

Theoretical Study of Interaction of Urate with Li^+ , Na^+ , K^+ , Be^{2+} , Mg^{2+} , and Ca^{2+} Metal Cations

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The geometries and energetics of complexes of Li^+ , Na^+ , K^+ , Be^{2+} , Mg^{2+} , and Ca^{2+} metal cations with different possible uric acid anions (urate) were studied. The complexes were optimized at the B3LYP level and the 6-311++G(d,p) basis set. Complexes of urate with Mg^{2+} , and Ca^{2+} metal cations were also optimized at the MP2/6-31+G(d) level. Single point energy calculations were performed at the MP2/6-311++G(d,p) level. The interactions of the metal cations at different nucleophilic sites of various possible urate were considered. It was revealed that metal cations would interact with urate in a bicoordinate manner. In the gas phase, the most preferred position for the interaction of Li^+ , Na^+ , and K^+ cations is between the N_3 and O_2 sites, while all divalent cations Be^{2+} , Mg^{2+} , and Ca^{2+} prefer binding between the N_7 and O_6 sites of the corresponding urate. The influence of aqueous solvent on the relative stability of different complexes has been examined using the Tomasi's polarized continuum model. The basis set superposition error (BSSE) corrected interaction energy was also computed for complexes. The AIM theory has been applied to analyze the properties of the bond critical points (electron densities and their Laplacians) involved in the coordination between urate and the metal cations. It was revealed that aqueous solvation would have significant effect on the relative stability of complexes obtained by the interaction of urate with Mg^{2+} and Ca^{2+} cations. Consequently, several complexes were found to exist in the water solution. The effect of metal cations on different NH and CO stretching vibrational modes of uric acid has also been discussed.

Introduction

Uric acid (UA) is a naturally occurring antioxidant. In human blood plasma, it exists in considerably high concentrations.^{1–8} However, excess UA causes gout, which is due to the deposition of crystals of sodium urate in joints.^{9,10} Owing to the vast biochemical activity of UA, different experimental and theoretical investigations have been performed on this molecule.^{1–11} UA has several possible coordination sites. It interacts with biometallic ions such as cations of Mg ,^{12,13} Ca ,^{14,15} and Fe .^{16,17} However, information dealing with the synthesis and physical and structural properties of pure metal urate salts is limited. On the other hand, considerable amount of attention has been devoted to the preparation and structural characterization of metal ion complexes with other purines owing to their importance in the medical and pharmacological arena.^{18–19}

The involvement of metal ions in biological processes is well documented.²⁰ Alkali metal cations are very abundant in biological systems. Alkali metal cations as well as other hard metal ions have a poor ability to form covalent bonds and are therefore less likely to have a definite binding site. These metal ions prefer to bind to oxygen centers that are available in many biological processes. Their primary influence is to neutralize the negative charges in the surrounding environment. Metal ions may play a direct role, for instance in the oxidation–reduction reactions, or may serve as an indirect function like inducing conformational changes. Although metal ions are essential for

many processes, however, undesired results can be observed in the presence of the wrong metal or even the essential metals in the wrong concentration.²¹

There have been several theoretical studies investigating the interaction of metal cations with DNA and RNA bases.^{22–26} Burda et al.²² on the basis of interaction of different metal cations with adenine and guanine at the Hartree–Fock level have shown that the intermolecular distances between the metal cations and the N_7 site of adenine to be shorter than the those of the corresponding distance in metal–guanine complexes. The interaction of metal cations with the O_6 site of guanine provided extra stabilization of guanine complexes than those of the adenine complexes.²² On the basis of the theoretical investigations of gas-phase affinities of tautomers of DNA and RNA bases for Li^+ , Na^+ , and K^+ metal ions, the importance of rare tautomers of nucleic acid bases in explaining the experimental data have been suggested.^{23–25}

