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CHRACTERIZATION OF THE COMPLEXATION BETWEEN INDIUM(III) AND ZIROCNIUM(IV) IONS WITH THE DRUG PROCAINE: SPECTRAL ANALYSIS, THERMAL PROPERTIES, AND MICROSCOPIC IMAGING

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ABSTRACT. This paper investigates the complexation behavior of the drug procaine towards forming stable metal-based complexes. The study examines the chemical reaction between procaine (PC) and two metal ions (In^{3+} and Zr^{4+}). Controlling the temperature at 70 °C, the pH at approximately 8.5, and the stoichiometry at 1:3 for In^{3+} ion and 1:2 for Zr^{4+} ion, the reaction generated white, stable PC-In and PC-Zr complexes. To provide a comprehensive understanding of the structural, compositional, morphological, and thermal properties of the formed metal-procaine complexes, a variety of physicochemical techniques were employed to thoroughly characterize the synthesized complexes, including CHN elemental analysis, conductivity, ultraviolet/visible and Fourier-transform infrared spectroscopies, powder X-ray diffraction, transmission electron microscopy, and thermogravimetry. The study reveals that the manufactured complexes of In^{3+} and Zr^{4+} can be represented by the formulae $[In(PC)_3(H_2O)_3].Cl_3$ and $[ZrO(PC)_2(H_2O)_2].Cl_2.4H_2O$, respectively. These formulas correspond to the overall compositions of $C_{39}H_{66}N_6Cl_3O_9In$, and $C_{26}H_{52}N_4Cl_2O_{11}Zr$, respectively. The high-quality and well-focused TEM images demonstrate that the complexes possessed a uniform and well-structured morphology. The investigation of the complexation behavior of procaine with In^{3+} and Zr^{4+} ions provide valuable insights into the formation and properties of these stable complexes, which can have potential applications in the pharmaceutical and biomedical fields.

KEY WORDS: Drug procaine, Metal ion, Spectral analysis, Thermal decomposition, TEM

INTRODUCTION

The reaction of metal ions with inorganic and organic molecules gives rise to an essential class of chemical compounds, namely metal complexes or metal-based complexes [1-5]. When metal ions interact with biologically active molecules, the resulting products are known as metallodrugs or metal-based drugs, exhibiting a wide array of pharmaceutical and medical applications [6, 7]. Metal complexes play a pivotal role in numerous scientific disciplines, including medicine, pharmacology, chemistry, biology, material sciences, physics, and catalysis [8, 9]. Researchers have shown considerable interest in the synthesis, characterization, and application of metal-based complexes [10-19], as their crucial role in investigating the chemical reactions between bioactive molecules and metal ions is integral to the design and development of novel metallodrugs, underscoring the value of their contributions to various benefits such as: (i) Enhancing the biological and pharmaceutical properties of numerous drugs and natural active products through metal complexes. (ii) Mitigating the severe adverse effects associated with existing metal-based

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drugs. (iii) Overcoming the challenge of metal-based drugs resistance. (iv) Investigating novel metal-based complexes with potential therapeutic properties to combat emerging diseases like COVID-19.

Procaine is a synthetic local anesthetic drug belonging to the amino ester family. This compound induces a reversible loss of sensation by decreasing the conduction of sensory nerve impulses [20]. Its IUPAC name is 2-ethyl-4-aminobenzoate, and its chemical structure is depicted in Figure 1. Procaine was first synthesized in 1905 and introduced under the trade name Novocaine as the initial injectable synthetic local anesthetic. Prior to the discovery of procaine, cocaine was the most widely used local anesthetic. Furthermore, since Koller's pioneering use of cocaine to anesthetize a cornea in 1844, local anesthetics have been continuously developed. Procaine exhibits low toxicity and minimal stimulatory effects, and it is not toxic to the central nervous system [21]. Procaine is widely employed as a pharmacological agent in life sciences and clinical therapeutic research, and it is primarily used to alleviate pain associated with the intramuscular administration of penicillin. Additionally, it finds application in various dental procedures, such as numbing the gums during fillings, extractions, and root canals [22]. Procaine is a versatile and commonly used local anesthetic drug that has been an important part of the development of local anesthesia in medicine and dentistry.

