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Design and synthesis of two armed molecular receptor for recognition of Gd³⁺ metal ion and its computational study

 ¹ Department of Chemistry, Kurukshetra University, Kurukshetra 136119, India
 ² J. Heyrovsky Institute of physical Chemistry, Academy of Sciences of the Czech Republic, Dolejškova 2155/3, 182

23 Prague 8, Czech Republic
³ Department of Botany, Bioinformatics and Climate Change Impacts
Management, University School of Sciences, Gujarat University, Ahmedabad, Gujarat 380009, India

Correspondence

Brij Mohan, Department of Chemistry, Kurukshetra University Kurukshetra-136119, India. Email: brizharry17@gmail.com

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University Grants Commission, New Delhi, India, Grant/Award Number: Sch./ S-I/14/1179; Grant Agency of the Czech Republic, GAČR, Grant/Award Number: 17-18108S New receptor Phenylene-Bis-Methylfuran-yl-2-Methyele Acetohydrazide (PBMMA) has been synthesized by condensation of hydrazide and 5-methyl furfural. Synthesized receptor has been fully characterized by IR, ¹H NMR, ¹³C NMR, mass spectroscopic and thermo gravimetric analysis. The receptor **PBMMA** shows selective recognition potential towards Gd³⁺ ion when tested with several metal ions such as Na⁺, K⁺, Mg²⁺, Cu²⁺, Cd²⁺, Hg²⁺, Y³⁺, La³⁺, Eu³⁺, Sm³⁺, Gd³⁺, Re⁶⁺ and Th⁴⁺ ion as their sulfates by UV-visible and fluorescence spectroscopic studies. Binding nature of **PBMMA** with Gd³⁺ ion was further studied by mass spectroscopic and cyclic voltammetric studies. The stoichiometry of **PBMMA-**Gd³⁺ ion has been established, 1:1 by Benesi-Hildebrand plot method and method of continuous variation (Job's plot) with association affinity $K = 6.491 \times 10^4 M^{-1}$. In addition to these, molecular docking, molecular dynamic stimulation and binding energy of complex; through Density Function theory -595.66 kcal/mol has also indication of strong binding. The electron transfer energy of Higher occupied molecular orbital (HOMO) to Lower unoccupied molecular orbital (LUMO) is about 4.186 eV and 295 nm for PBMMA-Gd³⁺ Complex.

KEYWORDS

DFT, fluorescence, mass spectroscopy, receptor, UV-visible

1 | INTRODUCTION

In recent years, development of multifunctional receptors^[1] or sensors is growing area of research due to their potential applications in sensing, separation, catalysis, function of enzyme and ion channels etc.^[2–4] Receptors with two arms or multi arms^[5] are expected to play role as novel sensing platforms^[6,7] due to their better chelating opportunities through apparent convergence of functionalities that can wrap the target toxicant, metal ions and molecules.^[8–13] Now a days, receptors with different

structures have been synthesised for metal ions by using supramolecular interactions.^[14,15]

Metals specially lanthanides are found to have important role in the field of medical and biochemical science.^[16] Gadolinium is found to be used as contrast agent in Magnetic Resonance Imaging (MRI).^[17] Gadolinium in form of intravenous injection is utilized to enable sensitive identification of a number of pathologies such as vascular abnormalities, cardiac infarcts and tumors.^[18,19] The use of metal ligand complexes especially chelates in medicine is a developing field in novel therapeutic and in treatment of many diseases, also two armed molecular receptors with electron rich sites are found to coordinate with metal ions.^[20–22]

Vital role of gadolinium complexes in medical chemistry has motivated researchers for the development of new gadolinium specific receptors.^[23-27] Furfural based organic compounds are found to interact with gadolinium metal ion.^[28] The utilization of such type of organic framework as hosts is key to design highly sensitive and selective receptor for gadolinium ion.

Herein, we synthesized a two armed receptor with good thermal stability and also that selectively binds with gadolinium ions among various metal ions in solvent system. The synthesized receptor PBMMA shows good absorption and emission spectra in methanol-water solvent system and spectra changes upon addition of gadolinium metal ions only among a series of metal ions used as sulfate salts. The receptor is found to be a good photo sensor for gadolinium. The cyclic voltammetric studies introduce the reversible binding of PBMMA-Gd³⁺. Computational studies of PBMMA and PBMMA-**Gd**³⁺ ion gives a valuable information about the results of main singlet vertical electron transition energies (ΔE), wavelengths (λ), oscillator Strengths (f), and % contribution calculated at the TDDFT/CAMB3LYP level. Molecular docked structure defined the binding mode of Gd³⁺ with **PBMMA**. More interestingly the results obtained out from computational studies are similar to the observed experimental results of UV/Vis studies.