The interaction of different metal cations with urate has been investigated experimentally.^{27–31} Koksharova²⁶ synthesized and investigated the structural and physicochemical properties of complexes of urate with 3d-metal cations Mn^{2+} , Fe^{2+} , Co^{2+} , and Ni^{2+} using different spectroscopic methods and has shown that in these complexes metals were found to be coordinated through the oxygen and nitrogen atoms of the urate. Moawad²⁷ has studied the interaction of urate with some divalent and trivalent metal cations experimentally and suggested that the N_7 site of urate is one of the mandatory sites of metal–ligand binding. Further, it was found that at least two uric acid molecules are involved in the complex formation. Mandel and Mandel²⁸ have studied the crystal structure of sodium mono-

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hydrate. Dubler et al.²⁹ have studied the crystal structure of uric acid salt of magnesium. Carmona³⁰ has studied the crystal structure and infrared (IR) and Raman spectra of the hydrate of calcium urate. Davies et al.³¹ have shown that uric acid forms a stable coordination complex with iron cations. The formation of this complex plays an inhibit role in the iron cation catalyzed ascorbate oxidation and lipid peroxidation.

The present investigation, to the best of our knowledge, is the first theoretical work in which the interaction between the some of the first and second group metal cations (Li^+ , Na^+ , K^+ , Be^{2+} , Mg^{2+} , and Ca^{2+}) and different urate obtained by the deprotonation of different sites of the uric acid are considered. A systematic density functional theory and the second-order Moller–Plesset perturbation theoretical investigation has been performed with the objective to determine the most reactive binding sites of urate in interaction with metal cations, nature of interactions, and structure of complexes, which are necessary to develop an understanding of metal complex formation with urate.

Computational Methods

Geometry optimizations and harmonic vibrational frequency calculations of different complexes were performed using Becke's³² three-parameter nonlocal hybrid exchange potential (functional) with the nonlocal correlation functional of Lee, Yang, Parr (B3LYP).³³ The 6-311++G(d,p) basis set was used in the study. Harmonic vibrational frequency analysis suggested that optimized geometries belong to minima at the respective potential energy surfaces. It is well-known that a linear scaling to the zero point vibrational energy (ZPE) is necessary for the total energy correction. The scaling factor of 0.9877 suggested for the B3LYP/6-311++G(d,p) level of theory³⁴ have been used in the present work. Complexes of urate with Mg^{2+} , and Ca^{2+} metal cations were also optimized at the MP2/6-31+G(d) level. The single point energy calculations were also performed at the MP2/6-311++G(d,p) level using the B3LYP and MP2 optimized geometries. The binding energies for the complexes were computed as the differences between the total energies of the complexes and the energies of the isolated monomers and have been corrected for the basis set superposition error (BSSE) using the standard counterpoise method.³⁵ The effects of the aqueous solvation on the relative energy of complexes were modeled with the use of Tomasi's PCM model.³⁶ All calculations were performed using the Gaussian98 program.³⁷ The atoms-in-molecules (AIM) theory of Bader³⁸ was used to analyze the nature of interaction of metal cations with different possible urate. The AIM calculations were performed using the AIM2000 program.³⁹

Results and Discussion

Geometries of different metal–urate complexes were obtained by the interaction of metal cations with the N_1 , N_3 , N_7 , and N_9 sites of the corresponding anion (UAN_1^- , UAN_3^- , UAN_7^- , and UAN_9^- , respectively) of the uric acid. It should be noted that metal cations were also coordinated with the nearby carbonyl group in the corresponding urate. The atomic numbering schemes and the geometries of different complexes are shown in Figure 1.

