Dispersion-Corrected Density Functional Theory Study of the Noncovalent Complexes Formed with Imidazo[1,2-a]pyrazines Adsorbed onto Silver Clusters

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ABSTRACT: Imidazo[1,2-a]pyrazines are cyclic amidine-type compounds composed of α-amino acid residues. A full structural identification of these molecules constitutes an analytical challenge, especially when imidazo[1,2-a]pyrazines are obtained from physical processes (e.g., sublimation and pyrolysis of amino acids). A valuable source of molecular information can be obtained from absorption spectrosopies and related techniques encompassing the use of metallic substrates. The aim of this study is to provide new knowledge and insights into the noncovalent intermolecular interactions between imidazo[1,2-a]pyrazines and two Ag𝑛 (𝑛 = 4 and 20) clusters using density functional theory (DFT) methods. Semiempirical DFT dispersion (DFT-D) corrections were addressed using Grimme’s dispersion (GD2) and Austin–Petersson–Frisch (APF) functionals in conjunction with the 6-31+G(𝑑,𝑝) + LANL2DZ mixed basis set. These DFT-D methods describe strong interactions; besides, in all cases, the APF dispersion (APF-D) energies of interaction appear to be consistently overestimated. In comparison with B3LYP calculations, the mean values for the difference in the energies of interaction calculated are 2.25 (GD2) and 6.24 (APF-D) kcal mol−1 for Ag𝑛−molecules, and 2.30 (GD2) and 8.53 (APF-D) kcal mol−1 for Ag50−molecules. The effect of applying GD2 and APF-D corrections to the noncovalent complexes is nuanced in the intermolecular distance calculated, mainly in the Ag−N(amidine) bonding, which appears to play the most important role for the adsorptive process. Selective enhancement and considerable red shifts for Raman vibrations suggest strong interactions, whereas a charge redistribution involving the metallic substrate and the absorbate leads to a significant rearrangement of frontier molecular orbitals mainly in the Ag50−molecule complexes. Finally, time-dependent DFT calculations were carried out to access the orbital contributions to each of the transitions observed in the absorption spectrum. The corresponding UV–vis spectra involve transitions in the visible region at around 400 and 550 nm for the Ag4−molecule and the Ag50−molecule complexes, respectively.

INTRODUCTION

Imidazo[1,2-a]pyrazines are heterocyclic structures composed of α-amino acid residues contained into a five-membered imidazole fused to a six-membered pyrazine ring with a bridgehead nitrogen atom. These unusual molecules are of great interest from the point of view of amino acid bridgehead nitrogen atom. These unusual molecules are of imidazole fused to a six-membered pyrazine ring with a bridgehead nitrogen atom. These unusual molecules are of amidine chemistry.1 The natural occurrence of imidazo[1,2-a]pyrazines was discovered in bioluminescence sea organisms2 involving luciferine 3 and coelenterazine 4,5 systems, which constitute the most representative natural imidazo[1,2-a]pyrazines compounds. Their ability to luminesce under the action of oxidants has allowed the development of chemiluminescent sensors based on the determination of peroxides,6 glucose,7 and chemiluminescent immunoassay.8 A variety of biological activities (e.g., antibacterial, anti-inflammatory, antiulcer, antituberculous, cardiac stimulating, and inotropic properties) and cytotoxic effects on cancer cell lines have been also reported for synthetic imidazo[1,2-a]pyrazines derivatives.9−16 Several methods from wet-chemistry16 to sublimation17 and pyrolysis18−21 of amino acids are used to prepare imidazo[1,2-a]pyrazines. However, one of the major difficulties to study these molecules is lack of an adequate technique for a full structural identification. Combinatorial techniques such as gas-phase Fourier transform infrared spectroscopy coupled to gas chromatography and mass spectrometry17−21 identified some derivatives, but such methods also exhibited disadvantages because in situ decomposition of imidazo[1,2-a]pyrazines is very notable.18−21 The interest to study these cyclic amidine-type molecules lies in the fact that derivatives of glycine have failed to be detected by these techniques. The latter fact can be directly associated with the selective detection, thermochem-

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Published: December 27, 2019

DOI: 10.1021/acsomega.9b03127
ACS Omega 2020, 5, 561−569

ACS Omega 2020, 5, 561−569

http://pubs.acs.org/journal/acsdof
tical stability, or simply because cycle-condensation reactions of amino acids are not able to produce enough amounts of imidazo[1,2-α]pyrazines. Previous quantum chemical calculations\textsuperscript{25} suggested that the formation of imidazo[1,2-α]-pyrazines can proceed overcoming a high reaction barrier of about 49 kcal mol\textsuperscript{−1} and only supported by a silica-catalyzed process. This has opened up an area of great doubt about the formation and the spectroscopic properties\textsuperscript{23−25} of imidazo-[1,2-α]pyrazines, which deserves more definitive answers and novel approaches for experimental identification.

