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Physicochemical properties, molecular docking and global reactivity descriptors of manganese carbonyl complexes with imidazole ligands

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In this study, it was investigated that the solution behavior of two carbon monoxide releasing molecules; $Mn(CO)_3(bpy)(N\text{-imidazole})]PF_6$ (**1**), $[Mn(CO)_3(bpy)(N\text{-methylimidazole})]PF_6$ (**2**) which showed anticancer activity via zetasizer properties such as measuring particle size, electrophoretic mobility and zeta potential as a function of pH and determined the global reactivity descriptors and molecular docking poses via computational chemistry. The activities of molecules in the different pHs were checked by UV/Vis spectrophotometer.

Keywords: Particle size, mobility, zeta potential, molecular docking, global reactivity descriptors, manganese carbonyl, imidazole.

Introduction

Recently, it was reported that carbon monoxide releasing molecules (CORMs) have been investigated for their pharmacological properties for many human diseases. *In vitro* experiments of newly synthesized novel imidazole CORMs exhibited cytotoxic effect on breast cancer cells[1,2]. Physicochemical properties of particles such as particle size, shape and surface charge are very important in the cellular uptake of particles. Particle surface charge controls binding to the tissue, while particle size plays key role for particle passing through the cell wall[3].

The zetasizer measurements such as particle size, mobility and zeta potential give information about the stability and charge of particles in solution. The size and surface chemistry of micron scale particles are of fundamental importance in studies of biotechnology applications. Meanwhile, zeta potential which is the electro-kinetic potential in the interfacial double layer at the location of the slipping plane versus a point in the bulk fluid away from the interface explains the potential difference between the dispersion medium and the stationary layer of fluid attached to the dispersed particle and used for the characterization of double-layer properties. Zeta potential (ζ) measurement can provide information about the material surface-solution interface. It can be used to predict and control the stability of solutions and the understanding dispersion and aggregation processes. The presence, or absence of charged groups/moieties on the surface of materials, as revealed by their ZP, can directly affect their performance and processing characteristics in solution. The sign and magnitude of ZP affects process control, quality control, product specification[4].

Computational chemistry provides useful information about the properties of the molecules before the synthesis of the molecules[5]. Information that obtained by theoretical calculations on many topics such as reactivity, spectroscopic and crystallographic properties of the molecules have ensured labor, money and environmental protection[6]. These advantages have given rise to new improvements in the field of computational chemistry[7]. The interpretation of the theoretical results in relation with the several experimental results leads to the use of computational chemistry in larger areas[8].

Chemical potential (μ), global hardness (η), chemical softness (S), and electrophilicity index (ω) are known as global reactivity descriptors[9]. These expressions, which are calculated based on electron numbers and external potential variation, are used to interpret the activity of molecules. The aim of this study is to use the DFT-based calculation results for the evaluation of zeta potential analysis.

In this current work, $[M(CO)_3L(bpy)]PF_6$ {M: Mn; bpy: 2,2′-bipyridyl; L: imidazole (**1**), methylimidazole (**2**)} type molecules which were previously synthesized and characterized[2] were analyzed with molecular docking approximations, optimized by using ORCA package program and also global reactivity descriptors were calculated. As there are no previous studies on the use of these metal carbonyl complexes in solution, it was necessary to evaluate the stability and activity potential of these compounds in solution. The aggregation process *in vitro* and *in vivo* measurements is affected by several environmental factors such as concentration, pH, ionic strength and temperature. For this purpose, the particle size, mobility and zeta potential of these molecules were measured as a function of pH to determine the stability of the molecules in solution. The pH effect on the activity of these molecules were determined via UV/Vis.

Materials and method:

$Mn(CO)_3$(bpy)(N-imidazole)]PF_6 (**1**), [$Mn(CO)_3$(bpy)(N-methylimidazole)]PF_6 (**2**) were synthesized freshly[2]. NaOH and HCl (Merck, Germany) were used to adjust pH of solutions. The particle size, mobility and zeta potential of solutions was also measured by 90Plus Particle Size Analyzer, Brookhaven Instruments Corporation (BTC) and 90Pals (Phase Analysis Light Scattering) Zeta Potential Analyzer as a function of pH. The activity of these molecules in different pH solutions was checked by Shimadzu UVmini-1240 UV.

Zetasizer measurements:

Zetasizer measurements are consisting of particle size, mobility and zeta potential of particles. Particle size of particles can be determined by measuring the random changes in the intensity of light scattered from a suspension or solution. The particle size calculations are handled by instrument software. The sign of mobility shows the surface charge of particles. A positive mobility of a particle means the surface is positively charged; negative mobility means the surface is negatively charged. The zero-mobility value shows the velocity is zero and electrostatic repulsion is small.

