



Nontemplate synthesis, characterization and theoretical study of tetraazamacrocycles

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Abstract The syntheses of new tetraaza macrocyclic compounds of variable ring sizes by non-template methods and their characterization with the help of elemental analysis and spectroscopic techniques (FT-IR, ¹H-NMR, and ¹³C-NMR) have been reported in detail. The vibrational frequencies determined experimentally are compared with those obtained theoretically from density functional theory (DFT) and Hartree-Fock (HF) calculations. The comparisons between the experimental and theoretical results indicate that B3LYP level with both the 3-21G(d) and 6-31G+(d,p) basis sets is able to provide satisfactory results for predicting IR properties. The frontier molecular orbital diagrams and molecular electrostatic potential maps of title compounds have been also calculated and visualized at the B3LYP/6-31G+(d,p) level of theory.

Keywords: Macrocyclic ligands, Computational methods, DFT, HF, ab-initio

1. Introduction

Nature prefers macrocyclic derivatives for many fundamental biological processes such as photosynthesis, transfer of oxygen in mammalian and all respiratory systems [1]. The synthesis and applications of polyaza macrocycles have attracted a considerable interest in recent years because of their ability to interact with both metal cations and anionic species [2-5]. Many of the synthetic routes to these systems use high dilution techniques [6] or template synthesis [7], but last one to the synthesis of metal complexes of macrocyclic ligands and their subsequent release has serious limitations in the case of a number of metal ions, notably iron [8].

Computational chemistry is the science of representing molecular structures numerically and simulating their behavior with the equations of quantum and classical physics [9]. Computational chemistry programs allow scientists to generate and present molecular data including geometries, energies, electronic properties, and spectroscopic properties [10-12].

Herein, we would like to report the preparation of new tetraaza macrocyclic compounds of variable ring sizes by non-template synthetic methods [13,14] and their characterization with the help of

elemental analysis and spectroscopic techniques (FT-IR, ¹H-NMR, and ¹³C-NMR). Moreover, theoretical calculations have been performed using the Gaussian 03 program [15] at various levels of theory to investigate the structural and physical properties of title macrocycles [16].

2. Experimental and computational methods

All chemicals were purchased from Sigma-Aldrich or Fluka Chemical Company with a stated purity of greater than 99% and it was used as such without further purification. The FT-IR spectra were recorded in the region of 400–4000 cm⁻¹ on Perkin-Elmer Spektrum 100 BX, FT-IR spectrophotometer. The spectrum was recorded at room temperature, with scanning speed of 30 cm⁻¹ min⁻¹ and the spectral resolution of 2.0 cm⁻¹. Melting points were determined in open capillary tubes using Electrothermal IA-9200. ¹H-NMR spectra were recorded in deuterated chloroform using tetra methyl silane (TMS) as an internal reference standard on BRUKER DPX-400 NMR spectrometer.

The calculations of geometrical parameters in the ground state were performed using the Gaussian 03 suite of programs at DFT and HF levels with

both 6-31G(d) and 3-21G(d) basis sets [15]. Initial geometry generated from standard geometrical parameters was minimized without any constraint in the potential energy surface at AM1 semiempirical level. This geometry was then re-optimized again at both HF and DFT levels. The optimized structural parameters were used in the vibrational frequency calculations at both HF and DFT levels to characterize all stationary points as minima. Then, vibrationally averaged nuclear positions of compounds studied herein were used for harmonic vibrational frequency calculations resulting in IR frequency together with intensities.

3. Results and Discussion

3.1. Synthesis of 1,2-Bis{(2-aminobenzoyl)amino}propane (**5**) and its computational results

A solution of (0.1 mol) of 1,2-diaminopropane (**2**) in water and (0.2 mol) of isatoic anhydride (**1**) was added and stirred for 4 hr. The reaction mixture was stirred and the temperature raised slowly until a moderate evolution of CO₂ gas occurred. This was usually between 60 and 70 °C. After letting the mixture cool to room temperature, it was poured over crushed ice (**Scheme 1**).

