Nature of Metal–Drug Bond in Some Antitumor Active Complexes of Coinage Metal Ions

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ABSTRACT: N-Heterocyclic carbene and phosphine can be labeled as solid σ-donor ligands and can contribute to stable complexes. In addition, the constructed complex can accommodate a wide variety of applications, such as pharmaceutical products. In the light of this, a theoretical analysis was carried out on the existence of metal–drug interactions of group 11 metal ions in coordination with symmetrical unsaturated N-heterocyclic carbones [NHC(R)(R′)] and monodentate phosphine (PR₃). The R substitutes on N atoms in NHC and phosphines are identical, and R′ substitutes are located on two noncarbenic carbon atoms (C₄ and C₅) in the heterocycle complexes. All complexes are in general formula, [Tgt → ML] (where M = Cu(I), Ag(I), Au(I), Tgt = 2,3,4,6-tetra-O-acetyl-1-thio-β-d-glucopyranoside, L= [NHC(R)(R′)], and PR₃; R = F, Cl, Br, H, CH₃, C₂H₅, SiH₃, 2,6-disopropylphenyl; R′ = H and Ph) at the PBE-D3/def2-TZVP level of theory. Findings show greater tolerance for the release of drugs in the presence of Ag(I) metal ions than the other metal ions studied here. Applying natural bond orbital (NBO), atoms in molecules (AIMs), energy decomposition analysis (EDA), and extended theory. Findings show greater tolerance for the release of drugs in the presence of Ag(I) metal ions than the other metal ions studied here. Applying natural bond orbital (NBO), atoms in molecules (AIMs), energy decomposition analysis (EDA), and extended theory. Findings show greater tolerance for the release of drugs in the presence of Ag(I) metal ions than the other metal ions studied here. Applying natural bond orbital (NBO), atoms in molecules (AIMs), energy decomposition analysis (EDA), and extended theory.

1. INTRODUCTION

N-Heterocyclic carbones (NHCs), which can be considered as ligands featuring a singlet carbon donor, possess a single lone pair orbital at the carbon atom described as carbon (II). Furthermore, they are also known as potent σ-donor ligands in metal transition complexes.¹−³ Taking this into account, the strong NHC σ-donor properties will contribute to the development of metal–NHC complexes with high chemical and thermal stability.⁴,⁵ Such complexes were initially synthesized by Öfele⁶ and Wanzlick⁷ nearly at the same time in 1968. In addition, in 1991,⁸ the first free carbene has been isolated by Arduengo. Nowadays, metal–NHC complexes have already been known to be a major area of research for the development of new metallodrugs because of their high stability and ease of derivatives. It is worth noting that the biological potential of metal–NHC complexes has been considered to be one of the most important areas in bio-organometallic chemistry.⁹−¹⁹

Regarding this subject, over the last few years, a lot of research has been done, a substantial number of papers have been published, and plenty of metal–transition complexes containing NHC ligands have been identified as possible antitumor products.¹⁰−¹⁶,¹⁸,²¹−²⁴ Cisplatin and other platinum species have also been used in clinics considered effective anticancer medicines. The side effects, however, prompted scientists to look for new anticancer medicines. Recently, nonplatinum medications have gained a great deal of coverage as cancer chemotherapy to discover novel therapies of efficacy and clinical profiles.²⁰−²² By virtue of the fact that the NHCs have potent σ-donating potential to be bound to metal ions like phosphine, N-heterocyclic carbene complexes have been considered as good alternatives to phosphines.²³ In addition, imidazolium salt precursors are also more easily synthesized compared to phosphines. In addition, when NHC ligands and other metal ions are combined, the consequence is an interesting biological profile. In comparison, there seems to be a different process for metal–NHC complexes than platinum-based drugs that can hardly reach DNA.²⁰,²²−²⁵

On the other hand, tertiary phosphines (PR₃) are accessible ligands of numerous transition metals and nontransitional metal ions. By making modifications in R groups, the electronic and...
steric properties of phosphines can be modified systematically and consistently. In contrast to amines, phosphines are administered with unmatched features; that is, they act as π acids. Additionally, phosphine ligands can stabilize transition-metal ions in low oxidation states. A number of theoretical studies on the structure and function of metal ligand bonding in transition metals and nontransitional NHC complexes have recently been published.

In this content, for the first time, a comparative theoretical study on the effects of changing ligands (N-heterocyclic carbenes NHCC(R)(R′) and monodentate phosphine PR3) and also metal ions [Cu(I), Ag(I), Au(I)] on drug release and the nature of the metal–drug bond in some antitumor active complexes of coinage metal ions with N-heterocyclic carbenes [NHCC(R)(R′)] and monodentate phosphine (PR3) with general formula [Tgt → ML], [M = Cu(I), Ag(I), Au(I)] Tgt = 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside; R = F, Cl, Br, H, CH3, C2H5, SiH3, 2,6-diisopropylphenyl; R′ = H and Ph] at the PBE-D3/def2-TZVP level of theory is reported. In addition, R′ substitutes are given on two noncarbenic carbon atoms (C4 and C5) in NHC.

2. COMPUTATIONAL DETAILS

In this study, the [Tgt → Au(IPr)]]IPr = bis-(2,6-diisopropylphenyl)-imidazolin-2-ylidene] complex was applied using eight density functional methods, namely, B3LYP, BLYP, BP86, Cam-B3LYP, M06, M05-2X, M06-2X, and PBE in combination with D3 dispersion corrections is examined. Furthermore, the obtained structural results were compared with the equivalent experimental values gained by the X-ray structure.

Results obtained using rms methodological findings suggest that PBE-D3, the most relevant function of the above-mentioned methods, has the largest association between quantitative and experimental structural data (see Table 1).

Table 1. Comparison between the Performances of Eight Density Functional Methods of Au–C and Au–S Bond Lengths (Å) of [Tgt → Au(NHC(2,6-Diisopropyl Phenyl))] Complex

| method      | Au–C (Å) | Au–S (Å) | rms  |
|-------------|----------|----------|------|
| B3LYP-D3    | 2.027    | 2.328    | 0.040|
| BLYP-D3     | 2.032    | 2.343    | 0.051|
| BP86-D3     | 2.022    | 2.313    | 0.031|
| CAM-B3LYP-D3| 2.016    | 2.318    | 0.030|
| M06-D3      | 2.026    | 2.333    | 0.043|
| M05-2X-D3   | 2.004    | 2.309    | 0.020|
| M06-2X-D3   | 2.047    | 2.341    | 0.057|
| PBE-D3      | 2.008    | 2.314    | 0.025|
| Exp         | 1.986    | 2.287    |        |

“Data derived from ref 29.

In this article, three types of complexes are reported with the formulas [Tgt → MNHC(R)(R′)] and [Tgt → MP(R3)], [M = Cu(I), Ag(I), Au(I); R = F, Cl, Br, H, CH3, C2H5, SiH3, 2,6-diisopropylphenyl; R′ = H and Ph]. Additionally, these substituents are given in the heterocycle (C4 and C5) on two noncarbenic carbon atoms (see Scheme 1). All calculations were carried out at the PBE-D3/def2-TZVP level of theory using the GAUSSIAN 09 software. The vibrational frequency study reveals that the optimized structures at stationary points, determined at the same theoretical level, correspond to the local minima with no imaginary frequency.