The distance between metal cations and the coordinating sites of urate in the complexes are shown in Table 1. For the urate and the Li^+ , Be^{2+} , Mg^{2+} , and Ca^{2+} metal cation complexes, except for a few exceptions, the $\text{M}^+\text{--O}$ distances are generally shorter than the corresponding $\text{M}^+\text{--N}$ distances, where M^+ represents the cation. However, for the Na^+ and K^+ metal

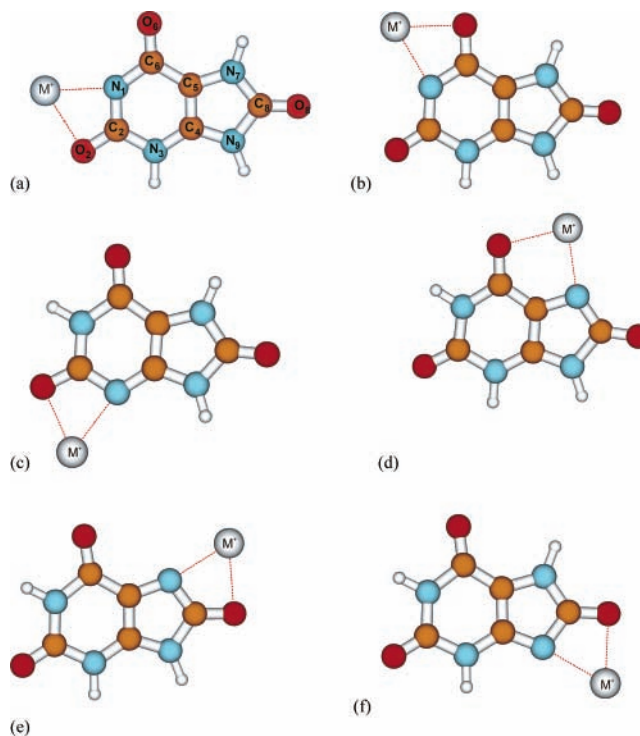


Figure 1. Optimized structures of the urate complexes with M^+ ($\text{M}^+ = \text{Na}^+$, Li^+ , K^+ , Be^{2+} , Mg^{2+} , and Ca^{2+}) cations at (a) N_1O_2 , (b) N_1O_6 , (c) N_3O_2 , (d) N_7O_6 , (e) N_7O_8 , and (f) N_9O_8 sites of the respective urate at the B3LYP/6-311++G(d,p) level.

cations and urate complexes, the $\text{M}^+\text{--O}$ distances are generally longer than the corresponding $\text{M}^+\text{--N}$ distances, except for the Na^+ –urate complexes bicoordinated between the N_3 and O_2 and between N_9 and O_8 atomic sites of the urate and K^+ –urate complexes bicoordinated between the N_1 and O_6 and between N_9 and O_8 atomic sites of the urate (Table 1). The analysis of metal–urate coordination distances among most stable complexes (which were obtained by the interaction of mono cations between the N_3 and O_2 sites and dications between the N_7 and O_6 sites of urate in the gas phase and are discussed later) reveals that the $\text{M}^+\cdots\text{N}$ distance is longer than the corresponding $\text{M}^+\cdots\text{O}$ distance, except for the Mg^{2+} cation where opposite trend is found. Further, for alkali and alkaline metal cations with increase in the atomic number within the same group of elements, the coordination distance was found to be increased while in going from the alkali metal cations to alkaline metal cations in the same row of periodic table, the coordination distances were found to be decreased (Table 1). Thus, the computed trend regarding the change of the coordination distances is in accordance with the generally known properties of the first and second group elements of the periodic table that in going from the top to bottom in the same group the electronic affinity decreases, while in going from the left to right within the same row the electronegativity increases.

