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Carbene→N^+ Coordination Bonds in Drugs: A Quantum Chemical Study

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Abstract. Coordination chemistry of bonds between main group elements and electron donating ligands as in L→E (where E is electron acceptor centre like C^0, Si^0, N^1, P^1, As^1, B^1 and L is an electron donating N-heterocyclic carbene) has been recently gaining attention. Many important drugs have nitrogen atom as an electron acceptor center and can be represented by two general formulae: $(L{\rightarrow}N{\leftarrow}L)^{\oplus}$ and L→N-R. Divalent N^1 compounds possess two lone pairs at central nitrogen and low nucleophilicity associated with them is found to be of importance. In this article, electronic structure analysis of drug molecules like picloxydine, chlorhexidine, and moroxydine was performed at B3LYP/6-311++G(d,p) level of theory. Evaluation of electron localization function (ELF), molecular orbitals, charge density, nucleophilicity, proton affinity and complexation energy estimation confirms the presence of coordination bonds $(L{\rightarrow}N{\leftarrow}L)^{\oplus}$ in the above mentioned drug molecules in their cationic state. Further, electronic structure analysis of drugs like clonidine, apraclonidine, brimonidine and xylazine indicated the presence of electronic structure similar to L→N-R systems.

Keywords. Divalent N^1 compounds; Coordination bonds; Main group elements; Biguanides; Drugs; DFT.

1. Introduction

Main group elements are known to form covalent bonds by sharing of electrons. Coordination bond among main group elements represented by the general formula L→E, is a very latest concept, which led to interrogation of bonding environment in many novel compounds.[1,2] This exploration using combined theoretical and experimental studies led to the identification of C^0 (**I**) systems which are known as carbones.[3] Such carbon centers are characterized by the presence of two lone pairs of electrons and high nucleophilicity. Similarly boron systems were reported, which carry boron in B^1 (**II**) state with one lone pair of electrons and are known as borylenes,[4] such boron systems behave as Lewis bases. On the similar lines, Si^0, Ge^0 and Sn^0 systems were also reported to carry such unusual bonding environment.[5] More intriguing are compounds with $(L{\rightarrow}E{\leftarrow}L)^{\oplus}$ (**III**) where E is an element of group V.[6,7] Compounds with L→E-E←L (**IV**) are also known (Figure 1).[8]

Divalent N^1 compounds named as nitreones were identified by our research group as novel compounds, which carry this unusual electronic character at central 'N' and can be represented by the general formula $(L{\rightarrow}N{\leftarrow}L)^{\oplus}$.[9,10] Divalent N^1 compounds are characterized by the presence of a central nitrogen atom, which accepts electron density from strong electron donating ligands like CO, N_2, PR_3, cyclic (alkyl)(amino)carbene (CAAC), N-heterocyclic carbenes (NHC), *etc*. Similarly, dinitrogen systems coordinated with two electron donating ligands L→N-N←L (**VIII**) were studied theoretically and experimentally.[8c,11] The central nitrogen atom of these species carries two lone pairs of electrons, low nucleophilicity and low oxidation state of 1. Structure **V** represents $(L\text{-}N\text{-}L)^+$ system with imidazol-2-ylidene as ligand, whereas **VI** and **VII** are (L→N-R) class of compounds with hidden divalent N^1 character.[12,13] Besides their applications in traditional organic chemistry (phase transfer catalysis and organocatalysis),[10c,14] study of these compounds becomes important from medicinal chemistry perspective. Most of the drugs containing biguanide exhibit therapeutic action in their cationic state. In their cationic state, these drugs were found to possess divalent N^1 character. One of the reasons for their applicability in medicinal chemistry is the low nucleophilicity shown by these