Zeta potential is the key parameter that controls electrostatic interactions in particle dispersions and aids in predicting long-term stability. Zeta potential, ζ was determined ten times for each sample. Results were automatically calculated by the zeta potential analyzer using the following Smoluchowski equation[10]:

$$\mu_e = (\varepsilon\zeta)/\eta$$

where μ_e is electrophoretic mobility, ε is the dielectric constant and η is the viscosity of electrolyte. High positive or negative zeta potentials greater than 30 mV lead to monodispersity. On the other hand, low values, smaller than 5 mV, can lead to agglomeration. Zeta potential is affected not only by the properties of nanoparticles, but also the nature of the solution, such as pH and ionic strength[10].

Calculation method:

DFT/TDDFT calculations for full unconstrained geometry optimizations tricarbonyl complexes were carried out with ORCA version 3.0.3[5,11] using the exchange functional according to Becke and the correlation functional suggested by Perdew hereafter called BP[12], with the resolution-of-the-identity (RI) approximation, a TZVP basis set[13], and the tightscf and grid4 options. To speed up the calculations, TZVP/J auxiliary basis set was used. HOMO and LUMO energies of optimized geometries were used for calculating global reactivity descriptors. Global reactivity descriptors were also calculated by using HOMO and LUMO energies of optimized molecules and gOpenMol was used for all the graphical illustrations.

Molecular docking studies were performed by AutoDockVina version 1.1.2. Protein crystal structure was downloaded from the RCSB Protein Data Bank (PDB entry code: 1N5U)[14]. The optimized molecule was docked into serum albumin after conversion to pdbqt file format by AutoDockTools[15]. The receptor was kept rigid and only polar hydrogens were added to docking process. The analyzed poses were visualized by Discovery Studio 4.1.0.

Results and discussion

The physicochemical properties of **1** and **2** molecules in solution were determined as a function of pH. The particle size, polydispersity and mobility of these molecules were given in Table 1.

Table 1. Particle size, polydispersity and mobility of $[M(CO)_3L(bpy)]PF_6$ {M: Mn; bpy: 2,2′-bipyridyl; L: imidazole (**1**), methylimidazole (**2**)}

pH	Particle size (nm)		Polydispersity		Mobility	
	1	**2**	**1**	**2**	**1**	**2**
1	320	370	0.478	0.144	0.52	2.06
2	285	380	0.439	0.122	0.17	0.96
3	160	340	0.541	0.173	–0.67	0.62
4	180	250	0.634	0.156	–0.57	–0.42
5	175	225	0.166	0.240	–0.77	–0.85
6	185	250	0.173	0.105	–1.72	–1.59
7	195	230	0.187	0.842	–1.37	–2.23
8	185	260	0.222	0.339	–1.51	–2.81
9	200	230	0.220	0.310	–1.34	–2.98
10	190	350	0.207	0.432	–1.63	–2.66
11	190	250	0.245	0.346	–0.99	–2.64
12	225	270	0.478	0.144	–0.93	–2.66

As the pH value of the solution changes from acidic to alkaline, particle size of molecule **2** is bigger than molecule **1**, particle size distributions of two molecules are monodisperse and particles show a significant change from plus to minus mobility values. According to mobility values, molecule **1** is negatively charged between pH 1 and pH 2, after pH 3 positively charged while molecule **2** is negatively charged between pH 1 and pH 3, after pH 4 positively charged.

To determine the stability and activity of these molecules in solution, the zeta potential and UV/Vis measurements of them were done in the different pHs. The zeta potential and activity changes of two molecules as a function of pH were given Fig. 1 and Fig. 2, respectively. According to Fig. 1, the zeta potential of molecule **2** is bigger than **1** at all pHs. The zeta potentials of molecule **1** is positive values up to pH 3, after pH 3, molecule **1** has negative zeta potential values while the zeta potentials of molecule **2** is positive values up to pH 4, after pH 4, molecule **2** has negative zeta potential values. To compare the zeta potential of these molecules, molecule **2** has bigger zeta potential values than molecule **1**. According to zeta potential values of the molecules, molecule **2** has more stability than molecule **1** in solution. *In vitro* experiments, the zeta potential when dispersed in culture medium for cell culture is about –15 to –20 mV regardless of the type of substance. This information supports results of this study.

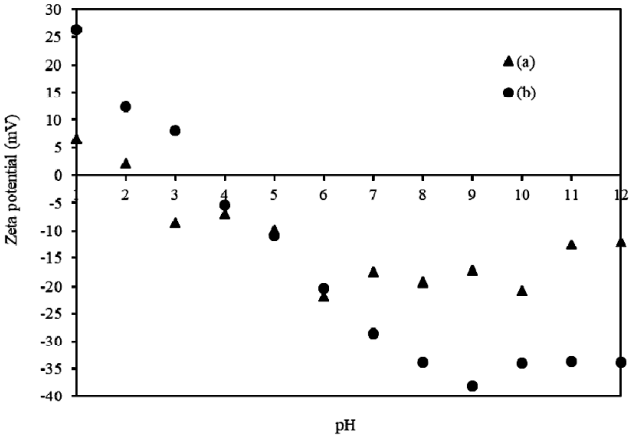


Fig. 1. Zeta potential changes of $M(CO)_3L(bpy)]PF_6$ {M: Mn; bpy: 2,2′-bipyridyl; L: imidazole (**1**) (a), methylimidazole (**2**) (b)} as a function of pH.