2 | EXPERIMENTAL

2.1 | Chemicals and reagents

All HPLC grade reagents and solvents were used without further purification during synthesis and evaluation of receptor. Thin-layer chromatography was performed using silica-aluminium plates and the plates were visualized using ultraviolet light both long range and short range.

2.2 | Instruments

All glassware was dried in an oven for 12 hrs before use. Open capillaries were used to determine melting point and are thus found uncorrected. Thermal Gravity Analysis was observed at Perkin Elmer TGA 4000 by heating at the rate of 5 °C per minute. IR spectra were recorded on ABB MB 3000 IR Spectrophotometer. NMR data were recorded on a Bruker AV (III)-400 MHz. All samples were analyzed in CDCl₃/DMSO- d_6 . Mass spectra were recorded on a Xevo G2-S Q-Tof spectrometer (Waters, USA), capable of recording high-resolution mass spectrum (HRMS) in the electrospray ionization (ESI) modes. The reference values for the residual solvent were taken as $\delta = 2.601$ (DMSO-d₆) for ¹H-NMR and $\delta = 77.1$ (CDCl₃), $\delta = 40$ (DMSO-d₆) for ¹³C-NMR. The abbreviations: s = singlet, d = doublet, m = multiplets were used for multiplicities of coupled signals given in hertz. Electronic spectra of receptor and metal ions with receptor were recorded on T 90 (PG Instruments Ltd) UV/Vis spectrometer in the region 700–200 nm CH₃OH:H₂O in 1:1 as solvent system and emission spectra were recorded on Shimadzu-5301pc spectrofluorophotometer in CH₃OH:H₂O in 1:1 as solvent system. Cyclic voltammetry measurements were recorded on Ivium Stat Electrochemical Analyzer by using KCl as supporting electrolyte.

2.3 | Synthesis of receptor

Compound 1 i.e. (diethyl 2,2'-(1,3-phenylenebis (oxy)) diacetate) was synthesized with slightly modification in the reported process^[15] by refluxing the mixture of resorcinol (0.0182 mol), ethyl bromoacetate (0.0363 mol) and K_2CO_3 (0.1097 mol) as catalyst in anhydrous acetonitrile for 24 hrs. Compound 2 i.e. (2,2'-(1,3-phenylenebis (oxy))di (acetohydrazide)) was synthesized with a slightly change in reported process^[15]; to a solution of compound 1 0.658 g (2.63 mmol) in methanol, hydrated hydrazine 0.920 g (18.4 mmol, 99%) was added and the reaction mixture was stirred at room temperature for 10 hrs.

2.3.1 | Synthesis of receptor 2,2'-(1,3phenylenebis (oxy))bis (N'-((E)-(5methylfuran-2-yl)methylene) acetohydrazide) (Phenylene-Bis-Methylfuran-yl-2-Methyele Acetohydrazide (PBMMA)

0.278 g (1.04 mmol) of hydrazide 2 and 0.229 g (2.1 mmol) of 5-methyl furfural and 2-3 drops of glacial acetic acid as catalyst was refluxed in ethanol for 30 hrs (Scheme 1). The reaction progress was noticed with the help of thin layer chromatography in petroleum-ether:ethyl-acetate solvent system. The contents were cooled at room temperature to obtain precipitates, which was filtered and washed with cold ethanol to yield **PBMMA** a light yellow solid; Yield: 60%. The melting point was observed by open capillary instrument and found to be uncorrected. Melting point: 220–225 °C. IR ($v = cm^{-1}$): 3256 (NH stretching), 2885 (CH stretching), 2824 (CH stretching), 1759 (C=O stretching), 1643 (C=N stretching), 1605; ¹H NMR (Figure S1) (400 MHz, DMSO- d_6): δ (ppm) 11.356 (s, 0.6H, NH), 11.017 (s, 0.40H, NH), 8.418 (s, 0.64H, CH=N), 8.208 (s, 0.39H, CH=N), 7.760 (d, 0.49H, furan),



SCHEME 1 (i) K₂CO₃/acetonitrile/ refluxed 24 hours (ii) NH₂NH₂.H₂O/ methanol/stirred 10 hrs (iii) 5-methyl furfural/acetic acid glacial/ethanol/ refluxed 30 hrs