In order to obtain bond properties, the AIM 2010 package was used. To perform AIM calculations, wave function files were generated from Gaussian output files at the PBE-D3/def2-TZVP level of theory.30

In this context, the objective was to conduct a natural bond orbital (NBO) analysis31 with the GAUSSIAN 09 internal module at the theoretical level described above. Energy decomposition analysis (EDA) measurements have been carried out to evaluate the nature of the bonding of S → M at the BP86-D3/TZ2P (ZORA)/PBE-D3/def2-TZVP level of theory using the ADF 2009.01 software package.

3. RESULTS AND DISCUSSION

3.1. Structural Studies. Figures 1−3 display the optimized configurations of [Tgt → MNHC(R)(R′)] and [Tgt → MPR3] [M = Cu(I), Ag(I), Au(I); R = F, Cl, Br, H, CH3, C2H5, SiH3, 2,6-diisopropylphenyl; R′ = H and Ph] as these substituents are given on two noncarbenic carbon atoms (C4 and C5) in the heterocycle complexes at the PBE-D3/def2-TZVP level of theory. As can be seen in Figures 1−3 and Table S1, the length of the M ← S bond is larger than the length of the M ← C bond in the [Tgt → MNHC(R)(R′)] complexes, with different substituents. For example, in [Tgt → CuNHC(H)(H)] the value of M ← S and M ← C bonds is 2.17 Å and 1.89 Å, respectively. In addition, by changing the substituent R from F to Br, the bond lengths of M ← S and M ← C are slightly increased (see Figure 1−3 and Table S1).

On the other hand, by changing the R substituent from F to Br, in [Tgt → MPR3] complexes which are similar to M ← S and M ← C bond lengths in [Tgt → MNHC(R)(R′)] complexes,

M = Cu, Ag, Au
R = H, F, Cl, Br, CH3, C2H5, SiH3, 2,6-diisopropylphenyl
R′ = H, Ph

Scheme 1. Schematic Representation of the [Tgt → MNHC(R)(R′)] and [Tgt → MP(R3)] Complexes [M = Cu(I), Ag(I), Au(I); R = F, Cl, Br, H, CH3, C2H5, SiH3, 2,6-Diisopropylphenyl; R′ = H and Ph]
the value of the $M \leftarrow P$ bond length also increased marginally (see Figure 1−3 and Table S1).

Eventually, the minimum values of $M \leftarrow C$ and $M \leftarrow S$ bond lengths in $[\text{Tgt} \rightarrow \text{MNHC}(R)(R')]$ complexes are observed in
Figure 2. Optimized structures of $[\text{Tgt} \rightarrow \text{MP}(\text{R})]_3$ $[\text{M} = \text{Cu(I)}, \text{Ag(I)}, \text{Au(I)}; \text{R} = \text{F, Cl, Br, H, CH}_3, \text{C}_2\text{H}_5, \text{SiH}_3, 2,6\text{-diisopropylphenyl}]$ complexes of the investigated here at the mentioned level of theory.
Figure 3. Optimized structures of $[\text{Tgt} \rightarrow \text{MNHC(R)}(\text{Ph})]$ $[\text{M} = \text{Cu(I)}, \text{Ag(I)}, \text{Au(I)}; \text{R} = \text{F, Cl, Br, H, CH}_3, \text{SiH}_3, 2,6$-$\text{diisopropylphenyl}; \text{R'} = \text{Ph}]$ complexes of the investigated here at the mentioned level of theory.
Table 2. Corrected $\Delta E_{\text{int}}$ (kcal mol$^{-1}$) Considering the BSSE Values for [Tgt $\rightarrow$ M-NHC(R)(R')] and [Tgt $\rightarrow$ M{P(R)3}] [M = Cu(I), Ag(I), Au(I); R = F, Cl, Br, H, CH$_3$, SiH$_3$, 2,6-Diisopropylphenyl; R' = H and Ph] at the PBE-D3/def2-TZVP Level of Theory

| R         | M        | [Tgt $\rightarrow$ CuNHC(R)(H)] | [Tgt $\rightarrow$ CuP(R)3] | [Tgt $\rightarrow$ CuNHC(R)(Ph)] |
|-----------|----------|---------------------------------|-----------------------------|----------------------------------|
|           |          | $\Delta E_{\text{int}}$ (kcal mol$^{-1}$) | $\Delta E_{\text{int}}$ (kcal mol$^{-1}$) | $\Delta E_{\text{int}}$ (kcal mol$^{-1}$) |
| H         | Cu       | $-156.89$                        | $-162.81$                    | $-150.11$                        |
|           | Ag       | $-145.66$                        | $-154.45$                    | $-136.05$                        |
|           | Au       | $-161.74$                        | $-173.07$                    | $-152.30$                        |
| F         | Cu       | $-157.34$                        | $-179.49$                    | $-150.27$                        |
|           | Ag       | $-149.05$                        | $-170.88$                    | $-136.05$                        |
|           | Au       | $-166.37$                        | $-192.99$                    | $-158.97$                        |
| Cl        | Cu       | $-155.84$                        | $-171.31$                    | $-147.79$                        |
|           | Ag       | $-148.69$                        | $-161.94$                    | $-137.03$                        |
|           | Au       | $-161.57$                        | $-181.02$                    | $-155.15$                        |
| Br        | Cu       | $-156.20$                        | $-169.50$                    | $-148.85$                        |
|           | Ag       | $-147.74$                        | $-157.00$                    | $-138.79$                        |
|           | Au       | $-159.65$                        | $-177.78$                    | $-156.28$                        |
| CH$_3$    | Cu       | $-153.68$                        | $-151.27$                    | $-148.35$                        |
|           | Ag       | $-145.03$                        | $-140.36$                    | $-137.93$                        |
|           | Au       | $-159.07$                        | $-154.07$                    | $-150.39$                        |
| SiH$_3$   | Cu       | $-155.92$                        | $-153.35$                    | $-145.74$                        |
|           | Ag       | $-144.89$                        | $-142.61$                    | $-135.08$                        |
|           | Au       | $-161.70$                        | $-158.65$                    | $-151.16$                        |
| 2,6-diisopropyl phenyl | Cu | $-148.03$                        | $-133.06$                    | $-145.13$                        |
|           | Ag       | $-137.22$                        | $-124.87$                    | $-134.06$                        |
|           | Au       | $-154.13$                        | $-138.05$                    | $-149.00$                        |
| C$_2$H$_5$ | Cu     | $-148.55$                        | $-136.38$                    | $-151.45$                        |

$\Delta E_{\text{int}} = E_{\text{AB}} - (E_{\text{A}}^A + E_{\text{B}}^B)$

From this perspective, it should be said that $E_{\text{AB}}$ represents the electrical energy of [Tgt $\rightarrow$ MNHC(R)(R')] and [Tgt $\rightarrow$ MPR$_3$] complexes and $E_{\text{A}}^A$ and $E_{\text{B}}^B$ represent the electrical energies of the two interactive fragments in the optimized structure of the complexes. Uncorrected $\Delta E_{\text{int}}$ for all complexes is shown in Table S5.
Table 3. WBIs of M–C and M–S Bonds and Natural Charges of M and S Atoms and [Tgt]− Fragment in [Tgt → MNHC(R)(R')] and [Tgt → MP(R)], [M = Cu(I), Ag(I), Au(I); R = F, Cl, Br, H, CH₃, SiH₃, 2,6-Diisopropylphenyl; R' = H and Ph] Complexes at the PBE-D3/def2TZVP Level of Theory

