Studies on compounds of Ca, Sr and Ba-chlorides with ephedrine hydrochloride  

Section A-Short Communication

Preliminary Studies on the Reaction of Ca\textsuperscript{II}, Sr\textsuperscript{II} and Ba\textsuperscript{II} Chlorides with Ephedrine Hydrochloride

Moamen S. Refat\textsuperscript{[a,b,c]*} and Abeer A. El-Habeesb\textsuperscript{[e]}

Keywords: Ephedrine HCl, infrared spectra, Raman spectra, \textsuperscript{1}H–NMR.

Ephedrine hydrochloride complexes of Ca(II), Sr(II) and Ba(II) non-transition metal ions were prepared. The compounds formed contains various amount of crystalline water (6, 8 and 4 for Ca, Sr and Ba, respectively) and were studied by IR, Raman and NMR methods. Electrolytic conductivity measurements showed that the complexes decompose into ionic particles in DMSO. The compounds show unusual high thermal stability.

* Corresponding Authors
E-Mail: Email: msrefat@yahoo.com  
[a] Department of Chemistry, Faculty of Science, Port Said, Port Said University, Egypt  
[b] Department of Chemistry, Faculty of Science, Taif University, 888 Taif, Kingdom Saudi Arabia  
[c] Department of Chemistry, Faculty of Science, Princess Nora Bint Abdul Rahman University, Riyadh, Kingdom Saudi Arabia

Introduction

Ephedra is a Phanerogame-Gymnosperme family from the family of Gnetaceen. Specially ephedra vulgaris, ephedra equisetina and ephedra sinica contain ephedrin with its other isomers. A certain ephedra species has been used in ancient Chinese medicine since ages. The pharmacological studies have indicated that ephedrine is a sympathomimetic agonist at both α and β-adrenergic receptors, which determine an increase of cardiac rate and contractility, peripheral vasoconstriction, bronchodilatation and central nervous system (CNS) stimulation.\textsuperscript{1,2} However, severe contraindications have been given for individuals with hypertension or other cardiovascular diseases, glaucoma, diabetes and hyperthyroidism. Products containing \textit{E. sinica} (or another botanical source of ephedrine) were among the most popular dietary supplements on the market, until their sale was banned by the U.S. Food and Drug Administration (FDA) in April 2004. After the ban of \textit{Ephedra} products, “Ephedra-free” dietary supplements for weight loss were introduced. However, Ephedra-free is not necessarily danger-free.\textsuperscript{3} \textit{Citrus aurantium} is an ingredient in many of these Ephedra-free dietary supplements. The main active constituent of \textit{C. aurantium} fruit extracts is (\textsuperscript{2}-methylamino)\textsuperscript{1}\textsuperscript{2}phenylpropanol (Eph) used in this study was obtained from the Egyptian International Pharmaceutical Industrial Company (EIPICO). All other chemicals used in the preparations were of analytical reagent grade, commercially available from different sources (Fluka Co. and Aldrich Co.). All the metal salts hydrated calcium, strontium and barium used as chloride. All solvents are used as it is without further purification.

Experimental

Reagents

Ephedrine \textit{(2-(methylamino)-1-phenylpropan-1-ol hydrochloride) (Eph) used in this study was obtained from the Egyptian International Pharmaceutical Industrial Company (EIPICO). All other chemicals used in the preparations were of analytical reagent grade, commercially available from different sources (Fluka Co. and Aldrich Co.). All the metal salts hydrated calcium, strontium and barium used as chloride. All solvents are used as it is without further purification.}

Synthesis of ephedrine HCl complexes

All the complexes were prepared by molar ratio 1:1 (1 mmol M\textsuperscript{II}; 1 mmol Eph) in water/ethanol (50/50\%) solution. The resulting mixtures were heated under reflux for 2 hr. and filtered suddenly after precipitation. The complexes were separated from the reaction mixture and washed with boiling ethanol and dried in vacuo over CaCl\textsubscript{2}.

Equipment and measurements

Carbon and hydrogen content was determined at the Microanalytical Unit of Cairo University. The analysis of metal ions and their conjugated anion (chloride) were carried out according to standard methods.\textsuperscript{10} IR spectra were recorded on a Genesis II FT–IR spectrophotometer (KBr – discs) in the ν = 400 – 4000 cm\textsuperscript{-1} range. Raman laser spectra of samples were measured on the Bruker FT-Raman with laser 50mW at Taif University, Saudi Arabia. \textsuperscript{1}H–NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer using d\textsuperscript{6}-DMSO as solvent and TMS...
as internal standard. The molar conductivities of freshly prepared 1.0x10^{-3} mol cm^{-3} DMSO solutions were measured for the soluble complexes using Jenway 4010 conductivity meter. The number of crystalline water molecules was estimated upon thermogravimetric analysis.

**Results and Discussion**

The analytical data of all the white color isolated complexes were displayed on Table 1. All the complexes are stable in air. The higher melting point of all isolated anhydrous complexes (> 300 °C) than the integral ligand (190 °C) may reflect their relative stability. All the complexes are insoluble in water, soluble to very limited extent in common organic solvents but considerable extent in dimethylformamide (DMF) and DMSO. The metal chelates solutions in DMSO showed slightly low conductance (49-63 Λm ohm^{-1}cm^{2}mol^{-1}) supporting the non-electrolyte nature of the complexes. The ephedrine compounds formed contains various amount of crystalline water (6, 8 and 4 for Ca, Sr and Ba, respectively) upon thermogravimetric analysis.