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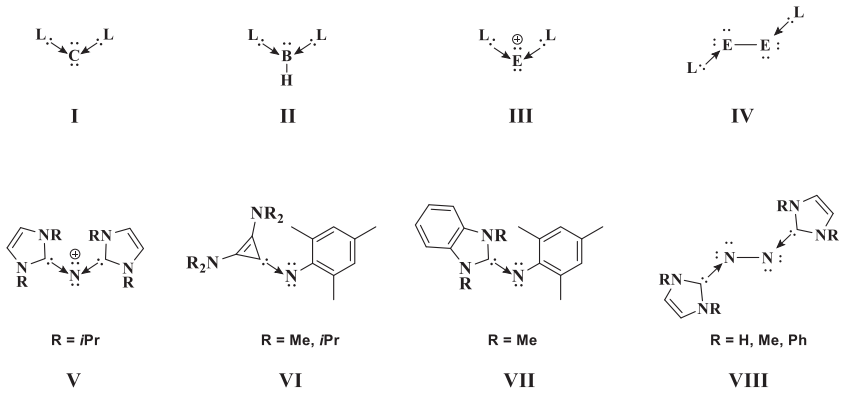

Figure 1. Representative structures of the compounds with L→E coordination bonds, where E = C, Si, N, P, Ge.

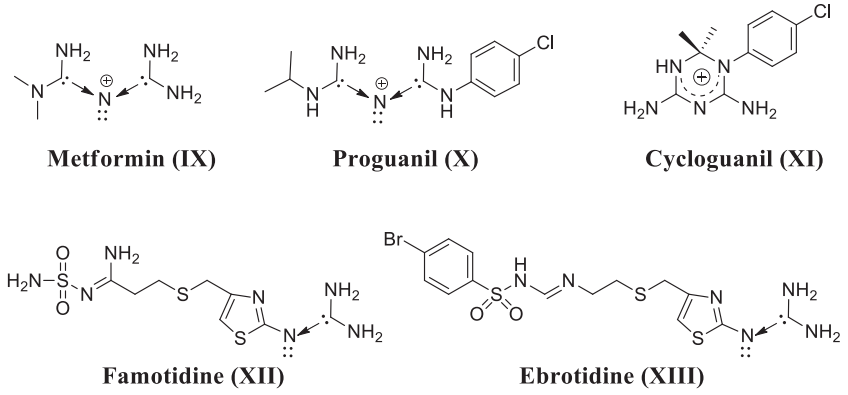

Figure 2. Structure of the drugs with reported divalent N^I character.

compounds despite having two lone pairs on central nitrogen. Hydrochloride salts of many drug molecules such as metformin (**IX**), proguanil (**X**), cycloguanil (**XI**), have been proven to posses divalent N^1 character, whereas famotidine (**XII**) and ebrotidine (**XIII**) were found to exhibit L→N-R system in their neutral state (Figure 2).[9g,11] Bharatam *et al*., recently observed divalent N^1 character in the therapeutically important species containing bis(azole)amines and showed that the molecular modeling of these species in their divalent N^1 state leads to better correlation with experimental studies.[9c] Thus, the nature of 'N' in these type of species is unique and the properties of molecules containing divalent N^1 nitrogen are expected to be distinct from compounds with classical 'N' atom. Hence, in this context, it became necessary to identify the appropriate electronic nature of the compounds so as to establish the proper pharmacophoric features.

Moroxydine (**1**) is an antiviral agent[15] whereas picloxydine (**2**) and chlorhexidine (**3**) are antibacterial agents (Figure 3).[16,17] All these compounds are biguanide derivatives very similar to metformin. These four compounds are known to show their therapeutic action in their corresponding salt form and they are marketed as their HCl salts for improved oral bioavailability. In our previous work, it was established that metformin and cycloguanil carry divalent N^1 character as in **III**.[9g] These three drug molecules, **1**, **2** and **3** may also carry divalent N^1 character in their salt form. Similarly, drugs like clonidine,[18] apraclonidine,[19] brimonidine[20] and xylazine[21] are also expected to show divalent N^1 character in their neutral state. Clonidine (**4**) is an antihypertensive agent[18] whereas apraclonidine (**5**) and brimonidine (**6**) are used for the treatment of glaucoma.[19,20] Xylazine (**7**) is used as veterinary anaesthetic.[21] In this article, quantum chemical calculations were carried out to explore the L→N coordination bonds. The results are compared with the already reported divalent N^1 compounds and compounds with hidden divalent N^1 character.