7.645 (d, 0.82H, furan), 7.211–7.168 (m, 0.97H, Ar-H), 6.824 (t, 0.80H, Ar-H), 6.672 (t, 0.58H, Ar-H), 6.561 (m, 0.72H), 6.520 (m, 0.54H), 6.203 (s, 0.84H), 6.106 (s, 1.03H), 4.588 (s, 1.21H, COCH₂), 4.562 (s, 0.92H, COCH₂), 2.424 (s, 2.89H, -CH₃), 2.380 (s, 3.42H, -CH₃); ¹³C NMR (Figure S2) (75 MHz, CDCl3): δ (ppm) 149.87, 147.50, 134.57, 129.75, 118.77, 115.44, 114.67, 108.91, 108.12, 101.85, 67.21, 64.80, 13.71. Mass spectroscopy is found to be in good agreement with the proposed structures of receptor **PBMMA;** MS-ESI-TOF (m/z) (Figure S3) [M + Na⁺] (m/z) 461.1422.

2.4 | General procedure for the detection of cations by spectrophotometry

Stock solutions of 5-methyl furfural derivative tweezer **PBMMA** (17 μ M) and the sulfate salts (17 μ M) of various metal ions (Na⁺, K⁺, Mg²⁺, Cu²⁺, Cd²⁺, Hg²⁺, Y³⁺, La³⁺, Eu³⁺, Sm³⁺, Gd³⁺, Re⁶⁺ and Th⁴⁺) were prepared in CH₃OH:H₂O (1:1 ν/ν) solvent system. In a 5 ml volumetric flask, 2.5 ml of the solution **PBMMA** and 2.5 ml of metal salt stock solutions were combined so that the effective concentrations of both **PBMMA** and metal ions were same. Absorption studies were performed using the as prepared solutions. A Benesi-Hildebrand plot (Figure 6) and Job's plot (Figure 7) were obtained based on the absorption studies to establish the stoichiometry and association affinity of receptor-metal. Mass analysis (Figure S4) was also characterized to know binding of Gd³⁺ with **PBMMA**.

For fluorescence study of **PBMMA** (3×10^{-4} M) with metal ions (3×10^{-4} M), a stock solution of the receptor **PBMMA** and metal sulfates were prepared in CH₃OH: H₂O (1:1 ν/ν) solvent system. In a 5 ml volumetric flask, 2.5 ml of the solution **PBMMA** and 2.5 ml of metal salts stock solutions were combined so that the effective concentrations of both **PBMMA** and Gd³⁺ metal ion

were same and the emission spectra were recorded on Shimadzu-5301pc spectrofluorophotometer.

2.5 | Computational methodology

2.5.1 | Molecular docking

The binding potency of chosen guest with appropriate host can be decipher by molecular docking approach. Geometry optimized three dimensional structure of both host (**PBMMA**) and guest (Gd³⁺) pertained to figure out the best binding pose and binding energy in Hex 8.0.0 software.^[29] The Accelrys Discovery Studio visualizer version 16 was employed to measure various interactions found between host-guest docking which reveals the potency of binding formation.

2.5.2 | Molecular dynamics simulation

Molecular dynamics simulation was performed based on identical simulation protocol of Desmond v3.6 package to model the different states of host-guest (PBMMA- Gd^{3+}) complex for 10 ns time trajectory with 1 ns integration step.^[30] Optimized Potentials for Liquid Simulations (OPLS) all-atom force field 2005 was applied for the cubic periodic box containing Simple Point Charge (SPC) (10 Å \times 10 Å \times 10 Å). This box also contains the van der Waals interactions computation cut off based on coulomb electrostatics distance which was 7.86, while other parameters were extensively computed by temperature at 298 K, pressure at 1 bar, pH 7.0, 0.9% NaCl, solvent density 0.997, pH 7.0, periodic boundaries.^[31] Methanol was chosen as solvent to equilibrate the host-guest complex with NPT ensemble system. In this event, various interactions were optimized to gauge the structural stabilization and conformational change feasibility.^[31]

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2.5.3 | DFT calculations

The Theoretical calculations were performed at density functional level of theory (DFT) using Becke's threeparameter hybrid exchange (B3LYP) in Gaussian 09 (G09) software package.^[32] In the calculation, the 6-31G(d,p) basis set was assigned to all elements with the exception of gadolinium, for which MWB53 basis set was employed. The geometric structures of the complex in the ground state (singlet) were fully optimized at the B3LYP in both gas and solvent phase methanol using the conductor-like polarizable continuum model (CPCM). Vibration frequency calculations were performed to ensure that the optimized geometries represent local minima associated with positive eigen values only. The ligands and metal complexes were demonstrated using Avogadro version 1.2.0 software. The single point energy calculations were carried out to calculate the strength of the complex in the term of binding energy. The binding energy of the PBMMA _Gd³⁺ complex was calculated by energies as mentioned as in equation (1).