The solid product were collected by filtration then fractionally recrystallized from dilute dioxane to give of compound (**5**) M.P. 178 °C; yield % 83; IR: 3468, 3277, 3057, 1624, 1578, 1533, 1487, 1446 cm⁻¹; ¹H-NMR (400 MHz, DMSO-*d*₆): δ=8.3, 7.5-6.4, 4.2, 3.3, 1.2; ¹³C-NMR (100 MHz, DMSO-

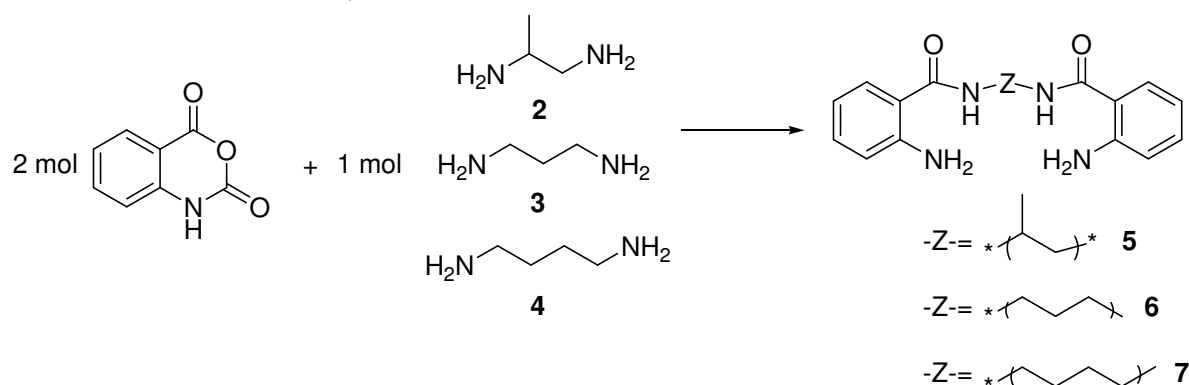
*d*₆) δ (ppm):169.45-168.69, 149.63-114.65, 45.06-44.06, 18.17. (see **Table 1**).

Table 1. The calculated frequencies (cm⁻¹) of **5** at HF/3-21G(d), HF/6-31+G(d,p), B3LYP/3-21G(d) and B3LYP/6-31+G(d,p) levels of theories. (R², a symbol for the coefficient of determination of a linear regression)

Experi- mental	HF/ 3-21G (d)	HF/ 6-31G +(d,p)	B3LYP/ 3-21G (d)	B3LYP/ 6-31G +(d,p)
1446	1456	1449	1462	1427
1487	1481	1494	1472	1487
1533	1537	1540	1536	1525
1578	1581	1558	1581	1567
1624	1624	1621	1610	1622
3057	3216	3192	3066	3051
3277	3278	3276	3231	3220
3468	3407	3394	3464	3538
R ²	0.995	0.996	0.999	0.999

3.2. Synthesis of 2-Amino-N-[3-[(2-aminobenzoylamino)propyl] benzamide] (**6**) and its computational results

A solution of (0.1 mol) 1,3-diaminopropane (**3**) in water and (0.2 mol) of isatoic anhydride (**1**) was added and stirred for 4 hr. The reaction mixture was stirred and the temperature raised slowly until a moderate evolution of CO₂ gas occurred. This was usually between 60 and 70°C. After letting the mixture cool to room temperature, it was poured over crushed ice (**Scheme 1**).



Scheme 1

The solid product were collected by filtration then fractionally recrystallized from dilute dioxane to give of compound (**6**). M.P. 171 °C; yield % 85; IR: 3478, 3067, 1623, 1537, 1488, 1447, 1364 cm⁻¹; ¹H-NMR (400 MHz, DMSO-*d*₆): δ=8.3, 7.6-6.4, 3.3, 1.7; ¹³C-NMR (100 MHz, DMSO-*d*₆) δ (ppm): 167.9, 145.6-116.2, 38.2, 29.4. (see **Table 2**).

Table 2. The calculated frequencies (cm⁻¹) of **6** at HF/3-21G(d), HF/6-31+G(d,p), B3LYP/3-21G(d) and B3LYP/6-31+G(d,p) levels of theories. (R², a symbol for the coefficient of determination of a linear regression)

Experi- mental	HF/ 3-21G (d)	HF/ 6-31G +(d,p)	B3LYP/ 3-21G (d)	B3LYP/ 6-31G +(d,p)
1364	1371	1375	1375	1362
1447	1441	1451	1419	1417
1488	1488	1464	1506	1487
1537	1541	1535	1538	1529
1623	1620	1631	1635	1621
3067	3222	3204	3054	3062
3478	3406	3395	3471	3542
R ²	0.994	0.994	0.999	0.999

3.3. Synthesis of 1,4-Bis{(2-aminobenzoyl)amino}butane (**7**) and its computational results

A solution of (0.1 mol) 1,4-diaminobutane (**4**) in water and (0.2 mol) of isatoic anhydride (**1**) was added and stirred for 5 hr. The mixture was stirred and the temperature raised slowly until a moderate evolution of CO₂ gas occurred. This was usually between 60 and 70 °C. After letting the mixture cool to room temperature, it was poured over crushed ice (**Scheme 1**).