2. Computational details

Density Functional (DFT) calculations were carried out using the Gaussian09 package.[22] Geometry optimizations were carried out using Becke–Lee–Yang–Parr (B3LYP) level of theory with 6-311++G(d,p) basis set[23] on various tautomers, isomers and corresponding protonated states. Frequencies were computed analytically for all the optimized species to characterize each stationary point as a minimum or

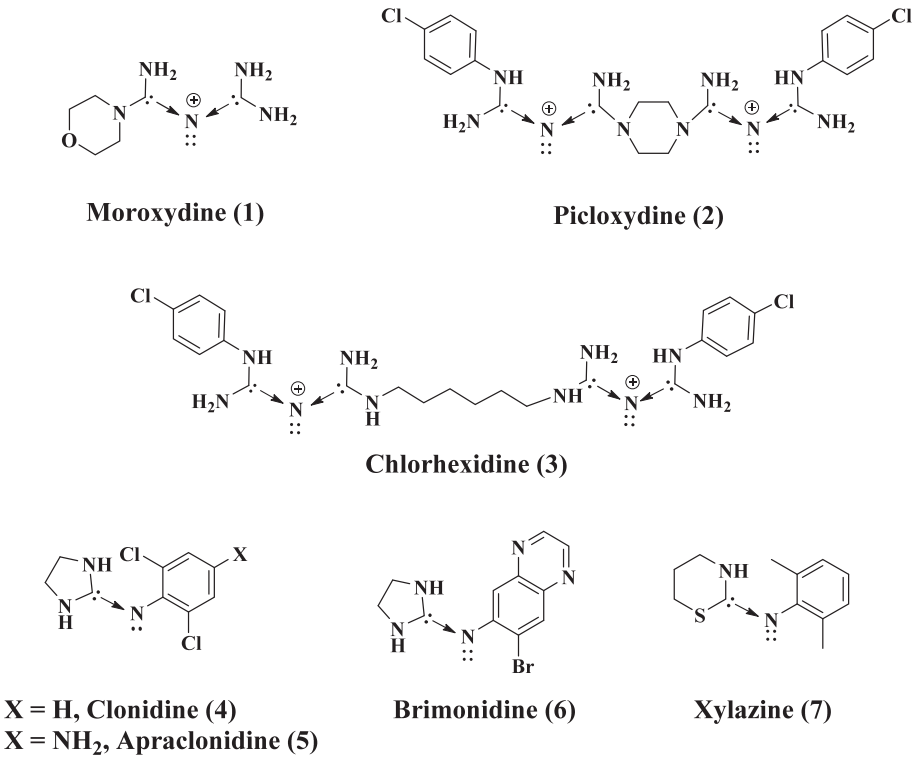

Figure 3. Structures of the drug molecules **1–7** considered in this study.

a transition state. Gibbs free energy was calculated for all the optimized structures. Natural Bond Orbital (NBO)[24] analysis was also carried out to estimate the partial atomic charges. To confirm the basicity of the central nitrogen atom, absolute proton affinity (APA) values were estimated in gas phase using eq. 1.

$$\mathrm{APA} = H_{298}(\mathrm{B}) + H_{298}(\mathrm{H}^+) - H_{298}(\mathrm{BH}^+) \quad (1)$$

Where, H_{298} is the enthalpy of the free base (B), its conjugate acid (BH^+), and the proton (H^+) at 298.15 K. ELF (Electron Localization Function)[25] calculations were performed using Multiwfn software[26] to evaluate the extent of electron density localization on central nitrogen atom. Complexation energies with AuCl were also estimated for the protonated state. The AuCl coordination chemistry was explored using mixed basis set 6-311++G(d,p) plus def2-TZVPP[27] where Au is treated with def2-TZVPP basis set with associated effective core potential, while rest of the molecule is optimized using 6-311++G(d,p). Nucleophilicity index (N) was estimated using the formula recently reported by Domingo *et al.*: $N_b = E_{\mathrm{HOMO(Nu)}} - E_{\mathrm{HOMO(TCE)}}$; where tetracyanoethylene (TCE) was chosen as reference. The local nucleophilicity index was calculated using $N_k^- = N_b * F_k^-$; where F_k^- is Fukui function at a given atomic center.[28]

