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Nature of metal–NHC bonds in some potential anticancer $[(NHC(R))_2{\rightarrow}M]^+$ (M = Cu^I, Ag^I, Au^I, R = *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl) complexes

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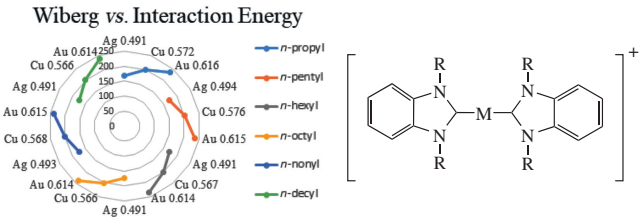
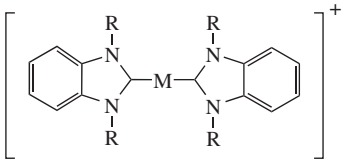
A theoretical study of the structures and nature of the M←C bonds in NHC Cu^I, Ag^I and Au^I cation complexes with two *N*,*N*′-dialkylbenzimidazolin-2-ylidene ligands was performed using natural bond orbital (NBO), atoms in molecules (AIM), energy decomposition analysis (EDA), and extended transition-state natural orbital for chemical valence (ETS-NOCV) analysis. Results demonstrated that the nature of M←C bonds in the complexes is more electrostatic. The complexes studied may be regarded as potentially anticancer agents.



Keywords: N-heterocyclic carbenes, copper complexes, silver complexes, gold complexes, anticancer agents, theoretical studies.

N-Heterocyclic carbenes (NHC) are the neutral two-electron donors which can bond to metal ions in high and low oxidation states, that is performed through σ-donation more than π back-donation.[1–5] Metal–NHC complexes were firstly synthesized by Öfele[6] and Wanzlick[7] almost at the same time in 1968. Lately, metal–NHC complexes have been recognized as a significant research field for developing new metallodrugs due to their high stability and ease of derivatives.[8–14] Recently Haque and his co-workers confirmed that the silver complexes of NHC ligands studied here with general formula $[(NHC(R))_2{\rightarrow}Ag]^+$ (where R = *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl) have *in vitro* anticancer activity against the HCT-116 cancer cell.[15] Also, we have reported several investigations on the structures and nature of metal–NHC bonds in various types of complexes.[16–19]

Herein, a theoretical survey is presented on nature of metal–NHC bonds of group 11 metal ions in coordination with symmetrical unsaturated N-heterocyclic carbenes **1**–**3** with ligands of *N*,*N*′-dialkylbenzimidazolin-2-ylidene type, with *n*-alkyl groups varying from C_3 to C_{10}. The structures of the complexes are optimized at the PBE/def2-SVP level of theory (see Online Supplementary Materials, Figure S1). The minimum and maximum amounts of M←C bond lengths in the complexes are observed around 1.92 and 2.09 Å in copper (**1a**–**h**) and silver (**2a**–**h**) ones, respectively.



1a–**h** M = Cu
2a–**h** M = Ag
3a–**h** M = Au

a R = *n*-C_3H_7 **b** R = *n*-C_4H_9 **c** R = *n*-C_5H_{11} **d** R = *n*-C_6H_{13} **e** R = *n*-C_7H_{15} **f** R = *n*-C_8H_{17} **g** R = *n*-C_9H_{19} **h** R = *n*-$C_{10}H_{21}$

The interaction energies (ΔE_{int}) between the investigated M^+ and ligands pieces in the optimized structures of the complexes were computed at PBE/def2-TZVP//PBE/def2-SVP level of theory, the corrected values having been in the ranges of 200.4–202.2 kcal mol^{-1} for **1a**–**h** (Cu^I), 167.8–173.1 kcal mol^{-1} for **2a**–**h** (Ag^I) and 235.4–237.7 kcal mol^{-1} for **3a**–**h** (Au^I) complexes, respectively (Table 1). The data showed that elongation of the carbon chain of R substituent from *n*-propyl to *n*-decyl caused a slight increase in the quantities of ΔE_{int} in the complexes. For example, the values of ΔE_{int} for compounds **1a** and **1f** are about –200.4 and –202.2 kcal mol^{-1}, respectively. Also, the data revealed that drug releases were slightly facilitated by changing R substituent from *n*-decyl to *n*-propyl (Table 1). The results showed that the interaction energies (ΔE_{int}) of M←C bond in complexes **1**–**3** are substantial and follow the popular V-shaped trend for first, second and third rows of the transition metals as: $Ag^I < Cu^I < Au^I$. The results confirmed that the Ag^I complexes have the smallest and Au^I complexes have the highest levels of metal–ligand interaction strength. Therefore, relative to

Table 1 The corrected interaction energies values (kcal mol^{-1}) for complexes **1**–**3** at the PBE/def2-TZVP//PBE/def2-SVP level of theory.