The solid product were collected by filtration then fractionally recrystallized from dilute dioxane to give of compound (**7**). M.P. 201 °C; yield % 84; IR: 3470, 3292, 3056, 1623, 1578, 1532, 1487, 1445 cm⁻¹; ¹H-NMR (400 MHz, DMSO-*d*₆): δ=8.2, 7.5-6.4, 3.6, 3.3, 1.7; ¹³C-NMR (100 MHz, DMSO-*d*₆)

δ (ppm): 168.76, 149.5-114.5, 40.1, 26.7. (see **Table 3**).

Table 3. The calculated frequencies (cm⁻¹) of **7** at HF/3-21G(d), HF/6-31+G(d,p), B3LYP/3-21G(d) and B3LYP/6-31+G(d,p) levels of theories. (R², a symbol for the coefficient of determination of a linear regression)

Experi- mental	HF/ 3-21G (d)	HF/ 6-31G +(d,p)	B3LYP/ 3-21G (d)	B3LYP/ 6-31G +(d,p)
1445	1453	1450	1423	1450
1487	1478	1488	1494	1488
1532	1537	1549	1537	1549
1578	1546	1563	1574	1563
1623	1620	1619	1635	1632
3056	3202	3169	3054	3169
3292	3295	3276	3323	3276
3470	3406	3395	3472	3395
R ²	0.996	0.997	0.999	0.997

3.4. Synthesis of Okso₄Bzo₂-(6-metil)-[15]dien-N₄ (**9**)

(0.01 mol) Compound **5** was dissolved in 30 mL methanol and transferred to (0.01 mol) of diethyl malonate was dissolved in 30 mL methanol taken in a dropping funnel. Both were fitted to a three necked flask containing 100 mL methanol and fitted with a reflux condenser. The reaction mixture was boiled for 6 h and then the solvent was removed completely under vacuum. The solid left was recrystallized from methanol until pure products (by TLC) were obtained (**Scheme 2**). M.P. 273-274 °C; yield % 82; IR: 3468, 3053, 1624, 1577, 1537, 1487, 1447 cm⁻¹; ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) =8.12, 7.45-6.3, 4.2, 3.55, 3.35, 1.2; ¹³C-NMR (100 MHz, DMSO-*d*₆) δ (ppm): 169.3-168.6-166.95, 149.5-114.5, 52.10-44.92-38.86, 18.0. (see **Table 4**).

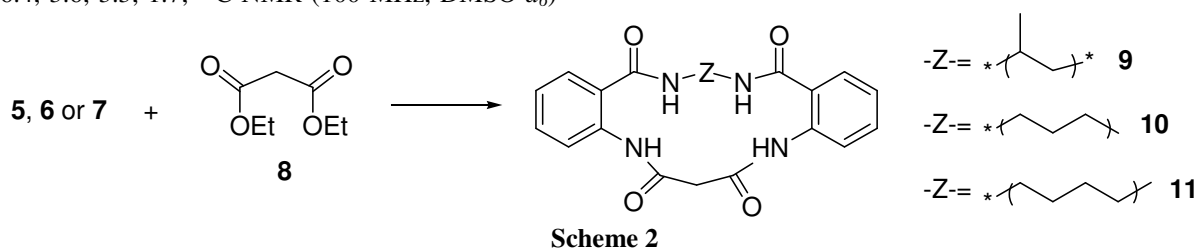


Table 4. The calculated frequencies (cm^{-1}) of **9** at HF/3-21G(d), HF/6-31+G(d,p), B3LYP/3-21G(d) and B3LYP/6-31+G(d,p) levels of theories.