Vibrational spectroscopy (e.g. Raman) can be the technique of choice for such a molecular identification. In particular, surface-enhanced Raman spectroscopy (SERS)\textsuperscript{26,27} dramatically can improve the limit of detection using metallic substrates, resulting in detection even at a single-molecule-level concentration.\textsuperscript{28} Under such a scenario, it is important to study the adsorptive processes to attempt surface-enhanced Raman detection. Of particular interest is the study of noncovalent intermolecular interactions with metal clusters\textsuperscript{29} because no mechanism was put forward to account for the adsorption of imidazo[1,2-α]pyrazines onto silver clusters. In the present study, the molecular properties of the noncovalent complexes formed with imidazo[1,2-α]pyrazines and Ag\textsubscript{n} (n = 4 and 20) clusters were studied using density functional theory (DFT) methods. The chosen Ag clusters represent to simple 4 and 20) clusters were studied using density functional theory (DFT) calculations were carried out to access the orbital contributions to each of the transitions observed in the absorption spectrum, and molecular excitation energies were obtained for both isolated molecule and metallic cluster-organic compounds. ARISING FROM SUBLIMATION OF α-AMINOACIDS (E.G., GLYCINE), BI AND TRICYCLIC IMIDAZO[1,2-α]PYRAZINES PREPARED REQUIRE THE FORMATION OF A FIRST INTERMEDIATE.\textsuperscript{25} THE CURRENT SERIES OF MOLECULES STUDIED CORRESPOND TO GLYCINE (GLY, 1), Piperazine-2,5-dione (DKP, 2), Hexahydroimidazo[1,2-a]pyrazine-3,6-dione (BCA, 3), and Hexahydroimidazo[1,2-a]imidazo[1,2-d]pyrazine-3,8-dione (TCA, 4) which are all depicted in Scheme 1.

**Scheme 1.** Chemical Structures of Glycine (1), Piperazine-2,5-dione (DKP, 2), Imidazo[1,2-a]pyrazine-3,6-dione (BCA, 3), and Imidazo[1,2-a]imidazo[1,2-d]pyrazine-3,8-dione (TCA, 4)

### RESULTS AND DISCUSSION

In this study, the noncovalent intermolecular interactions occurring on the metallic substrates were addressed using two sizes for the silver clusters, namely, Ag\textsubscript{n} (n = 4 and 20). Similarity and differences for these Ag clusters were reported elsewhere.\textsuperscript{30−39} In particular, the Ag\textsubscript{4} and Ag\textsubscript{20} clusters were chosen because they are the most stable structures in the potential energy surface, respectively, for small-sized clusters (n < 10) and medium-sized clusters (12 < n < 22).\textsuperscript{34} Substantial differences with other clusters is the relatively lower symmetry that can lead to metastable isomers. Several DFT methods predicted the global minimum for the neutral Ag\textsubscript{4} and Ag\textsubscript{20} clusters to be rhombic (D\textsubscript{3h}) and tetrahedral (T\textsubscript{d}) structures, respectively. Ag\textsubscript{20} (T\textsubscript{d}) is a relaxed fragment of the face-centered cubic lattice of bulk silver, whereas Ag\textsubscript{4} (D\textsubscript{3h}) is a subdomain located at the vertex of Ag\textsubscript{20} cluster. Because Ag\textsubscript{4} (D\textsubscript{3h}) represents the local minima with respect to other isomers (e.g. T\textsubscript{d} C\textsubscript{2v}, see the Supporting Information), this structure was used as a structural criterion for a respective comparison between both clusters. The energy gap between highest occupied molecular orbital (HOMO) and lowest