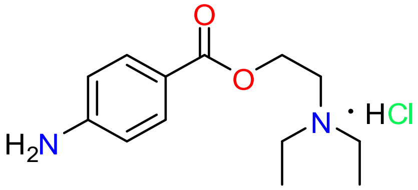

Figure 1. Molecular structure of procaine (HCl form).

This paper investigates the formation of metal-based complexes using procaine (abbreviated as PC) as an organic ligand and two metal ions (In^{3+} and Zr^{4+}). Initially, the researchers conducted a series of chemical reactions between PC and the investigated metal ions at a 1:3 stoichiometry for In^{3+} ion and 1:2 for Zr^{4+} ion, a pH of approximately 8.5, and a temperature of 70 °C, resulting in the formation of the corresponding metal complexes ([InPC] and [ZnPC]). Subsequently, the researchers employed a variety of physicochemical techniques to thoroughly characterize the synthesized complexes, including CHN elemental analysis, ultraviolet/visible (UV-Visible) and Fourier-transform infrared (FT-IR) spectroscopies, powder X-ray diffraction (XRD), transmission electron microscopy (TEM), and thermal measurements. The researchers used these techniques to provide a comprehensive understanding of the structural, compositional, and thermal properties of the formed metal-procaine complexes.

EXPERMENTAL

Chemicals

All chemicals used in this work were of analytical grade and were obtained from Sigma-Aldrich (St Louis, MO, USA) at the highest purity available. The ligand employed in the preparation of metal-based complexes is procaine in hydrochloride form (PC; $C_{13}H_{21}N_2O_2Cl$; 272.77 g/mol). The investigated metal ions are In^{3+} and Zr^{4+} in the form of chloride salts. ($InCl_3$; 221.18 g/mol; purity 98%) and ($ZrOCl_2 \cdot 8H_2O$; 322.25 g/mol; purity $\geq$ 99.5%). Deionized water from a water purification unit and HPLC-grade methanol were the solvents utilized in the preparation. The deionized water was used to dissolve the ligand, while the HPLC-grade methanol was employed to dissolve metal chlorides.

Preparation

Complexes of the PC ligand with In^{3+} and Zr^{4+} ions were synthesized as reported in the referenced sources [2-5]. Briefly, a 6 mmol solution of the PC ligand in methanol was stirred for 2-4 min. Subsequently, a solution of $InCl_3$ in deionized water (2 mmol) was added dropwise. The PC-In mixture was then continuously stirred at 70 °C, and the pH was adjusted to approximately 8.5 using a few drops of NH_3 (5%). The mixture was stirred for an additional 5-7 min and left to evaporate until the solution volume was halved. After standing overnight, white, dense precipitates formed. The precipitates were collected, filtered, and thoroughly washed with hot deionized water, diethyl ether, and methanol. The PC-In complex was then oven-dried at 75 °C. The PC-Zr complex was prepared using the same method but with $ZrOCl_2 \cdot 8H_2O$ (3 mmol) instead of $InCl_3$. Both the PC-In and PC-Zr complexes were stored in a desiccator containing anhydrous $CaCl_2$. The synthesis process involved several key steps, including the initial mixing of the PC ligand and metal ion solutions, pH adjustment, evaporation, and precipitation. The resulting PC-In and PC-Zr complexes were then purified and dried for further analysis and characterization.

Identification techniques

A Nicolet iS10 Fourier transform infrared spectrometer (FTIR) and a Perkin-Elmer Lambda 25 ultraviolet-visible (UV/Vis) spectrophotometer were used to collect the FT-IR spectra and electronic absorption spectra, respectively, of the PC-In and PC-Zr complexes. A HACH digital conductivity meter was employed to measure the molar conductivities of the PC-In and PC-Zr complexes, while a Perkin-Elmer 2400 series II CHNS Elemental Analyzer was utilized to determine the elemental compositions of the complexes. A Shimadzu TGA–50H thermal analyzer and a JEM-2010 JEOL Transmission Electron Microscope (TEM) were used to collect the thermal behavior and morphological characteristics, respectively, of the PC-In and PC-Zr complexes. Finally, a Philips X'Pert X-ray diffractometer was utilized to obtain the powder X-ray diffraction patterns of the PC-In and PC-Zr complexes.

