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Mechanochemical Synthesis, Characterization and Antifungal Studies of Organotin (iv) Carboxylates Obtained from Citric Acid

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Abstract
The morbidity and mortality caused by invasive fungal infections are increasing across the globe due to developments in transplant surgery, the use of immunosuppressive agents, and the emergence of drug-resistant fungal strains, which have led to a challenge in terms of treatment. This study investigates the mechanochemical synthesis, characterization, and antifungal properties of organotin (IV) citrate complexes. Four complexes were synthesized via solvent-free grinding: Bu2SnCTR-30, Bu2SnCTR-60, Bu3SnCTR-30, and Bu3SnCTR-60. Characterization using FTIR, thermal analysis, XRF, and PXRD confirmed successful synthesis and provided structural insights. Longer reaction times improved yields, crystallinity, and tin content. Antifungal studies revealed activity against Aspergillus niger and A. flavus, with Bu2SnCTR-60 showing the highest potency (MIC: 12.5 mg/mL, MFC: 25 mg/mL). The complexes were inactive against Candida albicans, indicating potential for targeted applications. This green synthesis approach offers an environmentally friendly alternative for producing antifungal organotin compounds, with implications for agricultural and medicinal use. Further optimization of reaction conditions, expanded antifungal testing, and toxicity assessments are recommended for future research.
Keywords: Mechanochemistry, organotin carboxylates, antifungal activity, green synthesis, characterization

Introduction

The industrial and agricultural sectors have extensively employed organotin compounds across diverse applications, particularly as pesticides, fungicides, and antifouling agents, owing to their distinctive characteristics and chemical reactivity [1]. Research has demonstrated the efficacy of organotin (IV) compounds in controlling microorganisms, leading to their deployment as fungicides, bactericides, and pesticides [2]. Contemporary investigations have expanded into exploring potential therapeutic applications, specifically examining antitumor and antimicrobial properties [3].

The scientific community maintains sustained interest in organotin (IV) compounds, with particular emphasis on organotin (IV) carboxylates, primarily due to their biological implications [4]. Their capacity to hinder cellular proliferation positions makes organotin (IV) carboxylate complexes promising candidates for cancer therapeutics [4]. The biological effectiveness of these compounds correlates strongly with their molecular architecture and the tin atom's coordination number [1]. This established relationship between structural characteristics and biological functionality has catalyzed extensive research into tin carboxylates. The remarkable biological efficacy of organotin (IV) compounds has accelerated their integration into pharmaceutical applications [4]. The economic advantages of organotin complexes further enhance their appeal. Their implementation in clinical medicine promises reduced costs, lower dosage requirements, and enhanced therapeutic outcomes. These factors have motivated research into organotin (IV) carboxylate synthesis for novel pharmaceutical developments.

Mechanochemistry represents an emerging methodology that harnesses mechanical energy to facilitate solid-state reactions efficiently, requiring minimal or no solvent intervention. This environmentally conscious approach eliminates solvent requirements and minimizes waste generation. The process offers multiple advantages, including high yields [5], scalability [2], expedited reaction times [6], and cost-effectiveness [3]. Studies have confirmed the feasibility of synthesizing coordination complexes through solvent-free grinding techniques, achieving outcomes comparable to conventional methodologies [7]. Mechanochemistry, using mechanical energy to induce chemical reactions, has emerged as a promising approach in green chemistry. Although this method can be traced back to prehistoric times, it has gained renewed interest in recent decades due to its potential to reduce or eliminate the use of solvents in chemical synthesis [8,9]. Some key advantages of mechanochemical synthesis include reduced solvent use [10], improved yields [5], shorter reaction times [6], cost-effectiveness [3], and unique reactivity [11]. Recent

advancements in mechanochemistry have expanded its applications in various fields, including organic synthesis, materials science, and pharmaceutical development. For instance, Hernández and Bolm [12] demonstrated the mechanochemical synthesis of pharmaceutically relevant compounds, highlighting the method's potential in drug discovery and development.

Organotin compounds are organometallic compounds containing at least one tin-carbon bond. These compounds have found numerous applications in industry, agriculture, and medicine due to their diverse properties and reactivity [3]. The general formula for organotin compounds is RnSnX(4-n), where R represents an organic group (e.g., methyl, butyl, phenyl), X is an anionic species (e.g., halide, oxide, hydroxide), and n ranges from 1 to 4. The properties and reactivity of organotin compounds are largely influenced by the number and nature of the organic groups attached to the tin atom [13]. Organotin compounds have been extensively studied for their biological activities, including antifungal properties [2], antitumor activity [3], and antibacterial potencies [13]. However, concerns about the environmental persistence and toxicity of some organotin compounds have led to restrictions on their use in certain applications, particularly as antifouling agents in marine paints. This has prompted research into developing more environmentally friendly organotin compounds and exploring new applications in areas such as medicine and materials science [13].

