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Mercury(II) Complexes of Vitamin B_1

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Abstract

Mercury(II) complexes of thiamine and its derivatives have been synthesized and characterized by elemental analysis, conductivity measurements, infrared, proton and carbon-13 nuclear magnetic resonance spectra. These new complexes have been formulated as either $M(Th)X_3$ with a possibility of direct Hg(II)–N(1′) interaction or as ionic compounds of the type $(MX_3)^-(Th)^+$ where M = Hg, Th = thiamine, X = Cl, Br or I and (M(Th)(OAc)X)X where X = SCN and OAc = acetato group.

Introduction

Recently, we and others demonstrated [1–7] by way of ^1H, ^{13}C NMR, IR spectroscopy and X-ray crystallography that metal–thiamine complexes do actually exist. It was earlier suggested that there are several areas in which complexing might be an important facet of the chemistry of thiamine [8]. For instance, complex formation is a possible mechanism for the prevention of cadmium [9, 10], manganese [11, 12] or mercury [13] poisoning in the biological system. To this end, we have synthesized mercury(II) complexes of thiamine and its derivatives and now we wish to report some of their properties.

Experimental

Thiamine derivatives, thiamine·HX_2 (X = Br, I or SCN) were prepared [14] by mixing a warm aqueous solution of either the potassium or sodium salts of X (1:5 molar ratio) with thiamine chloride hydrochloride. The chloro, bromo, iodo and thiocyanato complexes were prepared employing the general synthetic route [15]. However, unlike the latter, mercury(II) acetate solution was added dropwise with constant stirring so as to discourage the formation of multiple products [16]. Table 1 lists some of the analytical data of the complexes.

The conductivity measurements were carried out in DMSO with an Electronic Conductivity Model MC-1, Mark V while the IR spectra were taken in KBr discs using a Perkin-Elmer 983 spectrometer in the range 4000–200 cm^{-1}. The NMR spectra were run in d_6-DMSO on a Nicolet 200 MHz High Resolution Spectrophotometer while the melting points were determined by a Gallenkamp Melting point apparatus and were uncorrected.

Results and Discussion

The elemental analysis of the complexes shows 1:1 metal-to-ligand stoichiometry supporting either

TABLE 1. Analytical data for mercury(II) complexes

Compound	Colour	Melting point (°C)	Conductivity	C (%)	H (%)	N (%)	Halogen (%)
Hg(thiamine)CH_3	light yellow	140–142	37	25.17 (25.25)	2.97 (2.89)	9.79 (9.63)	18.59 (18.44)
Hg(thiamine)Br_3	dull white	176–178	43	20.43 (20.85)	2.41 (2.37)	7.94 (7.79)	33.99 (34.04)
Hg(thiamine)I_3	yellow	138–140	45	17.02 (16.97)	2.01 (1.98)	6.62 (6.71)	44.98 (44.69)
[Hg(thiamine)(OAc)SCN]SCN	white	136–138	67	29.88 (29.64)	3.12 (3.07)	13.07 (3.11)	

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$M(Th)X_3$ or $(MX_3)^-(Th)^+$ formulation. These complexes are soluble in dimethyl sulphoxide and dimethyl formamide. The electrical conductances (37–45 ohm^{-1} cm^2 mol^{-1}) in dimethyl sulphoxide, though slightly lower than normally expected for a 1:1 electrolyte [17] may be supportive of $(MX_3)^-$-$(Th)^+$ rather than $M(Th)X_3$ formulation for the chloro, bromo and iodo complexes while a value of 67 ohm^{-1} cm^2 mol^{-1} observed for the thiocyanato complex confirms the proposed structure, (Hg(Th)-(OAc)SCN)SCN.