$$BE = E_{(M-Complex)} - (E_L + E_M)$$
(1)

Where, $_{(M-complex)}$ is the energy of the metal complex (**PBMMA**-Gd³⁺) and $E_{\rm L}$ and $E_{\rm M}$ are the energies of the **PBMMA** and Metal ion Gd³⁺, respectively.

Time dependent-Density functional Theory (TD-DFT) level of calculation was also performed for absorption spectra calculation. The effect of solvent (Methanol) was also monitored for all step using conductor-like Polarizable Continuum Model (CPCM).

3 | RESULTS AND DISCUSSIONS

The current section is organized as follows. Thermo gravimetrical analysis TGA of **PBMMA** was analyzed. The metal cation binding nature of **PBMMA** was determined by treating various metal ions as their sulfates with the help of UV-visible and fluorescence spectroscopic techniques. **PBMMA-Gd³⁺** ion binding was further studied with the help of mass spectroscopy and cyclic voltammetric studies. The geometric and energetic features associated with the binding of **PBMMA-Gd³⁺** were discussed by computational studies. Finally, we found that the results of absorption spectra at TDDFT level of calculation and experimental UV-visible spectra changes are almost same for interaction between the **PBMMA** and Gd³⁺ ion.

3.1 | Thermal studies

Thermal study^[33] of **PBMMA** was analyzed in nitrogen environment (Figure 1). Thermo gravimetric analysis (TGA) data (Figure S5 and Figure S6) for all the samples were obtained in the standard form of % weight loss as function of temperature at heating rate 5 °C min⁻¹ is shown in Figures 1. There was no weight loss was observed up to 120 °C. The major weight loss observed was found in two stages. In stage first, major weight loss of 57.76% (calc. 56.20%) occurred in the temperature range 120-311 °C. This weight loss was due to the decomposition of methyl furfural hydrazine moiety. In second stage weight loss of 38.36% (calc. 43.80%) was occurred in between the temperature range 311-790 °C at a constant rate due to loss of benzene, carbonyl and other part of the compound. At the temperature 790 °C the remaining yield of the PBMMA was found 3.88%.

3.2 | UV-visible spectroscopic studies

UV–visible spectroscopic studies provide a vital evidence for absorption behaviour of the receptor and receptorcation complexes. Sensitivity and selectivity of the synthesized receptor can be evaluated by observing changes in their UV–visible spectra of receptor by evaluating with different metal ions in $CH_3OH:H_2O$ (1:1) solvent system.

3.2.1 | Interaction of cations with receptor PBMMA by UV-visible studies

17 μ M solution of receptor **PBMMA** in CH₃OH:H₂O gives a very good absorption spectra due to electronic transactions and absorption maxima was observed at 312 nm with a hump near 358 nm due to n- π^* and $\pi - \pi^*$ transition (Figure 2). The cation binding



FIGURE 1 TGA curves of PBMMA at heating rates of 5 °C min⁻¹



FIGURE 2 UV-visible spectra of receptor **PBMMA** (17 μ M) with metal Gd³⁺, Na⁺, K⁺, Mg²⁺, Cu²⁺, Cd²⁺, Hg²⁺, Y³⁺, La³⁺, Eu³⁺, Sm³⁺, Re⁶⁺ and Th⁴⁺ in CH₃OH:H₂O (1:1 ν/ν) as solvent system. UV-visible (electronic spectra) of receptor and metal ions with receptor was recorded on T 90 (PG Instruments Ltd) UV/VIS spectrometer in the region 700–200 nm

