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Molecular docking and electronic transition analysis of novel [Re(bbim)(bpy)(CO)$_3$]OTf complex as a CO-releasing molecule

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Synthesis of CO-releasing molecules that safely deposit/transport CO has attracted great attention after the discovery of therapeutic properties of carbon monoxide, which is known to be a toxic gas. Metal carbonyl complexes seem to be the most important alternative as CO-releasing molecules. Recent developments in computational chemistry make it possible to gain many information about the properties of complexes before being synthesized. On the other hand, molecular docking methods can also give valuable information about the interaction of the molecules with tissue. The metal carbonyl complexes that were synthesized as a CO-releaser interact primarily with blood proteins when they enter the tissue; therefore, the theoretical analysis of the interaction of complexes with blood proteins can give useful information. In this study, [Re(bbim)(bpy)(CO)$_3$]OTf (bbim: benzylbenzimidazole; bpy: 2,2′-bipyridyl, OTf: SO_3CF_3) complex was synthesized, characterized, analyzed by DFT/TDDFT based calculation method and docked into human serum albumin.

Keywords: Molecular docking, DFT/TDDFT, rhenium complexes, CO-releasing molecules.

Introduction

The cytoprotective effect of the induced heme oxygenase (HO-1) enzyme is well known. This enzyme, which induces the destruction of the free hem molecule separated from the injured and dead cells, enables the formation of Fe^{2+}, bilirubin and free carbon monoxide (CO)[1]. The latter is a very important signaling molecule akin to NO and H_2S and these molecules are generally defined as gasotransmitters[2]. CO displays anti-inflammatory, anti-thrombotic and anti-proliferative effects, like HO-1, by administration from an external source meaning that CO is a therapeutic agent as demonstrated in animal models of vascular and inflammatory diseases, organ transplantation and some other diseases[3].

There are many difficulties about CO-based therapy. The strong binding affinity of hemoglobin is the biggest obstacle to CO inhalation for medicinal application. Although it has been tested in animal models and human clinical trials; necessity of large amounts of CO in the systematic circulation for observing the biological effects and lack of tissue specificity are important disadvantages of the inhalation method. Synthetic prodrugs called CORMs (CO-releasing molecules) have been tried as an effective releasing method and the most important candidate for this purpose is metal carbonyl complexes (MCC)[4]. The ideal CORM must protect itself in circulation, target the required organ and release CO by triggering on intended tissue. CORM firstly interacts with the plasma proteins after entering systematic circulation and human serum albumin (HSA) which plays important roles for transporting the endogenous and exogenous circulated molecules is the most common one[5].

Interaction of an MCC with serum albumin can occur in three different ways. The first one is the substitution reaction between the ligand and MCC; this strong interaction provokes effective CO-release to the blood stream. The second one is

the metal-ligand exchange reaction, which induces more limited and slower CO-release than the first one. The third is the non-covalent interaction between the protein and the MCC, which does not result in CO-release because of the resistance to decomposition of MCC[5]. Therefore, it is important to know the interaction properties of the candidate CORM molecule and plasma proteins. These studies are also important for evaluation of therapeutic functions, prodrug-plasma protein interactions, pharmacokinetic properties and ADMET parameters[6].

The work presented here focused on the synthesis and characterization of a new [Re(bbim)(bpy)$(CO)_3$]OTf (bbim: benzylbenzimidazole; bpy: 2,2′-bipyridyl, OTf: SO_3CF_3) complex. The optimization and the evaluation of electronic transitions of the complex were analyzed by DFT/TDDFT based calculation method. The potential binding interactions between the synthesized compound and human serum albumin was explored using molecular docking studies.

Material and method:

General remarks:

All reactions were carried out under argon using standard Schlenk and vacuum techniques. Solvents were freshly distilled after refluxing over metallic sodium or phosphorous pentoxide for 3–4 days. NMR spectra were recorded on a Bruker Ultra Shield 300 MHz spectrometer. Chemical shifts δ in ppm indicate a downfield shift relative to tetramethylsilane (TMS) and were referenced relative to the solvent signals. Coupling constants *J* are given in Hertz. IR spectra were recorded on solid samples with a Shimadzu IRAffinity-1 ATR spectrometer. Band intensities are marked as strong (s), medium (m), weak (w), or shoulder (sh). Absorption spectra were measured using a Shimadzu UV-1800 spectrophotometer equipped with quartz cuvettes (d = 1 cm). LC-MS was carried out on an Agilent 1100 Series instrument. All chemicals were purchased from Sigma Aldrich and used without further purification.