RESULTS AND DISCUSSION

Analysis results from UV-Visible spectroscopy and molar conductance studies

Figure 2 illustrates the UV-Visible spectra of the free PC ligand and its complexes with In^{3+} and Zr^{4+} ions. All three compounds were dissolved in dimethylsulfoxide (DMSO) solvent, and their UV-Visible spectra were recorded over the wavelength range from 200 to 800 nm. The uncomplexed PC ligand exhibits a broad absorption profile spanning 200 to 570 nm, with two prominent and wide absorption bands centered at 336 and 428 nm. The band at 336 nm is slightly more intense than the 428 nm band, and both are approximately the same width. The ligand also displays a narrow, medium-intensity absorption band at 206 nm, which can be attributed to $\pi \rightarrow \pi^*$ transitions, while the 336 and 428 nm bands are assignable to $n \rightarrow \pi^*$ transitions. Upon the complexation of the PC ligand with In^{3+} ions, the 336 nm absorption band maintains its position, intensity, and width as in the free ligand. However, the 428 nm band undergoes a significant decrease in intensity. Similarly, the absorption bands at 336 and 428 nm are still present in the PC-Zr complex, but their intensities are reduced, and the 428 nm band becomes broader than in the free ligand. These spectral changes can be attributed to the complexation process between PC ligand and the metal ions, and potentially to metal-to-ligand charge transfer (MLCT) transitions. The observed changes in the UV-Visible spectra of the PC ligand upon complexation with In^{3+}

and Zr^{4+} ions suggest that the coordination of the metal ions to the PC ligand has a significant impact on the electronic structure and optical properties of the resulting complexes. The free PC ligand and its complexes were dissolved in DMSO solvent at a specific concentration (10^{-3} M), and their conductivities were measured using a HACH digital conductivity meter. The molar conductance values for the free PC ligand, PC-In complex, and PC-Zr complex were 21.28, 165.24, and 120.75 S cm^2 mol^{-1}, respectively. The ligand exhibited non-conducting behavior in the DMSO solution, as indicated by these values. Furthermore, the conductance values suggest the electrolytic nature of the PC-In and PC-Zr complexes, implying the presence of chloride ions either outside or within their coordination spheres. This reveals the distinct electrical properties of the PC ligand and its complexes, with the free ligand being non-conducting and the complexes exhibiting electrolytic behavior, likely due to the presence of chloride ions.

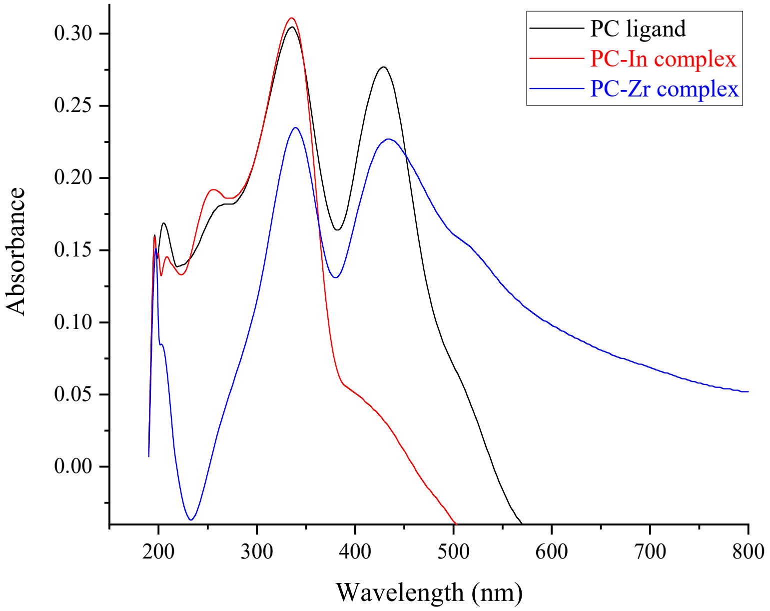

Figure 2. UV-Visible spectra of free PC ligand and its complexes with In^{3+} and Zr^{4+} ions.