The analysis of the geometry of urate and those of metal–urate complexes suggests that the geometry of urate in the metal cation complexes differs slightly from the geometry of the isolated urate. The most prominent changes influenced by monovalent metal cations are revealed in the six-membered ring of the urate. All but $\text{C}_4\text{--C}_5$ and $\text{C}_2\text{--O}_2$ bond lengths of the six-membered rings were found to be shorter than those in the isolated urate. The double bond nature of the $\text{C}_4\text{--C}_5$ bond is found to be increased to help compensate the metal ion attraction at the N_3 site while the $\text{C}_2\text{--O}_2$ bond length is increased due to the strong attraction for the oxygen to metal cation. The divalent

TABLE 1: Bond Distances (in Angstroms) of the Optimized Urate Metal Complexes Obtained at the B3LYP/6-311++G(d,p) Level

	N ₁	O ₂	N ₁	O ₆	N ₃	O ₂	N ₇	O ₆	N ₇	O ₈	N ₉	O ₈
Li ⁺	1.914	1.896	1.913	1.878	1.944	1.844	1.913	1.933	1.912	1.907	1.943	1.858
Na ⁺	2.246	2.272	2.246	2.253	2.301	2.197	2.242	2.284	2.243	2.272	2.287	2.213
K ⁺	2.575	2.602	2.583	2.575	2.667	2.496	2.581	2.632	2.574	2.587	2.649	2.507
Be ²⁺	1.576	1.536	1.565	1.515	1.575	1.518	1.561	1.541	1.567	1.554	1.575	1.530
Mg ²⁺	1.975	1.974	1.971	1.951	1.994	1.932	1.956	1.963	1.967	1.980	1.990	1.945
Ca ²⁺	2.229	2.191	2.232	2.164	2.278	2.128	2.226	2.216	2.220	2.192	2.265	2.139

metal cations Be²⁺, Mg²⁺, and Ca²⁺ were found to induce changes throughout the entire molecule, but the six membered ring is the most affected. The bond distances between C₅–C₆, N₁–C₆, and N₃–C₄ were found to be decreased; however the bond distances between C₂–N₃, N₁–C₂, C₄–C₅, and C₆–O₆ were found to be increased with respect to the corresponding distance in the isolated urate.

The relative ground-state total energies of urate–metal complexes in the gas phase and in aqueous media are presented in Table 2. This table shows that in general, alkali metal cations (Li⁺, Na⁺, and K⁺) energetically prefer to form bicoordinated complex with urate through the N₃ and O₂ positions both in the gas phase and in water solution without considering explicit water molecules. The complexes obtained by the coordination the alkali metal cations to the N₉ and O₈ sites of urate are second most stable in the gas phase and in the water solution. Data corresponding to the relative energy shown in Table 2 suggest that these complexes would also be present in the gas phase and in aqueous solution in significant proportions. On the other hand the divalent alkaline metal cations (Be²⁺, Mg²⁺, and Ca²⁺) energetically prefer to bicoordinate at the N₇ and O₆ positions of urate in the gas phase. Significant change in the relative stability of different divalent alkaline metal complexes with urate is revealed in the water solution modeled using the PCM solvation model. This is especially true for complexes containing the Mg²⁺ and Ca²⁺ cations (Table 2). At the B3LYP/6-311++G(d,p) level in the water solution, several complexes containing Mg²⁺ and Ca²⁺ cations were found to have similar stability and the similar results were also revealed at the MP2/6-311++G(d,p)//B3LYP/6-311++G(d,p) level. However, the most stable complexes were found to be different at these two levels of calculations. Therefore, we also optimized geometries of these complexes at the MP2/6-31+G(d) level, and single point energy calculations were performed at the MP2/6-311++G(d,p)//MP2/6-31+G(d) level. It is clear from the data shown in Table 2 that the complexes of Mg²⁺ and Ca²⁺ obtained by the bicoordination with N₃ and O₂ sites of urate will be the most stable in the water solution. However, other complexes will also be present in the water solution. The computed stability of other complexes in the water solution compared to that in the gas phase indicates that Mg²⁺ and Ca²⁺ cations are efficiently screened in the bulk water. However, the effective screening of metal cations in the bulk water (modeled using PCM model) would depend on the size of cation and the binding site in the urate.