properties of receptor PBMMA was investigated by evaluating sulfate salts of Na⁺, K⁺, Mg²⁺, Cu²⁺, Cd²⁺, Hg²⁺, Y³⁺, La³⁺, Eu³⁺, Sm³⁺, Gd³⁺, Re⁶⁺ and Th⁴⁺ metal ions and their UV-visible spectra were recorded. Receptor **PBMMA** showed negligible response to Na⁺, K⁺, Mg²⁺, Cu²⁺, Cd²⁺, Hg²⁺, Y³⁺, La³⁺, Eu³⁺, Sm³⁺, Re⁶⁺ and Th⁴⁺ metal ions (Figure 2), changes were observed only with Gd³⁺ metal ion. On addition of Gd³⁺ ions, there was a decrease in the intensity of absorbance at 312 nm and 358 nm with generation of a new band at 295 nm as well as hypsochromic shift of 17 nm respectively along with appearance of an isosbestic point at 301 nm (Figure 2). The shifting of λ_{max} toward lower wavelength could be due to interaction between receptor N, O atoms electrons with metal ions to form metal ion complexes. It is evident that 1:1 (receptor:metal) formation of complex by Benesi-Hildebrand plot (Figure 6) and method of continuous variation i.e. Job's plot (Figure 7) with association affinity^[34,35] K = 6.491×10^4 M⁻¹ for Gd³⁺.

The effect of different metal^[36] ions with respect to gadolinium metal ion was also checked at the same concentration (Figure 3). The results showed that the presence of other metal ions (Na⁺, K⁺, Mg²⁺, Cu²⁺, Cd²⁺, Hg²⁺, Y³⁺, La³⁺, Eu³⁺, Sm³⁺, Re⁶⁺ and Th⁴⁺) with Gd³⁺ metal ions had a minimal effect on the absorption spectra of ions **PBMMA + Gd³⁺** ion.

3.3 | Fluorescence spectroscopic study

PBMMA acts as sensors for gadolinium ion, as sensors are part of modern research areas within the field of supramolecular chemistry. Detection of ions by molecular



FIGURE 3 Observed interference study of the metal cations (Na⁺, K⁺, Mg²⁺, Cu²⁺, Cd²⁺, Hg²⁺, Y³⁺, La³⁺, Eu³⁺, Sm³⁺, Re⁶⁺ and Th⁴⁺) with ions **PBMMA + Gd³⁺** (17 μ M; CH₃OH:H₂O in 1:1 ν/ν) as solvent system at same concentration

receptors using fluorescence spectroscopy was found to be important biologically in *vitro-vivo* and sensors as light-emitting diodes.^[37–40] **PBMMA** has been used for detection of Gd³⁺ due to metal chelating sites that lead photo physical properties.^[41,42]

3.3.1 | Interaction of cations with receptor PBMMA by fluorescence spectral studies

Fluorescence spectroscopic studies of **PBMMA** $(3 \times 10^{-4} \text{ M})$ with metal ions $(3 \times 10^{-4} \text{ M})$ were carried out in CH₃OH:H₂O (1:1) solvent system (Figure 4). This emission of **PBMMA** shows a weak emission spectra band near 405 nm at excited wavelength 312 nm due to photoinduced electron transfer (PET) mechanism from electron denser part (N and O atoms) of receptor to the acceptor part. Further binding studies of receptor



FIGURE 4 Fluorescence emission spectra of receptor **PBMMA** $(3 \times 10^{-4} \text{ M})$ and with metal Gd³⁺, Na⁺, K⁺, Mg²⁺, Cu²⁺, Cd²⁺, Hg²⁺, Y³⁺, La³⁺, Eu³⁺, Sm³⁺, Re⁶⁺ and Th⁴⁺ ions $(3 \times 10^{-4} \text{ M})$ in $1:1(\nu/\nu)$ CH₃OH:H₂O $(1:1 \nu/\nu)$ as solvent system

PBMMA were conducted with various metal ions (Na⁺, K⁺, Mg²⁺, Cu²⁺, Cd²⁺, Hg²⁺, Y³⁺, La³⁺, Eu³⁺, Sm³⁺, Gd³⁺, Re⁶⁺ and Th⁴⁺); none of these showed significant change in fluorescence emission spectra, expect Gd³⁺ metal ion. Upon addition of Gd³⁺ ions to receptor **PBMMA**, fluorescence enhancement was observed with two new emission bands near 355 nm and 485 nm were observed at excited wavelength 312 nm (Figure 4). The mechanism of fluorescence was attributed to chelation-enhanced fluorescence mechanism (CHEF).^[43] Due to chelation of Gd³⁺ metal ion with receptor **PBMMA**, photoinduced electron transfer (PET) prevented and chelation-enhanced fluorescence.^[43,44]

The receptor **PBMMA** is specific for Gd^{3+} metal ion among various metal cations when studied under UV– visible (Figure 2) and fluorescence spectroscopic studies (Figure 4) in CH₃OH:H₂O (1:1) solvent system. The complexation of **PBMMA** with Gd^{3+} metal ion suggests that the complexation is result of the structural rearrangements and chelation binding of Gd^{3+} and this is also supported by computational studies (Figure 9). The binding feasibility of **PBMMA** with Gd^{3+} ion is due size and charge complementary that leads interaction and found less likely with other metal cations (Na⁺, K⁺, Mg²⁺, Cu²⁺, Cd²⁺, Hg²⁺, Y³⁺, La³⁺, Eu³⁺, Sm³⁺, Gd³⁺, Re⁶⁺ and Th⁴⁺).