All the new complexes have lower melting points (136–178 °C) than some solid thiamine complexes reported earlier [1–7] but comparable to those reported by Hadjliadis *et al.* [18]. The bromo complex has the highest melting point (176–178 °C). This is not surprising as it has been observed that in molecular compounds, the bromo compound has a higher melting point than the chloro compound whereas in ionic compounds, the chloro compound has a higher melting point than the bromo analogue, according to the halogen properties (Cl > Br > I). Further support for the molecular nature of the chloro, bromo and iodo complexes is reflected in their non-solubility in water. This is definitely a sharp contrast to the zinc(II) and cadmium(II) analogues reported earlier [1, 2, 4]. It is worth noting that Zn(II), Cd(II) and Hg(II) complexes are four coordinate with three 'X' ligands and an atom N-1′ of the pyrimidine ring of thiamine molecule completing an unusual tetrahedral coordination about the metal(II) ion. Unlike the zinc and cadmium analogues, however, many attempts focussed at isolating single crystals suitable for X-ray analysis of the Hg(II) complexes had proved abortive.

Infrared Spectra

Table 2 lists the major IR bands of thiamine·HCl_2 and the complexes. The ligand and all the complexes show strong bands in the region 3500–3000 cm^{-1} due to the $\nu(OH)$, $\nu(NH_2)$ and $\nu(CH)$ aliphatic or aromatic stretching motions [5–7, 19]. In the chloro compound, the same bands appear at 3447, 3400, 3290 and 3089 cm^{-1} while these bands appear at 3450, 3360, 3270 and 3040 cm^{-1} in the bromo analogue. The spectrum of the iodo compound shows these bands at 3430, 3324, 3207 and 3050 cm^{-1} while in the thiocyanato compound the same bands are located at 3440, 3320, 3299 and 3150 cm^{-1}. The variation in the position of these bands in all the complexes may be due to the varying degree of intermolecular hydrogen bonding between the hydrogen atoms of the amino group and the endocyclic nitrogen (N-3′) and an 'X' atom in each

TABLE 2. Selected infrared frequencies of thiamine·HCl_2 and its mercury(II) complexes

Thiamine·HCl_2	$Hg(Th)Cl_3$	$Hg(Th)Br_3$	$Hg(Th)I_3$	[Hg(Th)(OAc)SCN]SCN	Assignment
3450s	3447s	3450s	3430s	3440s	$\nu(OH)$
3435s	3400s	3360s	3324s	3320s	$\nu_{as}(NH_2)$
3270s	3290s	3270s	3207s	3290s	$\nu_s(NH_2)$
3075s	3089s	3040s	3050s	3150s	$\nu(CH)$
				2107s 2072s	$\nu(CN)$
				1678s	$\nu(C{=}O)$
1658vs 1608s	1655vs 1618s	1660s 1613s	1651s 1618s	1658s 1604s	$\nu(NH_2) + \nu(OH)$
1538s 1505sh	1550s 1466m	1570s 1482m	1556w 1533s 1470m	1555s 1479m	$\nu(C{=}C) + \nu(C{=}N)$
1035s	1075m	1060m	1050m 1040m	1385vs 1069	$\delta(OH)$
			824m 780m		
667m 637m	668m 634m	667m 634	667m 635m	668m 635m	$\nu(C{-}S)$ thiazolium ring
	522w	505w	545m	535w	ν(Hg–N pyrm)
				450w	$\delta(NCS)$
					$\nu(Hg{-}O)$
	322m 305m	320m 285m	315m 308m 290m	300m	$\nu(Hg{-}X)$

complex. Cramer *et al.* [1,3] had demonstrated by X-ray crystallography such hydrogen bonding in Cd(thiamine)$Cl_3O \cdot 6H_2O$ and Cu(thiamine)Cl_2 complexes.