| R          | M      | WBI M–C | WBI M–S | M    | [Tgt]− | S    | WBI M–P | WBI M–S | M    | [Tgt]− | S    | WBI M–C | WBI M–S | M    | [Tgt]− | S    |
|------------|--------|---------|---------|------|--------|------|---------|---------|------|--------|------|---------|---------|------|--------|------|------|
| H          | Cu     | 0.629   | 0.686   | 0.293| −0.533 | −0.302| 0.615   | 0.773   | 0.242| −0.240 | −0.355| 0.627   | 0.703   | 0.297| −0.528 | −0.303|
| Ag         | 0.555  | 0.635   | 0.286   | −0.531| −0.320 |      | 0.495   | 0.681   | 0.308| −0.204 | −0.392| 0.546   | 0.674   | 0.269| −0.517 | −0.307|
| Au         | 0.646  | 0.693   | 0.186   | −0.450| −0.248 |      | 0.610   | 0.729   | 0.156| −0.257 | −0.320| 0.654   | 0.715   | 0.159| −0.423 | −0.240|
| F          | Cu     | 0.606   | 0.749   | 0.329| −0.489 | −0.293| 0.783   | 0.819   | 0.099| −0.329 | −0.339| 0.660   | 0.739   | 0.330| −0.499 | −0.297|
| Ag         | 0.493  | 0.663   | 0.318   | −0.511| −0.305 |      | 0.658   | 0.714   | 0.169| −0.297 | −0.373| 0.505   | 0.702   | 0.302| −0.497 | −0.301|
| Au         | 0.631  | 0.730   | 0.221   | −0.413| −0.228 |      | 0.773   | 0.732   | 0.051| −0.325 | −0.315| 0.632   | 0.754   | 0.184| −0.390 | −0.220|
| Cl         | Cu     | 0.629   | 0.721   | 0.310| −0.497 | −0.289| 0.621   | 0.799   | 0.247| −0.181 | −0.335| 0.624   | 0.731   | 0.314| −0.500 | −0.290|
| Ag         | 0.505  | 0.647   | 0.284   | −0.498| −0.299 |      | 0.478   | 0.695   | 0.312| −0.154 | −0.373| 0.516   | 0.683   | 0.273| −0.497 | −0.297|
| Au         | 0.653  | 0.725   | 0.188   | −0.410| −0.224 |      | 0.644   | 0.744   | 0.150| −0.198 | −0.290| 0.652   | 0.749   | 0.146| −0.387 | −0.215|
| Br         | Cu     | 0.619   | 0.706   | 0.304| −0.479 | −0.290| 0.592   | 0.792   | 0.279| −0.132 | −0.329| 0.617   | 0.703   | 0.304| −0.490 | −0.292|
| Ag         | 0.499  | 0.637   | 0.270   | −0.476| −0.298 |      | 0.459   | 0.703   | 0.302| −0.132 | −0.349| 0.511   | 0.648   | 0.260| 0.484  | −0.299|
| Au         | 0.644  | 0.721   | 0.173   | −0.408| −0.219 |      | 0.626   | 0.744   | 0.166| −0.143 | −0.280| 0.646   | 0.720   | 0.123| −0.384 | −0.216|
| CH₃        | Cu     | 0.614   | 0.682   | 0.281| −0.548 | −0.307| 0.642   | 0.731   | 0.188| −0.335 | −0.373| 0.619   | 0.710   | 0.286| −0.526 | −0.299|
| Ag         | 0.522  | 0.632   | 0.259   | −0.529| −0.310 |      | 0.515   | 0.637   | 0.239| −0.297 | −0.397| 0.523   | 0.651   | 0.269| −0.520 | −0.307|
| Au         | 0.642  | 0.699   | 0.128   | −0.432| −0.229 |      | 0.636   | 0.708   | 0.055| −0.376 | −0.315| 0.646   | 0.731   | 0.123| −0.412 | −0.230|
| SiH₃       | Cu     | 0.604   | 0.694   | 0.309| −0.521| −0.304| 0.499   | 0.757   | 0.202| −0.192 | −0.368| 0.617   | 0.731   | 0.304| −0.501 | −0.290|
| Ag         | 0.490  | 0.627   | 0.274   | −0.510| −0.314 |      | 0.385   | 0.678   | 0.341| −0.165 | −0.388| 0.507   | 0.672   | 0.272| −0.496 | −0.299|
| Au         | 0.637  | 0.713   | 0.145   | −0.406| −0.219 |      | 0.537   | 0.777   | 0.127| −0.247 | −0.284| 0.646   | 0.743   | 0.131| −0.389 | −0.217|
| 2,6-diisopropyl phenyl | Ag     | 0.499   | 0.640   | 0.254| −0.512| −0.316| 0.339   | 0.624   | 0.234| −0.540 | −0.427| 0.451   | 0.643   | 0.279| −0.500 | −0.317|
| Au         | 0.639  | 0.747   | 0.092   | −0.395| −0.211 |      | 0.545   | 0.756   | −0.006| −0.404 | −0.298| 0.626   | 0.742   | 0.134| −0.402 | −0.212|
| C₂H₅      | Cu     | 0.641   | 0.730   | 0.177   | −0.345 | −0.376 |      | 0.507   | 0.613   | 0.225 | −0.319 | −0.411 | 0.643   | 0.703   | 0.036 | −0.404 | −0.323 |
Table 4. EDA\textsuperscript{a} Analysis (BP86-D3/TZ2P(ZORA)//PBE-D3/def2-TZVP) of the [Tgt \to MNHC(R)(R')] and [Tgt \to MP(R)\textsubscript{3}] Complexes [M = Cu(I); R = F, Cl, Br, H, CH\textsubscript{3}, C\textsubscript{2}H\textsubscript{5}, SiH\textsubscript{3}, 2,6-Diisopropylphenyl; R' = H and Ph]

