Study of Polymorphism in Calcium Halides Complexes of Pharmaceutically Important Ligands

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Summary: The synthesis of calcium halides complexes of pharmaceutically important ligands have been reported. The ESR spectra have been measured at X- and Q-band, of manganese (II) ions doped at a nominal 1% in the lattices of Ca (glycine)$_4$ Cl_2, Ca(acetamide)$_4$ Cl_2 and Ca (acetamide)$_4$ Br_2. For the first time, in the ESR spectra of all these complexes, the Mn (II) ions have been found distributed between two lattice sites, suggesting the presence of two polymorphic forms for each of the complex. Further, in each case the polymorphic form with lower D value was always found to be formed in larger quantity than that with higher D value.

Introduction

The occurrence of polymorphic forms of a drug is by no means unusual. Many pharmaceutically important compounds can exist in more than one crystalline form, a property known as polymorphism. The molecules of these compounds exhibit different space-lattice arrangements in the crystal from one polymorph to another. Although such pharmaceutically important compound is chemically indistinguishable in each form, polymorphic forms differ significantly with respect to a number of properties such as density, melting point, solubility and dissolution rate. It has been reported that one-third of all organic compounds can exist in at least two crystal forms and one-half of 22 barbaturate derivatives and 11 of 16 steroids that were investigated were found to display polymorphism [1]. Similarly, the acetamide has also been reported to exist in two different structural forms [2]. These pharmaceutically important compounds, when treated with metal salts, may form the polymorphic complexes.

The determination of stereochemistry of different polymorphic forms, without recourse to X-ray diffraction, is usually more difficult for main group metal complexes than for those of transition metal complexes. In recent years the use of manganese (II) ions as a stereochemical probe has made the ESR spectroscopy a very useful tool to determine the stereochemistry of those bivalent metal ions complexes, which, because of an empty or completely filled d shell, are not amenable to study by the usual physical techniques [3-7].

Here we report the preparation of polymorphic complexes formed by calcium halides with pharmaceutically important ligands, which include Ca (glycine)$_4$ Cl_2, Ca (acetamide)$_4$ Cl_2 and Ca (acetamide)$_4$ Br_2. All these complexes have been characterized by elemental analysis and the ESR spectra of manganese (II)) ions doped into the lattices of all of these complexes have been obtained at both X- and Q-band frequencies to study their structures.

Results and Discussion

All the calcium halides complexes of pharmaceutically important ligands, synthesized in the present work are reported in Table-1. ESR spectra have been measured at both X-and Q-band frequencies for 1% of Mn(II) ions doped into the complexes Ca (glycine)$_4$ Cl_2, Ca (acetamide)$_4$ Cl_2 and Ca (acetamide)$_4$ Br_2.

Table-1: Zfs parameters of Mn (II) in calcium halides complexes.

Complex	D(Cm^{-1})	λ
Ca (glycine)$_4$ Cl_2	0.082	0.178
	0.086	0.144
Ca (acetamide)$_4$ Cl_2	0.128	0.010
	0.135	0.007
Ca (acetamide)$_4$ Br_2	0.391	0.012
	0.414	0.020

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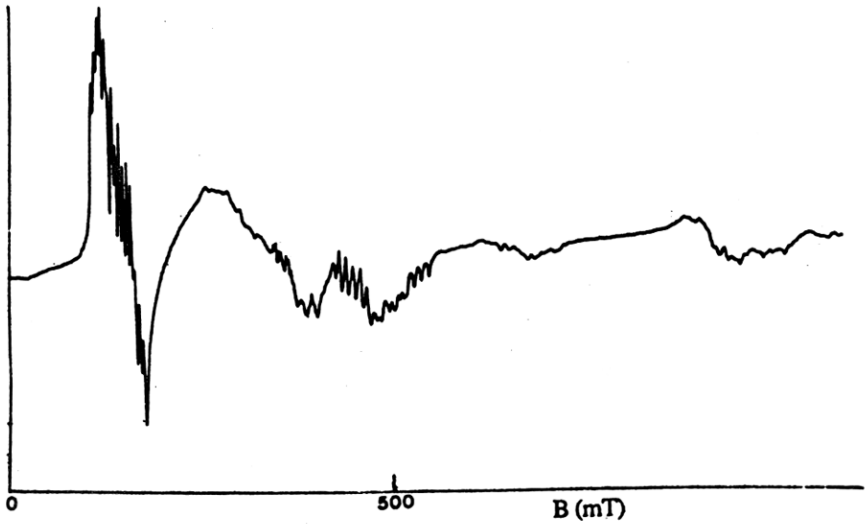