| complexes | B3LYP ΔE| Grimme-D2 ΔE| APF-D ΔE|
|-----------|---------|-------------|---------|
| Ag\textsubscript{4} | 1.77 | 1.85 | 1.86 |
| Ag\textsubscript{4}-Gly | 9.69 | 1.48 | 11.62 | 1.48 |
| Ag\textsubscript{4}-DKP | 7.03 | 1.56 | 10.02 | 1.52 |
| Ag\textsubscript{4}-BCA | 9.05 | 1.51 | 14.07 | 1.50 |
| Ag\textsubscript{4}-TCA | 8.20 | 1.48 | 14.25 | 1.57 |
| Ag\textsubscript{20} | 2.49 | 2.49 | 2.50 |
| Ag\textsubscript{20}-Gly | 14.40 | 2.93 | 18.75 | 2.43 |
| Ag\textsubscript{20}-DKP | 11.97 | 2.43 | 18.43 | 2.43 |
| Ag\textsubscript{20}-BCA | 14.55 | 2.43 | 21.81 | 2.43 |
| Ag\textsubscript{20}-TCA | 13.44 | 2.33 | 20.29 | 2.27 |

HOMO−LUMO gap energies are reported in eV for each level of theory.
the Fermi level to the vacuum state. For the large size cluster, Ag20, respectively. Such a di

from Figure 1, it becomes evident that mainly two bonds stabilize the adsorptive processes, in which the noncovalent (DKP) bonds. As a result, one can observe that molecules (1–4) can be adsorbed mainly by cooperative interactions with the participation of NH2 and COOH groups. The unique

Figure 2. Schematic of the frontier orbital bonding HOMO and LUMO for the complexes formed between Gly and its related imidazo[1,2-a]pyrazines (DKP, BCA, and TCA) when adsorbed onto metallic clusters. (A) Interaction of molecules with the Ag4 cluster (A) and interaction of molecules with the Ag20 cluster (B).

occupied molecular orbital (LUMO), and the Fermi energy level were calculated to characterize the metallic substrates. The HOMO–LUMO gap energies, $\Delta_{\text{GAP}}$ (see Table 1), were calculated to be about 1.8 and 2.5 eV, respectively, for the isolated Ag4 and Ag20 clusters. It is well known that the large energy gap corresponds to the higher stability for close-shell electron configurations; therefore, Ag20 is more stable than Ag4 (see Table 1). Empirical dispersion does not affect the properties of the wavefunction and thus GD2 and APF-D calculations result in similar values for HOMO–LUMO gap energies. The Fermi level ($E_F$, see the Supporting Information) was calculated to be about -4.36 and -4.44 eV for Ag4 and Ag20, respectively. Such a difference can be related with a different work function for transferring one electron from the Fermi level to the vacuum state. For the large size cluster, the value calculated is approximately similar for the bulk metal as obtained from photoelectric measurements on the (111) surface of silver metal surfaces.

Figure 1 shows the geometries at the stationary points as obtained using DFT-D methods. It was assumed that molecules (1–4) interacted with an ad-atoms site located at the vortex of the silver clusters. Previous studies showed that this orientation is more stable ($\sim$2.3 kcal mol$^{-1}$) that on-top binding onto one of the four faces (111) of the Ag20 cluster. From Figure 1, it becomes evident that mainly two bonds stabilize the adsorptive processes, in which the noncovalent interaction occurs along the Ag···N (BCA and TCA) or Ag···O (DKP) bonds. As a result, one can observe that molecules (1–4) can be adsorbed mainly by cooperative interactions with the participation of NH2 and COOH groups. The unique

Table 1 shows the energies of interaction for the noncovalent complexes, $\Delta E_{\text{NCO}}$, calculated in terms of an adiabatic two-state process using B3LYP, GD2 and APF-D functionals (absolute energies are reported in the Supporting Information). In particular, both GD2 and APF-D values account for empirical correction on dispersion through either electron pair bond formation, charge transfer, or polarization mechanisms, whereas B3LYP values represent the level of interaction when dispersion corrections are not taken into account. Therefore, GD2 and APF-D interaction energies were benchmarked against B3LYP energies. The mean values calculated for the Ag4–molecule complexes are 8.5, 12.5, and 14.7 kcal mol$^{-1}$, respectively, for B3LYP, GD2, and APF-D, whereas the mean value calculated for the Ag20–molecule complexes are 13.6, 19.8, and 22.1 kcal mol$^{-1}$, respectively, for B3LYP, GD2, and APF-D. It is observed that empirical dispersion correction using the APF-D functional resulted in severe strong interactions because in all cases such energies

