the C1 system and the results show that such a coordination does not



SCHEME 1.

give a stable complex. It collapses in an in-plane N, O bi-coordinated system during the optimization procedure. For this reason, and since also the analogous complexes with the alkali metal cations gave minima that were very high in energy with respect to the in-plane situations [10, 11], we have omitted study to this kind of coordination mode.

The main structural data for the found minima are collected in Figures 1 and 2, whereas energetic parameters are reported in Table II.

For the most stable tautomers of uracil and thymine (U1 and T1), the only suitable interaction sites for the manganese cation are those on O4 and O2 (see Scheme 1) atoms. Both correspond to a mono-coordinated situation and all the attempts to localize a stable complex failed. So we concluded that this kind of coordination is not possible for a cation like Mn^{2+}. On the contrary, the bi-coordination possible in the tautomers U2, U3, T2, and T3 yields stable complexes.

It is worth noting that in both cases, although the free tautomers differ considerably in energy, their corresponding metalated complexes are practically isoenergetic with energy differences less than 0.3 kcal/mol. The distances in all the uracil and thymine complexes are quite similar with the Mn–O bond shorter, in all cases, than the Mn–N one.

Cytosine is an interesting case because of the existence of four tautomers in a narrow range of energy (2.3 kcal/mol). They can be generated in a given physicochemical situation (e.g., high temperature) and infrared spectroscopy has revealed the presence, in the gas phase, of both amino-oxo (C1) and amino-hydroxy (C2) forms [21 – 24]. For this reason it is of great importance to take into account many isomers in the MIA prediction. The experimental

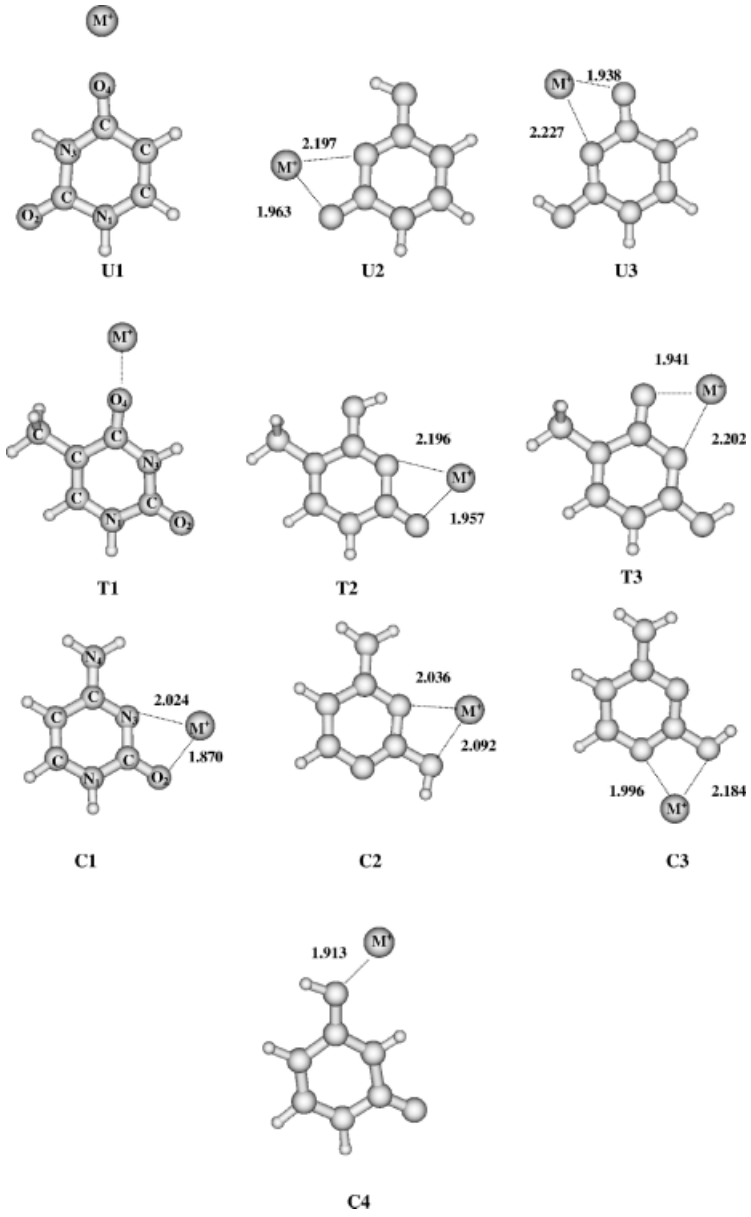


FIGURE 1. B3LYP/6-311+G(2*df*, 2*p*) optimized structures of uracil, thymine, and cytosine complexes with manganese cation. Distances are in Å.