Experi- mental	HF/ 3-21G (d)	HF/ 6-31G +(d,p)	B3LYP/ 3-21G (d)	B3LYP/ 6-31G +(d,p)
1447	1448	1442	1448	1459
1487	1488	1478	1484	1486
1537	1538	1542	1542	1533
1577	1572	1596	1566	1561
1624	1623	1630	1620	1622
3053	3206	3177	3044	3047
3468	3473	3450	3455	3527
R ²	0.997	0.997	1.000	0.999

3.5. Synthesis of Okso₄Bzo₂[16]dien-N₄ (10**)**

(0.01 mol) Compound **6** was dissolved in 30 mL methanol and transferred to (0.01 mol) of diethyl malonate was dissolved in 30 mL methanol taken in a dropping funnel. Both were fitted to a three necked flask containing 100 mL methanol and fitted with a reflux condenser. The reaction mixture was boiled for 6 h and then the solvent was removed completely under vacuum. The solid left was recrystallized from methanol until pure products (by TLC) were obtained (**Scheme 2**). M.P. 265-266 °C; yield % 85; IR: 3473, 3066, 1626, 1603, 1579, 1532, 1489, 1433 cm^{-1} ; ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) =8.19, 7.45-6.3, 3.35, 1.4; ¹³C-NMR (100 MHz, DMSO-*d*₆) δ (ppm): 167.9, 149.5-114.5, 40.1, 29.1, 26.3. (see **Table 5**).

Table 5. The calculated frequencies (cm^{-1}) of **10** at HF/3-21G(d), HF/6-31+G(d,p), B3LYP/3-21G(d) and B3LYP/6-31+G(d,p) levels of theories. (R², a symbol for the coefficient of determination of a linear regression)

Experi- mental	HF/ 3-21G (d)	HF/ 6-31G +(d,p)	B3LYP/ 3-21G (d)	B3LYP/ 6-31G +(d,p)
1433	1428	1434	1418	1437
1489	1501	1489	1489	1487
1532	1529	1531	1531	1519
1579	1580	1578	1578	1562
1603	1612	1606	1615	1615
1626	1625	1627	1629	1624
3066	3213	3192	3052	3063
3473	3466	3409	3479	3476
R ²	0.997	0.996	0.999	0.999

3.6. Synthesis of Okso₄Bzo₂[17]dien-N₄ (11**)**

(0.01 mol) Compound **7** was dissolved in 30 mL methanol and transferred to (0.01 mol) of diethyl malonate was dissolved in 30 mL methanol taken in a dropping funnel. Both were fitted to a three necked flask containing 100 mL methanol and fitted with a reflux condenser. The reaction mixture was boiled for 8 h and then the solvent was removed completely under vacuum. The solid left was recrystallized from methanol until pure products (by TLC) were obtained (**Scheme 2**). M.P. 291-293 °C; yield % 80; IR: 3480, 3292, 3056, 1621, 1579, 1535, 1474, 1445 cm^{-1} ; ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) =8.15, 7.45-6.3, 3.35, 1.4. (see **Table 6**).

Table 6. The calculated frequencies (cm^{-1}) of **11** at HF/3-21G(d), HF/6-31+G(d,p), B3LYP/3-21G(d) and B3LYP/6-31+G(d,p) levels of theories. (R², a symbol for the coefficient of determination of a linear regression)

Experi- mental	HF/ 3-21G (d)	HF/ 6-31G +(d,p)	B3LYP/ 3-21G (d)	B3LYP/ 6-31G +(d,p)
1445	1445	1445	1425	1467
1474	1460	1458	1482	1475
1535	1540	1526	1544	1527
1579	1609	1560	1577	1572
1621	1618	1620	1627	1621
1735	1740	1732	1739	1739
3056	3195	3161	3056	3052
3292	3300	3296	3280	3262
3480	3471	3445	3494	3519
R ²	0.997	0.998	0.999	0.999

In order to obtain the spectroscopic signature of the title structures, we have performed the vibrational frequency calculations at a series levels. The experimental and theoretical frequencies are shown briefly in **Tables 1–6** to compare with each other. The structures show the presence of N—H stretching vibrations experimentally above 3000 cm^{-1} in accordance with computational calculations which is the characteristic region for ready identification of these structures. The stretching vibration of C=O group occurs in the region 1626–1576 cm^{-1} .