Fig.1. X-band ESR spectrum of Ca (Mn)acetamide)$_4$ Br_2

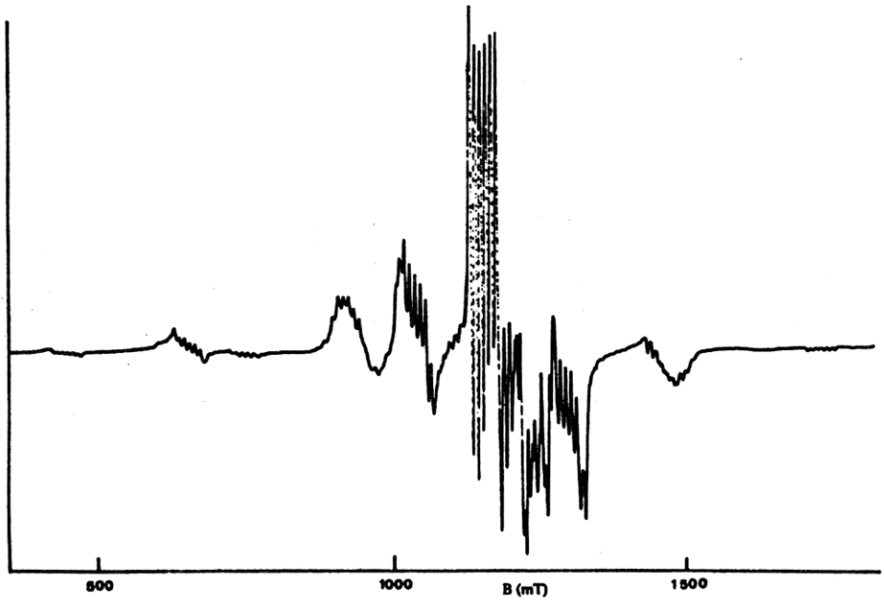

Fig.2. Q-band ESR spectrum of Ca (Mn) (acetamide)$_4$ Cl_2

At X-band all these complexes gave good quality but very complicated spectra with considerable overlapping of transitions and on the basis of only X-band spectra, the detailed interpretation was very difficult. The highest bands observed around 720 mT, in the spectrum of complex Ca (glycine)$_4$ Cl_2 and around 940 mT in the spectrum of Ca(acetamide)$_4$ Cl_2 suggested D values of about 0.09 and 0.13 cm^{-1} respectively. The X-band spectrum of Ca (acetamide)$_4$ Br_2 is much simpler in form (Fig.1), with the main intensity near $g_{eff} = 6$, indicating a much higher value of D and a low but finit λ. In the spectral profiles, at X-band, of all these complexes many more lines were observed than can

Table-2: Q-band ESR spectrum (mT) of Ca (Mn) (glycine)$_4$ Cl_2

Calculated for D= 0.086 cm^{-1} λ = 0.144			Observed (v=33.900 GHZ)	Calculated for D= 0.082 cm^{-1} λ = 0.178		
Levels	Field Direct	B.		B.	Field Direc.	Levels.
			438.0			
2--1	Z	843.5	843.9			
			862.6	863.1	Z	2--1
			949.8	949.0	Y	6--5
6--5	Y	1026.4	1027.5			
			1036.8	1035.8	Z	3--2
5--4	Y	1074.6	1073.4	1073.4	Y	5--4
5--4	X	1148.3	1148.3			
4--3	X	1192.7	1194.0	1193.5	X	4--3
4--3	Y	1201.0	1201.3	1202.7	Y	4--3
4--3	Z	1209.9	1210.0	1209.5	Z	4--3
3--2	Y	1335.0	1337.0			
			1340.0	1338.4	Y	3--2
			1385.0	1384.3	Z	5--4
5--4	Z	1394.2	1394.0			
2--1	Y	1478.6	1479.5			
			1482.5	1481.9	Y	2--1
			1561.8	1560.7	Z	6--5
6--5	Z	1579.8	1581.0			

be expected for a single set of zero-field splitting (zfs) parameters, D and λ, and suggest the presence of manganous ions in more than one lattice environment.

The Q-band spectra of all of these complexes were very well resolved and, therefore, were used to determine the precise value of D and λ (=E/D), for the individual complexes in the Spin Hamiltonian (i).

$$H = g\beta BS+D (S^2_z-1/3 S (S+1)) +E (S^2_x-S^2_y) \text{ ---- (i)}$$

The observed resonance fields fitted very well with those calculated, using the programme ESRS [8], by exact diagonalization of the matrix derived from (i) with g_{iso} =2.00 (Tables 2-3).