Findings from elemental analysis

To confirm the composition of the PC ligand and the studied metal ions, the levels of carbon, hydrogen, nitrogen, and the metal, as well as the water content were measured in the produced PC-In and PC-Zr complexes. An elemental analyzer was used to determine the percentages of C, H, N, and Cl, while the metal and water contents were obtained through gravimetric analysis. The specific measurements and results from these analyses are presented below. The microanalytical analysis of the PC-In complex revealed the following calculated elemental composition: indium at 11.67%, water at 5.49%, nitrogen at 8.54%, chlorine at 10.82%, carbon at 47.60%, and hydrogen at 6.76%. The corresponding experimental data for these elements were: indium at

11.82%, water at 5.60%, nitrogen at 8.79%, chlorine at 10.66%, carbon at 47.75%, and hydrogen at 6.91%. The experimental results closely matched the calculated values, indicating the reliability of the analysis. Similarly, the microanalytical examination of the PC-Zr complex showed the following calculated elemental composition: zirconium at 12.04%, water at 14.23%, nitrogen at 7.38%, chlorine at 9.34%, carbon at 41.14%, and hydrogen at 6.91%. The corresponding experimental data for these elements were: zirconium at 12.19%, water at 14.15%, nitrogen at 7.16%, chlorine at 9.55%, carbon at 40.97%, and hydrogen at 7.04%. The experimental results closely matched the calculated values, further validating the accuracy of the analysis. Based on the elemental analysis, the synthesized complexes of In^{3+} and Zr^{4+} can be represented by the formulae $[In(PC)_3(H_2O)_3].Cl_3$ and $[ZrO(PC)_2(H_2O)_2].Cl_2.4H_2O$, respectively. These formulas correspond to the overall compositions of $C_{39}H_{66}N_6Cl_3O_9In$ (984.15 g/mol), and $C_{26}H_{52}N_4Cl_2O_{11}Zr$ (758.84 g/mol), respectively. The elemental composition data suggest a 1:2 metal-to-ligand stoichiometry for the PC containing Zr^{4+} ions, and a 1:3 metal-to-ligand stoichiometry for the PC complex containing In^{3+} ions.

Analysis results from FTIR spectroscopy

Infrared spectroscopic analysis provides valuable insights into the coordination site within the ligand and reveals distinct differences in the spectra of the resulting metal-based complexes. Figure 3 displays the full FT-IR spectra of the free PC ligand and its corresponding metal-based complexes. A comprehensive comparison of the relevant IR spectral bands of the free PC ligand with the corresponding bands in the IR spectra of the isolated PC-In and PC-Zr complexes clearly indicates that several of the characteristic bands of the PC molecule exhibit notable shifts in frequency and significant changes in their band intensities. These observed shifts in position and intensity of some of the bands can be directly attributed to the expected changes in symmetry and electronic structure of the PC units in the formed PC-In and PC-Zr complexes compared to the free PC molecule.