The significance of antifungal research has intensified due to mounting challenges in human health and agriculture [2]. Several factors necessitate enhanced antifungal solutions, including climate-driven changes, globalization impacts, compromised immune populations [5], emerging resistance patterns [3], limited therapeutic options, and agricultural productivity concerns [6]. Global mortality rates attribute over 1.5 million annual deaths to fungal infections [5]. Cryptococcus, Candida, and Aspergillus represent the primary fungal pathogens associated with human mortality and morbidity [14]. Certain strains demonstrate resistance to contemporary antifungal treatments. The escalation in transplant procedures, immunosuppressive therapy, and resistant fungal strains have intensified treatment challenges globally [15]. Additionally, the mechanisms of antifungal action for many organotin (IV) carboxylates remain to be fully elucidated. Also, concerns about potential toxicity and environmental persistence of some organotin compounds necessitate careful evaluation of their safety profiles alongside their antifungal efficacy [13]. Despite these challenges, the promising antifungal activities observed in many organotin (IV) carboxylates continue to drive research in this field. The development of new synthesis methods, such as mechanochemical approaches, may facilitate the discovery and optimization of novel organotin (IV) carboxylate complexes with enhanced antifungal properties and improved safety profiles.

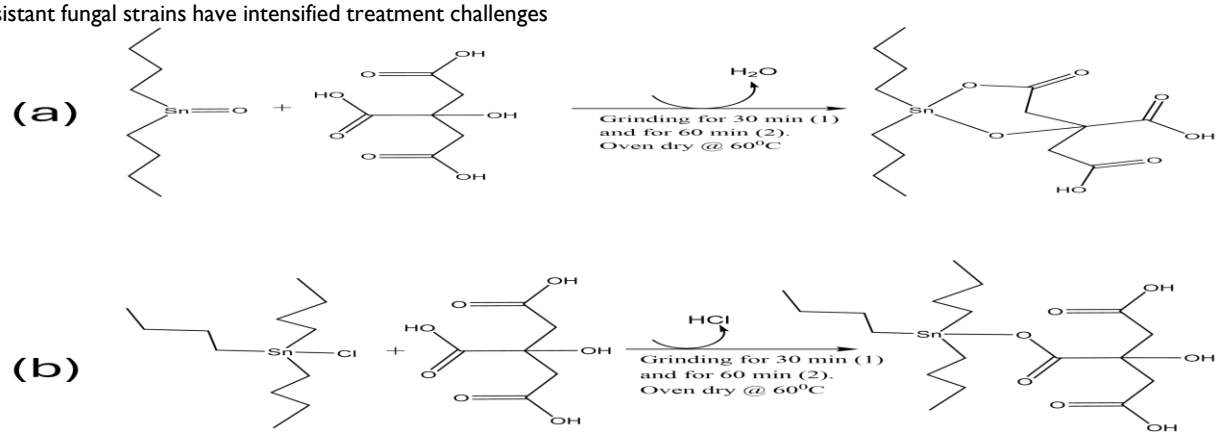
Materials and Methods

Chemicals and Equipment

All chemicals used in this study were of analytical grade and obtained from Sigma-Aldrich. The main reagents included tributyltin (IV) chloride (Bu_3SnCl), dibutyltin (IV) oxide (Bu_2SnO), citric acid, methanol, ethanol, acetone, dimethylformamide (DMF), and dimethylsulfoxide (DMSO). Others were distilled water, nutrient broth, and nutrient agar for microbial studies.

Synthesis of Organotin (IV) Complexes

The organotin (IV) citrate complexes were synthesized using a solvent-free mechanochemical method, adapted from the procedure described by [16] with modifications. Two dibutyltin (IV) citrate complexes were synthesized (Scheme 1a): Bu_2SnCTR-30 (S1): Dibutyltin (IV) oxide (1.0000 g, 4.02 mmol) and citric acid (0.7713 g, 4.02 mmol) were combined in an agate mortar and ground vigorously for 30 minutes. Bu_2SnCTR-60 (S2): The same procedure was followed, but the grinding time was extended to 60 minutes. Similarly, two tributyltin (IV) citrate complexes were synthesized (Scheme 1b): Bu_3SnCTR-30 (S3): tributyltin (IV) chloride (1.0000 g, 3.07 mmol) and citric acid (0.5898 g, 3.07 mmol) were combined in an agate mortar and ground vigorously for 30 minutes. Bu_3SnCTR-60 (S4): The same procedure was followed, but the grinding time was extended to 60 minutes. After synthesis, all complexes were dried in an oven at 60°C for 2 hours and stored in airtight containers for further analysis.



Scheme 1: Synthetic protocol for the synthesis of S1 and S2 (a) and protocol for S3 and S4 (b)

Characterization Techniques

FTIR spectra were recorded using a Perkin Elmer Spectrum Two FTIR Spectrometer. Samples were prepared as KBr pellets, and spectra were collected in the range of 4000-400 cm^-1 with a resolution of 4 cm^-1. Thermal analyses were performed using a Perkin Elmer STA 6000 Simultaneous Thermal Analyzer. Samples (5-10 mg) were heated from 30°C to 800°C at a rate of 10°C/min under a nitrogen atmosphere. Powder XRD patterns were obtained using a Bruker D8 Advance X-ray Diffractometer with Cu Kα radiation (λ = 1.5406 Å). Scans were performed in the 2θ range of 10° to 70° with a step size of 0.02°. Elemental analysis of tin content was conducted using a Spectro XEPOS XRF Spectrometer. Samples were prepared as pressed pellets for analysis.

