SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDIES OF NOVEL ORGANOBIsmuth(III) COMPLEXES

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Abstract- The Present Manuscript deals the synthesis of some novel organobismuth(III)aryloxyacetates followed by their characterization by melting points, elemental analysis, U.V., I.R and NMR spectral analysis to confirm their structures and geometry. The compounds were also screened for their antibacterial and antifungal efficacy against pathogenic bacterial and fungal strains. It was found that these compounds exhibit higher activity than the standard drug for bactericidal and fungicidal activity.

Keywords- Organobismuth, aryloxyacetates, antibacterial, antifungal.


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Introduction

The acetates in organic derivatives of group 15 elements could behave as monodentate, bidentate or as bridging ligands depending on the oxidation state (+3 or +5); physical state of the compound (solid or solution) and the various substituents present on the acetate group itself [1-10]. It has been found that major influences in determining mode of bonding, geometry and stability of the acetate system in general are the absence of ligand atom trans to an organic group; the preservation of the preferred angle of 120° at bounded oxygen atom and maximizing of secondary bonding via a bridging for acetate. Another important group of ligand which has not attracted much attention, but closely resembles to carboxylates is aryloxyacetates. However unlike acetate, aryloxyacetates has one extra donor site i.e. Ax-O, in addition to the -C=O functionality. It is noteworthy that despite such a great variety of structural possibilities, as discussed above exhibited by organometallic carboxylates and by the variety of metals for which such derivatives have been synthesized, corresponding aryloxyacetates are mainly confirmed to transition metal derivatives [11] with an occasional reference on organotin and organoantimony [12] derivatives. A perusal of the literature further reveals that the complexes of aryloxyacetates; in case of organotin possess intramolecular O->Sn coordination; particularly for alkyl tin derivatives and the compounds are monomeric in solid state. In sharp contrast to this triaryltin derivatives having pentacoordination, were found to be polymeric with bridging carboxyl group [13-19]. On the basis of ultraviolet and infrared spectra it has been concluded that aryloxyacetate behave as monodentate ligand towards bismuth. The principal objective of this work was to synthesize and characterized biomedically unreported organobismuth(III) aryloxyacetate derivatives; to investigate the role of ethereal oxygen of aryloxyacetate group i.e. whether it participates in bonding or not and thus raising the coordination number of bismuth(III) beyond three; to ascertain the mode of bonding of aryloxyacetate group towards bismuth i.e. whether the acetate group (s) acts as monodentate or bidentate group or as a both; to compare and contrast the behavior of aryloxyacetate ligand with that of acetate and to evaluate the newly synthesized organobismuth compounds for their biomedicinal importance against various pathogenic diseases.

Experimental

The diorganobismuth (III) chloride, R₂BiCl and organobismuth (III) dichloride, RBiCl₂ was prepared by the redistribution reaction [20]. The syntheses of some representative compounds are as follows.

Reaction of (C₆H₅)₂Bi(III)Cl with (C₆H₅OCH₃COOH) (1)

In the stirring solution of diphenylbismuth(III)chloride (0.398gm;1mmol), phenoxyacetic acid (0.152gm;1mmol) was added in presence of triethylamine (1 ml) in benzene and was stirred in anhydrous oxygen free, nitrogen conditions for 6h, followed by refluxing for 2h to ensure completion of the reaction. A flocculent white precipitate of Et₃N.HCl (M.P.240°C) was formed which was filtered off. The filtrate on concentration gave a light brown solid which was recrystallised by petroleum ether (40°-60°C).

Reaction of (C₆H₅)₂Bi(III)Cl with (p-CH₃C₆H₄OCH₃COOH) (2)

In the stirring solution of diphenylbismuth(III)chloride (0.398gm;1mmol), p-methyl phenoxyacetic acid (0.166gm;1mmol) was added in presence of triethylamine (1ml) in benzene and was stirred in anhydrous oxygen free, nitrogen atmosphere for 6h, followed by refluxing for 2h to ensure completion of the reaction. A flocculent white precipitate of Et₃N.HCl (M.P.240°C) was formed which was filtered off. The filtrate on concentration afforded a light brown solid which was recrystallised by petroleum ether (40°-60°C).