| R          | \[Tgt \to CuNHC(R)(H)] \Delta E | \[Tgt \to CuP(R)\textsubscript{2}] \Delta E | \[Tgt \to CuNHC(R)(Ph)] \Delta E |
|------------|---------------------------------|---------------------------------|---------------------------------|
| H          | \(-161.86\)                      | \(-168.07\)                      | \(-155.73\)                     |
|            | \(105.91\)                      | \(104.27\)                      | \(106.93\)                      |
|            | \(-188.69\) \(70.50\%)         | \(-190.64\) \(70.0\%)          | \(-180.96\) \(68.90\%)         |
|            | \(-69.5\) \(26.00\%)           | \(-73.47\) \(27.0\%)           | \(-69.76\) \(26.56\%)          |
|            | \(-9.58\) \(3.60\%)            | \(-8.22\) \(3.1\%)             | \(-11.94\) \(2.51\)            |
|            | \(-34.52\)                      | \(-43.14\)                      | \(-35.00\)                      |
|            | \(-23.40\)                      | \(-15.72\)                      | \(-22.12\)                      |
|            | \(-10.43\)                      | \(-10.50\)                      | \(-11.50\)                      |
| F          | \(-162.61\)                     | \(-186.72\)                     | \(-155.63\)                     |
|            | \(95.31\)                       | \(105.00\)                      | \(96.68\)                       |
|            | \(-181.21\) \(70.30\%)         | \(-199.01\) \(68.3\%)          | \(-174.35\) \(69.10\%)         |
|            | \(-70.02\) \(27.20\%)          | \(-83.20\) \(28.6\%)           | \(-69.90\) \(27.70\%)          |
|            | \(-6.69\) \(2.60\%)            | \(-9.51\) \(3.3\%)             | \(-8.07\) \(3.20\%)            |
|            | \(-37.20\)                      | \(-47.92\)                      | \(-36.40\)                      |
|            | \(-24.43\)                      | \(-23.00\)                      | \(-24.25\)                      |
|            | \(-9.40\)                       | \(-12.14\)                      | \(-10.25\)                      |
| Cl         | \(-160.32\)                     | \(-177.17\)                     | \(-153.55\)                     |
|            | \(99.46\)                       | \(106.68\)                      | \(98.61\)                       |
|            | \(-181.87\) \(70.00\%)         | \(-192.37\) \(67.8\%)          | \(-173.02\) \(68.62\%)         |
|            | \(-69.10\) \(26.60\%)          | \(-81.46\) \(28.7\%)           | \(-69.19\) \(27.44\%)          |
|            | \(-8.11\) \(3.40\%)            | \(-10.02\) \(3.6\%)            | \(-9.95\) \(3.95\%)            |
|            | \(-35.61\)                      | \(-47.09\)                      | \(-34.65\)                      |
|            | \(-22.55\)                      | \(-21.15\)                      | \(-23.18\)                      |
|            | \(-9.92\)                       | \(-11.35\)                      | \(-8.16\)                       |
| Br         | \(-161.51\)                     | \(-175.32\)                     | \(-155.55\)                     |
|            | \(104.57\)                      | \(107.81\)                      | \(103.22\)                      |
|            | \(-184.49\) \(69.4\%)          | \(-190.63\) \(67.4\%)          | \(-175.86\) \(67.96\%)         |
|            | \(-71.85\) \(27.0\%)           | \(-81.55\) \(28.8\%)           | \(-71.34\) \(27.57\%)          |
|            | \(-9.73\) \(3.7\%)             | \(-10.96\) \(3.9\%)            | \(-11.56\) \(4.4\%)            |
|            | \(-34.50\)                      | \(-47.17\)                      | \(-30.80\)                      |
|            | \(-26.16\)                      | \(-17.59\)                      | \(-25.19\)                      |
|            | \(-11.91\)                      | \(-11.57\)                      | \(-10.47\)                      |
| CH\textsubscript{3} | \(-157.72\)                     | \(-154.84\)                     | \(-154.42\)                     |
|            | \(103.39\)                      | \(107.08\)                      | \(107.41\)                      |
|            | \(-185.41\) \(71.00\%)         | \(-182.54\) \(69.7\%)          | \(-177.48\) \(67.79\%)         |
|            | \(-64.87\) \(24.9\%)           | \(-69.66\) \(26.6\%)           | \(-69.38\) \(26.50\%)          |
|            | \(-10.83\) \(4.2\%)            | \(-9.72\) \(3.8\%)             | \(-14.96\) \(5.7\%)            |
|            | \(-32.76\)                      | \(-41.04\)                      | \(-34.94\)                      |
|            | \(-19.71\)                      | \(-13.73\)                      | \(-22.12\)                      |
|            | \(-11.74\)                      | \(-10.61\)                      | \(-12.74\)                      |
| SiH\textsubscript{3} | \(-160.25\)                     | \(-156.51\)                     | \(-151.68\)                     |
|            | \(99.97\)                       | \(104.82\)                      | \(102.48\)                      |
|            | \(-181.85\) \(69.9\%)          | \(-180.74\) \(69.0\%)          | \(-172.14\) \(67.73\%)         |
|            | \(-67.44\) \(26.0\%)           | \(-71.24\) \(27.2\%)           | \(-69.49\) \(27.34\%)          |
|            | \(-10.92\) \(4.2\%)            | \(-9.36\) \(3.6\%)             | \(-12.53\) \(4.9\%)            |
|            | \(-33.74\)                      | \(-42.22\)                      | \(-35.32\)                      |
|            | \(-19.99\)                      | \(-13.92\)                      | \(-22.22\)                      |
|            | \(-11.21\)                      | \(-10.38\)                      | \(-10.11\)                      |
| 2,6-diisopropyl phenyl | \(-151.41\)                     | \(-139.97\)                     | \(-152.27\)                     |
|            | \(107.77\)                      | \(116.02\)                      | \(111.43\)                      |
|            | \(-174.03\) \(67.2\%)          | \(-165.89\) \(64.8\%)          | \(-172.85\) \(65.5\%)          |
|            | \(-67.70\) \(26.2\%)           | \(-69.20\) \(27.0\%)           | \(-68.80\) \(26.0\%)           |
|            | \(-17.45\) \(6.8\%)            | \(-20.90\) \(8.1\%)            | \(-22.06\) \(8.3\%)            |
|            | \(-33.55\)                      | \(-40.49\)                      | \(-33.04\)                      |
|            | \(-21.62\)                      | \(-12.48\)                      | \(-22.31\)                      |
|            | \(-13.63\)                      | \(-14.17\)                      | \(-14.16\)                      |
| C\textsubscript{2}H\textsubscript{4} | \(-153.03\)                     | \(-108.76\)                     | \(-79.56\)                      |
|            | \(-179.56\) \(68.4\%)          | \(-86.75\) \(26.2\%)           |
Furthermore, the objective was to gain correct results on the basis of the fixed superposition error (BSSE) and to use the counterpoise method, as proposed by Boys and Bernardi (see Tables S2–S4). In this sense, to minimize the BSSE, this procedure can determine a correction term using the same basis set for the molecule and its subunits. The theoretically corrected and uncorrected $\Delta E_{\text{int}}$ for all of the complexes analyzed is given in Tables 2 and S5, respectively.

When we have the same M atom and R substituent (R = F, Cl, Br, H, CH$_3$, C$_2$H$_5$, SiH$_3$, 2,6-diisopropylphenyl) in [Tgt $\rightarrow$ MNHC(R)(R')] complexes and when the R’ from H is changed in to Ph for noncarbon atoms (C$_4$ and C$_5$) in the heterocycle, we also observed a decrease in the value of $\Delta E_{\text{int}}$. In this sense, in the case of [Tgt $\rightarrow$ CuNHC(H)(H')] $\Delta E_{\text{int}}$ values in the presence of R’ = H and Ph are about 156.9 and 150.1 kcal mol$^{-1}$, respectively.

In addition, the $\Delta E_{\text{int}}$ values of metal–drug (M $\leftarrow$ S) bond in [Tgt $\rightarrow$ MNHC(R)(R')] and [Tgt $\rightarrow$ MPR$_3$] complexes are significant and support the well-known V-shape pattern for the transition metals of the first, second, and third rows as described in the following order: Ag(I) $< $ Cu(I) $< $ Au(I) (see Table 2).

In addition, the same findings concerning the bond interaction of NHC(R) with Group 11 of the transition-metal complexes, in the presence of electron-withdrawing substituents, that is, F, Cl, Br, and H, the strength of M $\rightarrow$ S bond in [Tgt $\rightarrow$ MPR$_3$] have the smallest and largest levels of interaction energies, respectively. On the other hand, in [Tgt $\rightarrow$ MPR$_3$] complexes, the [Tgt $\rightarrow$ AuP(2,6-diisopropylphenyl)] and [Tgt $\rightarrow$ AuP$_3$] have the smallest and largest values of $\Delta E_{\text{int}}$ of the metal–drug (M $\leftarrow$ S) bond, respectively.

The analysis of the associated findings shows that the highest quantity of $\Delta E_{\text{int}}$ in the complexes corresponds to the electron-withdrawing substitutions F and Au ions of metal and that the smallest quantity corresponds to the electron-donating substituents 2,6-diisopropylphenyl and Ag ions of metal (see Table 2).