**Infrared spectra and chelation mode**

A comparison of the most intense band positions in the free ligand (ephedrine hydrochloride) and the formed precipitates are listed in Table 2. The spectrum of free ligand displays a series of significant bands as: 3330, 2972, 1591 and 1395 cm^{-1} which may assign to υ(OH), υ(NH), δ(NH) and δ(OH) in plane. The lower appearance shinned on bands of –OH and –NH groups supports of the presence of intraligand H–bonding (Fig. 1) between the two neighboring groups. This is expected due to the distribution of –OH and –NH groups, which primates this behavior as appeared from Molecular Modeling for the minimum internal energy structure (3.385 kcal/mol) by the use of MM^+ 11 force – field as implemented in hyperchem 5.1. According to elemental analysis and thermogravimetric studies, all the complexes obtained contain coordinated and crystalline water as well. The bands observed at 900 – 950 and 810 – 850 cm^{-1} can be assigned to coordinated water molecules.13

The new bands assigned for υ(M-N) and υ(M-O) are easily characterized in the low frequency field except υ(M-Cl) which cannot detected in the scanning range but detectable in Raman spectra.

**Resonance Raman spectra**

Figure 2 displays the Raman spectra of investigated complexes in solid state as Ca(II), Sr(II) and Ba(II) complexes. As can be seen, all the complexes show a very similar pattern. The significant spectral similarity among the bivalent metal complexes reflects the same nature of the ligand in coordination with all metal ions. Table 2 summarizes the observed vibrational wavenumbers aggregated with infrared spectral data. The resonance Raman spectra of Ca(II), Sr(II) and Ba(II) complexes show band profile characteristic of compounds.

![Figure 1: The Modeling and 3D structures of ephedrine hydrochloride](image-url)
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Table 1: Analytical and Physical data for the Ephedrine complexes and its metal complexes

<table>
<thead>
<tr>
<th>Compound/Empirical formula (M. Wt.)</th>
<th>Color</th>
<th>Elemental analysis (%) Calcd. (Found)</th>
</tr>
</thead>
</table>

Table 2: Assignments of the IR (Raman) Essential Spectral bands (cm⁻¹) of ephedrine HCl and its metal complexes

<table>
<thead>
<tr>
<th>Compound</th>
<th>νOH</th>
<th>νNH</th>
<th>δOH</th>
<th>νC-O</th>
<th>δOH</th>
<th>δNH</th>
<th>νM-C</th>
<th>νM-N</th>
<th>νM-O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine (Eph.HCl)</td>
<td>3330</td>
<td>2972</td>
<td>751</td>
<td>1051</td>
<td>1395</td>
<td>1591</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>(3500)</td>
<td>(3064)</td>
<td>(725)</td>
<td>(1044)</td>
<td>(1303)</td>
<td>(1654)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CaCl₂.Eph.HCl.6H₂O</td>
<td>3245</td>
<td>3013</td>
<td>741</td>
<td>1017</td>
<td>1385</td>
<td>1569</td>
<td>--</td>
<td>409</td>
<td>540</td>
</tr>
<tr>
<td>(-) (3008)</td>
<td></td>
<td>(672)</td>
<td>(1045)</td>
<td>(1304)</td>
<td>(1598)</td>
<td>(213)</td>
<td>(466)</td>
<td>(566)</td>
<td></td>
</tr>
<tr>
<td>SrCl₂.Eph.HCl.8H₂O</td>
<td>3246</td>
<td>3012</td>
<td>740</td>
<td>1014</td>
<td>1324</td>
<td>1566</td>
<td>--</td>
<td>444</td>
<td>533</td>
</tr>
<tr>
<td>(-) (3008)</td>
<td></td>
<td>(658)</td>
<td>(1045)</td>
<td>(1304)</td>
<td>(273)</td>
<td>(472)</td>
<td>(546)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BaCl₂.Eph.HCl.4H₂O</td>
<td>3242</td>
<td>3013</td>
<td>740</td>
<td>1017</td>
<td>1262</td>
<td>1569</td>
<td>--</td>
<td>576</td>
<td>--</td>
</tr>
<tr>
<td>(-) (3008)</td>
<td></td>
<td>(672)</td>
<td>(1038)</td>
<td>(1304)</td>
<td>(1551)</td>
<td>(279)</td>
<td>(466)</td>
<td>(526)</td>
<td></td>
</tr>
</tbody>
</table>

1H-NMR of SrCl₂.Eph. HClH₈O complex

1H-NMR spectrum of the strontium(II) complex was recorded in DMSO and compared with the ligand one to confirm the binding of active sites towards the metal ion. The spectrum showed a multiplet in the region δ = 0.77 – 0.78 ppm, which has been assigned for methyl protons (CH₃ –CH₃). A singlet peak in the region δ = 2.46 – 2.49 ppm for the other methyl protons (CH₃ –NH). Singlet peaks appeared at region δ = 3.12 – 3.13 and 4.93 – 4.92 ppm were assigned for CH proton of MeCH-NH and PhCH(OH) groups, respectively. In the region δ = 7.25 – 7.27 ppm were assigned chemical shifts for hydrogen of symmetrical aromatic ring of the ligand.

Figure 2: Raman spectrum of the calcium(II) chloride – ephedrine hydrochloride complex

The position of the OH and NH peaks in the SrCl₂.Eph. HClH₈O complex are relatively unaffected in comparing with that in free ligand, this is suggesting their participation after the removal of intraligand hydrogen bonding between the two groups causing their appearance as more or less unshifted. Although, the usual behavior is the downfield appearance for the peaks assigned for the coordinating groups due to the deshielding caused coherently with the movement of unchained paired of electrons towards the metal ion to form a coordinate bonds. Due to flexibility of the structural variations in these type of compounds formed, the studies on the nature of chemical bond, coordination mode and number of the ligands and other structural features are in progress.

References

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