3. Results and Discussion

3.1 *Tautomerism Studies*

Compounds **1–7** were evaluated for the possible tautomers on the potential energy surface (PES). The relative Gibbs free energy values (ΔG_T) for the global minimum structure (**a**) and its nearest amine isomer (**b**) with 3D structures are given in Figure 4. Among the various isomers evaluated, the imine form was found to be the global minimum (~1.00 to 23.00 kcal/mol) at B3LYP/6-311++G(d,p) level of theory. For compounds **1**, **2** and **3**, the tautomeric energy difference (ΔG_T) was found to be 10.82, 23.59 and 17.80 kcal/mol, respectively in favour of imine tautomer. Similarly, the difference between imine and amine tautomer for compounds **4**, **5**, **6** and **7** was found to be 7.13, 5.55, 3.38 and 1.18 kcal/mol, respectively (Figure 4). These observations clearly establish that the structures represented by the imine form should be considered for the drug design studies. The optimized structures for compounds **1–3** exhibit almost coplanar rearrangement around the central nitrogen atom (N1). In case of compounds **4–7**, the substituents around N1 nitrogen atom were found to be orthogonal to each other.

The optimized geometries for the most stable structure of **1–3** showed the N1-C1 bond lengths in the

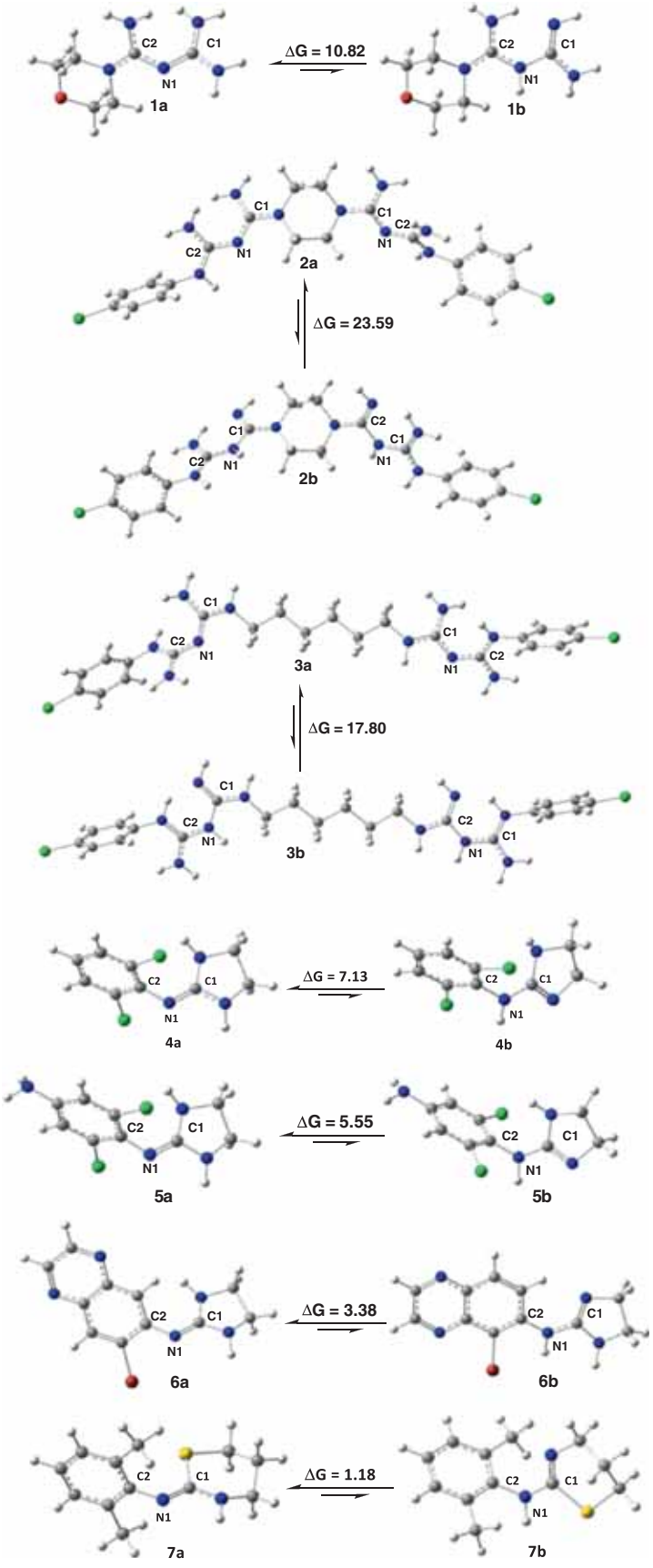

Figure 4. 3D structures of the optimized imine (**1a**–**7a**) and nearest amine forms (**1b**–**7b**) of **1**–**7** identified on the PES, ΔG is in kcal/mol.

range of 1.32 Å, while the N1-C2 bond lengths were in the range of 1.34 Å. Similarly, for compounds **4**–**7**, the N1-C1 bond lengths varied from 1.27 to 1.29 Å, whereas the N1-C2 bond lengths were found to be 1.38 to 1.41 Å (Table 1). In case of compounds **1a**–**3a**, the observed bond lengths are clearly deviating from the regular C=N bond lengths. However, for compounds **4a**–**7a**, N1-C1 bond lengths were comparable to regular C=N bond lengths, while N1-C2 bond lengths were shorter than the regular single bond but longer than the C=N double bond.

3.2 *Divalent N[1] Character*