Consequently, it can be inferred that in the presence of the same M metal ion and R = F, Cl, Br, and H substituents, the group 11 metals can generate stronger bonds with [Tgt$^-$]–drug in the form [Tgt $\rightarrow$ MPR$_3$] than [Tgt $\rightarrow$ MNHC(R)(R')] complexes (see Table 2).

### 3.3. AIM Analysis.

Bader’s theory of atoms in molecules (AIM theory) was used to investigate the bond critical points (BCPs). In the present paper, we attempt to analyze the BCPs at M $\leftarrow$ C and M $\leftarrow$ S bonds in [Tgt $\rightarrow$ MNHC(R)(R')] as well as M $\rightarrow$ P and M $\rightarrow$ S bonds in [Tgt $\rightarrow$ MPR$_3$] [M = Cu(I), Ag(I), Au(I); R = F, Cl, Br, H, CH$_3$, C$_2$H$_5$, SiH$_3$, 2,6-diisopropylphenyl; R’ = H and Ph] (as these substituents are given on two noncarbenic carbon atoms (C$_4$ and C$_5$) in the heterocycle) complexes using AIM theory.

As can be seen in Tables S6–S8, the topological properties of the interactions have been calculated at the BCPs. The $V^2\rho$ (laplacian of electron density) and $-G_c/V_c$ ($G_c$ is the kinetic energy and a positive quantity, $V_c$ is the potential energy and a negative quantity) values have also been used to study the nature of the interaction. The effects of the substituents on the values of electron density ($\rho$) of M $\leftarrow$ C and M $\leftarrow$ S bonds in [Tgt $\rightarrow$ MNHC(R)(R')] as well as M $\rightarrow$ P and M $\rightarrow$ S bonds in [Tgt $\rightarrow$ MPR$_3$] are also investigated.

According to the acquired findings, it can be argued that the changing in the R substituents may not have a significant impact on the electron density values ($\rho$) of on M $\leftarrow$ C, M $\leftarrow$ P and M $\leftarrow$ S bonds studied here (see Tables S6–S8).

Figures 4 and 5 represent a satisfactory correlation between the calculated $E_{\text{int}}$ and the corresponding electron density ($\rho$) for the M $\leftarrow$ S bond in [Tgt $\rightarrow$ MNHC(R)(R')] and [Tgt $\rightarrow$ MPR$_3$] complexes. The aforementioned results, which are strongly in agreement with $\Delta E_{\text{int}}$, confirm the well-known V-shaped trends of electron
Table 5. EDA$^a$ Analysis (BP86-D3/TZ2P(ZORA)//PBE-D3/def2-TZVP) of the [Tgt $\rightarrow$ MNHC(R)(R')] and [Tgt $\rightarrow$ MP(R)$_3$] Complexes [M = Ag(I); R = F, Cl, Br, H, CH$_3$, C$_2$H$_5$, SiH$_3$, 2,6-Diisopropylphenyl; R' = H and Ph]

| R      | $\Delta E_{\text{int}}$ | $\Delta E_{\text{presh}}$ | $\Delta E_{\text{rest}}$ | $\Delta E_{\text{disp}}$ |
|--------|--------------------------|---------------------------|---------------------------|---------------------------|
|        | [Tgt $\rightarrow$ AgNHC(R)(H)] | [Tgt $\rightarrow$ AgP(R)$_3$] | [Tgt $\rightarrow$ AgNHC(R)(Ph)] |
| H      | -146.81                  | -155.84                   | -137.44                   |
|        | 105.98                   | 104.16                    | 107.08                    |
| F      | -187.23 (73.60%)         | -202.06 (71.80%)          | -179.26 (72.13%)          |
| Cl     | -187.38 (72.60%)         | -193.28 (71.10%)          | -177.63 (71.77%)          |
|        | -60.93 (23.60%)          | -71.61 (26.40%)           | -60.92 (26.41%)           |
| Br     | -11.67 (4.20%)           | -11.90 (4.30%)            | -10.99 (4.32%)            |
| CH$_3$ | -144.19                  | -141.39                   | -140.58                   |
|        | 106.73                   | 111.76                    | 114.52                    |
| SiH$_3$| -146.24                  | -142.86                   | -137.40                   |
| 2,6-diisopropyl phenyl | -137.94                  | -127.74                   | -137.33                   |
| C$_2$H$_5$| -178.90 (71.37%)        | -60.78 (24.25%)           |
Table 5. continued

| R                | [Tgt → AgNHC(R)(H)] | [Tgt → AgP(R)₃] | [Tgt → AgNHC(R)(Ph)] |
|------------------|---------------------|-----------------|---------------------|
|                  | ΔE_{disp}           | ΔE_{o treatments} | ΔE_{o treatments}   |
|                  | −10.99 (4.38%)      | −36.64          | −13.69              |
|                  | −10.32              |                  |                     |
|                  | −13.69              |                  |                     |

“All energy values are at kcal mol⁻¹.”

densities (ρ) of M ← C and M ← S bonds in the [Tgt → MNHC(R)(R’)] complex and the same is for M ← P and M ← S bonds in [Tgt → MPR₃] complexes, respectively. The results indicate that the M ← C and M ← S bonds in [Tgt → MNHC(R)(R’)] as well as M ← P and M ← S bonds in [Tgt → MPR₃] complexes are partly covalent (V²ρ > 0 and −G₋/V₋ < 1, see Tables S6–S8).

3.4. NBO Analysis. The natural bond orbital (NBO) analysis, which focuses on a technique for optimizing the transformation of a given wave function into a localized shape, corresponds to the Lewis structure of the chemist’s one-center “lone pair” and two-center “bond” elements. Assuming that the Lewis structures are bonding templates, the NBO approach was commonly accepted as understanding the bonding state. It is worth noting that the results obtained are very robust to the alteration of the basis set, which is the most significant advantage of the NBO analysis.

Based on NBO calculations at the PBE-D3/def2-TZVP level of theory, the nature of M ← C, M ← S, and M ← P bonds in the complexes studied here is analyzed. The values of the partial charge on S and M atoms and also the total charge of S atoms in [Tgt → MNHC(R)(R’)] complexes are investigated (see Tables S6–S8).

As can be seen in Table 3, acquired findings demonstrate that the M atoms carried positive charge for Au in [Tgt → AuP(2,6-diisopropylphenyl)] complex and S atom and M atoms carried positive charge (except for Au in [Tgt → AuP(2,6-diisopropylphenyl)] complex). The natural charge values of S atoms in [Tgt → MNHC(R)(H)] complexes and [Tgt → AgNHC(R)(H)] complexes are larger than those in [Tgt → MPR₃] complexes (see Table 3).

Moreover, in the presence of the Cu and Au metal centers and changing the R substitutes from F to Br, the partial positive charge values for Cu atoms [Tgt → CuPR₃] are approximately 0.099e, 0.247e, and 0.279e, respectively (see Table 3).

It is worth mentioning that in the presence of the same R substituent in [Tgt → MNHC(R)(H)], the partial natural charge value on M in [Tgt → MPR₃], unlike those obtained for [Tgt → CuNHC(C₂H₅)(R)] complexes increased. For example, in the presence of F, Cl, and Br, the partial positive charge values for Cu atoms [Tgt → CuPR₃] are about 0.293 and 0.242, respectively.