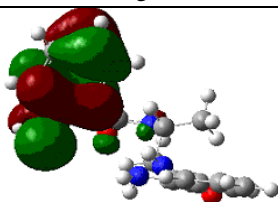
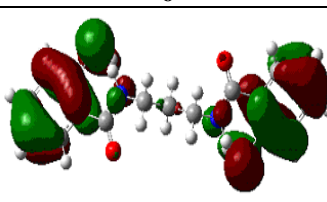
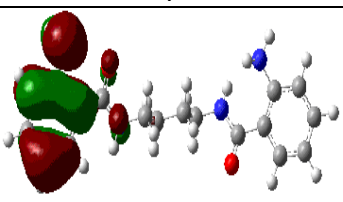
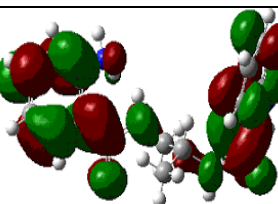
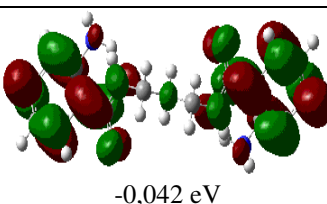
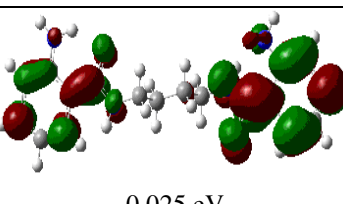
Molecule	5	6	7
HOMO	 -0,202 eV	 -0,227 eV	 -0,197 eV
LUMO	 -0,032 eV	 -0,042 eV	 -0,025 eV

Fig. 1. HOMO and LUMO orbitals of **5**, **6**, and **7** at B3LYP/6-31G+(d,p) level of theory.

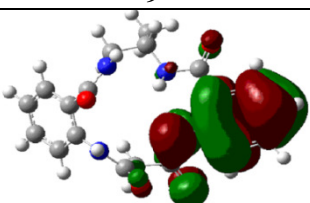
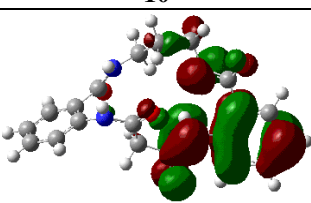
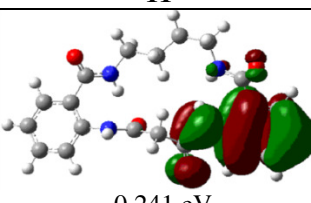
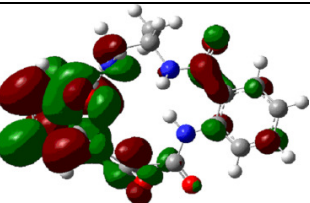
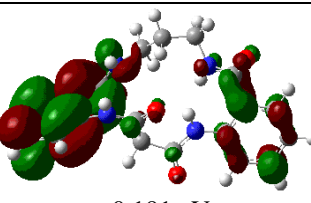
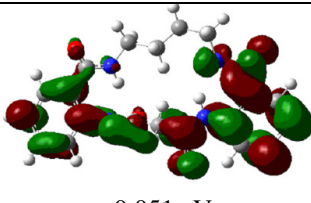
Molecule	9	10	11
HOMO	 -0,236	 -0,327 eV	 -0,241 eV
LUMO	 -0,064	 -0,191 eV	 -0,051 eV

Fig. 2. HOMO and LUMO orbitals of **9**, **10**, and **11** at B3LYP/6-31G+(d,p) level of theory.

From the calculations of the title structures at HF/3-21G(d), HF/6-31+G(d,p), B3LYP/3-21G(d) and B3LYP/6-31+G(d,p) levels of theories, we also found about 1450 cm^{-1} for C=C stretching. According to calculated correlation coefficient values, especially B3LYP/3-21G(d) method is in better agreement with the experimental C=C stretching frequency than others. As can be seen from R^2 values depicted in Tables 1-6, we found good agreement between theory and experiment.

The frontier molecular orbitals (highest occupied molecular orbital-HOMO and lowest unoccupied molecular orbital-LUMO) of chemical species are of prime importance to describe chemical reactivity and stability. It is known that the HOMO-LUMO gap also is a critical parameter for electric, optical and other prosperities of molecular admittance, as well as in UV-Vis spectra and chemical reactions [16-20]. A molecule with a small frontier orbital gap is more polarizable and is

generally associated with a high chemical reactivity, low kinetic stability and is also termed as a soft molecule. Theoretical calculations at B3LYP/6-31+G(d,p) theory of level for structure of **5**, **6**, **7**, **9**, **10** and **11**, are presented for the HOMO-LUMO gap with relevant energies in **Fig 1** and **2**.