The thiocyanato complex, (Hg(Th)(OAc)SCN)-SCN shows a very strong band around 2000 cm^{-1}. Interestingly, this band is conspicuously absent in the chloro, bromo and iodo complexes. It is therefore assigned to the ν(C=N) mode. In coordination compounds the thiocyanate ion can be bound to the central metal atoms in three ways; through the nitrogen atom (M–NCS), through the sulphur atom (M–SCN) or by means of a bridging structure (M–NCS–M). A very strong band is characteristic of a monodentate N-bonded [20] thiocyanate group. In our thiocyanato complex this strong band is split into two at 2107 and 2072 cm^{-1}, respectively. This splitting [21] may be due to a possible bridging structure (M–NCS–M) where the metal is bound to both the N and S donor atoms of the SCN group. Another possibility is that there may be two kinds of SCN group; one in the first coordination sphere and the other in the second coordination sphere of the metal ion. The more intense peak at 2107 cm^{-1} is most likely due to the SCN group in the first coordination sphere while the less intense peak at 2072 cm^{-1} is due to the SCN in the second coordination sphere. Interestingly, the conductivity value (67 ohm^{-1} cm^2 mol^{-1}) observed for the thiocyanato complex in DMSO falls in the range (65–90 ohm^{-1} cm^2 mol^{-1}) expected for a 1:1 electrolyte [17]. This observation lends support to the assumption that one SCN group is in the first coordination sphere while the other SCN is in the second coordination sphere. Another interesting feature of the thiocyanato complex is another strong peak at 1678 cm^{-1}. This band is again conspicuously absent in the chloro, bromo and iodo complexes. It is therefore unequivocally assigned to the carbonyl oxygen of the acetato group in the first coordination sphere of the metal ion (see Fig. 2b).

Another region of interest is around 1600 cm^{-1}. In thiamine$\cdot HCl_2$ two bands appear at 1658 and 1608 cm^{-1} which are assignable to NH_2 bending and ring stretching coupling [22]. In the chloro, bromo, iodo and thiocyanato complexes the same bands appear at 1655 and 1618, 1660 and 1613, 1651 and 1618, and 1658 and 1604 cm^{-1}, respectively. The bands at 1538 and 1505 cm^{-1} ascribed to the ν(C=C) and ν(C=N) modes appear at 1550 and 1466, 1570 and 1482, 1556, 1533 and 1447, 1555 and 1478 cm^{-1} in Hg(Th)Cl_3, Hg(Th)Br_3, Hg(Th)I_3 and (Hg(Th)(OAc)SCN)SCN, respectively. The shift in this region is indicative of complex formation [5,7]. The non-involvement in bonding of the OH group with mercury is confirmed by the non-removal of the ν(OH) band of the ligand in the complexes [23,24]. This band which appears at 1035 cm^{-1} in the ligand is located at 1075 and 988, 1060, 1050 and 1069 cm^{-1} in the chloro, bromo, iodo and thiocyanato complexes, respectively. The shift in the position of this band in all the complexes relative to its position in the ligand may be due to hydrogen bonding, the extent of which depends on the identity of X in the order Cl > SCN > Br > I.

The stretching vibration mode for the C–S group in the ligand can be assigned to the two medium bands at 667 and 637 cm^{-1}. In the chloro, bromo, iodo and thiocyanato complexes, the same two bands appear at 668 and 634, 667 and 634, 667 and 635, and 668 and 635 cm^{-1}, respectively. Since there are no changes in the positions of these two bands in these complexes relative to the ligand, it could be concluded that the sulphur donor atom is not involved in coordination. The new weak bands at 522, 505, 545 and 535 cm^{-1} in the chloro, bromo, iodo and thiocyanato complexes, respectively, suggest ν(Hg–N(pyrimidine)) vibrations. Furthermore, in the chloro complex, the weak bands at 322 and 305 cm^{-1} are ascribed to the ν(Hg–Cl) mode while in the bromo analogue the ν(Hg–Br) mode appears at 320 and 285 cm^{-1}. In the iodo complex, the bands at 315, 308 and 290 cm^{-1} are assigned to the ν(Hg–I) mode while in the thiocyanato complex, the ν(Hg–NCS) mode appears at 300 cm^{-1}. There is another band at 358 cm^{-1} in the thiocyanato complex, which is not present in the chloro, bromo and the iodo complexes. This band is ascribed to the ν(Hg–O) mode.