Antifungal Activity Studies

The antifungal activity of the synthesized complexes was evaluated against Candida albicans, Aspergillus niger, and Aspergillus flavus using the agar well diffusion method [17,18]. Minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) were determined using the broth dilution method [19].

Results

Synthesis and Physical Properties

Four organotin (IV) citrate complexes were successfully synthesized: Bu2SnCTR-30 (S1), Bu2SnCTR-60 (S2), Bu3SnCTR-30 (S3), and Bu3SnCTR-60 (S4). Yields ranged from 71.68% to 88.38%, with higher yields observed for longer reaction times. The physical properties of the synthesized organotin complexes and their percentage yields are presented in Table 1. The data obtained confirmed the formation of the complexes, as their observed colours matched the expected ones. For instance, the synthesized organotin complexes S1 and S2 were off-white while S3 and S4 were white. The complexes had good yields ranging from 71.68% to 88.38%. The highest yields were from complexes S1 and S2 (87.54% and 88.38%), while complex S3 had the lowest yield (71.68%). Interestingly, the longer reaction time resulted in higher yields for S2 and S4. The complexes were formed according to Scheme 1.

Table 1: Physical properties of the synthesized organotin complexes

Complex	Formula weight ($gmol^{-1}$)	Decomposition temperature (°C)	Colour	Yield (%)
Bu_2SnCTR-30 (**S1**)	422.92	96–98	Off white	87.54
Bu_2SnCTR-60 (**S2**)	422.92	83–85	Off white	88.38
Bu_3SnCTR-30 (**S3**)	481.00	86–89	White	71.68
Bu_3SnCTR-60 (**S4**)	481.00	71–73	White	79.83

FTIR Spectroscopy

The analysis of the infrared spectral data of the complexes reported has provided sufficient evidence for a better understanding of the coordinating modes in the organotin complexes. FTIR analyses were conducted on the synthesized metal complexes, with the spectra data in Table 2 and the spectra shown in Figures 1 – 3. The absorption band due to ν(C=O) was observed at 1687 – 1717 cm−1 in the spectra of the organotin complexes indicating the incorporation of the ligands to form the complexes [20]. This is supported by the vibrational frequencies at ca. 2913 – 2927 cm-1 in the spectra of the complexes. This indicates the presence of the C-H group. The fact that the peaks appeared in a similar position rationalizes the similarity of the corresponding S1 and S2, and S3 and S4 which are only different in the reaction time. The presence of bands at ca. 3491 – 3496 cm-1 in the spectra of all the complexes suggests the presence of the O–H group. Interestingly, bands associated with the organometallic bond (Sn–C) were observed at ca. 660 – 690 cm-1 in the spectra of the complex compounds while peaks observed in the range of 762 – 779 cm-1 were ascribed to the Sn-O vibration in the respective citric acid complexes. The findings in the present study are consistent with those of other researchers for similar kinds of materials [20,21].

Table 2: FTIR spectra data for the synthesized organotin complexes

Complex/bands (cm^{-1})	O-H	C-H	C=O	C-O	Sn-C	Sn-O
Bu_2SnCTR-30 (**S1**)	3492	2913	1691	1235	779	659
Bu_2SnCTR-60 (**S2**)	3492	2918	1717	1228	775	664
Bu_3SnCTR-30 (**S3**)	3491	2923	1695	1131	767	691
Bu_3SnCTR-60 (**S4**)	3496	2927	1687	1140	762	686

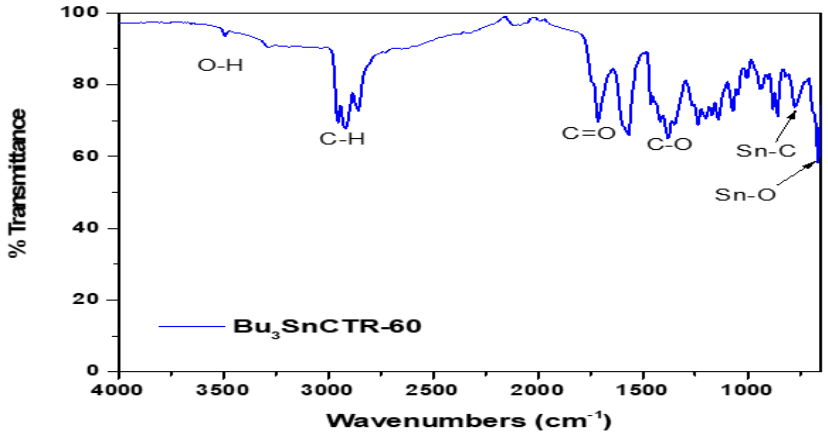


Fig. 1: FTIR spectrum of Bu_2SnCTR-60 (S2)