MIA measurements obtained in previous works for the alkali metal–nucleic acid base interaction have interpreted for cytosine in terms of metalation of C1 isomer. Our computations on this subject have demonstrated that, for a correct assignment of the spectroscopic data [11, 14] to a structural situation, it is mandatory to take into consideration all four low lying tautomers. Indeed, for these systems the theoretical MIA closest to the experimental value is obtained as the interaction of the cation occurs with C2 or C3 tautomers [11, 14].

The stability order of cytosine–Mn^{2+} complexes, Mn^{2+}–C1 > Mn^{2+}–C3 > Mn^{2+}–C2 > Mn^{2+}–C4, is different than that found for alkali metal–DNA (RNA) bases. Furthermore, the relative energy differences (ΔE) with respect to the most stable system Mn^{2+}–C1 are in this case very high so that the MIA values range from a maximum of 190.8 kcal/mol for Mn^{2+}–C1 to a minimum of 157.2 kcal/mol for Mn^{2+}–C4 complexes. The Mn^{2+}–C4 mono-coordinated complex is also a stable structure but its energy, as well as that corresponding to

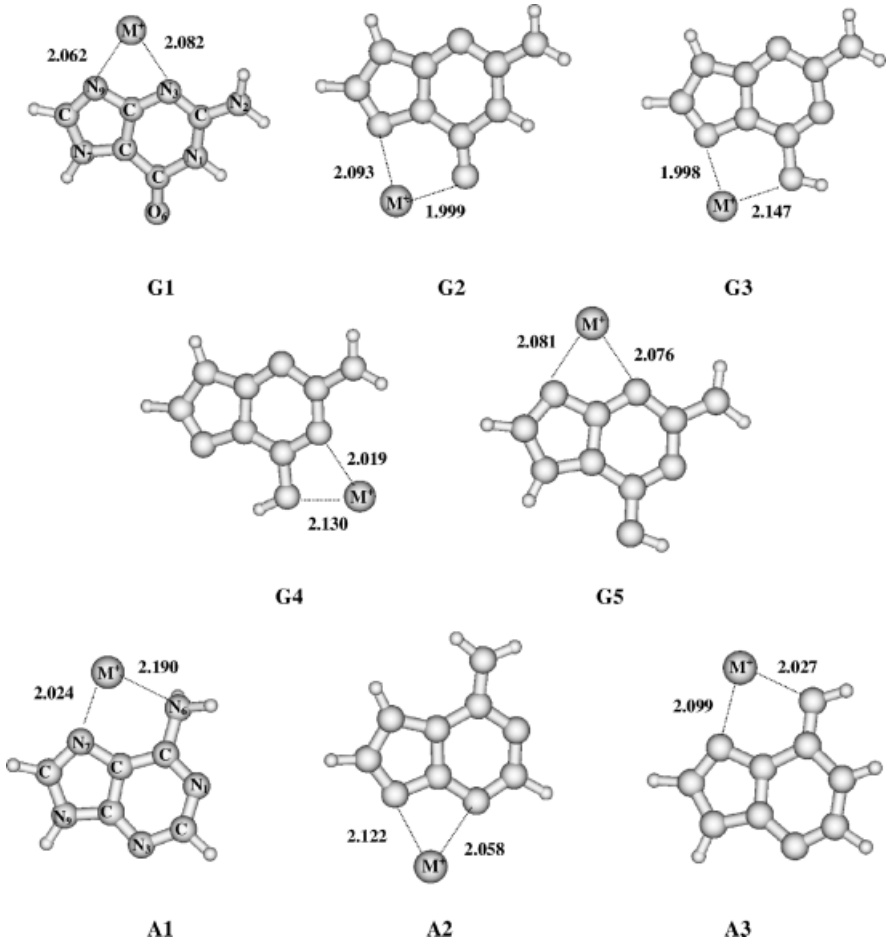


FIGURE 2. B3LYP/6-311+G(2*df*, 2*p*) optimized structures of guanine and adenine complexes with manganese cation. Distances are in Å.

the Mn^{2+}–C2 system, is very high, being more than 30 kcal/mol above that of the Mn^{2+}–C1 complex. The relative energy value of the Mn^{2+}–C3 complex is 20.95 kcal/mol and the corresponding MIA is 171.9 kcal/mol.

Concerning the geometrical structure, we note that the cation–oxygen length is slightly longer than the cation–nitrogen one when the oxygen is also involved in the formation of the hydroxyl bond.