NMR Spectra

The ^{1}H NMR chemical shifts of both the ligand and the complexes are given in Table 3 while Table 4 lists the ^{13}C NMR chemical shifts. Although the direction of the chemical shifts of these new complexes is similar to some of those already reported, there is a need to discuss some of the resonances for the purpose of comparison. For this comparison we have chosen Pt(II) and Pd(II) thiamine complexes reported [7] recently, since all these complexes have certain properties in common. For example, the Pt(II), Pd(II) and Hg(II) thiamine complexes are not soluble in water but soluble in DMSO and DMF. Both the ^{1}H and ^{13}C NMR spectra of these complexes were recorded in d_6-DMSO for effective comparison. Figure 1 shows a representative spectrum of the Hg(II)–thiamine complexes.

An examination of the ^{1}H NMR of these new complexes shows a negative shift of C6′–H signal, another evidence in support of lack of direct Hg(II)–N(1′) interaction. A positive shift of this signal which is adjacent to the assumed coordination site (N-1′) would be expected for direct Hg(II)–N(1′) interaction. In the Pt(Th)Cl_3 complex [7], the 2′-CH_3, C6′ and C2′ carbon resonances are shifted by 6.29, 8.48 and 3.95 ppm, respectively. In the Hg(Th)Cl_3 complex, however, the same resonances are shifted

TABLE 3. ^1H NMR spectra of thiamine·HCl_2 and its mercury(II) complexes

Proton	Thiamine·HCl_2	$Hg(Th)Cl_3$	$Hg(Th)Br_3$	$Hg(Th)I_3$	[Hg(Th)(OAc)SCN]SCN
C2-H	10.08s	9.85s	9.84s	9.84s	9.85s
C4'-NH_2	9.33s	8.36br	8.36br	8.37br	8.36br
C6'-H	8.47s	8.26s	8.27s	8.26s	8.27s
5'-CH_2	5.70s	5.44s	5.44s	5.43s	5.45s
OCH_2	3.67s	3.70t	3.70t	3.69t	3.70t
5-CH_2	3.10s	3.09t	3.10t	3.10t	3.09t
2'-CH_3	2.60s	2.50s	2.50s	2.50s	2.50s
4-CH_3	2.57s	2.50s	2.50s	2.50s	2.50s

s = singlet; t = triplet; br = broad.

TABLE 4. ^{13}C NMR of thiamine·HCl_2 and its mercury(II) complexes

Carbon	Thiamine·HCl_2	$Hg(Th)Cl_3$	$Hg(Th)Br_3$	$Hg(Th)I_3$	[Hg(Th)(OAc)SCN]SCN
C2'	163.00	164.15	164.09	164.11	164.13
C4'	161.23	162.57	162.60	162.61	162.63
C2	155.23	154.58	154.59	154.60	154.64
C6'	146.65	150.40	150.37	150.38	150.41
C4	142.13	141.98	141.92	141.94	141.97
C5	135.31	135.51	135.45	135.48	135.50
C5'	105.28	104.50	104.46	104.48	104.48
OCH_2	59.65	59.60	59.56	59.54	59.51
5'-CH_2	49.88	50.14	50.19	50.18	50.16
5-CH_2	29.33	29.30	29.29	29.36	29.29
2'-CH_3	21.13	22.98	22.96	22.95	22.97
4-CH_3	11.63	11.70	11.68	11.74	11.69

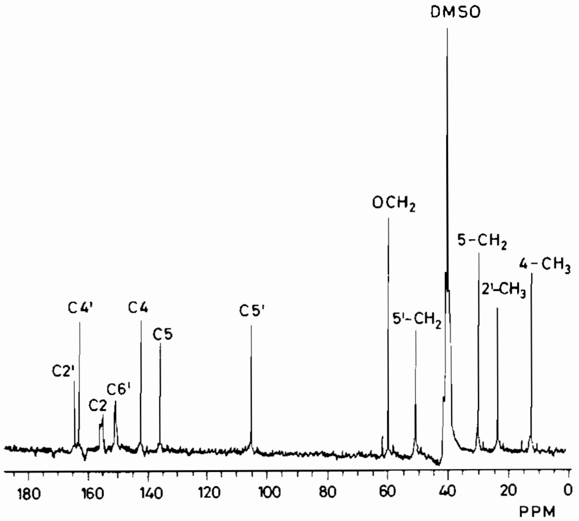

Fig. 1. Representative ^{13}C NMR spectrum of mercury(II)–thiamine complexes.