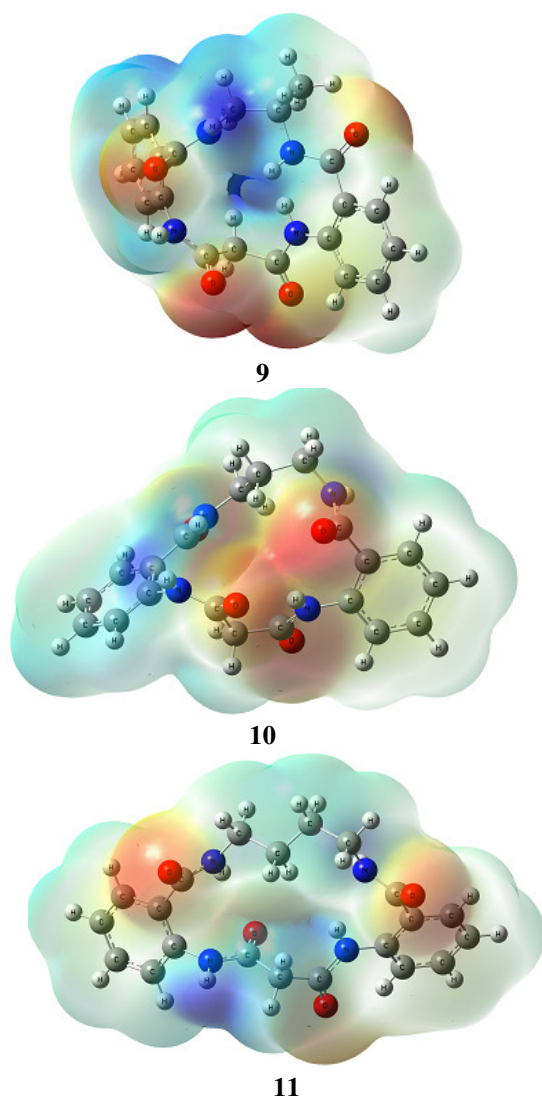


Fig. 3. Molecular electrostatic potential maps of **9**, **10**, and **11** calculated at B3LYP/6-31+G(d,p) level.

It can be easily seen that HOMO of the structures of **5**, **6**, and **7**, are mainly on one benzene ring, whereas lowest unoccupied molecular orbital

(LUMO) of the structures substantially localized on another benzene ring of title molecules. The **6** has the highest HOMO-LUMO gap ($\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$) with 0.185 eV, whereas the lowest one is on the **10** (0.136 eV). The small energy separation means low excitation energies for many of the excited states and low chemical hardness for **10**.

The molecular electrostatic potential (MEP) is used widely for deciding sites molecular reactivity, intermolecular interactions, molecular recognition, nucleophilic reactions, electrophilic attack, and a variety of chemical phenomena as well as hydrogen-bonding interactions [20-22]. Visualization of MEP is a suitable way to explain the charge distribution within a molecule. MEPs of the optimized three local minima of **9**, **10**, and **11**, shown in Fig. 3, were calculated at the B3LYP/6-31+G(d,p) level, respectively. In these figures, *blue* is partial negative (electron rich), and *red* is partial positive (electron deficient). On the other hand, the negative (red and yellow) and the positive (blue) regions in the MEP were related to electrophilic reactivity and nucleophilic reactivity, respectively. As can be seen in the diagrams, the negative regions of the title structures were observed around the N atoms, whereas a maximum positive region is localized on the O atoms for the **9**, **10**, and **11** at the B3LYP/6-31+G(d,p) level in **Fig. 3**.

4. Conclusions

The development of the compounds **5**, **6**, **7**, **9**, **10**, and **11**, is interesting as the search for supramolecular interactions between the solid complex species and covalent molecules and/or counter ions both in solid state and solution is the field of current importance [23-25]. Experimental and theoretical vibrational analyses of **5**, **6**, **7**, **9**, **10**, and **11**, have also been performed for the first time. Calculated vibrational frequencies have been compared with that obtained from the experimental IR spectrum. Experimental fundamentals are found to have slightly a better correlation for DFT than for HF method.

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6. References

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