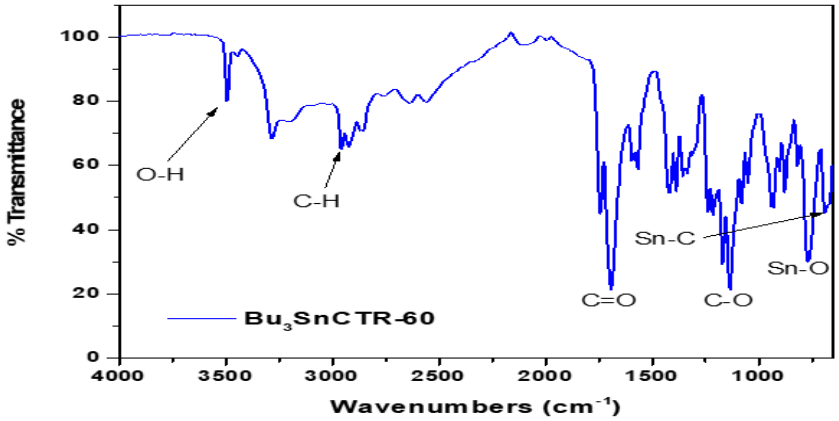


Fig. 2: FTIR spectrum of Bu_3SnCTR-60 (S4)

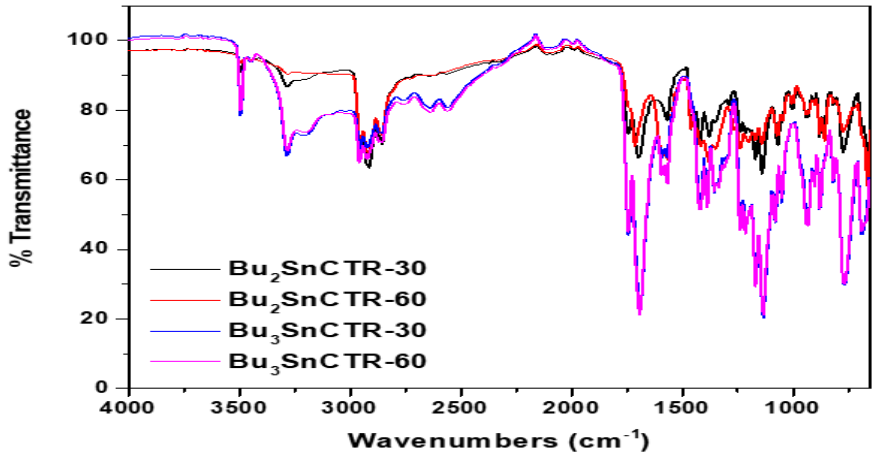


Fig. 3: Stacked FTIR spectra of S1, S2, S3, and S4

Thermal Analysis

Differential thermal analysis (DTA) is a technique used to monitor the temperature difference between a sample and a reference material over time or temperature. The sample is heated in a specified atmosphere, and its temperature is programmed. In this analysis, the organotin complexes were examined from 30 to 800 °C in a controlled atmosphere. In analyzing the DTA plots (Figures 4), exothermic and endothermic events occurred within the samples across a programmed temperature range. In the endothermic process shown in the DTA thermogram, the sample's temperature falls below the reference temperature, resulting in a downward peak on the graph. On the other hand, during the exothermic process, the sample's temperature exceeds the reference temperature, leading to a minimum observed on the graphical plot. The analysis was done between 30 °C and 800 °C with air as the atmosphere for all samples and data presented in Table 3. The DTA curve of S1 showed an endothermic peak at about 264 °C, corresponding to the evaporation of the absorbed water [22]. Another endothermic peak at approximately 331 °C occurred in DTA, which might be associated with the decomposition of organic residues. The appearance of two exothermic peaks at approximately 427 and 501 °C can be assigned to the degradation of impurities and the completion of the reaction respectively. Thus, 501 °C has been assigned as the calcination temperature for S1.

Table 3: Differential thermal analysis data (◦C) of the synthesized organotin complexes

Complex	Endothermic peaks	Exothermic peaks	Calcination temperature
Bu_2SnCTR-30 (**S1**)	264, 331	427, 501	501
Bu_2SnCTR-60 (**S2**)	224	448, 613	613
Bu_3SnCTR-30 (**S3**)	252, 318	409, 477, 528	528
Bu_3SnCTR-60 (**S4**)	251, 325	401, 455, 595	595

The DTA plot of S2 appeared to have an endothermic peak assignable to absorbed water evaporation at about 224 °C and two exothermic peaks at approximately 448 and 613 °C which can be ascribed to a combination of activities viz, decomposition of organic residues, degradation of impurities and completion of the reaction. The peak at 613 °C thus forms the calcination temperature of S2. Interestingly, a similar pattern was observed in the thermograms of S3 and S4 except that three exothermic peaks were observed in these scenarios. This could be ascribed to structural differences in the compounds and the presence of fewer impurities in the latter group. For instance, the structure of S1 or S2 contains two units of the Sn-O moieties while that of the S3 or S4 analogues contains one. Consequently, 528 and 595 °C were assigned to be the calcination temperatures of the complexes S3 and S4 respectively [23].