It is well-known that under the physiological conditions, these metals cations are heavily hydrated and hydrated cations interact with biological molecules, e.g., nucleic acid bases.⁴⁰ Further, the nature and strength of hydration is also different for different cations. For example, the dehydration of hydrated Mg²⁺ requires more energy than that of the hydrated Ca²⁺.⁴¹ The coordination number for hydration is found to depend on concentration and temperature. In the calcium ion, the coordination number is found to decrease with increase in concentration but increase with increase in the temperature.^{42,43} Therefore, it is necessary

to study the interaction of hydrated alkaline cations with urate, which we will perform in the near future. Further, it is true that in the bulk aqueous environment, both the cation and the urate moiety will be solvated. However, the effect of hydration on metals cations will be stronger and localized due to the charge localization while on the urate moiety effect of hydration will be comparatively weaker due to the charge delocalization. In other theoretical investigations also, the hydration of metal cations is found to be more favorable than the hydration of ligands.⁴⁴ The hydration characteristics of the first group metal cations are different than second group cations.⁴⁵ Further, all second group metal cation–urate complexes are singly positively charged. Therefore, effect of hydration on the relative energies of first and second group metal cation–urate complexes would be different.

The BSSE corrected interaction energy at the B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p)//B3LYP/6-311++G(d,p) levels are presented in Table 2. It is evident that complexes formed by the interaction of metals cations to the N₇ and O₆ sites of urate have the largest interaction energy. The most stable alkali metal–urate complexes formed by the bicoordination of metal cations to the N₃ and O₂ sites do not have the largest interaction energy. It should be noted that Moawad²⁷ has experimentally suggested that some divalent and trivalent metal cations interact with urate through the N₇ site of the molecule. Our finding for divalent metals such as Be²⁺, Mg²⁺, and Ca²⁺ are in agreement with those findings. Data presented in Table 2 show that such metal have the greatest interaction at the N₇ site of the molecule. In general, the coordinations of metal cations with urate in the crystals are found to be complex. More than one urate molecules and a few water molecules were found to be involved coordinating with metal cations.^{26–29} It appears that the crystal field effect and the presence of water molecules play an important role in the interaction of metal cation with urate in the crystalline form. The large interaction energy (Table 2) partially results from the bicoordination nature of the interaction in the studies complexes. This point is clear from the study of Kumar et al.,⁴⁶ in which authors have performed theoretical investigations of the interaction of proton and lithium cation with different diamines. The energy difference between mono- and bidentate complexes was found to be significantly large. The effect of lithium cation was found to be about three times larger than that of proton in such energy differences. In other words, the interaction energies computed for bidentate complexes were found to be significantly larger than that in the corresponding monodentate complexes.

The relative stability appears to be more important than the interaction energy in the present investigation. In the present work, we have studied the interaction of metal cations with four possible anions of uric acid. The relative energy of uric acid anions follows the order^{11a} N₃[−] (0.0) > N₉[−] (0.7) > N₇[−] (17.4) > N₁[−] (19.4), where N_n represents the site of deprotonation and values in parentheses are relative energies in kcal/mol at the B3LYP/6-311++G(d,p) level. Therefore, there are two main

TABLE 2: Relative Total Energies (ΔE , kcal/mol) of Metal–Urate Complexes in the Gas Phase and in Water Solution and the BSSE Corrected Interaction Energy (ΔE_{int}) in the Gas Phase at the B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p)//B3LYP/6-311++G(d,p) Levels^a