The activity changes of the molecules in different pH solutions is checked via the peak about 380 nm[6]. The molecule **1** has the highest activity at pH 7, the lowest activity at pH 11 while the molecule **2** has the highest activity at pH 5, the lowest activity at pH 12.

The properties of the frontier orbitals of the molecules could be considered for the evaluation of reactivity. The atoms in which the frontier orbitals are located could be appreciated as reactivity center of molecules. It is seen from the results of DFT-based calculations made for this study that HOMO orbitals mostly consist of central manganese metal with the small contribution of carbonyl orbitals while all the LUMO orbitals of the molecules consist of 2,2-bipyridyl ligand (Fig. 3). This could be an indication of that the molecules accept electron over bipyridine while the molecules donate electron through manganese metal. The HOMO and LUMO energies obtained by using the DFT-based calculations are used for the relative evaluation of the reactivity properties of the molecules. Ionization potential (IP), electron affinity (EA), electronegativity (χ) and chemical potential (μ) of the molecules that identified as global reactivity descriptors are also calculated by using the HOMO/LUMO energies. The global reactivity descriptors of the molecules in this study shows that complex **2** has the highest ionization potential. In addition, global softness (S) and chemical hardness (η) are also approved as evaluation criteria for the reactivity of molecules.

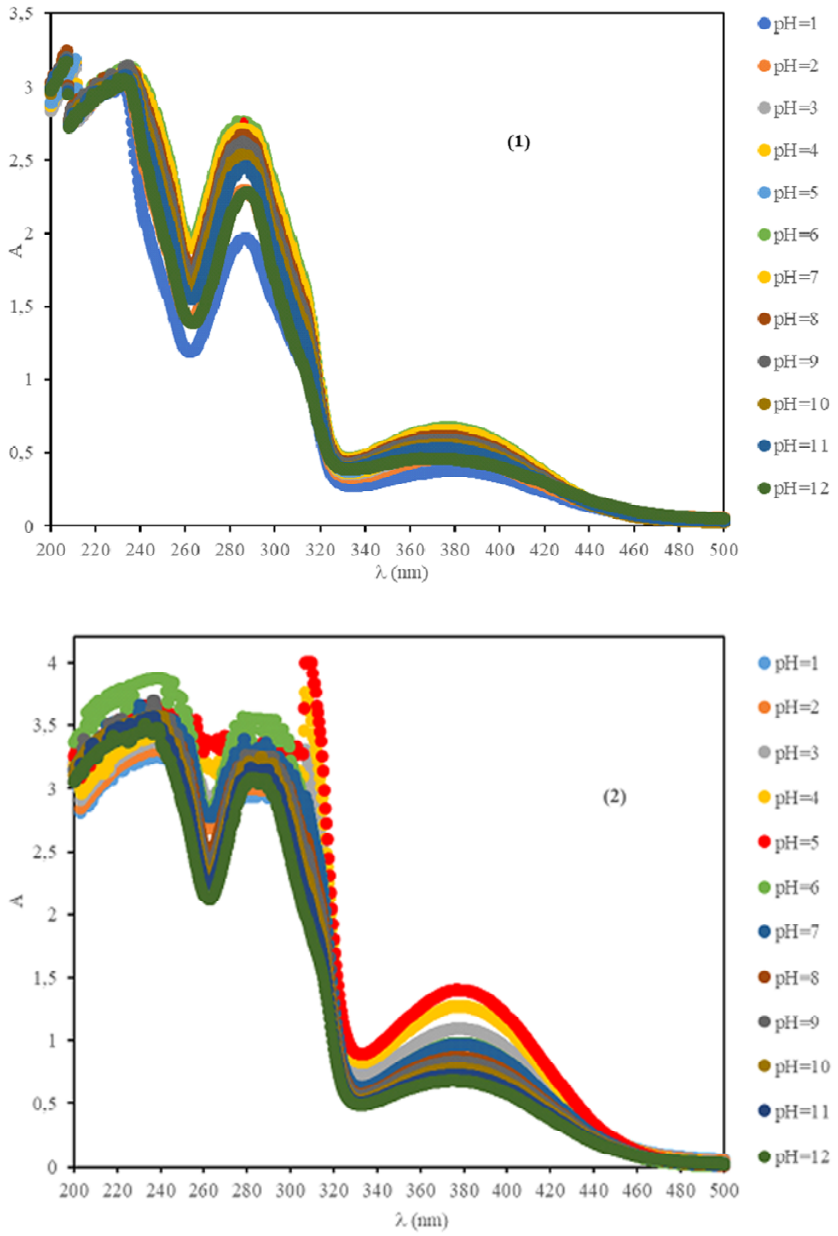
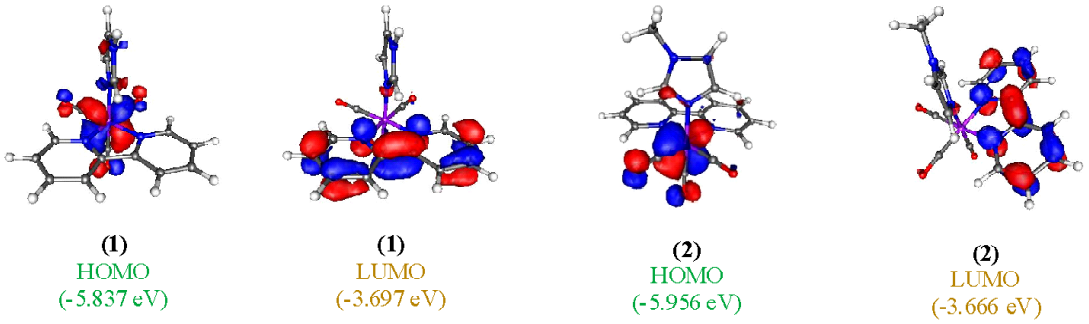