Patel *et al.*, reported the coordination chemistry of metformin in which the central nitrogen atom is shown to exhibit the N^1 oxidation state with $(L{\rightarrow}N{\leftarrow}L)^{\oplus}$ type of bonding environment.[9i] Similarly, Bruns *et al.*,[13] and Bhatia *et al.*,[12] reported the coordination chemistry of compounds with L→N-R type of bonding environment as represented by the structure **VI** and **VII** (Figure 1). **1a**–**3a** contain diaminocarbene or substituted diaminocarbene interacting with the N1 nitrogen atom. **4a**–**7a** contain imidazole-2-ylidene or thiazine based carbene on one side and substituted phenyl on the other side. The carbene units in the above species can be considered as electron donating ligand designated as L, whereas the non-carbenic *i.e.*, substituted phenyl in **4a**–**7a** can be designated as R. Therefore, the compound **1a**–**3a** and **4a**–**7a** may be envisaged as examples of $(L{\rightarrow}N{\leftarrow}L)^{+}$ and L→N-R system, respectively. Moreover, the observed bond lengths in the optimized geometries are in favor of above mentioned character in the compounds under investigation. Therefore, to explore the potential of divalent N^1 character in **1a**–**7a**, various parameters were evaluated and compared with the established $(L{\rightarrow}N{\leftarrow}L)^{+}$ (**V**) and L→N-R (**VI**) systems.

Table 1. Comparison of observed bond lengths and bond angles of **1a**–**7a** at B3LYP/6-311++G(d,p) level of theory.

Compd. code	Bond length (Å)		Bond angle (°)
	N1-C1	N1-C2	C1-N1-C2
1a	1.32	1.34	126.17
2a	1.32, 1.32	1.34,1.34	125.82, 125.67
3a	1.32,1.33	1.34,1.33	126.10, 126.34
4a	1.28	1.38	121.99
5a	1.28	1.39	120.86
6a	1.28	1.38	121.95
7a	1.27	1.41	123.57
V	1.32	1.32	124.24
VI	1.28	1.41	119.19

3.2a *Molecular Orbital, ELF Analysis and Nucleophilicity*: The unique 'N' atom in divalent N^1 compounds is characterized by the presence of excess partial negative charge which increases with the increase in the electron donating capacity of L.[9g] The excess electronic charge can be demonstrated in the form of two lone pairs, which can be visualized by molecular orbital analysis. The molecular orbital analysis of **1a**–**7a** shows that the central nitrogen (N1) contains both σ-type and π-type of molecular orbitals (Figure 5). The quantitative values for the σ and π electron occupancies at the N1 nitrogen atom of **1a**–**7a** were ~1.71 and ~1.44, respectively (Table 2). However, the σ and π electron occupancy values for **6a** were relatively low.