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appear to be consistently overestimated in comparison with B3LYP calculations. Differences for the energies of interaction calculated with respect to B3LYP are 2.25 (GD2) and 6.24 (APF-D) kcal mol$^{-1}$ for Ag$_4$–molecules, and 2.30 (GD2) and 8.53 (APF-D) kcal mol$^{-1}$ for Ag$_{20}$–molecules. According to other studies, the dispersion term in the APF-D functional should probably be re-evaluated, because deviations can arise from some long-range dispersion that were double-counted by

Table 2. Principal Molecular–Cluster Complexes’ Excitation Energies As Obtained from TDDFT Calculations

| complex   | MOs$^a$ | energy/wavelength$^b$ | $f^c$ | wave function                      |
|-----------|---------|------------------------|-------|------------------------------------|
| Ag$_4$–Gly | 58 → 61 | 3.039/408              | 0.7952| 0.521 H → L + 2)                  |
|           | 58 → 65 | 3.609/344              | 0.2350| 0.569 H → L + 6)                  |
|           | 57 → 59 | 3.776/328              | 0.3328| 0.456 H → 1 → L)                  |
| Ag$_4$–DKP| 68 → 75 | 3.405/364              | 0.3103| 0.400 H → L + 6)                  |
|           | 68 → 75 | 3.421/362              | 0.6388| 0.506 H → L + 6)                  |
|           | 66 → 69 | 3.886/319              | 0.2111| 0.419 H → 2 → L)                  |
| Ag$_4$–BCA| 78 → 84 | 3.267/379              | 0.8792| 0.478 H → L + 5)                  |
|           | 78 → 88 | 3.811/325              | 0.1773| 0.654 H → L + 9)                  |
|           | 77 → 79 | 3.847/322              | 0.1541| 0.387 H → 1 → L)                  |
| Ag$_4$–TCA| 88 → 95 | 3.157/393              | 0.6007| 0.474 H → L + 6)                  |
|           | 88 → 96 | 3.521/352              | 0.2121| 0.508 H → L + 7)                  |
|           | 87 → 90 | 3.712/334              | 0.1105| 0.490 H → 1 → L + 1)              |
| Ag$_{20}$–Gly| 208 → 213 | 2.179/569           | 0.0137| 0.624 H → 2 → L + 2)              |
|           | 206 → 212 | 2.232/556           | 0.0187| 0.466 H → 4 → L + 1)              |
|           | 206 → 211 | 2.236/554           | 0.0209| 0.518 H → 4 → L)                  |
|           | 207 → 212 | 2.253/550           | 0.0181| 0.602 H → 3 → L + 2)              |
|           | 208 → 214 | 2.295/540           | 0.0155| 0.545 H → 2 → L + 3)              |
| Ag$_{20}$–DKP| 216 → 221 | 2.229/556           | 0.0132| 0.594 H → 4 → L)                  |
|           | 216 → 222 | 2.258/549           | 0.0109| 0.461 H → 4 → L + 1)              |
|           | 218 → 223 | 2.285/543           | 0.0250| 0.486 H → 2 → L + 2)              |
| Ag$_{20}$–BCA| 229 → 231 | 1.939/639           | 0.0138| 0.486 H → 1 → L)                  |
|           | 226 → 232 | 2.234/555           | 0.0170| 0.417 H → 4 → L + 1)              |
|           | 226 → 231 | 2.241/553           | 0.0136| 0.346 H → 4 → L)                  |
|           | 227 → 232 | 2.261/548           | 0.0133| 0.330 H → 3 → L + 1)              |
|           | 229 → 233 | 2.265/547           | 0.0238| 0.385 H → 1 → L + 2)              |
| Ag$_{20}$–TCA| 239 → 241 | 1.844/672           | 0.0107| 0.545 H → 1 → L)                  |
|           | 240 → 242 | 1.916/647           | 0.0192| 0.593 H → 1 → L + 1)              |
|           | 236 → 241 | 2.166/572           | 0.0129| 0.486 H → 4 → L)                  |
|           | 236 → 242 | 2.210/561           | 0.0163| 0.474 H → 4 → L + 1)              |
|           | 237 → 242 | 2.235/555           | 0.0135| 0.529 H → 3 → L + 1)              |