Reaction of (C₆H₅)₂Bi(III)Cl with (p-CIC₆H₄OCH₃COOH) (3)

In the stirring solution of diphenylbismuth(III)chloride (0.398gm;1mmol), p-chloro phenoxyacetic acid (0.186gm;1mmol) was added in presence of triethylamine (1ml) in benzene and was stirred in anhydrous oxygen free, nitrogen atmosphere for 6h, followed by refluxing for 2h to ensure completion of the reaction. A white
colour precipitate of Et₂N·HCl (M.P.240°C) was formed which was filtered off and the filtrate on concentration in vacuum afforded a light brown solid which was recrystallised by petroleum ether (40°C-60°C).

**Reaction of (CF₃)₂Bi(III)Cl with (C₆H₅OCH₂COOH) (4)**

In the stirring solution of bis(pentafluorophenyl) bismuth(III)chloride (0.578gm; 1mmol), phenoxycetic acid (0.152gm; 1mmol) was added in presence of triethylamine (1 ml) in benzene and was stirred in anhydrous oxygen free, nitrogen conditions for 6h, followed by refluxing for 2h to ensure completion of the reaction. A focoult white precipitate of Et₂N·HCl (M.P.240°C) was formed which was filtered off. The filtrate on concentration gave a light brown solid which was recrystallised by petroleum ether (40°C-60°C).

**Reaction of (CF₃)₂Bi(III)Cl with (p-MeC₆H₅OCH₂COOH) (5)**

In the stirring solution of bis(pentafluorophenyl) bismuth(III)chloride (0.578gm; 1mmol), p-methyl phenoxycetic acid (0.166gm; 1mmol) was added in presence of triethylamine (1ml) in benzene and was stirred in anhydrous oxygen free, nitrogen conditions for 6h, followed by refluxing for 2h to ensure completion of the reaction. A focoult white precipitate of Et₂N·HCl (M.P.240°C) was formed which was filtered off. The filtrate on concentration afforded a light brown solid which was recrystallised by petroleum ether (40°C-60°C).

**Result and Discussion**

All the reactions were conducted at room temperature and the products were recrystallised from petroleum ether (40°C-60°C) or in benzene. The complexes are off-white to light brown solids and obtained as a sticky mass which on treatment with sodium in dry benzene gets solidified and subsequently crystallized with benzene/pet-ether. The complexes are fairly stable on air and moisture and have sharp melting point. There is no regular trend of the melting point of the complexes and they melt without decomposition. Complexes are also soluble in chloroform and acetonitrile. They can be stored at room temperature without decomposition for several weeks. The consistency in melting points after repeated crystallization as well as TLC run in chloroform hexane mixture (1:1) with the observation of a single spot excluded the presence of mixture of reactants. The molar conductance value of 10-3 M solution of these compounds were recorded in methanol and found in the range of 15-25 Ohm⁻¹ cm⁻¹ mol⁻¹ indicating the absence of ionic species in solution. The complexes were found to be monomeric in nitrobenzene.

**IR Spectra**

As expected infrared absorptions inherent to phenyl and fluoroxy groups bound to bismuth have no difference appreciably and hence not discussed. The infrared absorptions having diagnostic value for organobismuth aryloxyacetates, related to the ligand, have been identified which on preliminary stage indicates the mode of bonding with aryloxy ligand. The characteristic ν(OH) absorption band of ligands which appeared around 3400 cm⁻¹ in the free ligand, was found missing in the newly synthesized complexes. A medium strong intensity band appearing at 1690-1700 cm⁻¹ can confidently be assigned to ν(OH) (OCO) mode while comparatively weaker band in the range 1380-1400 cm⁻¹ can be attributed to ν(C=O) (OCO) band. The deformation mode as a medium intensity band was found in the range 815-790 cm⁻¹. The absorption associated with the bismuth-oxygen appears in the range between 400-430 cm⁻¹ and the absorption due to bismuth-carbon corresponding to ν(C-O-C) mode occurs in the range 3400-1400 cm⁻¹. These values clearly indicated the formation of organobismuth (III) aryloxyacetates. The comparison of IR spectra of the compounds with those of respective ligands in solid and solution states did not show any significant shift in ν(C=O), ν(O-C-O) and ν(C-O-C) deformation bands which in turn showed the lack of coordination with bismuth through -C=O or C=O-Ar center of the ligand. Since the separation observed in the present compounds is fairly large (2000 cm⁻¹), monomolecular constitution seems to be most plausible whereas bismuth would be have a coordination number three. This observation is clearly sharp contrast to organol complexes of aryloxyacetates which have been found to be polymeric involving carboxylic bridges. In addition to this intermolecular interaction involving the ethereal oxygen has also been demonstrated in some cases particularly.