Synthesis of complex:

$Re(CO)_3$(bpy)Br was prepared according to literature methods[7]. $Re(CO)_3$(bpy)Br (200 mg, 0.395 mmol) were added into the solution of AgOTf (121.8 mg, 0.474 mmol) in acetone (10 mL). Precipitated AgBr was filtrated by Celite and the ligand was added after stirring for a day at room temperature. Acetone was evaporated under vacuum. Precipitated orange product was filtered and washed with 5 mL of cold methanol and 10 mL of cold diethyl ether. Yield: 251.4 mg (81.1%). ^{1}H NMR (400 MHz, DMSO) δ (ppm): 9.39 (d, *J* 5.1 Hz, 2H, $N_2C_{10}H_8$), 8.71 (d, *J* 8.1 Hz, 2H, $N_2C_{10}H_8$), 8.40 (t, *J* 7.8 Hz, 2H, $N_2C_{10}H_8$), 8.29 (s, 1H, NCHN), 7.90–7.83 (m, 2H, $N_2C_{10}H_8$), 7.80 (d, *J* 7.7 Hz, 1H, NC_6H_4N), 7.66 (d, *J* 7.4 Hz, 1H, NC_6H_4N), 7.36 (dt, *J* 14.5, 7.3 Hz, 3H, $NCH_2C_6H_5$), 7.27 (s, 2H, $NCH_2C_6H_5$), 6.97 (s, 2H, NC_6H_4N), 5.39 (s, 2H, $NCH_2C_6H_5$); ^{13}C NMR (400 MHz, DMSO) δ (ppm): 48.57 ($NCH_2C_6H_5$), 146.38 (NCHN), 155.63, 154.89, 141.70, 125.45, 129.15 ($N_2C_{10}H_8$), 129.25, 127.73, 124.86, 118.10 ($NCH_2C_6H_5$), 141.23, 135.66, 132.81, 128.65, 125.26, 113.08 (NC_6H_4N), 196.20, 192.76 (CO); LCMS: *m/z* 635.2 [M-OTf-]$^+$; IR (cm^{-1}, ATR): 1469.8 (C-H, s), 1442.7 (C-H, s), 1600.9 (s, C-N), 2009.8 (CO, s), 1879.9 (CO, sh), 1870.9 (CO, s).

Theory/calculation:

DFT calculations were carried out with ORCA version 3.0.3 using the BP86 functional with the resolution-of-the-identity (RI) approximation, a TZV/TZV/J basis set, the tightscf and grid4 options[8].

Molecular docking studies were performed by AutoDockVina version 1.1.29. Protein crystal structure was downloaded from the RCSB Protein Data Bank (PDB entry code: 1N5U)[10]. The optimized molecule was docked into serum albumin after conversion to pdbqt file format by AutoDockTools[9]. 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

[$Re(CO)_3$(bbim)]OTf, synthesized for this study was characterized by using ^{1}H NMR, ^{13}C NMR, LC-MS and IR spectroscopy. The bipyridyl structure bonded to centre transition metal is characterized by ^{1}H NMR spectra bands between 7.83 ppm and 9.89 ppm. The NCHN hydrogen of the benzimidazole ring is observed as a clean singlet at 8.29 ppm, while the hydrogens of CH_2, which link the benzene to benzimidazole are identified by the singlet band observed at 5.39 ppm. ^{13}C NMR spectroscopy is an important technique for identification of CO ligands of metal carbonyl complexes. Although there are three different carbonyls in the molecule,

it is characterized by two carbonyl bands observed at 196.20 ppm and 192.76 ppm because of the chemically different environment of carbonyls. ^{1}H NMR and ^{13}C NMR spectra of the molecule were also detailed in the Materials and methods. The carbonyls of the molecule are observed at 2036 cm^{-1}, 1944 cm^{-1} and 1931 cm^{-1} and the C-N bond is recorded at 1604 cm^{-1} in the IR spectrum.

DFT based calculation methods, which improved significantly in recent years, provide important information about the structure/activity properties of molecules and save time/funding/labor. The region, energies of the frontier orbitals and HOMO-LUMO energy gap are significant criteria for investigation of the reactivity properties of the molecules and these properties could be different in isolated form and in solution. In this study, the molecule in both isolated form and dissolved in acetonitrile (AcN) and DMSO that are generally used in bioactivity studies have been optimized. The molecular orbital energy diagrams in different forms are given in Fig. 1. The HOMO energy of the gas molecule is –8.41 eV and the LUMO energy is –6.54 eV, while the HOMO-LUMO energy gap corresponds to 663 nm. On the other hand, while HOMO energy in acetonitrile is –6.06 eV, LUMO energy was calculated as –3.74 eV. The calculation results in acetonitrile and in DMSO are similar to each other, and the HOMO-LUMO energy gaps are 534 nm and 532 nm, respectively. The HOMO orbitals of the molecule in all forms are mostly located in metal and carbonyl regions, while the LUMO orbitals are usually located on bipyridyl.