$^a$Molecular orbitals. $^b$In eV/nm. $^c$Oscillator strength.
the APF function and the spherical atom model. The HOMO–LUMO gap energies ($\Delta_{\text{gap}}$) are very similar for GD2 and APF-D calculations, and slightly close with those values calculated without dispersion (i.e., B3LYP). However, the HOMO–LUMO gap energies becomes smaller after complexation with molecules, and this is noticeable for those noncovalent complexes formed with the Ag4 cluster (in about 0.34 eV). Figure 2 shows the iso-surfaces for HOMO and LUMO (at 0.02 a.u.) depicting the frontier orbitals for the Ag−molecule complexes together with a simplified orbital energy diagram. In the case of Ag4−molecule complexes (Figure 2A), a small extended distribution occurred in HOMO orbitals, whereas in the Ag20−molecule complexes (Figure 2B) a large portion of HOMO is delocalized, suggesting the formation of electrostatic field gradients around the Ag20 cluster that can induce dipoles in the absorbates because of the changes in the surface charge density. In particular, a significant rearrangement of the frontier molecular orbitals occur in the Ag20−BCA and Ag20−TCA complexes. As regards spatial distribution of frontier orbitals, the following situations can be observed:

(1) HOMO is found exclusively on Ag metal clusters.
(2) Both HOMO and LUMO appear on the Ag4 metal cluster only.
(3) Traces of LUMO appear on BCA and TCA.
(4) LUMO is mainly localized in the imidazole ring of BCA and TCA.

According to these situations, one can suggest that imidazole rings are responsible for binding imidazo[1,2-α]pyrazines (i.e., BCA and TCA) to Ag clusters.

TDDFT calculations were carried out on 15 electronic transitions for the ground-state complexes. Table 2 shows the most important excitation energies (i.e., those with the largest oscillator strength) as calculated for vertical excitation at using DFT-D methods. It is observed that the Ag4−molecules complexes exhibited the highest oscillator strengths, whereas very small oscillator strengths were calculated for the Ag20−molecules complexes. On one hand, the excitations for

Figure 4. Simulated normal Raman scattering spectra of Gly, DKP, BCA, and TCA molecules as calculated at the APFD-B3LYP/MBS level of theory. Differential cross sections of molecules in units of 10−31 cm2/sr were calculated at an incident wavelength of 514.5 nm based on static polarizability derivatives. Bands are given a Lorentzian width of 20 cm−1. Frequencies were scaled with a 0.959 factor.

Table 3. Selected Gas-Phase Normal Raman Active Modes, Scattering Factors ($S_i$), Absolute Raman Cross Sections ($d\sigma/d\Omega$) at an Incident Wavelength of 514.5 nm Based on Static Polarizability Derivatives, Together with Their Corresponding Band Assignments for Gly (1)

| $\nu_i$ | $S_i^b$ | $d\sigma/d\Omega \times 10^{-31}$ | band assignment |
|--------|--------|-----------------|----------------|
| 66     | 0.31   | 0.21            | molecule deform |
| 162    | 3.32   | 0.46            | NH deform out-of-plane |
| 376    | 2.28   | 0.09            | molecule deform |
| 452    | 1.70   | 0.07            | COOH bending   |
| 494    | 3.82   | 0.11            | COO− bend + CH3 bend |
| 586    | 3.62   | 0.09            | C=C–C stretch  |
| 807    | 9.60   | 0.13            | COOH bending   |
| 1092   | 6.48   | 0.08            | NH deform out-of-plane |
| 1190   | 9.64   | 0.11            | C−H bending    |
| 1266   | 5.37   | 0.05            | C−H bending    |
| 1398   | 3.91   | 0.03            | C−H bending    |
| 1462   | 15.72  | 0.10            | C−H bending    |
| 1591   | 3.76   | 0.02            | NH bending     |
| 1674   | 6.16   | 0.03            | C=O stretch    |

*In cm−1. b In Å4/amu. *In cm2/sr.

Table 4. Selected Normal Raman Active Modes, Scattering Factors ($S_i$), Absolute Raman Cross Sections ($d\sigma/d\Omega$) at an Incident Wavelength of 514.5 nm Based on Static Polarizability Derivatives, Together with Their Corresponding Band Assignments for Piperazine-2,5-dione (2)

| $\nu_i$ | $S_i^b$ | $d\sigma/d\Omega \times 10^{-31}$ | band assignment |
|--------|--------|-----------------|----------------|
| 60     | 0.69   | 0.56            | ring deform    |
| 174    | 1.31   | 0.20            | ring deform    |
| 428    | 4.23   | 0.18            | ring deform    |
| 506    | 4.34   | 0.19            | CH3 stretch    |
| 577    | 6.31   | 0.16            | ring stretch   |
| 755    | 18.32  | 0.28            | ring breath    |
| 1125   | 3.39   | 0.04            | ring deform    |
| 1217   | 13.83  | 0.13            | CH3 rocking    |
| 1296   | 11.65  | 0.12            | CH3 wagging    |
| 1346   | 13.21  | 0.11            | CH3 bending, NH bending |
| 1427   | 8.59   | 0.09            | CH2 scissos, NH bending |
| 1477   | 11.77  | 0.10            | CH2 scissos    |
| 1642   | 15.43  | 0.08            | C=O stretch    |

*In cm−1. b In Å4/amu. *In cm2/sr.

