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Complexes of Theophylline with Divalent Metal Ions

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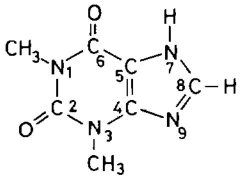
Abstract

Theophylline (Tp)–metal ion complexes of the type $M(Tp)_2(L)_2 \cdot XH_2O$, where M = Cu(II), Zn(II), and Cd(II), L = O, NH_3, Cl, Br, and X = 0, 1, 2 were examined in the IR 600–200 cm^{-1} region. Room temperature magnetic susceptibilities were acquired for the Cu(II) complexes. These values were slightly low, and when IR spectra of the above complexes were compared to similar compounds of known structure, the metal atoms in the above complexes appear to have distorted tetrahedral stereochemistries, with theophylline acting as a bridge for polymer formation. $CuTp_2$ exhibits a very low magnetic susceptibility, suggesting that extensive magnetic exchange interactions have occurred.

Introduction

The interaction of theophylline (Tp) with metal ions has been extensively studied in recent years [1–3]. We have prepared a series of theophylline metal ion complexes of the type $M(Tp)_2(L)_2 \cdot XH_2O$, where M = Cu(II), Zn(II), and Cd(II), L = O, NH_3, primary amines, and X = 0, 1, 2 [4–7]. Infrared spectra of these complexes in the 4000–650 cm^{-1} region indicate that, with the exception of $CuTp_2$, they are structurally similar [7]. C_6 carbonyl coordination to the central metal does not occur, but hydrogen bonding is present between C_6 and various other ligands. This is in agreement with previously studied theophylline–metal ion complexes [2, 3].



Theophylline

Recently, the IR spectra of a series of metal complexes of purine [8, 9] and xanthine, hypoxanthine, and guanine [10, 11] have been published. Various structures were proposed for the purine complexes, including a double bridged N(3), N(9) dimer or a N(3), N(9) bridged oligomer. Vestues and Sletten [12] have determined the structure of the copper–purine complex, $[Cu(C_5H_4N_4)(H_2O)_4]SO_4 \cdot 2H_2O$, to be a polymeric chain with copper atoms in an octahedral coordination binding equatorially to N(7) and N(9) of two purine rings. This binding is fairly common in simple imidazole and benzimidazole metal complexes [13] but has been previously unknown in neutral purines. The structure of metal complexes of xanthine, hypoxanthine, and guanine has also recently been proposed as polymeric chains, with bonding most likely occurring between the copper atom and N(7) and N(9) of two purine rings.

The compounds of interest here, $M(Tp)_2(L)_2 \cdot XH_2O$, form immediately in basic solution and are completely insoluble in organic solvents. Their synthesis and properties are similar to those for metal complexes of benzimidazole (Bz), such as $Cu(Bz)_2$ [13]. Bridging in imidazole and benzimidazole complexes involving N(7) and N(9) has been documented. When theobromine is substituted for theophylline in the above complexes, no reaction occurs [4]. Theobromine is blocked at the N(7) position with a methyl group, and thus offers no possibility for imidazole bridging for polymer formation involving N(7) and N(9). Undoubtedly, other factors are also involved in the unreactivity of theobromine to complex formation of this type, but theophylline may react similarly to imidazole and benzimidazole towards metal ions because of their common imidazole ring structure.

$CuTp_2Cl_2$ and $CuTp_2Br_2 \cdot H_2O$ were prepared following a procedure by Behrens and Goodgame [14]. Low frequency IR spectra (600–200 cm^{-1}) of these compounds were compared to those of the above complexes to gain more understanding of their structures.

Experimental

Metal ion–theophylline complexes were prepared as reported previously [4–7]. Infrared spectra

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were obtained as Nujol mulls between high density polyethylene windows (600–200 cm^{-1}) on a Perkin-Elmer 1430 spectrophotometer. Magnetic measurements were obtained at room temperature on a Gouy balance of standard design.