3.4 | Binding stoichiometry

To gain further information of the Gd^{3+} cation binding interaction with the receptor, UV-visible spectrophotometric titration studies has been performed. On successive addition of Gd³⁺ (0-5 equivalent) to receptor PBMMA (17 µM) the band at 312 nm changes with hypsochromic shift in its intensity with the appearance of a new band at 295 nm with isobestic point at 301 nm as shown in Figure 5. The inferred isobestic point in an evident for the formation of new species in the solution i.e. there is interaction between **PBMMA** and Gd^{3+} ion. Receptor **PBMMA** (17 μ M) when gradually titrated by Gd^{3+} metal ions (Figure 5) gave the spectra that have been used to draw a plot between $1/(A_0-A)$ vs. $1/[Gd^{3+}]$ using Benesi-Hildebrand equation. Linearity was observed by the Benesi-Hildebrand plot^[45] (Figure 6); also results observed from job's $plot^{[\overline{46}]}$ (Figure 7) indicated the formation of a 1:1 complex with association affinity $K = 6.491 \times 10^4 \text{ M}^{-1}$ for Gd^{3+} ion. Also complexation of **PBMMA-**Gd³⁺ ion was determined by MS-ESI spectroscopy and MS-ESI-TOF $(M^- + Gd^{3+})$; (m/z) for **PBMMA** + Gd^{3+} complex found 595.7167 and m/z 437.2372 for PBMMA (Figure S4). Mass spectroscopic studies have been found to be in good agreement with the proposed structures of receptor **PBMMA**-Gd³⁺



FIGURE 5 UV-visible spectra of receptor **PBMMA** (17 μ M) with increasing concentration of Gd³⁺ ions (0–5 equivalent) in CH₃OH:H₂O (1:1 v/v) as solvent system. UV-visible (electronic spectra) of receptor **PBMMA** and with increasing concentration of Gd³⁺ to **PBMMA** (0–5 equivalent) were recorded on T 90 (PG Instruments Ltd) UV/VIS spectrometer in the region 700–200 nm



FIGURE 6 Benesi-Hildebrand plot of **PBMMA** with Gd^{3+} metal ion at 312 nm in CH₃OH:H₂O (1:1 v/v) as solvent system. Using Benesi-Hildebrand method employing $1/(A - A_o) = 1/(A - A_f) + 1/K$ (A - A_f) [Gd³⁺] equation and observed linearity in the plot which indicated the formation of a 1:1 complex with association affinity $K = 6.491 \times 10^4 M^{-1}$

complex. The mass study of complexation is evident for 1:1 complexation of the **PBMMA**-Gd³⁺ complex.

3.4.1 | Job's plot

To perform method of continuous variation (Job's plot), stock solutions (100 ml) of receptor **PBMMA** and Gd^{3+} metal salts of same concentrations were prepared. Then 10 solutions with varying mole fractions of each receptor and metal ions were prepared in CH₃OH:H₂O (1:1 ν/ν) as solvent system, keeping over all concentration constant



FIGURE 7 Job's plot for **PBMMA** and Gd^{3+} ; ([**PBMMA**] + [Gd^{3+}]) = 13.694 × 10⁻⁵ M in 1:1(ν/ν) methanol-water solvent

as 13.694×10^{-5} M. UV-visible spectra were recorded to perform Job's plot. The stoichiometry^[46] of **PBMMA**-Gd³⁺ was determined by the method of continuous variation (Job's plot). The total concentration of the receptor **PBMMA**-Gd³⁺ was kept constant (13.694 × 10⁻⁵ M), with a continuous variable molar fraction of guest Gd³⁺. Figure 7 shows the Job's plot of compound for **PBMMA**-Gd³⁺ at 312 nm. The **PBMMA**-Gd³⁺ Complex concentration approaches a maximum when the molar fraction of **PBMMA**-Gd³⁺ is 0.5. It means that **PBMMA**-Gd³⁺ complex formed a 1:1 (Host:Guest) complex with association affinity K = 6.491 × 10⁴ M⁻¹.