Notwithstanding, the largest charge values on the M metal center in [Tgt → MNHC(R)(R’)] and [Tgt → MPR₃] complexes are found in [Tgt → CuNHC(2,6-diisopropylphenyl)(Ph)] and [Tgt → AgP(SiH₃)₃] complexes, whereas the smallest values can be found in [Tgt → AuNHC(2,6-diisopropylphenyl)(H)] and [Tgt → AuP(2,6-diisopropylphenyl)] complexes, respectively.

It is worthy of note that the partial natural charge value of S atoms in [Tgt → MNHC(R)(R’)] and [Tgt → MPR₃] complexes has also been addressed. The data confirm that the partial negative natural charge values of S atoms in [Tgt → MPR₃] complexes are larger than those in [Tgt → MNHC(R)(R’)] complexes (see Table 3).

Charge-transfer (CT) values from [Tgt]⁻ to [MNHC(R)-] and [MPR₃]⁺ fragments in [Tgt → MNHC(R)(R’)] and [Tgt → MPR₃] complexes are also analyzed.

As can be seen in Table 3, the CT values in [Tgt → MNHC(R)(R’)] complexes, in the presence of the same M metal center and R substitution, are greater than those in [Tgt → MPR₃] complexes, except for the 2,6-diisopropylphenyl substituent.

Results also demonstrate that, by changing the R substituent from the electron-donating to the electron-withdrawing groups, the values of CT are almost reduced in [Tgt → MNHC(R)(R’)] complexes (see Table 3). On the other hand, the maximum and minimum amounts of the CT in [Tgt → MNHC(R)(R’)] are found for [Tgt → CuNHC(CH₃)(H)] and [Tgt → AuNHC(CH₃)(H)] complexes, respectively.

In [Tgt → MPR₃] complexes, the maximum and minimum amounts of the CT are also found in the case of [Tgt → CuP(2,6-diisopropyl phenyl)] and [Tgt → AgP(Br)] complexes, respectively.
Table 6. EDA\(^e\) Analysis (BP86-D3/TZ2P(ZORA)//PBE-D3/def2-TZVP) of the \([\text{Tgt} \rightarrow \text{MNHC}(R)(R')]\) and \([\text{Tgt} \rightarrow \text{MP}(R)_3]\) Complexes \([M = \text{Au(I)}; R = \text{F, Cl, Br, H, CH}_3, \text{C}_2\text{H}_5, \text{SiH}_3, \text{2,6-Diisopropylphenyl}; R' = \text{H and Ph}]\)

| R   | \(\text{Tgt} \rightarrow \text{AuNH}(R)(H)\) | \(\text{Tgt} \rightarrow \text{Au}(R)\) | \(\text{Tgt} \rightarrow \text{AuNH}(R)(\text{Ph})\) |
|-----|--------------------------------|---------------------------------|--------------------------------|
| H   | \(\Delta E_{\text{tot}}\) | -163.71 | -177.38 | -156.91 |
|     | \(\Delta E_{\text{pauli}}\) | 147.40 | 148.73 | 149.84 |
|     | \(\Delta E_{\text{clatt}}\) | -216.39 (69.55%) | -226.53 (72.80%) | -209.74 (68.37%) |
|     | \(\Delta E_{\text{orb}}\) | -86.03 (27.65%) | -90.40 (24.70%) | -86.69 (26.69%) |
|     | \(\Delta E_{\text{disp}}\) | -9.17 (2.50%) | -10.32 (3.37%) |
|     | \(\Delta E_{\text{orb+disp}}\) | -53.78 | -62.66 | -53.44 |
|     | \(\Delta E_{\text{orb+disp+rest}}\) | -23.62 | -16.32 | -23.95 |
|     | \(\Delta E_{\text{orb+disp+rest}}\) | -8.11 | -8.42 | -10.14 |
| F   | \(\Delta E_{\text{tot}}\) | 143.84 | 150.58 | 151.01 |
|     | \(\Delta E_{\text{pauli}}\) | -217.93 (69.70%) | -238.17 (68.20%) | -214.05 (68.59%) |
|     | \(\Delta E_{\text{clatt}}\) | -89.31 (28.60%) | -101.38 (29.10%) | -90.19 (28.90%) |
|     | \(\Delta E_{\text{orb}}\) | -5.63 (1.80%) | -9.76 (2.80%) | -7.84 (2.51%) |
|     | \(\Delta E_{\text{disp}}\) | -55.30 | -67.37 | -54.80 |
|     | \(\Delta E_{\text{disp+rest}}\) | -25.75 | -20.32 | -26.03 |
|     | \(\Delta E_{\text{disp+rest}}\) | -8.92 | -10.35 | -10.40 |
| Cl  | \(\Delta E_{\text{tot}}\) | 145.42 | 154.55 | 152.09 |
|     | \(\Delta E_{\text{pauli}}\) | -215.28 (69.70%) | -229.49 (67.30%) | -212.09 (68.54%) |
|     | \(\Delta E_{\text{clatt}}\) | -87.77 (28.40%) | -101.61 (29.80%) | -88.79 (28.67%) |
|     | \(\Delta E_{\text{orb}}\) | -6.17 (2.00%) | -10.05 (3.00%) | -8.33 (2.85%) |
|     | \(\Delta E_{\text{disp}}\) | -54.05 | -69.61 | -53.61 |
|     | \(\Delta E_{\text{disp+rest}}\) | -25.49 | -18.61 | -25.44 |
|     | \(\Delta E_{\text{disp+rest}}\) | -9.13 | -9.86 | -10.61 |
| Br  | \(\Delta E_{\text{tot}}\) | -161.71 | -182.57 | -159.82 |
|     | \(\Delta E_{\text{pauli}}\) | 145.58 | 156.70 | 154.54 |
|     | \(\Delta E_{\text{clatt}}\) | -213.72 (69.50%) | -226.84 (66.90%) | -213.26 (67.84%) |
|     | \(\Delta E_{\text{orb}}\) | -87.03 (28.32%) | -101.96 (30.10%) | -89.34 (28.42%) |
|     | \(\Delta E_{\text{disp}}\) | -6.55 (2.10%) | -10.46 (3.10%) | -11.76 (3.74%) |
|     | \(\Delta E_{\text{disp+rest}}\) | -53.46 | -69.58 | -51.39 |
|     | \(\Delta E_{\text{disp+rest}}\) | -24.58 | -18.10 | -25.40 |
|     | \(\Delta E_{\text{disp+rest}}\) | -9.65 | -10.00 | -10.82 |
| CH₃ | \(\Delta E_{\text{tot}}\) | -160.63 | -158.60 | -152.76 |
|     | \(\Delta E_{\text{pauli}}\) | 149.02 | 158.35 | 153.84 |
|     | \(\Delta E_{\text{clatt}}\) | -216.84 (69.60%) | -216.36 (68.30%) | -210.29 (68.59%) |
|     | \(\Delta E_{\text{orb}}\) | -82.43 (26.50%) | -86.36 (27.30%) | -86.50 (28.21%) |
|     | \(\Delta E_{\text{disp}}\) | -10.39 (4.10%) | -14.24 (4.50%) | -9.22 (3.20%) |
|     | \(\Delta E_{\text{disp+rest}}\) | -49.56 | -58.04 | -52.72 |
|     | \(\Delta E_{\text{disp+rest}}\) | -21.22 | -13.63 | -23.37 |
|     | \(\Delta E_{\text{disp+rest}}\) | -10.69 | -12.57 | -10.74 |
| SiH₃ | \(\Delta E_{\text{tot}}\) | -165.90 | -162.85 | -153.89 |
|     | \(\Delta E_{\text{pauli}}\) | 150.06 | 159.45 | 153.09 |
|     | \(\Delta E_{\text{clatt}}\) | -217.41 (68.80%) | -217.55 (67.50%) | -208.54 (67.93%) |
|     | \(\Delta E_{\text{orb}}\) | -85.08 (27.00%) | -89.98 (28.00%) | -87.52 (28.51%) |
|     | \(\Delta E_{\text{disp}}\) | -13.53 (4.30%) | -14.77 (4.60%) | -10.92 (3.56%) |
|     | \(\Delta E_{\text{disp+rest}}\) | -50.73 | -61.52 | -52.85 |
|     | \(\Delta E_{\text{disp+rest}}\) | -21.66 | -13.86 | -23.32 |
|     | \(\Delta E_{\text{disp+rest}}\) | -12.04 | -10.57 | -11.65 |
| 2,6-diisopropyl phenyl | \(\Delta E_{\text{tot}}\) | -156.25 | -141.76 | -151.75 |
|     | \(\Delta E_{\text{pauli}}\) | 156.86 | 164.97 | 157.36 |
|     | \(\Delta E_{\text{clatt}}\) | -210.25 (67.20%) | -200.14 (65.25%) | -206.60 (66.84%) |
|     | \(\Delta E_{\text{orb}}\) | -84.61 (27.10%) | -87.16 (28.42%) | -84.68 (27.39%) |
|     | \(\Delta E_{\text{disp}}\) | -18.25 (5.90%) | -19.43 (6.33%) | -17.83 (5.77%) |
|     | \(\Delta E_{\text{disp+rest}}\) | -50.08 | -61.50 | -49.76 |
|     | \(\Delta E_{\text{disp+rest}}\) | -22.58 | -11.42 | -22.45 |
|     | \(\Delta E_{\text{disp+rest}}\) | -13.53 | -12.21 | -13.40 |
|     | \(\Delta E_{\text{disp+rest}}\) | -153.07 | 158.47 |
|     | \(\Delta E_{\text{disp+rest}}\) | -213.88 (68.65%) | -85.54 (27.46%) |
Finally, in the case of [Tgt → MPR₃] complexes, the well-known v-shaped attitude is shown for the CT values by considering the same R substituent and by changing the M metal center from Cu to Au in most cases and in compliance with the interaction energies ($\Delta E_{int}$) in the following order: Ag < Cu ∼ Au.