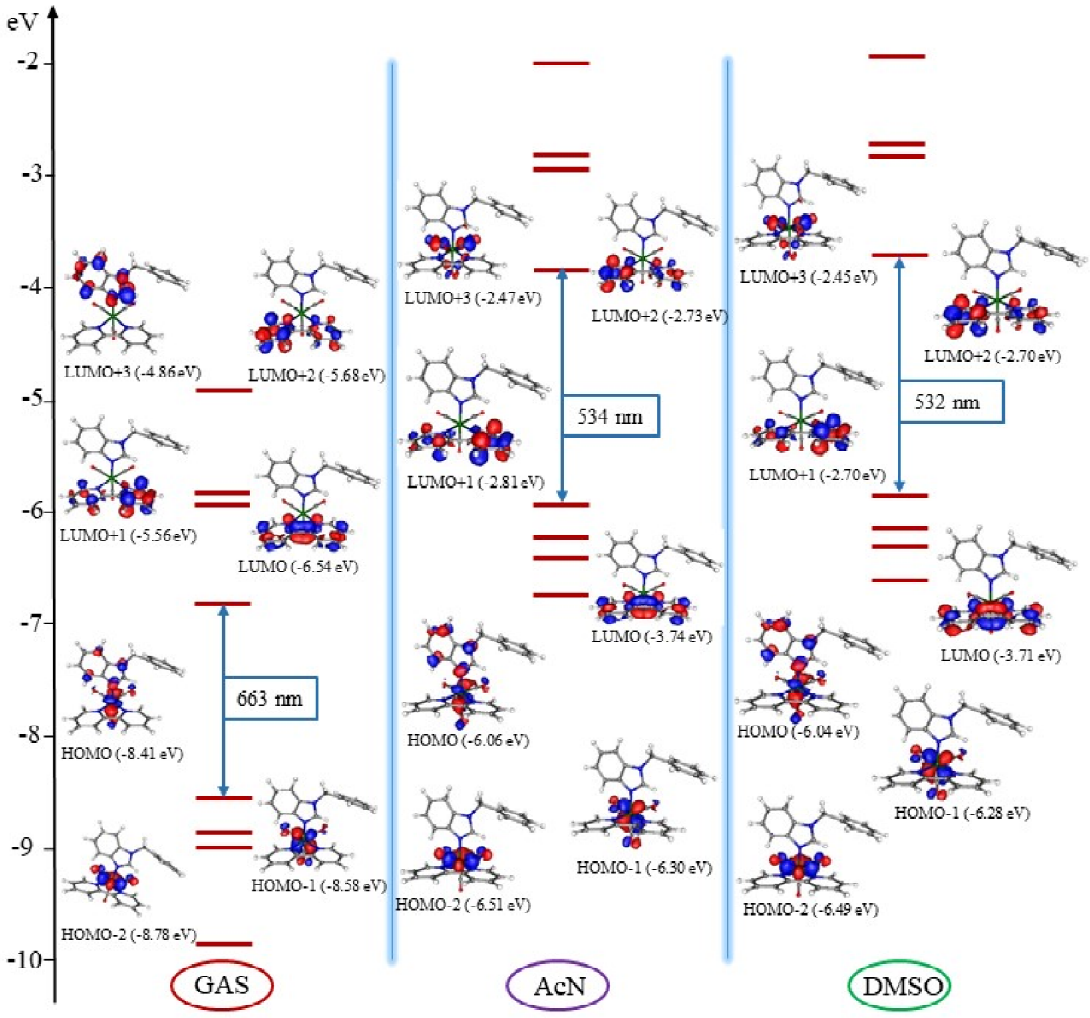

Fig. 1. Molecular orbital energy diagram of the complex in AcN, DMSO and gas form.

Table 1. Wavelength (in nm), oscillator strength (f_{osc}), main orbital contributions of the most important singlet excitations of $[Re(CO)_3(benzylbenzimidazole)(bpy)]OTf$ calculated with TDDFT/BP86