complex	ΔE		ΔE_{int}	
	gas phase	water solution	gas phase	water solution
Lithium Urate				
N ₃ O ₂	0.0 (0.0)	0.0 (0.0)	-149.8	-147.1
N ₉ O ₈	1.2 (0.3)	4.5 (3.6)	-150.0	-147.5
N ₇ O ₆	4.9 (5.1)	9.4 (8.5)	-164.9	-160.1
N ₁ O ₆	7.2 (8.5)	8.2 (9.0)	-162.3	-158.1
N ₇ O ₈	8.7 (6.9)	9.0 (7.2)	-159.8	-157.0
N ₁ O ₂	9.3 (9.6)	8.2 (8.4)	-160.6	-157.0
Sodium Urate				
N ₃ O ₂	0.0 (0.4)	0.0 (0.0)	-124.3	-121.3
N ₉ O ₈	0.5 (0.0)	0.4 (1.5)	-125.1	-122.4
N ₇ O ₆	4.9 (5.5)	6.6 (8.3)	-138.0	-133.3
N ₁ O ₆	7.3 (8.8)	7.1 (8.1)	-136.7	-132.4
N ₇ O ₈	7.5 (6.2)	7.6 (7.2)	-135.3	-132.1
N ₁ O ₂	8.9 (9.6)	6.6 (8.0)	-135.3	-131.8
Potassium Urate				
N ₃ O ₂	0.0 (0.6)	0.0 (0.0)	-107.1	-106.5
N ₉ O ₈	0.1 (0.0)	2.5 (1.8)	-108.2	-107.8
N ₇ O ₆	6.0 (6.3)	5.9 (4.9)	-119.3	-117.5
N ₁ O ₆	8.0 (9.5)	8.6 (9.0)	-118.9	-117.3
N ₇ O ₈	7.1 (6.1)	8.5 (6.1)	-118.2	-117.6
N ₁ O ₂	9.0 (10.1)	6.1 (6.6)	-117.9	-116.9
Beryllium Urate				
N ₇ O ₆	0.0 (0.0)	0.0 (0.0)	-544.8	-530.6
N ₁ O ₆	9.4 (11.8)	6.1 (8.0)	-530.6	-516.8
N ₃ O ₂	19.4 (19.8)	9.3 (9.0)	-497.7	-487.5
N ₁ O ₂	21.2 (21.1)	10.1 (9.2)	-516.7	-505.0
N ₉ O ₈	23.2 (21.8)	14.4 (12.5)	-495.4	-485.5
N ₇ O ₈	25.1 (23.1)	16.4 (13.4)	-511.1	-500.1
Magnesium Urate				
N ₇ O ₆	0.0 (0.0)	2.8 (2.6)	-389.0	-376.3
	0.0 [0.0]	2.6 [2.5]		
N ₁ O ₆	6.9 (8.1)	0.0 (0.8)	-381.4	-369.2
	8.5 [8.3]	5.4 [0.8]		
N ₃ O ₂	14.4 (13.3)	0.6 (0.1)	-357.5	-344.2
	13.0 [12.8]	0.0 [0.0]		
N ₁ O ₂	13.8 (13.2)	4.3 (4.3)	-374.3	-355.5
	13.0 [12.7]	3.6 [4.5]		
N ₉ O ₈	14.9 (12.0)	1.7 (0.0)	-354.7	-346.2
	11.7 [11.3]	2.4 [0.3]		
N ₇ O ₈	14.4 (11.4)	3.5 (0.6)	-372.5	-362.6
	10.9 [11.4]	3.0 [1.4]		
Calcium Urate				
N ₇ O ₆	0.0 (0.0)	2.3 (1.9)	-325.6	-312.8
	0.0 [0.0]	6.1 [2.2]		
N ₁ O ₆	3.5 (5.6)	1.4 (3.8)	-322.8	-309.5
	5.5 [5.4]	6.3 [2.5]		
N ₃ O ₂	8.1 (7.8)	0.0 (0.1)	-297.1	-286.9
	8.9 [8.3]	0.0 [0.0]		
N ₁ O ₂	8.3 (8.2)	0.6 (1.4)	-317.9	-306.7
	8.7 [8.6]	6.1 [3.0]		
N ₉ O ₈	7.4 (5.9)	0.9 (0.7)	-313.7	-289.3
	6.5 [5.7]	2.8 [0.7]		
N ₇ O ₈	6.6 (4.1)	1.3 (0.0)	-299.4	-306.7
	4.6 [4.5]	4.0 [1.2]		