The key characteristic FT-IR spectral bands of the free PC molecule were: 3346, 3312 υ_{as}(N-H), 3204 υ_s(N-H), 1728 υ_{as}(C=O), 1692 υ_s(C=O), 1602 δ_{def}(N-H), 1520 υ(C=C), 1269 υ(C–O), 1168 υ_{as}(C-N), 1112 υ_s(C-N). The experimental IR spectral data aligns with previously reported findings [23-25]. When the PC molecule interacts with the metal ions, the intensities and frequencies of the $-NH_2$ groups [υ_{as}(N-H), υ_s(N-H), δ_{def}(N-H)] are affected. The bands corresponding to the υ_{as}(N-H), υ_s(N-H), and δ_{def}(N-H) vibrations shifted to (3363 and 3300), 3230, and 1595 cm^{-1} in the PC-In complex, and to (3361 and 3302), 3233, and 1592 cm^{-1} in the PC-Zr complex, respectively. The complexation between the PC molecule and the metal ions did not significantly impact the C=O modes, as the frequencies of the C=O modes [υ_{as}(C=O) and υ_s(C=O)] were only slightly shifted or remained unchanged in the complexes compared to the free PC ligand. The substantial shifts in the characteristic bands due to the $–NH_2$ group of the PC ligand clearly suggest the involvement of this group in the complexation with In^{3+} and Zr^{4+} ions. The participation of $–NH_2$ in the chelation process with the metal ions resulted in the formation of new and weak bands in the IR spectra of PC-In and PC-Zr complexes. This band was observed at 497 cm^{-1} in the PC-In and at 493 cm^{-1} in the PC-Zr and could be assigned to the υ(M-N) vibrations [26]. The coordinated water molecules exhibit four angular deformation modes: $\delta_b(H_2O)$, $\delta_{rock}(H_2O)$, $\delta_{wag}(H_2O)$, and $\delta_{twist}(H_2O)$. The IR spectrum of the PC-In complex displays absorption bands at 1629, 845, 660, and 543 cm^{-1} that can be attributed to these respective motions. Likewise, the IR spectrum of the PC-Zr complex shows corresponding frequencies at 1642, 851, 664, and 570 cm^{-1} [27]. Based on the analytical and spectral data, the proposed structures of PC-In and PC-Zr are depicted in Figure 4.

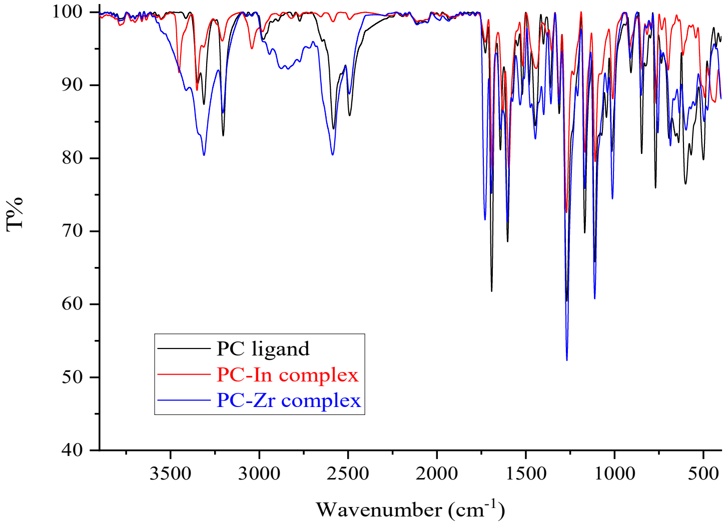

Figure 3. FT-IR spectra of free PC ligand and its complexes with In^{3+} and Zr^{4+} ions.

Findings from XRD and TEM analysis

The powder-free PC ligand and its complexes with In^{3+} and Zr^{4+} ions were analyzed using an X-ray diffraction instrument. The instrument operated at 40 kV and 30 mA, equipped with a Ge monochromator before the sample and a Cu $K_{\alpha 1}$ X-ray source with a wavelength of 0.154056 nm. The XRD patterns were recorded at 25 °C, covering an angular range of 10 to 70°. The obtained spectral data from the compounds' XRD patterns are listed in Table 1. The XRD diffractogram of the free PC ligand contains three characteristic XRD reflections: a very strong intensity line at 2θ 14.452°, and two medium-intensity diffraction patterns at 2θ 28.850° and 36.333°. The ligand also showed a group of six low-intensity lines. The XRD profile of the free ligand changed when it was complexed with the investigated metal ions. The XRD profile of the PC-In complex exhibited a single, highly prominent XRD reflection line at a Bragg's angle (2θ) value of 15.528°. This sole line indicates that the complex possessed a crystalline structure, suggesting a well-ordered atomic arrangement within the material. The complex resulting from the reaction of PC with Zr^{4+} exhibited two very strong XRD diffraction lines of approximately equal intensity, located at Bragg's angle 2θ values of 21.653° and 24.868°. The XRD patterns of the PC-Zr complex also showed a medium-intensity line at 16.496°. These reflections suggest that the PC-In and PC-Zr complexes had well-organized and well-defined structures. The full width at half-maximum (FWHM) of the strongest diffraction line for the free PC ligand, the PC-In complex, and the PC-Zr complex were 0.249°, 0.347°, and 0.284°, respectively. The corresponding values of the inter-planar spacing between the atoms (*d*-spacing) of the highest-intensity line were 6.12409 Å, 5.70203 Å, and 4.10098 Å, respectively.