downfield by 1.82, 3.75 and 1.15 ppm, respectively. The smaller ^{13}C NMR chemical shifts observed in these complexes may be due to either weak interaction between Hg(II) and N-1′ of the pyrimidine moiety of thiamine or lack of direct Hg(II)–N(1′) interaction in these complexes. It is also possible that these complexes partially decomposed in warm DMSO since a long time (~12 h) was required to obtain any decent spectrum.

In summary, establishing the actual complexing site most especially for ligands having a wide variety of donor sites, could be challenging and interesting. In thiamine there are three potential complexing sites (NH_2, N-1′ and S donor atom). Although the Hg(II) ion has a great affinity for NH_2 and S, it is very unlikely that Hg(II) ion binds to any of these two sites in this case. The 4′-oxocyclic amino substituent of the pyrimidine ring bears a partial positive charge across the pH span of 0–9 because the exocyclic nitrogen's unbonded pair of electrons is extensively overlapped with the electrons of the ring. This partial positive charge would repel protons or metal ions. The S donor atom of the thiazolium ring [25] has been shown to be unreactive probably due to the fact that some positive character is being transmitted to it by the N-3 atom of the thiazolium moiety. Even in thiazole (Fig. 2c), metals prefer to bind to the nitrogen donor atom. The fairly constant position of the ν(C–S) mode in all the complexes with respect to the ligand confirms the non-

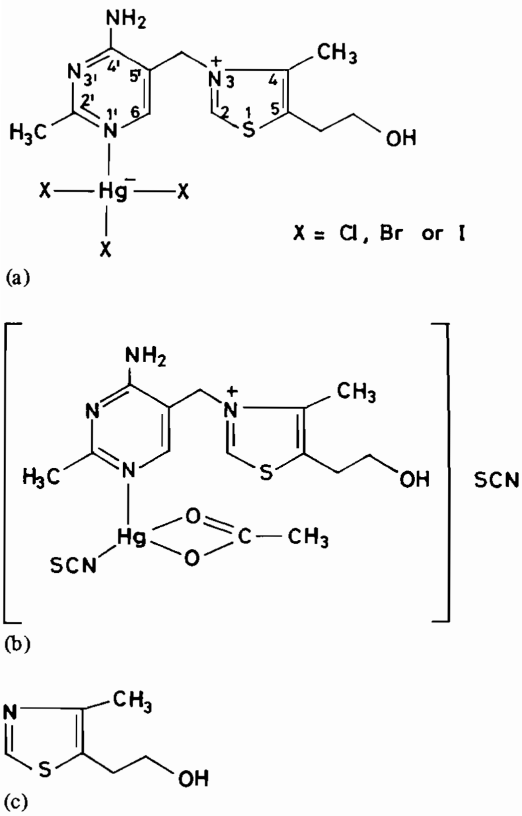

Fig. 2. The proposed structure for the chloro, bromo and iodo complexes (a) and the thiocyanato complex (b). The structure (c) is thiazole.

involvement of the sulphur donor atom in coordination.

The complexing site is most likely the N-1′ of the ligand as this is confirmed by a significant shift in the ν(C=C) and ν(C=N) modes in all the complexes relative to thiamine. The ν(M–X) and ν(M–N) modes observed in the complexes are further proof for complex formation. The small ^{13}C chemical shifts observed for these new complexes compared to those of Pt(II) and Pd(II) complexes reported earlier may be due to either weak interaction between the Hg(II) ion and N-1′ of thiamine or partial decomposition of these complexes in warm DMSO as a very long time (~12 h) was required to obtain any decent spectrum. It is equally possible that the new complexes are of the ionic type, $(MX_3)^-(Th)^+$.

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