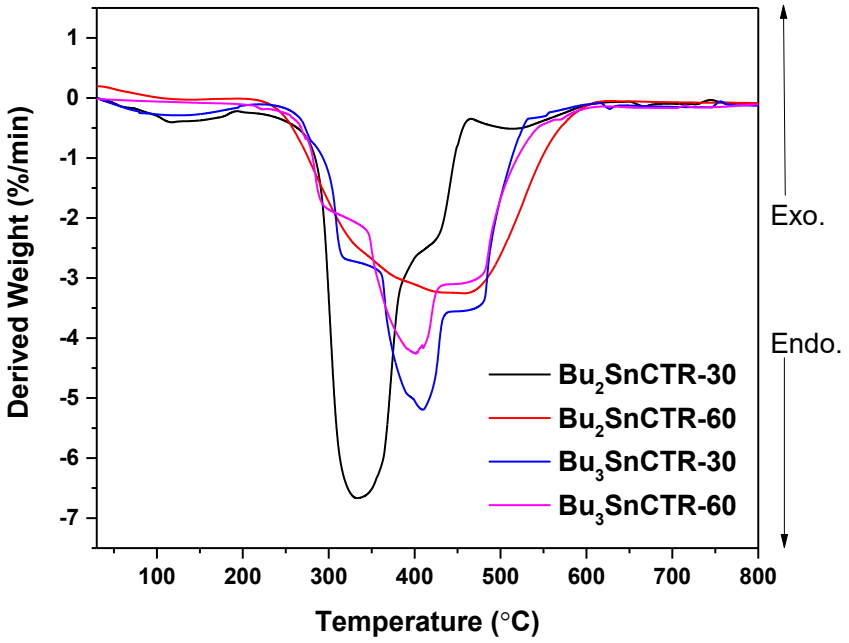


Fig. 4: Stacked DTA thermograms of S1, S2, S3, and S4

Thermogravimetric Analysis

The mass variation of a sample with temperature change is analyzed using thermogravimetric analysis [24]. This technique is commonly used to detect changes in weight percent as temperature changes. Thermal analysis methods have been widely used to study the thermal behaviour of metal complexes. Thus, thermogravimetric analysis (TGA) was carried out from 30 to 800 °C in the atmosphere to determine the changes that occurred during the heat treatment of the metal complexes. Table 4 shows the thermogravimetric data of the organotin complexes while their respective thermograms are presented in Figure 5.

Table 4: Thermogravimetric analysis data of the synthesized organotin complexes

Complex	% H_2O	% CTR	% Residue
Bu_2SnCTR-30 (**S1**)	2.30	92.00	5.70
Bu_2SnCTR-60 (**S2**)	2.45	78.91	18.64
Bu_3SnCTR-30 (**S3**)	2.28	89.02	8.70
Bu_3SnCTR-60 (**S4**)	2.98	78.18	18.84

The thermogram of the organotin complexes showed that an onset degradation temperature occurred at approximately 289, 308, 321, and 316 °C for S1, S2, S3, and S4 respectively. This mass loss has been attributed to dehydration with the loss of H_2O molecules representing about 2.30, 2.45, 2.28, and 2.98 % respectively for the organotin complexes. This may suggest the presence of water of hydration or crystallization in all the metal complexes [25]. The fact that the hydration water in S2 is higher than S1 and S4 greater than S3 infers that the reaction is better completed with a longer time. In addition, the thermograms showed a second mass loss occurring at approximately 295-445 °C, 315-525 °C, 321-469 °C, and 316-501°C for samples S1, S2, S3, and S4 respectively. These two events correspond to the decomposition of organic matter (Ligand) and the formation of the residues (SnO2) [26]. Thus, the percentage composition of the ligand and residues in the organotin complexes were observed to be 92.00 and 5.70 %, 78.91 and 18.64 %, 89.02 and 8.70 %, and 78.18 and 18.84 % for S1, S2, S3, S4 respectively. It is important to note that the percentage of mass loss attributed to S1 is lower than that of S2, even though the complexes are the same except for their reaction time (S1 was reacted for 30 minutes and S2 for 60 minutes). This suggests that a longer reaction time is more suitable for the mechanochemical synthesis of metal complexes. These thermal events further support the formation of the organometallic complexes. This observation is consistent with literature reports on similar [27-30].

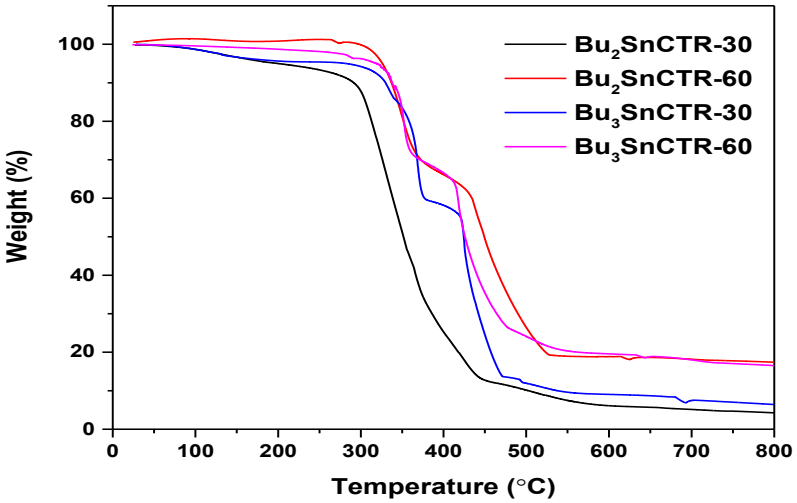


Fig. 5: Stacked TGA thermograms of S1, S2, S3, and S4

Differential Scanning Calorimetry Studies

Differential Scanning Calorimetry (DSC) methods are frequently used to determine non-isothermal transformation indices. This process enables us to measure the amount of heat absorbed from or released to the surroundings per unit time during isothermal processes or heating and cooling [31]. This allows for the measurement of heat capacities, melting points, transition temperatures, and more. The information mentioned above can offer an additional understanding of phase transitions, crystallization