State	λ_{nm}	f_{osc}	Main transitions	
1	599.8	0.0245	HOMO → LUMO (70.1%)	M → bpy (MLCT)
			HOMO-1 → LUMO (23.6%)	M/CO → bpy (MLCT/LLCT)
2	574.9	0.0207	HOMO-1 → LUMO (73.5%)	M/CO → bpy (MLCT/LLCT)
			HOMO → LUMO (18.3%)	M → bpy (MLCT)
7	464.1	0.0221	HOMO-6 → LUMO (95.2%)	bimid (benzyl) → bpy (LLCT)
12	387.8	0.0760	HOMO-1 → LUMO+2 (69.4%)	M/CO → bpy (MLCT/LLCT)
17	354.0	0.0263	HOMO-6 → LUMO+1 (13.5%)	bimid (benzyl) → bpy (LLCT)
			HOMO-5 → LUMO+1 (15.0%)	bimid (benzyl) → bpy (LLCT)
			HOMO-4 → LUMO+1 (60.9%)	bimid → bpy (LLCT)
24	324.9	0.0423	HOMO-1 → LUMO+3 (20.2%)	M/CO → bimid (MLCT/LLCT)
			HOMO → LUMO+3 (33.7%)	M → bimid (MLCT)
			HOMO → LUMO+4 (25.7%)	M → CO (MLCT)
27	297.1	0.0897	HOMO-8 → LUMO (28.0%)	bimid → bpy (LLCT)
			HOMO-7 → LUMO (29.9%)	bpy → bpy (ILCT)
			HOMO → LUMO+6 (20.6%)	M → bpy (MLCT)
28	294.9	0.0859	HOMO-7 → LUMO (22.6%)	bpy → bpy (ILCT)
			HOMO-1 → LUMO+5 (30.0%)	M/CO → CO (MLCT/ILCT)
			HOMO → LUMO+5 (15.4%)	M → CO (MLCT)
30	293.8	0.0485	HOMO-7 → LUMO (10.5%)	bpy → bpy (ILCT)
			HOMO-2 → LUMO+4 (14.9%)	M/CO → CO (MLCT/ILCT)
			HOMO → LUMO+6 (58.5%)	M → bpy (MLCT)
34	288.2	0.0218	HOMO → LUMO+5 (27.2%)	M → CO (MLCT)
			HOMO → LUMO+7 (27.5%)	M → benzyl (MLCT)

TDDFT based electronic transitions of the molecule were also calculated. The highest oscillated electronic transition of the molecule at 297.1 nm is comprised of MLCT and LLCT, wherein electron flows from both the benzimidazole and Re to the bpy ligand. The electronic transition with the second highest oscillator strength is mainly consisted of metal→CO electron flow. All electronic transitions with oscillator strengths higher than 0.02 are detailed in Table 1.

Molecular docking studies were performed to get insight into the interaction between synthesized molecules and plasma proteins. The molecule first interacts with serum albumin after entrance into the circulation, so the equilibrium of the molecules with serum albumin is important. In this study, interaction between HSA and the molecule is shown in Fig. 2. The most preferable pose has an inhibition constant of 654.74 nm with a binding energy of 8.44 kcal/mol. It is seen that the region formed by the amino acids Gln196, Lys199, Phe211, Trp214, Arg218, Leu238, His242, Cys245,

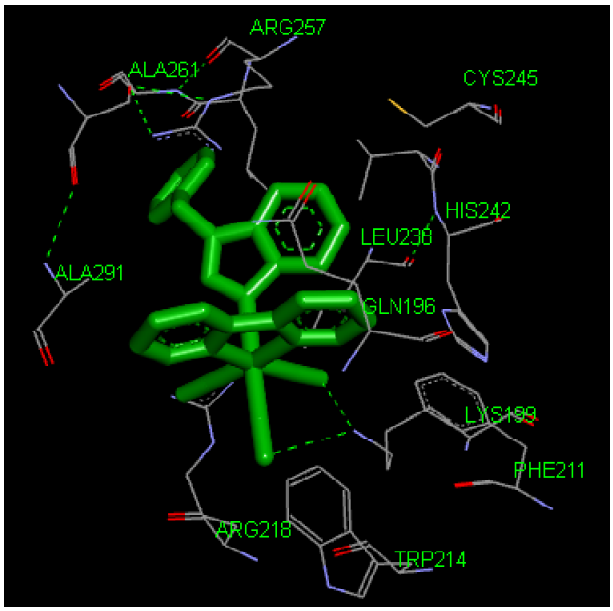

Fig. 2. Molecular docking figure of the molecule with human serum albumin (PDB ID: 1N5U).

Arg257, Ala261 and Ala291 makes the most effective interaction with the molecule. Two H-bonds between the HSA and the carbonyl region of the complex are remarkable: the first one between Lys199 and eq-CO is 2.23 Å, and the second between Lys199 and ax-CO is 2.12 Å. Furthermore, pi-alkyl non-bonding interactions of both benzimidazole and bipyridyl with benzene are noteworthy.

Conclusions

In recent years, the good agreement between the computational data and the experimental results has become a good motivation for applying theoretical methods in many fields. The calculations in this study show that substitution via bpy can make changes that are more effective. In further studies, it is planned to synthesize new complexes with substituted bpy ligands and different central atoms.

Acknowledgements

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