	Interaction energies		
Alkyl	Cu (**1**)	Ag (**2**)	Au (**3**)
n-propyl	–200.4	–167.8	–235.4
n-butyl	–200.9	–171.0	–235.7
n-pentyl	–201.4	–172.1	–236.4
n-hexyl	–201.7	–172.1	–236.8
n-heptyl	–202.0	–172.8	–237.4
n-octyl	–202.0	–172.9	–237.5
n-nonyl	–201.8	–172.6	–238.2
n-decyl	–202.2	–173.1	–237.7

other complexes studied here, drug releases tend to be best promoted in Ag^I complexes.

The nature of the M←C bonds in complexes **1–3** was studied by NBO analysis. The quantities of the partial charge on the C(carbene) and M^+ metal ions of the M←C bonds and the total charge of the NHC fragments in the complexes were also checked at the PBE/def2-TZVP//PBE/def2-SVP level of theory. The results showed that the natural charges of C(carbene) and M atoms involved in the complexes and the total charge of NHC fragments are positive. Hence, it can be deduced that there is a charge transfer from the $(NHC(R))_2$ fragments, as a Lewis base, to empty orbitals of the M^+ metal ion, as a Lewis acid. Regardless of the changing the R substituents, by changing the M from Cu^I to Au^I, the amount of charge transfer from NHC fragments into the empty orbitals of the M^+ metal ions decreased. This may related to the increase in the values of electrostatic interaction between the M^+ metal ion and NHC fragments in the complexes. The Wiberg bond indices (WBI) for the M←C bonds (M = Cu^I, Ag^I, Au^I) bonds in complexes **1–3** were also compared (Online Supplementary Materials, Table S4). The results showed that the amount of WBI's of M←C bonds are in a good agreement with the interaction energies (ΔE_{int}) and obey the well-known V-shaped trend for the transition metals of the first, second, and third rows in the following order: $Ag^I < Cu^I < Au^I$. Figure 1 represents a good correlation between the calculated and the corresponding Wiberg bond indices for C→M bonds in complexes **1–3**.

A natural hybrid orbital (NHO) analysis was also carried out based on the NBO analysis of the complexes. The data of NHO analysis between the M^+ metal ion and C atoms in C→M bonds in complexes **1–3** (see Online Supplementary Materials, Tables S6–S8) show that the occupancy of C atoms in the latter bonds is about 80% for Cu^I and Ag^I, and 70% for Au^I metal centers. The results verified the existence of σ bonding interaction from NHC as Lewis base to empty orbitals of M^+ metal ion as a Lewis acid in C→M bonds (see Tables S6–S8). In another way, the bond critical points (BCPs) of the M←C bonds in all complexes were also investigated at the PBE/def2-TZVP//PBE/def2-SVP level of theory. The values of $\nabla^2\rho$ and $-G_c/V_c$ have also been utilized to survey the nature of the interaction. As it is displayed in Table S5, the value of the electron density (ρ) of the M←C bonds with the same R substituent is in good agreement with the well-known V-shaped trends that were shown for ΔE_{int}. The results showed a satisfactory correlation between the electron density (ρ) and the corresponding ΔE_{int} as well as WBI's of C→M bonds in $[(NHC(R))_2{\rightarrow}M]^+$ complexes (see Online Supplementary Materials, Figures S2 and S3). The study of the nature of interactions in the complexes revealed that the C→M bonds in complexes **1–3** are almost covalent ($\nabla^2\rho > 0$ and $-G_c/V_c < 1$), see Online Supplementary Materials, Table S5.

The bonding analysis in terms of energy decomposition analysis (EDA) was also performed for the interaction between $[M]^+$ with NHC fragments in the optimized structure of all complexes at the BP86-D3/TZ2P(ZORA)//PBE/def2-SVP level of theory. Data proved that the values for the investigated complexes are very close to those obtained at PBE/def2-TZVP//PBE/def2-SVP. The results of EDA for complexes **1–3** showed that changing in the R substituent from *n*-propyl to *n*-decyl with considering the same metal ion leads to a slight increase in the amounts of interaction energies (see Online Supplementary Materials, Table S10). Also, the values of C→M bonds in complexes **1–3** are substantial and fit with the well-known V-shaped pattern for the transition metals of the first, second and third rows in the following order: $Ag^I < Cu^I < Au^I$.