Table 6. continued

| R   | Tgt → AuNHC(R)(H) | Tgt → AuP(R)₃ | Tgt → AuNHC(R)(Ph) |
|-----|------------------|---------------|--------------------|
| C₂H₅ | $\Delta E_{\text{disp}}$ | $\Delta E_{\text{disp}}$ | $\Delta E_{\text{disp}}$ |
|      | $\Delta E_{\text{orb},\sigma}$ | $\Delta E_{\text{orb},\pi}$ | $\Delta E_{\text{orb},\text{rest}}$ |
|      | $-12.13$ (3.89%) | $-13.43$ | $-12.95$ |

“All energy values are at kcal mol⁻¹.”

Figure 6. Deformation densities associated with the most important orbital interactions for [Tgt → CuNHC(CH₃)(H)] and [Tgt → CuP(CH₃)₃] complexes at the BP86-D3/TZ2P(ZORA)//PBE-D3/def2-TZVP level of theory.

Figure 7. Deformation densities associated with the most important orbital interactions for [Tgt → CuNHC(CH₃)(H)] and [Tgt → CuP(CH₃)₃] complexes at the BP86-D3/TZ2P(ZORA)//PBE-D3/def2-TZVP level of theory.
Using the Wiberg bond index (WBI) method, the chemical bond orders of M ← P and M ← S bonds in [Tgt → MPR3] complexes and M ← C and M ← S bonds in [Tgt → MNHC(R)(R')] complexes are also evaluated and as can be seen, the results are compared in the Table 3.

The obtained results have shown that by changing the M metal center in the presence of the same R and R' substituents in [Tgt → MNHC(R)(R')] complexes, which are in good agreement with the interaction energies (ΔEint), the well-known v-shaped attitude is shown for the WBI values of the M ← C bond in the following order: Ag(I) < Cu(I) < Au(I). Moreover, it is found that changing the R' substituent has no significant effect on the WBI values of M ← C bonds (see Table 3).

Afterward, by changing the R substituent from electron-donating to electron-withdrawing substituent, we can see an increase in the values of WBI's M ← S in [Tgt → MNHC(R)(H)] and [Tgt → MPR3] complexes.

Generally, the values of WBI's M ← S in [Tgt → MPR3] complexes are slightly larger than those in [Tgt → MNHC(R)(H)] complexes; Nonetheless, 2,6-diisopropylphenyl complexes are some examples of their exceptions. The obtained data showed that the smallest values of WBIs for M ← C and M ← P bonds in the complexes are found in [Tgt → AgNHNC(2,6-diisopropylphenyl)(Ph)] and [Tgt → AgP(2,6-diisopropylphenyl)] complexes and those for M ← S bonds are found in [Tgt → AgNHNC(SiH3)(H)] and [Tgt → AgP(C2H5)] complexes.

Based on the above findings, which are in good agreement with the metal–drug (M ← S) bond ΔEint it can be concluded that in comparison with PR3 ligands and Cu and Au metal centers in the complexes examined here, drug releases are better facilitated in the presence of the majority of NHC(R)(R) centers in the complexes examined, and also the results acceptor interactions as well as natural hybrid orbital (NHO) analysis between the M metal center and S, P, and C atoms in the latter bonds are found in [Tgt → AgNHNC(SiH3)(H)] and [Tgt → AgP(C2H5)] complexes.

Based on the above findings, which are in good agreement with the metal–drug (M ← S) bond ΔEint it can be concluded that in comparison with PR3 ligands and Cu and Au metal centers in the complexes examined here, drug releases are better facilitated in the presence of the majority of NHC(R)(R) centers in the complexes examined, and also the results acceptor interactions as well as natural hybrid orbital (NHO) analysis between the M metal center and S, P, and C atoms in the latter bonds are found in [Tgt → AgNHNC(SiH3)(H)] and [Tgt → AgP(C2H5)] complexes.

Based on the above findings, which are in good agreement with the metal–drug (M ← S) bond ΔEint it can be concluded that in comparison with PR3 ligands and Cu and Au metal centers in the complexes examined here, drug releases are better facilitated in the presence of the majority of NHC(R)(R) centers in the complexes examined, and also the results acceptor interactions as well as natural hybrid orbital (NHO) analysis between the M metal center and S, P, and C atoms in the latter bonds are found in [Tgt → AgNHNC(SiH3)(H)] and [Tgt → AgP(C2H5)] complexes.

3.5. EDA Analysis. Energy decomposition analysis (EDA) for the interaction energy interaction (ΔEint) of two or more chemical bonds between the fragments in the specific electronic reference state and the frozen molecular geometry.

The energy interaction can be divided into four main components eq 1.

\[ \Delta E_{\text{int}} = \Delta E_{\text{elstat orb Pauli dis}} + \Delta E_{\text{pauli}} + \Delta E_{\text{disp}} \]

where ΔEelstat is the electrostatic interaction, ΔE_{pauli} is Pauli repulsion, and ΔE_{disp} is the dispersion energy between the two investigated fragments.

In this research, the bonding analysis is defined as the interaction between [MNHC(R)(R')] and [MPR3]′ with [Tgt] fragments in the related optimized structures.