processes, and related phenomena. These thermodynamic parameters are essential for studying heat transport mechanisms in different solid-state compounds. Therefore, the thermodynamic properties of synthesized organotin complexes have been examined to understand their energy and determine specific thermodynamic parameters (refer to Table 5).

Table 5: Differential scanning calorimetric analysis of the synthesized organotin complexes

Complex	Melting range		Fusion temperature (°C)	C_p (KJg^{-1}°C^{-1})	Crystallization temperature (°C)
	T_i (°C)	T_f (°C)			
Bu_2SnCTR-30 (**S1**)	96.35	97.53	102.07	2.65	133.97
Bu_2SnCTR-60 (**S2**)	83.04	84.95	96.72	5.63	230.18
Bu_3SnCTR-30 (**S3**)	86.21	88.72	99.23	14.60	278.82
Bu_3SnCTR-60 (**S4**)	71.12	72.54	79.42	3.81	262.30

Figures 6 display the DSC curves of the synthesized organotin complexes. All the complexes showed endothermic processes. The area of the endothermic peak corresponds to the heat of fusion, and the peak temperature corresponds to the melting point. The melting ranges (Ti and Tf), temperatures of fusion, and temperatures of crystallization of the complexes are provided in Table 5. The heat capacities (Cp) of the complexes were calculated from DSC results and are all presented. It can be observed from the DSC data that the range of melting temperatures occurred at approximately similar domains in the respective curves of the organotin complexes. This could suggest that the synthesized metal complexes have similar structural motifs, hence their decomposition patterns as supported by TGA results. This claim is further supported by the values of temperatures of fusion of the complexes which are in similar domains at approximately 80 – 103 °C and crystallization which was observed at approximately 134 – 279 °C.

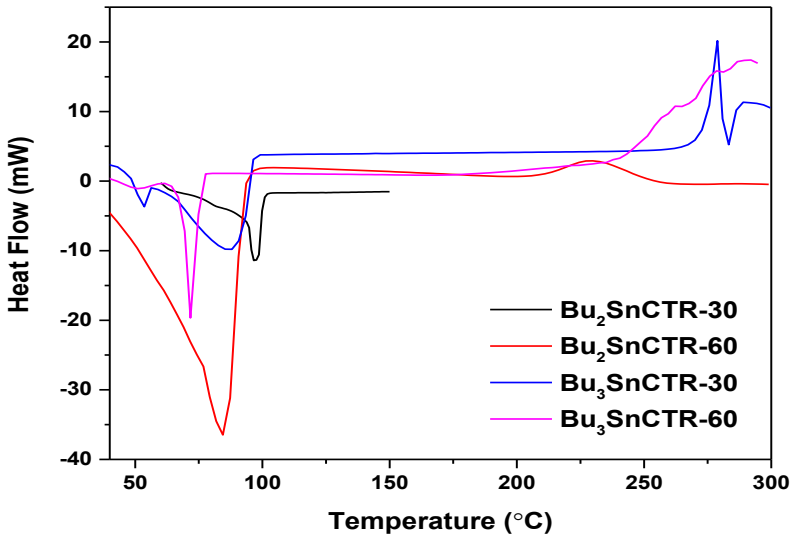


Fig. 6: Stacked DSC thermograms of S1, S2, S3, and S4

Interestingly, the specific heat capacities of the synthesized complexes fall in the range of approximately 2.65 – 14.60 kjg^{-1}°C^{-1} which is similar to complexes reported by other researchers [27,28,32]. It is important to note however that, some of the complexes have very high specific heat capacities. This indicates that complexes with a high specific heat capacity require more energy to change their temperatures. For example, the complex S3 showed very high specific heat capacities, approximately 14.60 Jg^{-1}°C^{-1}. This suggests that these complexes are the most thermally stable among all the synthesized complexes, making them potential candidates for biological applications where complex stability is crucial [27].

X-ray Fluorescence Analyses

The tin amounts in the complexes were determined using XRF measurements, as shown in Table 6. Based on these data, certain conclusions can be drawn, considering that the

metal centers were coordinated to the ligand moieties via the hydroxyl ends. A comparison of the complexes of the two metal substrates studied revealed a better reaction efficiency for the dibutyltin (IV) complexes, as the ligand was loaded more than in the corresponding tributyl analogue. This could suggest that steric requirements are a relevant factor in the coordination ability of these ligands [33]. Interestingly, the % Sn content in S3 (7.85 %, 0.07 mmol) is less than that in S4 (14.46 %, 0.12 mmol). This again suggests that the synthesis of the complex compounds is more effective with a longer reaction time. For instance, the synthesis of S3 proceeded for only 30 minutes, while S4 was allowed to react for 60 minutes. A similar scenario appears to be at play for S2 and S1. This rationalizes the suggestion further and the results here agree with those of TGA and DTA.