Preparation of CuTp$_2$Cl$_2$

0.5 mmol theophylline (0.90 g) and 5.0 mmol $CuCl_2 \cdot 2H_2O$ (0.85 g) were refluxed in methanol for 24 h, and allowed to cool at room temperature for one day. 2.1 g (85% yield) orange powder was recovered and dried under vacuum to constant weight. *Anal.* Calcd. for $(C_7H_7N_4O_2)_2CuCl_2$: C, 34.11; H, 2.84; N, 22.74; Cu, 12.89. Found: C, 34.18; H, 3.02; N, 22.59; Cu, 12.75%.

Preparation of CuTp$_2$Br$_2$·H$_2$O

The procedure outlined above produced 0.8 g (27%) dark brown-black powder after first concentrating the solvent. $CuTp_2Br_2$ was produced in anhydrous form by heating $CuTp_2Br_2 \cdot H_2O$ to constant weight at 130 °C. *Anal.* Calcd. for $(C_7H_7N_4O_2)_2CuBr_2 \cdot H_2O$: C, 28.04; H, 2.67; N, 18.69; Cu, 10.60. Found: C, 27.78; H, 2.87; N, 18.02; Cu, 10.66%.

Results and Discussion

$CuTp_2Cl_2$ and $CuTp_2Br_2 \cdot H_2O$ exhibit limited solubility in methanol, and rapidly decompose in water. All other complexes are insoluble; they decompose immediately in aqueous solution below pH 6.3, while $CuTp_2(NH_3)_2 \cdot 2H_2O$ and $CuTp_2(NH_3)_2$ undergo slow ligand exchange reactions with water above pH 6.3 [7].

Theophylline exhibits a number of ring vibrations in the 600–200 cm^{-1} region (Table I). Several of these are relatively unaffected upon metal complex formation, but the two lowest vibrations, at 292 cm^{-1} and 210 cm^{-1}, are shifted appreciably to higher frequencies upon complexation. In the $M(Tp)_2(NH_3)_2 \cdot XH_2O$ series the Cu(II) shift (331, 245 cm^{-1}) is greater than that of Zn(II) (317, 221 cm^{-1}) and Cd(II) (320, 220 cm^{-1}); these trends are similar to those observed for metal-pyridine complexes [15]. Other theophylline frequencies are relatively unaffected as the central metal ion varies from Cu(II) to Zn(II) and Cd(II), suggesting a similar stereochemistry is present in these complexes. The previously reported 4000–650 cm^{-1} IR spectra of these compounds are also closely similar [4–7]. Lattice water vibrations in $CuTp_2(NH_3)_2 \cdot 2H_2O$ and $Cd(Tp)_2(NH_3)_2 \cdot 2H_2O$ are not noticeable in the 600–200 cm^{-1} region; this may be due to masking by ligand bands. Distinct M–N stretching vibrations are not observed in this series. $M-NH_3$ bands may be obscured by theophylline vibrations, and M–N (theophylline) stretching may also be obscured, or may occur below 200 cm^{-1}, a situation found in complexes of p-toluidine, quinoline, and α and β-picoline [15].

The crystal structure of $ZnTp_2en$ (en = ethylenediamine) has recently been determined [16]. Zinc ion is tetrahedrally coordinated to ethylenediamine and two theophylline anions, with slight distortions from the ideal tetrahedral coordination angles of 109.5° due to steric factors and hydrogen bond interactions. Theophylline is bonded through N(7) to zinc and the relatively short Zn–N(7) bond length of 1.97 Å suggests that theophylline is present in the anionic form. Theophylline N(7) binding to the central metal has been previously proposed for $CuTp_2(NH_3)_2 \cdot 2H_2O$, $Zn(Tp)_2(NH_3)_2$ and $Cd(Tp)_2(NH_3)_2 \cdot 2H_2O$, and is known for many other metal ion complexes of theophylline [1–4]. Table I indicates the 600–200 cm^{-1} IR frequencies observed for $ZnTp_2en$. Excluding the peaks at 267 and 212 cm^{-1}, clear comparisons can be made between $ZnTp_2(NH_3)_2$ and $ZnTp_2en$, and indeed, also with $CuTp_2(NH_3)_2 \cdot 2H_2O$ and $CdTp_2(NH_3)_2 \cdot 2H_2O$. IR comparisons of these complexes suggests a similar structure, most likely that of a distorted tetrahedron. Goodgame and Haines [17] conclude that

TABLE I. Infrared (IR) Spectra (600–200 cm^{-1}) of Theophylline and Metal–Theophylline Complexes.