**1H NMR Spectra**

*H NMR spectra of these compounds was recorded in CDCl₃ using TMS as an
internal reference at 25°C. The disappearance of OH proton signals (89.1 ppm) present in the ligand clearly indicates the formation of aryloxyacetate derivatives. The appearance of singlet for -CH3 protons at 84.85 ppm showed the ligand is in one plane. The phenyl protons for both the derivatives appear as multiplets in the range 57.80-7.20 ppm.

UV Spectra

The electronic spectra obtained for representative compounds were recorded in chloroform in the range 200-400 nm. The UV absorption due to COO group appears at 274+6 and 294+2 are due to aryloxy moieties. Since there was no significant change in absorption peaks of the ligands indicates that -C=O and -C-O-Ar centre of aryloxyacetates are not coordinated to bismuth in any of the compounds. This also tends to support the fact that aryloxyacetates behave as monodentate ligand towards bismuth in +3 oxidation state.

<p>| Table-1 Phsyicochemical studies of organobismuth (III) aryloxyacetates |
|-------------------------------------------------|-------|-------|---------|-------|</p>
<table>
<thead>
<tr>
<th>S.N.</th>
<th>Compounds</th>
<th>Formula</th>
<th>M.P. (°C)</th>
<th>Color</th>
<th>Yield (%)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(C₆H₅)Bi(OOC.CH₂OCCH₃)</td>
<td>C₆H₅-OBi</td>
<td>190</td>
<td>Light Brown</td>
<td>60</td>
<td>Pet-ether</td>
</tr>
<tr>
<td>2</td>
<td>(C₆H₅)Bi(OOC.CH₂OCCH₂CH₃)</td>
<td>C₆H₅-OBi</td>
<td>156</td>
<td>Light Brown</td>
<td>75</td>
<td>Pet-ether</td>
</tr>
<tr>
<td>3</td>
<td>(C₆H₅)Bi(OOC.CH₂OCCH₂Cl)</td>
<td>C₆H₅-OBiCl</td>
<td>214</td>
<td>Light Brown</td>
<td>70</td>
<td>Pet-ether</td>
</tr>
<tr>
<td>4</td>
<td>(C₆F₅)Bi(OOC.CH₂OCCH₂Cl)</td>
<td>C₆F₅-OBiCl</td>
<td>184</td>
<td>Light Brown</td>
<td>65</td>
<td>Pet-ether</td>
</tr>
<tr>
<td>5</td>
<td>(C₆F₅)Bi(OOC.CH₂OCCH₂CH₃)</td>
<td>C₆F₅-OBi</td>
<td>176</td>
<td>Light Brown</td>
<td>60</td>
<td>Pet-ether</td>
</tr>
<tr>
<td>6</td>
<td>(C₆F₅)Bi(OOC.CH₂OCCH₂Cl)</td>
<td>C₆F₅-OBiCl</td>
<td>204</td>
<td>Light Brown</td>
<td>60</td>
<td>Pet-ether</td>
</tr>
<tr>
<td>7</td>
<td>(p-FC₆H₄)Bi(OOC.CH₂OCCH₂Cl)</td>
<td>C₆H₄-OBiCl</td>
<td>192</td>
<td>Light Brown</td>
<td>60</td>
<td>Pet-ether</td>
</tr>
<tr>
<td>8</td>
<td>(p-FC₆H₄)Bi(OOC.CH₂OCCH₂CH₃)</td>
<td>C₆H₄-OBi</td>
<td>182</td>
<td>Light Brown</td>
<td>75</td>
<td>Pet-ether</td>
</tr>
<tr>
<td>9</td>
<td>(p-FC₆H₄)Bi(OOC.CH₂OCCH₂Cl)</td>
<td>C₆H₄-OBiCl</td>
<td>198</td>
<td>Light Brown</td>
<td>70</td>
<td>Pet-ether</td>
</tr>
</tbody>
</table>