Table 7: X-ray fluorescence data for the tin content analysis of the organotin complexes

Complex	SnO_2 (%)	Sn (%)	Sn (mmol)
Bu_2SnCTR-30 (**S1**)	21.53	16.96	0.143
Bu_2SnCTR-60 (**S2**)	22.79	17.96	0.151
Bu_3SnCTR-30 (**S3**)	9.96	7.85	0.066
Bu_3SnCTR-60 (**S4**)	18.35	14.46	0.122

Powder X-ray Diffraction Studies

The Powder X-ray Diffraction (PXRD) data and its analysis can be found in Table 8 while the diffractograms are included in Figure 7. Both complexes showed similar peaks and Miller indices, supporting the conclusion that the complexes S3 and S4 are the same materials, with only the reaction time differentiating them. Furthermore, the most prominent peaks in the thermograms of S3 and S4 occurred at 2θ values of 26.59 and 34.27◦ degrees with d-spacings of 0.34 and 0.26 nm respectively. These peaks were used to estimate the average crystallite size of the organotin complexes by employing the Debye-Scherrer formula, $\delta = 0.9\lambda/ \beta \cos\theta$, where λ is the wavelength of the X-rays used for diffraction and β is full width at half maximum (FWHM) of the peak [34]. The average crystallite sizes of S3 and S4 were thus estimated to be 68.17 and 75.68 nm respectively. This observation provides evidence that the organotin complexes were formed with relatively high crystallinity as evidenced by the appearance of narrow and high-intensity peaks in the diffractograms. The most prominent peak in the two diffractograms is assigned the 201 Miller index which further supports the inference that S3 and S4 are a similar complex. Therefore, a monoclinic Bravais lattice system is proposed for the complexes being studied. Some of the low-intensity peaks observed in the diffractogram have been identified to be caused by ligands. This suggests that the ligands might not have completely reacted and thus remained in the sample in small quantities. It is important to note that the average crystallite size of S3 (68.17 nm) is less than that of S4 (75.68 nm). This further affirms that the mechanosynthesis of complex compounds is more efficient with a longer reaction time. For example, the synthesis of S3 was allowed to proceed for only 30 minutes, while S4 was allowed to react for 60 minutes. This conclusion is supported by the results of XRF, TGA, and DTA.

Table 8: Some lattice data of Bu_3SnCTR-30 (S2)

S/N	2θ (◦)	*d*-spacing (Å)	Peak Int. (cps)	FWHM	*hkl*
1	7.45	11.93	441	0.23	110
2	18.56	4.77	1161	0.15	101
3	20.12	4.44	491	0.13	111
4	24.00	3.68	237	0.76	200
5	26.59	3.35	2843	0.12	201
6	31.42	2.84	524	0.14	211
7	34.36	2.60	345	0.10	301
8	43.84	2.07	493	0.13	311

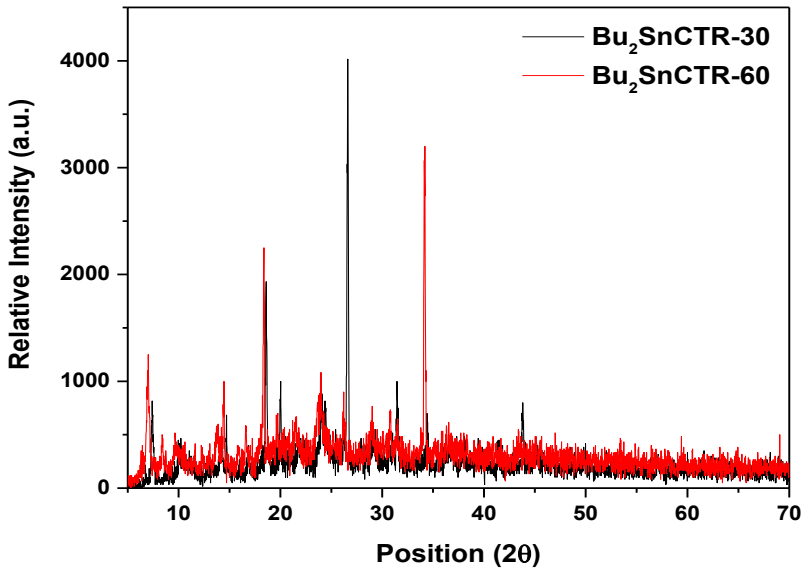
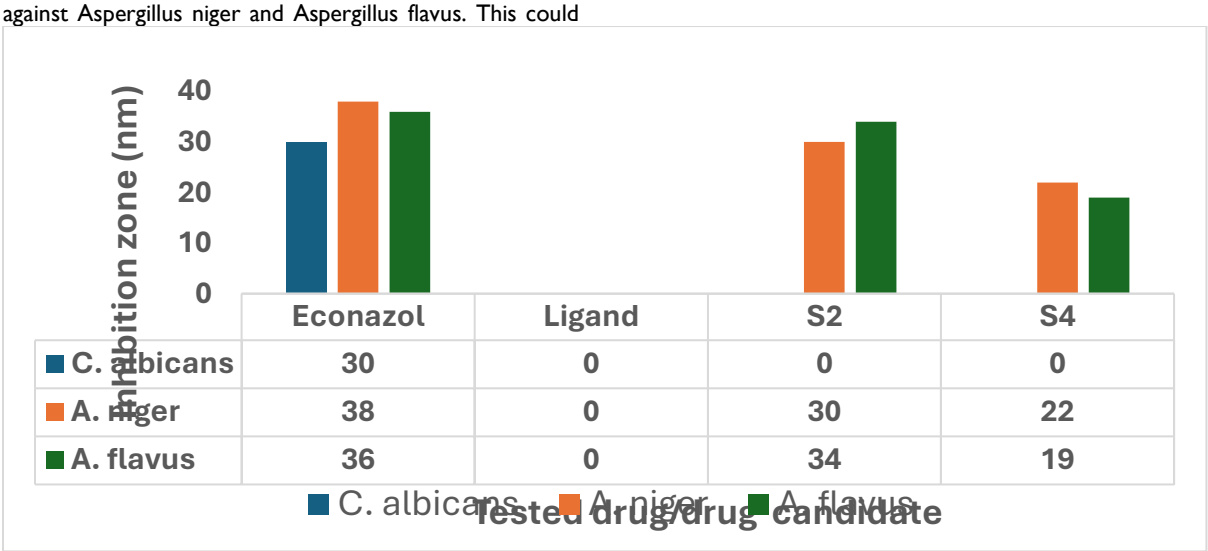