The particle sizes of the free PC ligand, the PC-In complex, and the PC-Zr complex were analyzed using a high-resolution transmission electron microscope (TEM). The captured TEM images were used to measure particle sizes and observe their morphology and distribution. Figure 5 depicts the TEM images of the free PC ligand, the PC-In complex, and the PC-Zr complex. The high-quality and well-focused TEM images of the PC molecule revealed that its particles have a mix of shapes, including irregularly rectangular, irregularly polygonal, and stone-like. The PC molecule particles are clustered, forming a tree branch-like structure. The introduction of In^{3+} ions into the PC molecule changed its particle morphology to a homogeneous elliptical-shaped and ovoid structure. The PC-In complex particles tend to be individual and exhibit diameters ranging from 50 to 150 nm. The introduction of Zr^{4+} ions into the PC molecule changed its particle morphology to a long rod-like shape. The PC-Zr complex rods have varying sizes and thicknesses, with an average length of approximately 1200 nm and an average width of approximately 500 nm. The TEM analysis indicated that the type of metal ion significantly affects the structural morphology of the PC ligand. While the PC-In complex particles exhibit a mix of elliptical-shaped and ovoid morphology, the PC-Zr complex particles have a clear rod-like shape. The particle size and morphological changes observed in the TEM analysis suggest that the interactions between the PC ligand and the metal ions play a crucial role in determining the final structural properties of the complexes. The shapes of the synthesized complexes depend on the metal ions in the chemical structure. The PC-Zr complex had a rod-like shape, while the PC-In complex had a mix of elliptical and ovoid particles. The metal ion properties, such as atomic radius, electronegativity, and coordination, determine the final shapes.

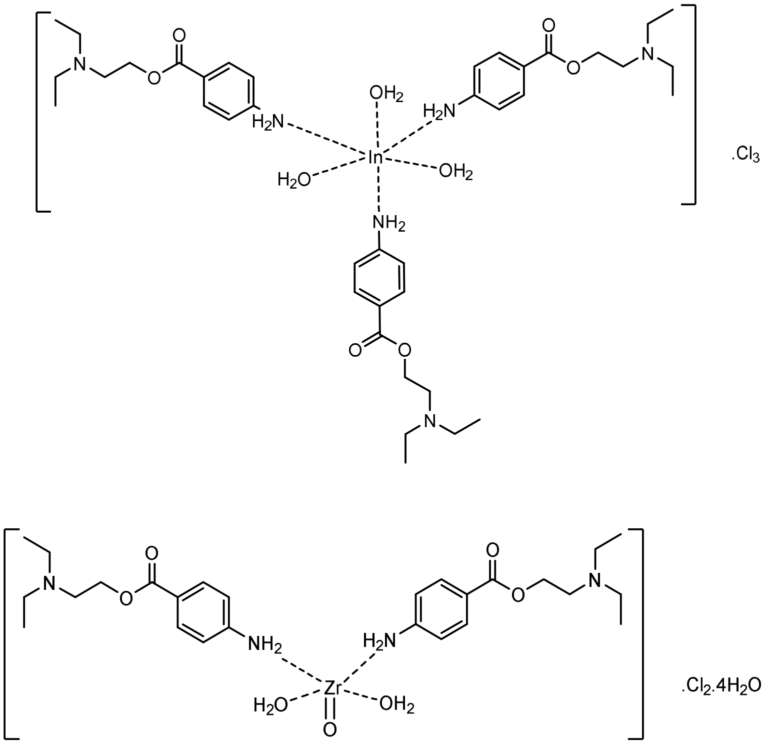

Figure 4. Proposed chemical structures of $[In(PC)_3(H_2O)_3].Cl_3$ and $[ZrO(PC)_2(H_2O)_2].Cl_2.4H_2O$ complexes.