Analogously to cytosine, the free molecule of guanine possesses different tautomers in a small energy range. In fact, we have selected the five isomers lying in a range of 4.38 kcal/mol. Also in this case, an infrared spectroscopy experiment has evidenced the presence of more than one isomer in gas phase [25]. The corresponding complexes with manganese cation are more separated in energy and their stability order is Mn^{2+}–G1 > Mn^{2+}–G5 > Mn^{2+}–G2 > Mn^{2+}–G3 > Mn^{2+}–G4 (see Fig. 2 for the geometrical structures). The results show that the N, N coordination is preferred over the N, O one and the N, O coordination is favored when the oxygen atom is not involved in the O–H bond. The manganese ion affinity for guanine goes from 207.1 kcal/mol (for the G1 isomer) to 166.5 kcal/mol (for the G4 isomer). Our previous study on the alkali metal ion affinity has pointed out that, also for this base, for a correct assignment of the experimental value all the isomers treated in this work should be considered.

The tautomers of adenine selected by us have relative energies, with respect to the absolute minimum A1, of 8.08 (A2) and 18.46 (A3) kcal/mol, respectively. The metalation process promotes the less favored tautomer to the most stable one, being 13.12 (A2) and 27.77 (A3) kcal/mol, the energy difference with respect to the other two complexes. In

TABLE II

Absolute (*E* in a.u.), relative (ΔE in kcal/mol) energies, and manganese ion affinity (MIA in kcal/mole) at 0 K for DNA and RNA bases computed at the B3LYP/6-311+G(2*df*, 2*p*) level.

	B		B–Mn^{++}		
	E_{SCF}	ΔE	E_{SCF}	ΔE	MIA
U1	−414.971535	0.00	—	—	—
U2	−414.952629	11.67	−1565.335556	0.00	173.2
U3	−414.940608	18.94	−1565.335242	0.04	180.5
T1	−454.303544	0.00	—	—	—
T2	−454.283101	12.65	−1604.676415	0.27	179.8
T3	−454.273749	18.26	−1604.676485	0.00	185.7
C1	−395.078564	0.00	−1545.490869	0.00	190.8
C2	−395.076865	1.31	−1545.435786	33.44	158.7
C3	−395.075619	2.07	−1545.456448	20.95	171.9
C4	−395.075776	2.34	−1545.432786	35.92	157.2
G1	−542.748120	0.00	−1693.185404	0.00	207.1
G2	−542.746912	0.70	−1693.152052	21.02	186.7
G3	−542.745155	1.82	−1693.134199	31.30	168.4
G4	−542.744504	2.26	−1693.115716	42.83	166.5
G5	−542.740761	4.38	−1693.154562	18.56	192.2
A1	−467.481162	0.00	−1617.859099	27.77	169.9
A2	−467.468537	8.08	−1617.882234	13.12	192.1
A3	−467.452252	18.46	−1617.904104	0.00	215.6

this case, all the possible coordination sites involve the nitrogen atoms and the most stable complex originates from the coordination of the cation to two N6–H and N7 atoms (Mn^{2+}–A3). The complexes in which the cation approaches N3 and N9 (Mn^{2+}–A2) and N6H2 and N7 (Mn^{2+}–A1) follow in energy the Mn^{2+}–A3 complex. A comparison with the alkali ion–adenine complexes shows a similar situation for the Li^+ cation which prefers to form the complex with A3 while Na^+ and K^+ prefer the A2 tautomer. The resulting MIA values are 169.9, 192.1, and 215.6 kcal/mol for Mn^{2+}–A1, Mn^{2+}–A2, and Mn^{2+}–A3, respectively.

The well known difficulties in the gas-phase experimental determination of the entropic contribution have been recently reviewed by Armentrout [26]. On the other hand they are mandatory to obtain reliable values of the free energy variations. The theoretical computations do not suffer from this problem and accurate values can be determined by the thermochemical analysis [27]. For this reason we have included this important term in our MIA evaluations. Results, collected in Table III, show that the $T\Delta S$ contribution is in any case not negligible (about 8 kcal/mol).

TABLE III

Enthalpy (ΔH = MIA), entropy ($T\Delta S$), and free energy (ΔG) variations for the formation process of B–Mn^{2+} complexes at 298 K, computed at the B3LYP/6-311+G(2*df*, 2*p*) level of theory.

Tautomer	ΔH^{298K} (kcal/mol)	$T\Delta S^{298K}$ (kcal/mol)	ΔG^{298K} (kcal/mol)
U1	—	—	—
U2	173.8	8.6	165.2
U3	181.1	8.7	172.4
T1	—	—	—
T2	180.4	8.6	171.8
T3	186.6	8.5	177.8
C1	191.4	9.2	182.2
C2	159.3	8.5	150.8
C3	172.5	8.6	163.9
C4	157.8	7.6	150.2
G1	207.7	9.1	198.6
G2	187.3	8.6	178.7
G3	169.0	8.5	160.5
G4	167.1	8.2	158.9
G5	192.8	8.7	184.1
A1	170.5	8.6	161.9
A2	192.7	8.7	184.0
A3	216.2	9.2	207.0

Furthermore, it is important to underline that between the different tautomers of a given nucleic acid base it does not vary significantly, 0.9 kcal/mol being the maximum variation in the case of guanine complexes.