Fig. 2. The activity changes of $M(CO)_3L(bpy)]PF_6$ {M: Mn; bpy: 2,2′-bipyridyl; L: imidazole (**1**), methylimidazole (**2**)} as a function of pH.

The stability of molecules decreases with the increasing of the global softness of the molecule while chemical hardness is just the reciprocal of global softness, so the higher the hardness, the lower the reactivity. It is clear from Fig. 3 that the reactivity of the molecules will be listed as **1** > **2**. Electrophilicity index (ω) is regarded as an indication of the electrophilic force of the molecular system against a nucleophile.

The interactions between the molecules and human serum albumin are analyzed by molecular docking method the most appropriate pose for molecule **2** is given in Fig. 4. The binding energy of the most appropriate pose was calculated 8.44 kcal/mol. Molecule **2** has the best interaction with the region constituted by Glu153, Gln196, Lys199, Arg218, Val241, His242, Arg257 and Ser287 amino acids. The H-bond between Lys199 and axial carbonyl is a significant interaction with a length of 2.47 Å. There are also pi-alkyl inter-



	IP	EA	χ	μ	η	S	ω
1	5.837	3.697	4.767	–4.767	1.070	0.467	10.619
2	5.956	3.666	4.811	–4.811	1.145	0.437	10.107

Fig. 3. Pictures and energies of HOMO/LUMO orbitals and global reactivity descriptors of the molecules.

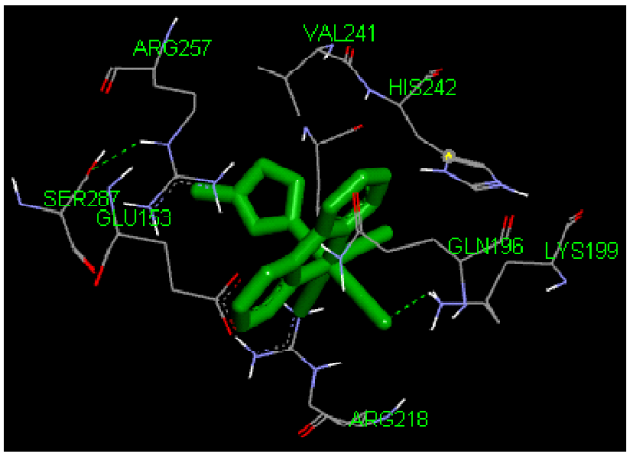


Fig. 4. Molecular docking pose of **2** in human serum albumin (PDB ID: 1N5U).

actions which are calculated with docking calculation, but which cannot be considered as bond.

Conclusion

Zetasizer measurements of synthesized/characterized two bioactive manganese carbonyl complexes of type $[Mn(CO)_3(bpy)L]PF_6$ were analyzed for particle size, electrophoretic mobility and also zeta potential as a function of pH. It is found that the activity of complexes are a bit decreasing, stabilities are increasing and they have more negative charges in alkaline media. With the aid of theoretical calculation methods, we had knowledge about frontier molecular orbitals and global reactivity descriptors of the molecules. It is clear that the reactivity of the molecules is **1** > **2**. The molecular docking methods are also confirmed that the molecule **2** has moderate binding energy with the human serum albumin.

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