(1) HOMO is found exclusively on Ag metal clusters.
(2) Both HOMO and LUMO appear on the Ag4 metal cluster only.
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(4) LUMO is mainly localized in the imidazole ring of BCA and TCA.
electronic transitions in Ag₄-molecule systems are found at energies in the proximity of the absorption maxima (i.e., 386 nm relative to the Ag₂₀ cluster), that is, Ag₄-Gly, 408 nm (f = 0.795); Ag₄-DKP, 362 nm (f = 0.639); Ag₄-BCA, 379 nm (f = 0.879); and Ag₄-TCA, 393 nm (f = 0.601). Therefore, these metal-molecule transitions should occur from orbitals below the HOMO (HOMO − N, with N = 1 and 2) of Ag₄ to the LUMO of each molecule. On the other hand, the calculated absorption spectrum for Ag₂₀—molecule complexes involves excitations in the visible region and they are very close to the absorption maxima (i.e., 537 nm, relative to the Ag₂₀ cluster); that is, Ag₂₀-Gly, 554 nm (f = 0.021); Ag₂₀-DKP, 543 nm (f = 0.025); Ag₂₀-BCA, 547 nm (f = 0.024); and Ag₂₀-TCA, 647 nm (f = 0.019). Figure 3 shows the simulated absorbance spectrum of the studied complexes. The absorption showed changes as a function of both the molecule and the cluster size. For the Ag₄—molecules complexes, the corresponding spectra involve transitions in the visible region that might occur at about 400 nm, which are blue-shifted regarding the transitions for the Ag₂₀—molecule complexes occurring at around 550 nm.

Theoretical Raman spectra for neutral Gly (1), DKP (2), BCA (3), and TCA (4) molecules obtained using DFT-D methods are shown in Figure 4. Frequencies at the gas-phase with the corresponding band assignments and the absolute Raman cross sections (dΩ/dν) are shown in Table 5. Absolute Raman cross sections (dΩ/dν) molecules systems are found at 400 and 1000 cm⁻¹ and bands within the range of 1000–2000 cm⁻¹. However, peak intensities at the second range are slightly smaller than the peaks located at the first range. Taking into account the basis set effect on fundamental frequencies, the wavenumber scaling was used for the full assignment on the vibrational modes. In particular, the Raman spectra profile of Gly (1) shows bands associated with COO⁻ bend + CH₃ bend at 494 and 586 cm⁻¹, stretching-type modes of CH₃ at 1190, 1398, and 1462 cm⁻¹, and stretching of C=O at 1674 cm⁻¹. In-plane deformation bending δ(C=O) was at 807 cm⁻¹, and δ(NH₂) and wagging ρ(CH₃) at 1092 and 1591 cm⁻¹, respectively. A number of additional bands because of CH₃ and C≡N vibrational modes are evident in the case of BCA (3) and TCA (4) molecules, whereas the spectra of DKP (2) showed the presence of NH bands that remained as the spectral characteristics of Gly (1). The fingerprint region (i.e., 200 and 800 cm⁻¹) for DKP, BCA, and TCA molecules is constituted by peaks corresponding to the bands that all belong to deformation modes involving ring distortions (i.e., deformations of pyrazine and imidazo rings) as well as in-plane and out-of-plane bending of C=O moieties. The strongest bands because of rings’ breathing of DKP, BCA, and TCA molecules are located at 755, 707, and 702 cm⁻¹, respectively.