According to this analysis, the optimized structure of the [Tgt → MNHC(R)(R')] and [Tgt → MPR3] complexes (Scheme 1) are performed with B3P86-D3/TZ2P-(ZORA)//PBE-D3/def2-TZVP and the program package ADF2009.01. As can be seen in Tables 4–6, the results obtained indicate that ΔE_{int} values of the studied complexes are identical to those obtained at PBE-D3/def2-TZVP.

Tables 4–6 represent the results of energy decomposition analysis (EDA) for [Tgt → MNHC(R)(R')] and [Tgt → MPR3] complexes.

According to the EDA results for [Tgt → MNHC(R)(R')] complexes with R = H and Ph (as these substituents are given on two noncarbenic carbon atoms (C4 and C5) in the heterocycle) complexes, it can be inferred that changing the R group from H to Ph has a relatively remarkable impact on the amount of interaction energy and also, in the plurality of cases for the same R substitution in [Tgt → MNHC(R)(Ph)] complexes, the amount of interaction energy is less than the corresponding value in [Tgt → MNHC(R)(H)] complexes (see Tables 4–6).

The results illustrate that the smallest values of ΔE_{int} in the complexes correspond to electron-donating substitutions (often 2, 6-diisopropylphenyl) and the greatest values correspond to the electron-withdrawing changes (mostly F) (see Tables 4–6).

In addition, in accordance with what has been addressed in Section 3.2 in the presence of the electron-withdrawing substituents F, Cl, and Br by considering the same M atom and changing the L ligand from NHNC(R)(R') to PR3, the strength of the M ← S bond in [Tgt → ML] complexes has increased. For example, as can be seen in Table 4, in the case of [Tgt → CuL] complex, the ΔE_{int} values in the presence of NHNC(F)(H/Ph) ligands are approximately 162.6 and 155.6 kcal mol⁻¹ and by changing the L ligand group to PF3, the ΔE_{int} value is approximately 186.7 kcal mol⁻¹ (see Table 4). Therefore, the findings obtained suggested once again that...
drug releases are more facilitated in the presence of NHC(R)-
(R′) ligands than the PR3 ligands studied here.

The EDA analysis results reveal that among the three attractive terms of energy decomposition analysis, the electrostatic energy ∆E_{elat} is the most critical energy with about 64–74%. Subsequently, ∆E_{elat} comes with a percentage in the range about 22–30% and ∆E_{disp} which arises from the instantaneous dipole–induced dipole forces between the two fragments having a little effect (about 2–9%) on ∆E_{tot} (see Tables 4–6).

The covalent bond between the two interacted fragments of [MNHC(R)(R′)]+ with [Tgt]− and also [MPR3]+ with [Tgt]− fragments in the optimized structure of the [Tgt → MNHC-(R)(R′)] and [Tgt → MPR3] {M = Cu(I), Ag(I), Au(I); R = F, Cl, Br, H, CH3, C2H5, SiH3, 2,6-diisopropylphenyl; R′ = H and Ph} as these substituents are given on two noncarbenic carbon atoms (C4 and C5) in the heterocycle} complexes is rendered apparent by the measured deformation densities ∆ρ. This function can be associated with significant orbital interactions between the fragments described above.

Using the EDA–NOCV method, the individual portions of the pairwise interactions are determinable. It should be remembered that there are only a few numbers of pairwise encounters that make a major contribution to ∆E_{tot}.

Regarding [Tgt → MNHC(R)(R′)] complexes and [Tgt → MPR3] complexes, the NOCV pairs account for an average of 69.3–90.8% and 75.2–94.5% in all the complexes. The EDA which were in agreement with NBO and support the critical deformation densities and also statistical results among eight density functional methods have been performed that the drug releases were more facilitated in the presence of NHC(R)(Ph) ligand than PR3 ligands studied here. In addition, it can be inferred that the group 11 metals form stronger bonds with the [Tgt]− drug in the [Tgt → MPR3] form than [Tgt → MNHC(R)(R′)] complexes in the presence of the same M metal ion and R = F, Cl, Br, and H substituents. The WBIs which were in good agreement with ∆E_{tot} of metal–drug (M → S) bond confirmed that the drug releases were more facilitated in the presence of most of the NHC(R)(R′) ligands and Ag metal center than PR3 ligands and Cu and Au metal centers in the complexes.

The results of EDA, which were in agreement with NBO and ∆E_{tot} of metal–drug (M → S) bond, not only confirmed that the drug releases were more facilitated in the presence of NHC(R)(R′) ligands than PR3 ligands for electron-withdrawing substituents but also confirmed that the electrostatic energy ∆E_{elat} was the most important energy among the three attractive terms of an energy decomposition analysis with about 64–74% in all the complexes. The EDA–NOCV confirmed that the interactions between the S atoms of the [Tgt]− fragment and M atoms of M-PR3 fragments in [Tgt → MPR3] complexes are better σ donors. Furthermore, they can be regarded as weaker π acceptors than the corresponding values in [Tgt → MNHC(R)(R′)] complexes.

4. CONCLUSIONS

The present study outlines a theoretical analysis on the complexes of the group 11 metals with general formula [Tgt → ML] in coordination with symmetrical unsaturated N-heterocyclic carbenees [NHC(R)(R′)] and monodentate phosphines (PR3) {M = Cu(I), Ag(I), Au(I); Tgt = 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside, L = NHC-(R)(R′) and PR3; R = F, Cl, Br, H, CH3, C2H5, SiH3, 2,6-diisopropylphenyl; R′ = H and Ph} at PBE-D3/def2-TZVP. The R′ substituents are located on two noncarbenic carbon atoms (C4 and C5) in the heterocycle complexes. Data obtained from rms statistical results among eight density functional methods have shown that PBE-D3 is the most appropriate function among these methods.

The ∆E_{elat} values of the metal–drug (M → S) bond in [Tgt → MNHC(R)(R′)] and [Tgt → MPR3] complexes confirmed that the drug releases are more facilitated in the presence of NHC(R)(Ph) ligand than PR3 ligands studied here. In addition, it can be inferred that the group 11 metals form stronger bonds with the [Tgt]− drug in the [Tgt → MPR3] form than [Tgt → MNHC(R)(R′)] complexes in the presence of the same M metal ion and R = F, Cl, Br, and H substituents. The WBIs which were in good agreement with ∆E_{elat} of metal–drug (M → S) bond confirmed that the drug releases were more facilitated in the presence of most of the NHC(R)(R′) ligands and Ag metal center than PR3 ligands and Cu and Au metal centers in the complexes.

The results of EDA, which were in agreement with NBO and ∆E_{tot} of metal–drug (M → S) bond, not only confirmed that the drug releases were more facilitated in the presence of NHC(R)(R′) ligands than PR3 ligands for electron-withdrawing substituents but also confirmed that the electrostatic energy ∆E_{elat} was the most important energy among the three attractive terms of an energy decomposition analysis with about 64–74% in all the complexes. The EDA–NOCV confirmed that the interactions between the S atoms of the [Tgt]− fragment and M atoms of M-PR3 fragments in [Tgt → MPR3] complexes are better σ donors. Furthermore, they can be regarded as weaker π acceptors than the corresponding values in [Tgt → MNHC(R)(R′)] complexes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c01471. Cartesian coordinates, calculated M–C and M–S bond lengths, topological properties critical points of M–C and M–S bonds, and uncorrected ∆E_{elat} investigated here (PDF).

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The authors declare no competing financial interest.

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