3.5 | Cyclic voltammetric study

Electrochemical studies^[47,48] of **PBMMA** (Figure S8) and **PBMMA-Gd³⁺ ion** (Figure S9) in solution, recorded in 3×10^{-3} M in CH₃OH:H₂O (1:1 v/v) as solvent system using KCl as supporting electrolyte at room temperature with scan rate of 0.1 V/s in the potential range – 1.0 to +3.0 V (Figure 8). It shows that it is quasi-reversible electron transfer redox process which exhibit two waves. The main anodic and cathodic peaks observed for **PBMMA** Epa = 0.0713 V and Epc = -0.1567 V; peaks observed for **PBMMA-Gd³⁺** ion are Epa = 0.4069 V and Epc = 0.7936 V. The observed peaks for **PBMMA** and **PBMMA-Gd³⁺** ion are different, this happens due to the binding of **PBMMA** with Gd³⁺ ion and change in electrochemical properties of receptor.

3.6 | Computational studies

3.6.1 | Molecular docking

The host and guest were docked with the binding energy -36.09 KJ/mol and two metal-acceptor bonding. This



FIGURE 8 Cyclic voltammetric study for **PBMMA** and **PBMMA + Gd³⁺** ion in 3×10^{-3} M in CH₃OH:H₂O (1:1 v/v) as solvent system

binding reveals the affinity of Gd^{3+} towards the **PBMMA** compound which depict the interactions with nitrogen and oxygen atom with 2.09 Å and 2.05 Å distance (Figure 9). There are two metal-acceptor bonds that describe the polarity of ligand toward metal ion.

3.6.2 | Molecular dynamics stimulation

The structural integrity and stability of docked complex (**PBMMA**-Gd³⁺) was evaluated through the molecular dynamics simulation during 10 ns time trajectory. The MD simulation executed by event and quality analysis (Table 1 and Figure S10). The Root Mean Square Fluctuation (RMSF) of ligand **PBMMA** described the frame by frame fluctuation confined by every atom which ranged between 1 to 3 Å (Figure S11) which reverse the fluctuations of ligand.

The conformational changes were identified by rotatable bonds (RB) present in host (**PBMMA**) and evaluated by torsions plot throughout the simulation trajectory (0 through 10 ns). The color-coded rotatable bonds were retained in 2D schematic diagram and accompanied by a dial plot and bar plots of the same color. The center of



FIGURE 9 Docked structure of PBMMA + Gd³⁺ ion

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TABLE 1 Simulation quality analysis								
Sr. No.	Properties	Average	Std. Dev.	Slope (ps ⁻¹)				
1	Total energy (kcal/mol)	1935.818	15.840	0.003				
2	Potential energy (kcal/mol)	-1818.760	53.710	-0.001				
3	Temperature (K)	295.778	2.794	0.000				
4	Pressure (bar)	-70.126	140.403	0.001				
5	Volume (cm ³)	61451.992	576.865	-0.011				

TABLE 2 Optimization details

		Optimization Energy				
Sr. No	Name	Optimization step	Gas Phase (Hatree)	Optimization step	Methanol (Hatree)	
1	PBMMA	69	-1521.376566	28	-1521.403284	
2	PBMMA _Gd ³⁺	40	-1556.720961	29	-1556.839791	

radial plot is the key point which related to the initiation of simulation event. However, dial plots (or radial plots) showed the conformation and density of torsion angle (Figure S12A and Figure S12B).

RMSD (Å), radius of Gyration (Å), intramolecular hydrogen bonds, Molecular surface area (Å), Solvent accessible surface area (Å), Polar surface area (Å) were different parameters observed during the quality analysis which revealed the ligand PBMMA compatibility to decipher the structural level integrity (Figure S13).

3.6.3 | DFT studies

Density functional theory calculations The geometry optimization of **PBMMA** and PBMMA_Gd³⁺ complex has been performed on both

gas phase (Figure S14) as well as solvent phase (Figure S15) and optimization energy details given in Table 2. The binding Energy of Complex (**PBMMA** Gd^{3+}) in Gas phase and solvent phase are -595.6679383 kcal/mol and - 498.0607959 kcal/mol, respectively. It shows that Strong binding between PBMMA and Gadolinium and also gives an outline about the stable complex formation during the geometry optimization in both gas and solvent phase.