Table 1. The XRD spectral data of the strongest lines for free PC, PC-In, PC-Zr complex.

Compound	2θ (deg)	*d*-spacing value (Å)	FWHM (deg)	Gross intensity
Free PC	14.452	6.12409	0.249	5211
	28.850	3.09215	0.279	3801
	36.333	2.47069	0.154	3478
PC-In	15.528	5.70203	0.347	856
PC-Zr	16.496	5.36954	0.280	655
	21.653	4.10098	0.284	517
	24.868	3.57754	0.331	444

Thermal analyses

The compositions and structures of the $[In(PC)_3(H_2O)_3].Cl_3$ and $[ZrO(PC)_2(H_2O)_2].Cl_2.4H_2O$ complexes were confirmed by thermal analysis (TG/DTG). The representative thermograms of the free PC ligand, the PC-In complex, and the PC-Zn complex were collected within the specified temperature range (TG/DTG) under an air atmosphere. Table 2 summarized the potential thermal degradation patterns for these compounds. The close correspondence between the calculated and experimental percentages of the moieties expelled from the synthesized complexes strongly supports the experimentally determined stoichiometry of the complexes. The thermogram of the free PC ligand indicates that it is thermally stable up to 200 °C, begins decomposing at around 200°C, and is completely decomposed at around 600 °C. Its thermal decomposition proceeds through a single degradation step with a DTG_{max} of 287 °C. The observed weight loss associated with this step is (observed; 99.80%, calculated; 100.0%), which can be attributed to the loss of the $C_{13}H_{21}N_2O_2Cl$ organic moiety ($6C_2H_2 + N_2 + CO_2 + 4H_2 + HCl$). The PC-In complex underwent thermal decomposition in roughly two steps within the 200-800 °C temperature range. The first mass loss (observed; 39.83%, calculated; 40.62%), peaking at DTG_{max} of 295 °C, corresponded to the release of $3H_2O$, PC, Cl_2, and HCl molecules. The second decomposition step (observed; 44.73%, calculated; 44.83%), with a maximum around 440 °C and occurring within the 350-800 °C range, was likely due to the removal of one PC molecule and the organic moiety $C_{13}H_{19}N_2$. The final decomposition product was indium(III) oxide (In_2O_3), free of any remaining carbon. The PC-Zr complex undergoes thermal decomposition in roughly three stages, within the temperature range of 70-800 °C. During the initial decomposition stage in 70-275 ºC temperature range, all the coordinated and uncoordinated water molecules were released. In the second stage from 275-400 °C (observed; 39.76%, calculated; 40.48%), the mass loss at the maximum rate of decomposition at DTG_{max} of 319 °C is reasonably attributed to the loss of the PC moiety and a Cl_2 molecule. Continuous mass loss in the thermogravimetric curve from 400-800 °C corresponds to the loss of the $C_{13}H_{20}N_2O$ moiety (observed; 28.76%, calculated; 29.00%) at a DTG_{max} of 432 °C. The third and final stage leaves behind ZrO_2 as the end product, free of any residual carbon.

Table 2. The potential thermal degradation patterns for the free PC ligand and its metal-based complexes.

Compound	Stages	TG range (°C)	DTG max. (°C)	TG% mass loss		Lost species
				Found	Calculated	
Free PC ligand	I	200-600	287	99.80	100.0	$6C_2H_2 + N_2 + CO_2 + 4H_2 + HCl$
PC-In complex	I	200-350	295	39.83	40.62	$3H_2O + PC + Cl_2 + HCl$
	II	350-800	440	44.73	44.83	$PC + C_{13}H_{19}N_2$
	Residue	-	-	14.74	14.10	$0.5In_2O_3$
PC-Zr complex	I	70-275	242	14.67	14.23	$6H_2O$