Figure 5 shows the effect of using Ag clusters on the Raman spectra of molecules (1–4). As observed, evident spectral differences resulted in bands that appeared at different wavenumbers. In particular, selective enhancement and considerable red shifts for several Raman vibrations suggest that for some signal enhancements such a result effectively corresponds to the presence of local interactions occurring between the active site of the adsorbate (i.e., imidazo ring) and the effective ad-atom of the metal surface. In particular, for the Ag₄—Gly complex, the bands observed are δ(NH₂), ρ(CH₃), δ(NH₂), and ν(C=O) located at 862, 1277, 1598, and 1672 cm⁻¹, respectively. Tenorio et al. calculated similar Raman spectra for glycine but using a silver eight-atom cluster. For the Ag₄—DKP complex, the most characteristic absorption bands present intense peaks at 764, 1306, 1354, 1454, and 1641 cm⁻¹ assigned to υ(NH), δ(CH₃), ν(NH), ν(N≡C), and ν(C=O) vibrations, respectively. For both Ag₄—BCA and Ag₄—TCA complexes, the most intense bands

Table 5. Selected Normal Raman Active Modes, Scattering Factors (S_i), Absolute Raman Cross Sections (dΩ/dν) at an Incident Wavelength of 514.5 nm Based on Static Polarizability Derivatives, Together with Their Corresponding Band Assignments for Hexahydroimidazo[1,2-a]pyrazine-3,6-dione (3)

| ν_i | S_i | dΩ/dν × 10⁻³³ | band assignment |
|-----|-----|--------------|-----------------|
| 55  | 0.86| 0.83         | rings deform    |
| 167 | 1.54| 0.27         | rings deform    |
| 202 | 1.24| 0.22         | rings deform, CH₂ rock |
| 233 | 1.62| 0.20         | rings deform, CH₂ rock |
| 416 | 6.56| 0.26         | pyrazine ring deform |
| 521 | 3.29| 0.16         | CH₂ rock, NH deform out-of-plane |
| 569 | 8.37| 0.26         | CH₂ rock, NH deform out-of-plane |
| 678 | 8.59| 0.30         | CH₂ rock, NH deform out-of-plane |
| 707 | 11.28| 0.27       | rings breath    |
| 1017| 2.31| 0.05         | pyrazine ring deform |
| 1133| 5.70| 0.07         | CH₂ rock        |
| 1211| 7.47| 0.13         | pyrazine ring deform |
| 1305| 11.39| 0.14       | CH₂ wagging     |
| 1360| 6.29| 0.10         | NH bending      |
| 1472| 16.24| 0.16       | CH₂ scissors    |
| 1627| 19.89| 0.15       | C≡N stretch     |
| 1669| 10.41| 0.09       | C≡O stretch     |

Table 6. Selected Normal Raman Active Modes, Scattering Factors (S_i), Absolute Raman Cross Sections (dΩ/dν) at an Incident Wavelength of 514.5 nm Based on Static Polarizability Derivatives, Together with Their Corresponding Band Assignments for Hexahydroimidazo[1,2-a]imidazo[1,2-d]pyrazine-3,8-dione (4)

| ν_i | S_i | dΩ/dν × 10⁻³³ | band assignment |
|-----|-----|--------------|-----------------|
| 44  | 1.11| 0.17         | pyrazine ring deform |
| 197 | 3.05| 0.52         | rings deform     |
| 236 | 3.04| 0.39         | rings deform     |
| 401 | 5.99| 0.20         | pyrazine ring deform |
| 509 | 3.23| 0.20         | rings deform     |
| 612 | 11.51| 0.32       | rings deform     |
| 702 | 15.97| 0.48       | rings breath     |
| 1019| 7.28| 0.10         | CH₂ rock        |
| 1134| 10.29| 0.13       | CH₂ wagging     |
| 1179| 5.15| 0.09         | CH₂ wagging     |
| 1235| 6.50| 0.14         | CH₂ wagging     |
| 1270| 4.29| 0.10         | CH₂ wagging     |
| 1325| 15.83| 0.17       | CH₂ wagging     |
| 1407| 35.42| 0.33       | CH₂ scissors    |
| 1469| 15.01| 0.17       | CH₂ scissors    |
| 1624| 32.29| 0.25       | C≡N stretch     |
| 1669| 20.85| 0.16       | C≡O stretch     |
were observed in a particular region between 1000 and 1500 cm$^{-1}$. Absorption bands were predicted corresponding to $\delta(CH_2)$ at 996 cm$^{-1}$, rings' deformations at 1013 cm$^{-1}$, bending $\delta(NH)$ at 1362 cm$^{-1}$, imidazo ring-deformation at 1424 cm$^{-1}$, bending $\delta(N=C)$ at 1613 cm$^{-1}$, and bending $\delta(C=O)$ at 1638 cm$^{-1}$. Finally, the Raman spectra of the molecules adsorbed onto the Ag$_{20}$ cluster are much more similar than those of isolated molecules. This is the case of the Ag$_{20}$−Gly complex, in which the most intense bands are $\delta(CCO)$, $\delta(NH_2)$, and $\delta(CH_2)$, $\nu(CH_2)$, $\delta(NH_2)$, and $\delta(C=O)$ located at 629, 1147, 1386, 1435, and 1628 cm$^{-1}$, respectively. The predicted absorptions for the interval between $\delta(NH_2)$ and $\delta(C=O)$ stretching is 193 cm$^{-1}$, whereas in the case of Ag$_{4}$−Gly, it was 74 cm$^{-1}$. In Ag$_{20}$−DKP, the principal absorption bands correspond to ring breathing (764 and 889 cm$^{-1}$), which is more evident than that in the Ag$_4$ complex. The bands $\delta(CH_2)$, $\nu(NH)$, and $\nu(N=C)$ were also observed at 1217, 1356, and 1429 cm$^{-1}$, respectively. However, C=O bands are much weaker and thus they cannot be distinguished in the predicted spectrum. Because BCA and TCA are molecules with the same chemical nature, the interaction energies are similar, and form noncovalent complexes through the same active site, the predicted Raman spectra for both Ag$_{20}$−BCA and Ag$_{20}$−TCA complexes showed similar bands in the 800−1500 cm$^{-1}$ region. According to the interaction energies calculated (~20 kcal mol$^{-1}$), it is expected that such values overpass a threshold required to observe the SERS effect. However, further studies should address other variables such as the effect of pH, charge of Ag clusters and molecules, different metallic substrates, as well as calculations of Raman activities using different laser wavelengths.