Conclusions

The manganese ion affinities for the uracil, thymine, cytosine, guanine, and adenine have been predicted by using the density functional approach in its B3LYP formulation in conjunction with the 6-311+G(2*df*, 2*p*) basis set. We have considered different tautomers of the free nucleic acid bases and various coordination topologies. Results show that bi-coordination is preferred and for this reason it seems that the more stable tautomers of uracil and thymine are not metalated. The manganese affinity for nucleic acid bases is found to be greater than that of the corresponding alkali ions. If we consider the most stable complexes, the metal ion affinity order for manganese cation is A > G > C > T > U. Since in other cases the measured affinity does not correspond to the theoretical value obtained for the most stable complex, the correct metal ion affinity order should be determined in the presence of experimental measurement that we hope to stimulate. In any case because we have considered all other low energy tautomers, any further work should be greatly facilitated.

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References

1. Loeb, L. A.; Zakour, A. R. Nucleic Acid–Metal Ion Interaction; Spiro, T. G., Ed.; Wiley: New York, 1980; pp. 115–144.
2. Sigel, A.; Sigel, H., Eds. Metal Ions in Biological Systems, Vol. 32; Interactions of Metal Ions with Nucleotides, Nucleic Acids and their Constituents; Dekker: New York, 1996; Sigel, A.; Sigel, H. Eds. Metal Ions in Biological Systems, Vol. 33; Probing of Nucleic Acids by Metal Ion Complexes of Small Molecules; Dekker: New York, 1996.
3. Lippard, S. J.; Berg, J. M. Principles of Bioinorganic Chemistry; University Science Books: Mill Valley, CA, 1994.
4. Kaim, W.; Schwedersky, B. Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life; Wiley: Chichester, 1994.
5. Kirk, B. W.; Kuchta, R. D. Biochemistry 1999, 38, 10126.
6. Horton, T. E.; Roxame Clardy, D.; De Rose, V. J. Biochemistry 1998, 37, 18094.
7. Lin, Y.; Nageswara Rao, B. D. Biochemistry 2000, 39, 3667.
8. Raghunathan, V.; Chau, M. H.; Ray, B. D.; Nageswara Rao, B. D. Biochemistry 1999, 38, 15597.
9. Cerda, B. A.; Wesdemiotis, C. J Am Chem Soc 1995, 117, 9734.
10. Rodgers, M. T.; Armentrout, P. B. J Am Chem Soc 2000, 122, 8548.
11. Russo, N.; Toscano, M.; Grand, A. J Phys Chem B 2001, 105, 4735.
12. Cerda, B. A.; Wesdemiotis, C. J Am Chem Soc 1996, 118, 11884.
13. Greco, F.; Liguori, A.; Sindona, G.; Uccella, N. J Am Chem Soc 1990, 112, 9092.
14. Russo, N.; Toscano, M.; Grand, A. J Am Chem Soc 2001, 123, 10272.
15. Marino, T.; Russo, N.; Toscano, M. J Inorg Biochem 2000, 79, 179.
16. Marino, T.; Russo, N.; Toscano, M. Inorg Chem 2001, 40, 6439.
17. Frisch, M. J.; et al. Gaussian, Inc.: Pittsburgh, PA, 1998.
18. Becke, D. J Chem Phys 1993, 98, 5648.
19. Lee, C.; Yang, W.; Parr, R. G. Phys Rev B 1988, 37, 785.
20. Clark, T.; Chandrasekhr, J.; Spitznagel, G. W.; Scheleyer, P. v. R. J Comput Chem 1983, 4, 294.
21. Szczpaniak, K.; Szczpaniak, M.; Kwaitkowski, J.; Kubulat, K.; Person, W. B. J Am Chem Soc 1988, 110, 8319.
22. Nowak, M. I.; Lapinski, L.; Fullara, J. Spectrochim Acta A 1989, 45, 229.
23. Brown, R. D.; Godfrey, P. D.; McNaughton, D.; Pierlot, A. P. J Am Chem Soc 1987, 111, 2308.
24. Dreyfus, M.; Bensaude, O.; Dodin, G.; Dubois, J. E. J Am Chem Soc 1976, 98, 2353.
25. Szczpaniak, K.; Szczpaniak, M.; Szajda, W.; Person, W. B.; Leszczynski, J. Can J Chem 1991, 69, 1718.
26. Armentrout, P. B. J Am Soc Mass Spectrom 2000, 11, 371.
27. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. Ab Initio Molecular Orbital Theory; Wiley: New York, 1986.