These values are significantly larger than the σ and π occupancies of divalent C^0 systems but comparable to reported divalent N^1 systems, which indicates strong localization of electrons at the N1 nitrogen.[3f] The calculated NBO charges for **1a**–**7a** are listed in Table 2 and were in comparison to the reported divalent N^1 systems **V** and **VI**. Further, the Electron Localization Function (ELF) analysis confirms the localization of excess electron density at N1 nitrogen of **1a**–**7a** with $V(N^1) \geq$ 3.00e. These values for the electron density are larger than the values for the conventional imine system where it is expected to be 2.00e. The calculated global (N) and local (N_k) nucleophilicity for **1a**–**7a** were found to be in the range of reported divalent N^1 compounds (Table 2). The estimated lower values of global nucleophilicity and comparative higher values of local nucleophilicity for N1 nitrogen in **1a**–**3a** were in accordance with the cationic nature of divalent N^1 systems.

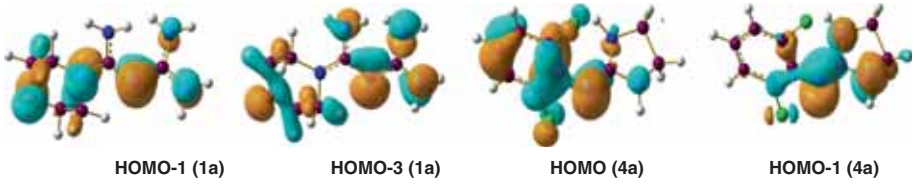

Figure 5. Molecular orbitals corresponding to the two lone pairs on central nitrogen (N1) in **1a** and **4a**. The corresponding molecular orbitals of **2a**, **3a**, **5a**, **6a** and **7a** are given in Figure S1 in supporting information.

Table 2. The comparison of NBO charges, nucleophilicity, lone pair occupancy and Electron Localization Function (ELF) of **1a**–**7a** with established $(L{\rightarrow}N{\leftarrow}L)^+$ (**V**) and L→N-R (**VI**) systems. All the values are in electrons.

S. No.	q_N	N	N_k^-	f_k^-	LP occupancy (σ)	LP occupancy (π)	ELF
1a	−0.637	0.20	0.02	0.11	1.69	1.50	3.10
2a	−0.640	1.43	0.01	0.01	1.75, 1.75	1.47, 1.47	3.12, 3.11
3a	−0.637	0.98	0.02	0.02	1.83, 1.83	1.47, 1.47	3.09, 3.09
4a	−0.584	3.63	0.71	0.20	1.70	1.45	3.00
5a	−0.587	4.30	0.46	0.13	1.70	1.44	3.00
6a	−0.810	3.65	1.50	0.41	1.48	1.22	2.98
7a	−0.564	4.10	0.51	0.13	1.72	1.36	2.81
V	−0.615	0.16	0.03	0.17	1.83	1.47	3.14
VI	−0.605	4.90	0.97	0.20	1.83	1.45	3.24

3.2b *Proton Affinity and Lewis Base Character*: Compounds with $(L{\rightarrow}N{\leftarrow}L)^+$ representations are known to show mild nucleophilicities, while the species with L→N-R representation show relatively high nucleophilicity. In order to quantify the relative electron donating ability in these systems, proton affinity and complexation energy with the Lewis acids like BH_3 and AuCl were calculated at B3LYP/6-311++G(d,p) level of theory. Table 3 lists the gas phase proton affinity (PA) values along with the complexation energies for **1a**–**7a** (the corresponding 3D geometries can be found in the Supporting Information). All the calculated values for PA and complexation energy are comparable to that of reported $(L{\rightarrow}N{\leftarrow}L)^+$ and L→N-R systems. The PA values for **1a**, **2a** and **3a** were 127.75, 139.33 and 193.37 kcal/mol, whereas the PA value for **4a**–**7a** were found to be ∼237 kcal/mol. Similar trend was observed for complexation energies. The free energy change for the complexation of BH_3 and AuCl with **1a**–**3a** were in the range of −10 to −14 and −27 to −44 kcal/mol, respectively. Correspondingly, the free energy change for the complexation of **4a**–**7a** with BH_3 and AuCl were found to be in the range of −25 to −28 and −44 to −47 kcal/mol, respectively (Table 3). The lower PA and complexation values for **1a**–**3a** can be rationalized due to the presence of positive charge on these type of systems, which resists donation of electron to the Lewis acids.[9g]