^a The MP2/6-311++G(d,p)//B3LYP/6-311++G(d,p) energies are in parentheses, the optimized MP2/6-31+G(d) level energies are in italics bold and the single-point MP2/6-311++G(d,p)//MP2/6-31+G(d) level energies are in italics bold brackets.

factors contributing to the stability of different complexes of a particular cation: (i) relative stability of different anions; (ii) stabilization of different anions due to a metal cation. It appears that relative stability of different anions have significant role in determining the stability of alkali metal cation–urate

complexes, but insignificant role for alkaline metal cation–urate complexes. Therefore, for first group atoms the complex obtained by the interaction of metal cations at the N₃ and O₂ sites of urate (N₃⁻ anion) is most stable among complexes, although the interaction energy is not the largest. Similar results were also obtained by Russo et al.²⁴ in the computational study of interaction of sodium and potassium cations with different tautomeric forms of nucleic acid bases (adenine, guanine, thymine, uracil, and cytosine). These authors have also found that there are no correlations between the stability of complexes and heat and free energy of formation, and the most stable complex does not necessarily have the largest heat or free energy of formation.

It is interesting that while the dipole moment of neutral uric acid was increased by about 50% in passing from the gas phase ($\mu \approx 2.8$ D) to a water environment ($\mu \approx 5.5$ D),^{11a} only minor changes were observed in electrostatic interactions (based on NPA charges of the given complex used in the Coulomb law) between the metal cation and the neighboring atoms of the corresponding urate anion. In the case of Mg²⁺ cation, the largest increase of electrostatic interaction was found for N₃O₂ site (nearly 40% increase) while only marginal change could be noticed in N₇O₆ site, which is the place where the most pronounced changes could be expected due to the dipole moment orientation of neutral uric acid. This short analysis demonstrates that the straightforward dipole-monopole interaction cannot be used in our model since cations do not form simple adduct to uric acid. Instead, proton replacement reaction in the studied process, where stability of the product is more complex function of electrostatic, polarization (charge transfer), and covalent forces.

To study the nature of the M⁺–O and M⁺–N bonds of the complexes, the atom in molecules (AIM) theory of Bader³⁸ was applied. The results obtained with the AIM theory confirm findings based on the geometrical data. In this study, the AIM calculations were performed at the B3LYP/6-311++G(d,p) level. Table 3 collects the electron densities (ρ) and corresponding Laplacian values ($\nabla^2\rho$) for the bond critical points (BCPs) of the urate metal complexes. The Laplacian of the densities ($\nabla^2\rho$) identifies the regions of the space wherein the electronic charge is locally depleted or collected. The former situation is typically associated with interactions between closed-shell systems and characterizes the ionic bonds, hydrogen bonds, and van der Waals interactions, whereas the latter characterizes covalent bonds, where the electron density concentrates in the internuclear region. For the alkali metals the electron densities of the BCP and Laplacian show that the strongest interaction is for the Li⁺. As the alkali metals increase in atomic number, the electron density and Laplacian values at BCP were found to be decreased (Table 3). A similar trend is also revealed for alkaline metal–urate complexes. It should be noted that the computed interaction energies for the urate–metal complexes also show the similar behavior (Table 2). Further, the alkaline earth metal–urate complexes have larger charge density and Laplacian than alkali–urate complexes, and this result is consistent with the computed interaction energy (Tables 2 and 3).

Different NH and CO stretching vibrational frequencies (unscaled) of uric acid and most stable urate metal cation complexes obtained at the B3LYP/6-311++G(d,p) level are shown in Table 4. It is evident from the data shown in Table 4 that the interaction of alkali metal cations with different urates does not influence any significant change in the stretching NH vibrational frequencies compared to that in the uric acid.

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