<p>| Table-2 Analytical studies organobismuth (III) aryloxyacetates |
|-------------------------------------------------|-------|-------|-------|-------|</p>
<table>
<thead>
<tr>
<th>S.N.</th>
<th>Compounds</th>
<th>Formula</th>
<th>Molecular weight</th>
<th>Elemental Analysis</th>
<th>In Absorption frequencies</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅-OBi</td>
<td>514</td>
<td>C (%)</td>
<td>H (%)</td>
<td>λmax (ODC)</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅-OBi</td>
<td>528</td>
<td>46.69</td>
<td>3.30</td>
<td>1695</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₅-OBiCl</td>
<td>548.5</td>
<td>43.76</td>
<td>2.92</td>
<td>1694</td>
</tr>
<tr>
<td>4</td>
<td>C₆F₅-OBiCl</td>
<td>594</td>
<td>34.58</td>
<td>1.51</td>
<td>1596</td>
</tr>
<tr>
<td>5</td>
<td>C₆F₅-OBi</td>
<td>708</td>
<td>35.59</td>
<td>1.27</td>
<td>1700</td>
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<tr>
<td>6</td>
<td>C₆F₅-OBiCl</td>
<td>728.5</td>
<td>32.94</td>
<td>0.82</td>
<td>1697</td>
</tr>
<tr>
<td>7</td>
<td>C₆F₅-OBiCl</td>
<td>590</td>
<td>43.64</td>
<td>2.72</td>
<td>1692</td>
</tr>
<tr>
<td>8</td>
<td>C₆F₅-OBiCl</td>
<td>564</td>
<td>44.68</td>
<td>1.01</td>
<td>1688</td>
</tr>
<tr>
<td>9</td>
<td>C₆F₅-OBiCl</td>
<td>584.5</td>
<td>41.06</td>
<td>2.39</td>
<td>1694</td>
</tr>
</tbody>
</table>

<p>| Table-3 Anti-bacterial activity of organobismuth (III) aryloxyacetates |
|-------------------------------------------------|-------|-------|-------|-------|</p>
<table>
<thead>
<tr>
<th>S. N.</th>
<th>Compounds</th>
<th>Control</th>
<th>Pseudomonas aeruginosa</th>
<th>Staphylococcus aureus</th>
<th>Klebsiella pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(C₆H₅)Bi(OOC.CH₂OCCH₃)</td>
<td>–</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>2</td>
<td>(C₆H₅)Bi(OOC.CH₂OCCH₂CH₃)</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>(C₆H₅)Bi(OOC.CH₂OCCH₂Cl)</td>
<td>–</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>4</td>
<td>(C₆F₅)Bi(OOC.CH₂OCCH₂Cl)</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>5</td>
<td>(C₆F₅)Bi(OOC.CH₂OCCH₂CH₃)</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>6</td>
<td>(C₆F₅)Bi(OOC.CH₂OCCH₂Cl)</td>
<td>–</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>7</td>
<td>(p-FC₆H₄)Bi(OOC.CH₂OCCH₂Cl)</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>8</td>
<td>(p-FC₆H₄)Bi(OOC.CH₂OCCH₂CH₃)</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>9</td>
<td>(p-FC₆H₄)Bi(OOC.CH₂OCCH₂Cl)</td>
<td>–</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