	II	275-400	319	39.76	40.48	Cl_2 + PC
	III	400-800	432	28.76	29.00	$C_{13}H_{20}N_2O$
	Residue	-	-	16.50	16.24	ZrO_2

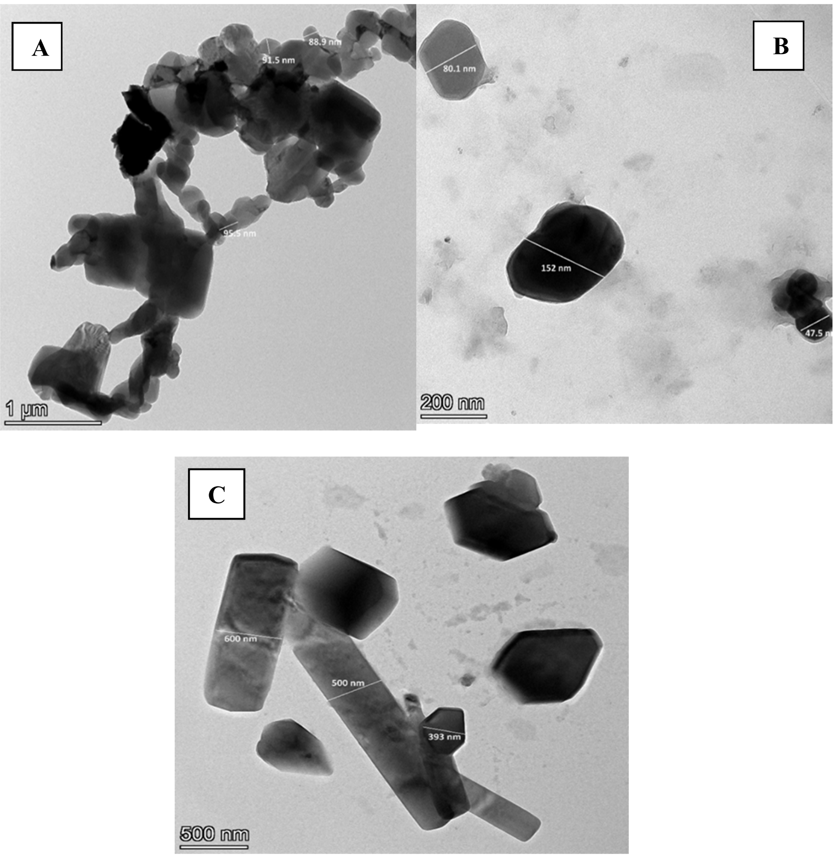

Figure 5. TEM images of A) the free PC ligand, B) the PC-In complex, and C) the PC-Zr complex.

CONCLUSION

This paper examines the complexation behavior of the drug procaine with the formation of stable metal-based complexes. The study investigates the chemical interaction between procaine (PC) and two metal ions (In^{3+} and Zr^{4+}). By controlling the temperature at 70 °C, the pH at approximately 8.5, and the stoichiometry at 1:3 for In^{3+} ion and 1:2 for Zr^{4+} ion, the reaction produced white, stable PC-In and PC-Zr complexes. A variety of physicochemical techniques, including CHN elemental analysis, conductivity, spectroscopic methods, powder X-ray diffraction (XRD), electron microscopy (TEM), and thermal analysis, were employed to provide a comprehensive understanding of the structural, compositional, morphological, and thermal properties of the formed metal-procaine complexes. The study reveals that the synthesized complexes of In^{3+} and Zr^{4+} can be represented by the formulas $[In(PC)_3(H_2O)_3].Cl_3$ and $[ZrO(PC)_2(H_2O)_2].Cl_2.4H_2O$, respectively. The high-quality and well-focused TEM images demonstrate the uniform and well-structured morphology of the complexes. Studying how procaine forms complexes with In^{3+} and Zr^{4+} ions provides valuable information about these stable complexes, which may have applications in pharmaceuticals and medicine. Future research will examine procaine's interactions with various metal ions, aiming to better understand its capacity to form stable complexes. Further studies of these interactions could yield new insights, enabling innovative applications in areas like catalysis, environmental remediation, and medicine.

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