Table 3. Comparison of proton affinity (PA) and complexation energies E (BH_3 and AuCl) for **1a**–**7a** with established $(L{\rightarrow}N{\leftarrow}L)^+$ (**V**) and L→N-R (**VI**) systems. All the energy values are in kcal/mol.

S. No.	PA	E_{BH3}	E_{AuCl}
1a	−127.75	−11.88	−27.75
2a	−139.33	−10.22	−43.95
3a	−193.37	−14.15	−44.56
4a	−235.17	−25.05	−45.56
5a	−242.05	−26.85	−47.52
6a	−234.36	−24.89	−47.15
7a	−237.71	−28.02	−44.54
V	−127.86	−15.07	−29.78
VI	−257.25	−31.00	−53.92

3.2c *L→N bond strength analysis*: As per the results and discussion in the above sections, all the evaluated parameters indicate the presence of C→N character. However, the valencies for nitrogen and carbon will only be satisfied, when the represented structures are shown with π bonds. Therefore, it is very important to clearly establish the nature of C-N bonds in these types of compounds. If there is a strong π-character in these compounds, they should have orthogonal π bonds, similar to allenes ($R_2C{=}N{=}CR_2$) but the bent shape of these optimized geometries (C1-N1-C2 bond angle ∼125°) evidently rules out this possibility. Further, if there is any traditional π character across these C-N bonds, the rotational barriers should be >30.00 kcal/mol. The rotation barriers of N1-C1 bond for **1a**–**7a** were found to be in the range of ∼4–12 kcal/mol. The rotational barriers for the N1-C2 in case of **1**–**3** were ∼4–12 kcal/mol. The observed rotational barriers clearly confirm the absence of C=N character and presence of C→N in these compounds.

4. Conclusions

Several drugs carry divalent N^1 character, such electronic character has already been established for the drugs like metformin, cycloguanil, famotidine and ebrotidine in their protonated state. In this work, we extended this concept to seven drugs: moroxydine, picloxydine, chlorhexidine, clonidine, apraclonidine, brimonidine and xylazine. An exhaustive electronic structure analyses for these drugs were performed. The tautomeric analysis of **1**–**7** indicated imine form to be the global minimum structure. The NBO analysis indicated localization of excess electron density at the N1

nitrogen center of the preferred tautomer. The excess electron density at N1 nitrogen in these drugs was confirmed through molecular orbital and ELF analysis, which were characterized in the form of two lone pairs. The proton affinity values and complexation energies were in comparison with the reported divalent N^1 systems. Further, the low rotational barriers around N1-C1 in **1a**–**7a** and N1-C2 in **1a**–**3a** confirm the absence of π character in these bonds. Taken together, all these parameters indicate that the drugs moroxydine, picloxydine, chlorohexidine can be classified into $(L\rightarrow N\leftarrow L)^+$ whereas clonidine, apraclonidine, brominidine and xylazine can be classified into L→N-R systems with L→N coordination bonds either in their global minima or highly accessible tautomeric states. The low nucleophilicity of these drugs makes them useful for human consumption. It is worth designing and synthesizing many drugs or leads with this kind of coordination bonds.

Supporting Information (SI)

The absolute free energies for all the optimized structures are provided. 3D-optimized geometries and coordinates of compounds discussed in the text at the B3LYP/6-311++G(d,p) level of theory are given. Molecular orbitals of **2a**, **3a**, **5a**, **6a** and **7a** are also given in Supporting Information, available at www.ias.ac.in/chemsci.

Acknowledgments

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