The positions and intensities of transitions observed, for all of these complexes, indicated the unequal distribution of manganese (II) ions between two lattice sites characterized by the zero-field splitting parameters:-

D = 0.082 cm^{-1}; λ = 0.178 and D = 0.086 cm^{-1}; λ = 0.144 for Ca (Mn) (glycine)$_4$ Cl_2;

D = 0.0.128 cm^{-1};λ = 0.010 and D = 0.135 cm^{-1}; λ = 0.007 for Ca (Mn) (acetamide)$_4$ Cl_2.

D = 0.391 cm^{-1};λ = 0.012 and D = 0.414 cm^{-1}; λ = 0.020 for Ca (Mn) (acetamide)$_4$ Br_2.

In each case the intensities of transitions observed for the lattice site with higher D value were comparatively weaker than those for the lattice site with lower D value.

The values of D and λ for these complexes are listed in Table 1. For the first time, in the ESR spectra of all of these complexes, the manganese (II) ions have been found distributed between two lattice sites characterized by two different sets of zero-field splitting parameters D and λ and indicate the presence of two polymorphic forms for each of the complex studied. In each case the intensities of transitions observed for the lattice site with higher D value were comparatively weaker than those for the lattice site with lower D value suggesting the formation of two polymorphic forms in unequal amounts. Further, in each case the polymorph with lower D value was always found to be formed in larger quantities than that with higher D value.

Table-3: Q-band ESR spectrum (mT) of Ca (Mn) (acetamide)$_4$ Cl_2

Calculated for D= 0.135 cm^{-1} λ = 0.007			Observed (v = 33.992 GHz)	Calculated for D= 0.128 cm^{-1} λ = 0.010		
Levels	Field Direct	B.		B.	Field Direc.	Levels.
2--1	Z	636.0	637.			
			665.	666.1	Z	2--1
3--2	Z	925.1	927.			
6--5	Y	941.9	941.	940.2	Z	3--2
			969.	969.0	X	6--5
5--4	Y	1052.3	1053.			
5--4	X	1057.6	1058.	1060.1	Y	5--4
			1067	1067.3	X	5--4
4--3	X	1180.5	} 1181			
4--3	Y	1181.5				
				1183.7	X	4--3
			1184	1185.0	Y	4--3
4--3	Z	1214.3	Region	1214.4	Z	4--3
			1324	1322.9	X	3--2
3--2	Y	1335.1	1336.			
			1489.	1488.5	Z	5--4
				1491.8	X	2--1
5--4	Z	1503.4	1503.			
2--1	X	1509.8	1511.			
2--1	Y	1521.5	1522.			
			1764.	1762.7	Z	6--5
6--5	Z	1792.6	1793.			

In case of acetamide complexes, the higher D value observed for the bromide complex, than for chloride analogue, indicates coordination of halide ions. Further, all of these complexes have lower D values than their urea analogues [9], suggesting a weaker field effect by glycine and acetamide than by urea. This result is in line with the previously reported higher Dq value of urea (860 cm^{-1}) [10] compared with acetamide (824 cm^{-1}) [11].

Experimental

Preparation of complexes

All the chemicals used in the present work were pure analytical grade and were used without further purification.

Ca (glycine)$_4$ Cl_2

The hot aqueous solutions of calcium chloride and glycine, in stoichiometric quantities, were prepared separately in minimum of water. The solutions were mixed together and the resulting solution was filtered off. The mixture was allowed to evaporate slowly at room temperature for several days. The white precipitates thus formed were washed with ether and dried in vacuo over P_2 O_5. Found; C, 22.82; H, 4.68; N, 13.13 Calculated for Ca(glycine)$_4$ Cl_2 : C,23.36; H, 4.87; N, 13.63.

Ca (acetamide)$_4$ X_2 (X= Cl or Br)

Both of these complexes were prepared by slow evaporation of aqueous solutions of equimolar ratios of calcium halides and acetamide, at room temperature, in vacuo over H_2 SO_4. Found: C, 27.75; H, 6.35; N, 16.03 Calculated for Ca (acetamide)$_4$ Cl_2: C, 27.67; H, 5.76; N, 16.13. Found: C, 22.99; H, 6.04, N, 13.38 Calculated for Ca (acetamide)$_4$ Br_2: C,22.83; H, 4.59, N, 12.84.

Analysis for % age composition of C, H and N were carried out by Imperial College pf Science, Technology and Medicine Microanalytical Laboratory.

X- band spectra were obtained using a varian E 12 spectrometer. Q-band spectra were obtained with a Bruker ER 200D-SRC spectrometer and an ER078 15-inch electromagnet. The ESR spectra were measured on powdered solid samples at room temperature. The Mn (II) 'doped' samples were obtained by preparing the host complex but using a solution of calcium halides to which a nominal 1% 'impurity' of corresponding manganese (II) halides had been added.

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