Fig. 7: Stacked X-ray diffractograms of S1 and S2

Antifungal Activity

A comparative evaluation of the antimicrobial activity of the ligand L, and the synthesized organotin (IV) complexes S2 and S4 was conducted based on the studies by Girish and Satish [17,18]. The evaluation was carried out against three strains of fungi as shown in Figure 8, Tables 9, and 10. The results showed that the ligand L is inactive against all three fungi strains. However, its activity is induced by complexation with the organotin (IV) moieties, especially against Aspergillus niger and Aspergillus flavus. This could infer that there is a synergistic effect between the ligand (citric acid) and the organotin (IV) precursors in the induced antifungal activity of the formed complexes [35]. Interestingly, Candida albicans showed resistance to the drug candidates but Aspergillus niger and Aspergillus flavus appeared to be susceptible to S2 and S4 suggesting that these complexes hold a strong potential in the development of alternative antifungal agents that can arrest the challenges of antimicrobial resistance [36].



	Econazol	Ligand	S2	S4
C. albicans	30	0	0	0
A. niger	38	0	30	22
A. flavus	36	0	34	19

Fig. 8: Inhibition zone of the ligands and organotin (IV) complexes

Table 9: Minimum Inhibitory Concentration (mg/mL) of the drug candidates against the Test Organisms

Test organism	L	S2	S4
	NA	NA	NA
Candida albicans			
Aspergillus niger	NA	12.50	50.00
Aspergillus flavus	NA	12.50	50.00

KEY: NA = No Activity.

Table 10: Minimum Fungicidal Concentration (mg/mL) of drug candidates against the Test Organisms

Test organism	L	S2	S4
Candida albicans	NA	NA	NA
Aspergillus niger	NA	25.00	##
Aspergillus flavus	NA	25.00	##

KEY: NA = No Activity, ## =No M.F.C.(The material is only fungistatic, not fungicidal).

This can further be rationalized from the results of inhibition zones as it can be observed that S2 demonstrated interesting potency against Aspergillus flavus which is almost at parity with the standard drug. Based on the minimum inhibitory and fungicidal concentrations, S2 proved to be the best drug candidate in this study as it showed the lowest concentration (12.5 and 25.00 mg/mL respectively) capable of inhibiting the growth and causing the death of Aspergillus niger and Aspergillus flavus. The citric acid ligand alone was inactive against all tested fungi. Complexes S2 and S4 showed activity against Aspergillus niger and A. flavus, with S2 being the most potent (MIC: 12.5 mg/mL, MFC: 25 mg/mL). All complexes were inactive against Candida albicans. The induction of antifungal activity through the complexation of citric acid with organotin moieties suggests a synergistic effect, a phenomenon observed in other metal-organic frameworks [37]. The differential activity against Aspergillus species versus Candida albicans indicates potential for targeted antifungal applications. The superior activity of the dibutyltin complex (S2) compared to the tributyltin complex (S4) may be attributed to structural differences affecting their interaction with fungal cell membranes [38]. This structure-activity relationship warrants further investigation for optimizing antifungal efficacy.

Conclusion

This study demonstrates the successful mechanochemical synthesis of organotin (IV) citrate complexes with promising antifungal activity, particularly against Aspergillus species. The green, solvent-free approach offers an environmentally friendly alternative to traditional solution-based methods. Longer reaction times improved various properties of the complexes, including yield, crystallinity, and potentially antifungal activity. The complexes showed selective antifungal activity, being effective against Aspergillus species but not Candida albicans. This selectivity could be advantageous in developing targeted antifungal treatments with potentially fewer side effects.

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