| Table-4 Anti-fungal activity of organobismuth (III) aryloxyacetates at 50 µg/ml conc. |
|-------------------------------------------------|-------|-------|-------|-------|
| S. N. | Compounds | Aspergillus flavus | % Inhibition | Aspergillus niger | % Inhibition |
|--- | --- | Coll. DIA (mm) | Coll. DIA (mm) | Coll. DIA (mm) | Coll. DIA (mm) |
| 1 | (C₆H₅)Bi(OOC.CH₂OCCH₃) | 0.7 | 76.6 | 0.6 | 70.0 |
| 2 | (C₆H₅)Bi(OOC.CH₂OCCH₂CH₃) | 0.2 | 93.3 | 0.7 | 65.0 |
| 3 | (C₆H₅)Bi(OOC.CH₂OCCH₂Cl) | 0.2 | 93.3 | 0.7 | 65.0 |
| 4 | (C₆F₅)Bi(OOC.CH₂OCCH₂Cl) | 0.5 | 83.3 | 0.4 | 90.0 |
| 5 | (C₆F₅)Bi(OOC.CH₂OCCH₂CH₃) | 0.2 | 93.3 | 0.7 | 65.0 |
| 6 | (C₆F₅)Bi(OOC.CH₂OCCH₂Cl) | 0.2 | 93.3 | 0.7 | 65.0 |
| 7 | (p-FC₆H₄)Bi(OOC.CH₂OCCH₂Cl) | 0.7 | 76.6 | 0.7 | 65.0 |
| 8 | (p-FC₆H₄)Bi(OOC.CH₂OCCH₂CH₃) | 0.8 | 73.3 | 0.8 | 60.0 |
| 9 | (p-FC₆H₄)Bi(OOC.CH₂OCCH₂Cl) | 0.8 | 73.3 | 0.8 | 60.0 |
| 10 | Control | 3.0 | – | 2.0 | – |

On the basis of IR, NMR and UV spectral analysis data, it may tentatively concluded that aryloxyacetate under the present study behaves as a monodentate ligand. Conductance measurement and molecular Wight data showed that these aryloxyacetates have monomeric nature and are non conducting in nature. The experimental data are thus consistent with three coordinate pyramidal structures.

Antibacterial activity

The organobismuth (III) aryloxyacetates were tested for antibacterial activity against three bacterial strains Pseudomonas aeruginosa, Staphylococcus aureus and Klebsiella pneumoniae using 10 µg/ml concentration of test compound. All the compounds showed higher to moderate activity against the bacterial strains. It was found that compounds having fluoro and pentafluorophenyl ring are more effective because of their water and lipid solubility. The fluorine containing compounds may generally form complexes with metalloenzymes, particularly those which responsible in basic physiology such as cytochrome oxidase. These compounds may react with peptidoglycan layer of bacterial cell wall and damage it by penetrating in such a manner that the phenyl ring gets entered inside the cell by puncturing it followed by death of bacterial cell. Sometimes these compounds in low concentration may cause bacteriostatic condition by slow down the growth of bacteria.
Synthesis, Characterization and Antimicrobial studies of Novel Organobismuth(III) Complexes

Antifungal Activity

The antifungal activity of organobismuth (III) compounds was tested against Aspergillus flavus and Aspergillus niger using 50 μg/ml concentration. The activity of these compounds was found variable at 50μg/ml concentration against fungal strains. Presence of nitrogen, phenyl and pentafluorophenyl ring along with bismuth in +3 oxidation state are considered for fungal activity. The role of different aryloxyacetates as ligands was also commendable. These compounds generally damage the fungal strains by puncturing the cell wall similarly as in the case of bacteria. Water and lipid solubility of these compounds, due to presence of fluorine, also increases the activity due to presence of fluorine.

Application of research: Applicable for study of antimicrobial activity of Organobismuth compounds

Research Category: Antibacterial activity

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University: Department of Chemistry, Mewar University, Chittorgarh, 312901, Rajasthan

Research project name or number: PhD Thesis

Author Contributions: All author equally contributed

Author statement: All authors read, reviewed, agree and approved the final manuscript

Conflict of Interest: None declared

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

References