The EDA results reveal that the most portions of ΔE_{int}, about 57–65%, are assigned to ΔE_{elstat}. Afterward, ΔE_{orb} has a percentage of ~31–37%, and ΔE_{disp}, which came from the instantaneous dipole–induced dipole forces between two pieces, have a small influence (2–5%) on ΔE_{int}.

The covalent bond between the two interacted parts of $[M]^+$ with NHC ligand in the optimized structure of complexes **1–3** can be seen from the calculated deformation densities $\Delta\rho$. The NOCV pairs related to complexes **1–3** contain an average of 82.19–89.56% of ΔE_{orb}. Figure 2 illustrates the critical deformation densities and the related energy amounts for complex **1a** (M = Cu, R = *n*-C_3H_7). Deformation densities for the other complexes are presented in Online Supplementary Materials, Figures S4–S11. As shown in Figure 2, the dominant term of ΔE_{orb} for complex **1a** arises from σ-orbital interactions. In this complex, the profiles of the orbital pairs $\Delta\rho1$ and $\Delta\rho4$ indicate the σ-orbital interactions between the lone pairs of C atoms of NHC fragments and empty orbital of M^+ metal ion as the donor and acceptor, respectively. In other words, the shapes of $\Delta\rho5$ represent the σ-back-donation (σbd) from M^+ metal ion into the NHC fragment in complex **1a**. The results showed that the σ-orbital interactions which account for complex **1a** are 64.38% of the ΔE_{orb} term, and the π donation constitutes 20.36% of ΔE_{orb} term. In this regard, $\Delta\rho2$, $\Delta\rho3$, and $\Delta\rho6$ are attributed to the associated energy stabilization for the π donations (see Figure 2).

In summary, the nature of M←C bonds in carbene cation Cu^I, Ag^I and Au^I complexes **1–3** with two *N*,*N*′-dialkylbenzimidazolin-2-ylidene ligands has been theoretically explored by NBO, AIM, EDA and ETS-NOCV analysis. The results proved that electrostatic energy ΔE_{elstat}) is the most significant energy among the three terms of an energy decomposition analysis within 57–65%. Furthermore, the interactions between C and M atoms of M←C bonds in these complexes are better σ donors rather than π acceptors.

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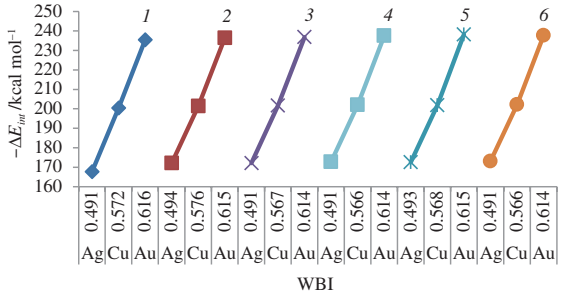

Figure 1 Calculated ΔE_{int} *vs.* Wiberg bond indices (WBI) for C→M bonds of selected Cu^I, Ag^I and Au^I complexes **1–3**: (*1*) R = *n*-C_3H_7, (*2*) R = *n*-C_5H_{11}, (*3*) R = *n*-C_6H_{13}, (*4*) R = *n*-C_8H_{17}, (*5*) R = *n*-C_9H_{19}, (*6*) R = *n*-$C_{10}H_{21}$.

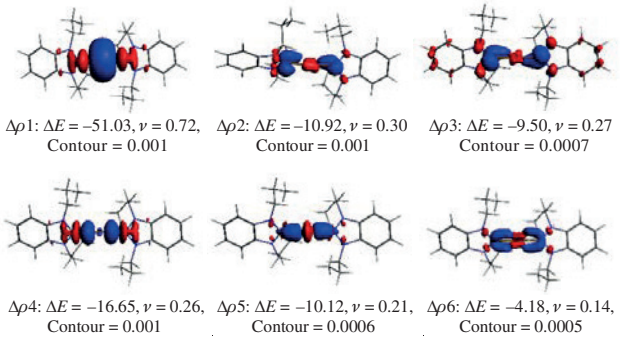

Figure 2 Deformation densities associated with the most important orbital interactions for copper(I) complex **1a** at the BP86-D3/TZ2P(ZORA)//PBE/def2-SVP level of theory.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2021.03.011.

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