**CONCLUSIONS**

Theoretical calculations of the noncovalent intermolecular interactions between imidazo[1,2-$a$]pyrazines and silver clusters were reported in the framework of dispersion-corrected DFT methods. The main conclusions can be summarized as follows:

- In terms of a computational modeling that compensates resource and time, the Ag$_{20}$ cluster is a very useful model to study the interactions of Ag nanoparticles with imidazo[1,2-$a$]pyrazines. In terms of an accurate prediction, dispersion-corrected DFT methods are required to estimate interaction energies in the non-covalent complexes studied.
- The mean values for the difference in the interaction energies calculated appeared to be consistently overestimated with APF-D, especially when complexes are formed with the Ag$_{20}$ cluster.
- Mulliken population analysis suggests a transfer of charge across the Ag···N(amine), red shifts for Raman vibrations suggest strong interactions, and charge redistribution involving HOMO and LUMO orbitals give rise to the formation of stable noncovalent complexes that can surpass a dissociation limit.
- These simulations constitute a useful and valuable first element for further experimental characterization of these unusual classes of cyclic amidines.

**COMPUTATIONAL METHODOLOGY**

To account for dispersive interactions in the electron density of the noncovalent molecule-metal cluster systems, all the electronic structure calculations were studied through DFT using the Grimme $^{30}$ and the APF $^{31}$ dispersion correction methods over the B3LYP functional. A mixed basis set (MBS)
was set using the 6-31G+(d,p) basis set for C, H, O, and N atoms plus the LANL2DZ basis set for Ag. Details of relative interaction energies, normal modes frequencies, Kohn–Sham HOMO and LUMO orbitals, vertical excitation energies, Raman intensities calculations, basis-set superposition error, and the details of the computational methodology adopted for the present work are given in the Supporting Information.

**ASSOCIATED CONTENT**

[Supporting Information](https://pubs.acs.org/doi/10.1021/acsomega.9b03127)

Details of computational methods; representative structures for Ag₈ clusters; total density-of-states calculated for Ag₈ (a) and Ag₈₋₁ (b) clusters; frontier orbitals HOMO and LUMO for molecules (1–4); absolute electronic energies (in Ha) for the isolated molecules (1–4) and metallic cluster-organic molecule systems HOMO and LUMO energies calculated for the isolated molecules; and Mulliken atomic charges for the Agₓ―molecule complexes (PDF)

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**Notes**
The author declares no competing financial interest.

**ACKNOWLEDGMENTS**

This work was partially supported by the National Council of Science and Technology of Mexico, CONACyT (grant 269399) and the School of Science and Engineering, Tecnológico de Monterrey. The author would like to express sincere gratitude to Prof. V.A. Basiuk for his encouragement in the realization of this study.

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