Absorption spectra at TDDFT level of calculation

TD-DFT level of studies highlighted the nature of the absorption spectra analysis. The experimental and theoretical transition from the topologies of the Kohn-sham orbital; Figure 10 shows frontier molecular orbitals (FMO's) of PBMMA and the maximum wavelength



FIGURE 10 Frontier molecular orbitals (HOMO and LUMO) of the PBMMA at CPCM-TD-cam-b3lyp/gen level of approximation

Sr.

1

2

Excitation Hypsochromic Oscillator % hypsochromic Contribution Shift No Name (eV) $\lambda_{excitation}$ Shift strength **Key transitions** λ_{exp} PBMMA 3.9872 310.96 1.8067 HOMO-1-- > LUMO 312 17 14.77 41.64 HOMO-- > LUMO+1 56.73 PBMMA-295 4 186 296.19 0.9255 HOMO-2-- > LUMO+1 8.91 Gd³⁺ HOMO-2-- > LUMO 3.37 +12HOMO--> LUMO+3 28.45 HOMO - > LUMO + 62.22 HOMO--> LUMO+7 4.92 HOMO - > LUMO + 1110.03 78.55 HOMO - > LUMO + 12HOMO - > LUMO + 132.68

HOMO - > LUMO + 15

HOMO-- > LUMO+17

TABLE 3 Main Singlet Vertical Electron Transition Energies (ΔE), Wavelengths (λ), Oscillator Strengths (f), and % contribution Calculated at the TDDFT/CAMB3LYP Level

absorption (λ_{max}) is presented in Table 3. The UV-visible spectra were emerged due to the transition from higher energy orbital (HOMO-1, and HOMO) to lower energy orbital (LUMO). The transition was obtained due to amalgam of FMO's which was presented in Table 3. On the other hand, The FMOs of **PBMMA-**Gd³⁺ can be found in Figure 11 and wavelength absorption (λ_{max}) is presented in Table 3. Note that the HOMO and LUMO were distributed on PBMMA moiety and Gd³⁺ metal ion, respectively. It was observed that the UV-visible

spectra developed due to the electronic transition of higher-energy orbitals (HOMO-1, and HOMO) to lower energy orbitals (LUMO, LUMO+1, LUMO+3, LUMO +6, LUMO+7, LUMO+11, LUMO+12, LUMO+13, LUMO+15, and LUMO+17). Among that, all transitions HOMO \rightarrow LUMO+12 and HOMO \rightarrow LUMO+3 contribute more than 28% so it plays a key role for the hypsochromic shift transition. It was clearly observed that the PBMMA gives a hypsochromic shift of 17 nm with Gd³⁺ metal ions due to complexation.

4.60

3.03

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FIGURE 11 Frontier molecular orbitals (HOMO and LUMO) of the Gd³⁺ complexes of PBMMA at CPCM-TD-cam-b3lyp/gen level of approximation

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4 | CONCLUSIONS

In conclusion, we have reported synthesis and recognition potential of molecular receptor PBMMA, which was characterized by various spectroscopic methods. TGA was also carried out to explain the thermal behavior of PBMMA. The receptor PBMMA has been found very efficient for the selective recognition of Gd³⁺ metal ions among various cations, such as Gd³⁺, Na⁺, K⁺, Mg²⁺, Cu²⁺, Cd²⁺, Hg²⁺, Y³⁺, La³⁺, Eu³⁺, Sm³⁺, Re⁶⁺ and Th⁴⁺ metal ions used as sulfates. The stoichiometry of the complex formed by receptor and Gd³⁺ metal ions was established to be 1:1 by Benesi-Hildebrand plot method and method of continuous variation (Job's plot) with association affinity $K = 6.491 \times 10^4 M^{-1}$ with a shift of 17 nm from 312 nm to 295 nm. In fluorescence study it was concluded that PBMMA acts as good sensor for Gd³⁺. Cyclic voltammetric study also gives crucial information with change in redox potential upon addition of Gd³⁺ ions to **PBMMA**. The binding modes and mechanism of **PBMMA** with Gd^{3+} was further explained by molecular docking. TDDFT study also prove that the hypsochromic shift of 17 nm appear due to the energy transfer from HOMO-LUMO's in a complex between **PBMMA** and Gd³⁺. In conclusion receptor has been found selective and good sensor for Gd³⁺ ions. However, for in vivo applications, there is further research to be undertaken to determine the biocompatibility of Gd³⁺ ion for medical functions.

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DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

ORCID

Brij Mohan D http://orcid.org/0000-0003-2414-9152 Krunal Modi D http://orcid.org/0000-0002-1151-1207

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