Compound	Metal sensitive Tp ring vibrations		ν(M–X)	ν(M–OH$_2$)	Ligand bands
Tp	292	210			550vw,503s,448s,421s,378s
$CuTp_2(NH_3)_2 \cdot 2H_2O$	331	245			550sh,510s,451s,424s,406m,222s
$CuTp_2(NH_3)_2$	330	250			550sh,514s,451s,422s,388m
$CuTp_2 \cdot 4H_2O$	330	250		430s	560w,512s,448sh,387sh
$CuTp_2$					550w,516s,500sh,456m,427s,385m
$CuTp_2Cl_2$			302s,288s		564w,511m,452m,421s,388m,361m
$CuTp_2Br_2 \cdot H_2O$			250s,230m	460sh	550m,510s,480s,420m,388m,361w
$ZnTp_2(NH_3)_2$	317	221			560w,511s,451s,423s,398s
$ZnTp_2en$	316	240			560w,510s,449s,419s,391s,267m,212m
$CdTp_2(NH_3)_2 \cdot 2H_2O$	320	220			560m,510s,455s,425s,395sh

dibenzimidazolatocopper(II), $CuBz_2$, possesses a distorted tetrahedral structure, similar to that reported for diimidazolatocopper(II) [18], where one half of the copper atoms have four coplanar N neighbors, and the remainder a flattened tetrahedral arrangement of four neighbors. The above theophylline complexes may have similar stereochemistries.

No appreciable change in the low frequency IR is noticed when $CuTp_2(NH_3)_2$ is compared to $CuTp_2(NH_3)_2 \cdot 2H_2O$. In fact, $CuTp_2(NH_3)_2$ is practically identical to $ZnTp_2(NH_3)_2$, with the exception of the two low frequency metal sensitive bands. The similarity of this IR with that of tetrahedral $ZnTp_2en$ (Table I) suggests a tetrahedral environment for Cu in this compound. When $CuTp_2 \cdot 4H_2O$ is compared to the above complexes, IR absorptions are similar except for a broad absorption at 430 cm^{-1}, attributed to two molecules of coordinated water replacing two ammine molecules [19]. Coordinated water can be clearly seen in the IR of this compound, but is not observed in the above aquated complexes. The absence of NH_3 in $CuTp_2 \cdot 4H_2O$ does not permit the assignment of $M-NH_3$ stretching in the above cases; apparently, this frequency is obscured by ligand bands. Excluding the water absorbance of 430 cm^{-1}, the spectra of $CuTp_2 \cdot 4H_2O$, $CuTp_2(NH_3)_2$ and $CuTp_2(NH_3)_2 \cdot 2H_2O$ are closely similar, suggesting that they are isomorphous. Magnetic susceptibility measurements (Table II) are also closely similar. Water and ammonia can be exchanged in these compounds resulting in little structural change. Indeed, the spectra indicate that the copper complexes are also isomorphous with $ZnTp_2(NH_3)_2$ and $CdTp_2(NH_3)_2 \cdot 2H_2O$.

TABLE II. Magnetic Susceptibilities (294 K) of Cu(II)–Theophylline Complexes.

Complex	μeff (B.M.)
$CuTp_2(NH_3)_2 \cdot 2H_2O$	1.72
$CuTp_2(NH_3)_2$	1.71
$CuTp_2 \cdot 4H_2O$	1.73
$CuTp_2$	0.93
$CuTp_2Cl_2$	1.78

Significant changes from the above are observed in the low frequency IR of $CuTp_2$. In particular, the metal sensitive theophylline bands at 292 cm^{-1} and 210 cm^{-1} disappear, and a broadening but not a shifting of the ligand bands occurs in the 500–400 cm^{-1} region. The magnetic susceptibility (Table II) undergoes a drastic change to 0.91 BM. This suggests a reordering of the copper stereochemistry away from the similar structures of the complexes above. Melnik [20] has suggested that structural changes occur in the first coordination sphere of copper when $CuTp_2 \cdot 2H_2O$ is dehydrated. This low magnetic moment is suggestive of magnetic exchange interactions, presumably of the superexchange type [21]. In fact, all of the other above complexes show slightly subnormal ambient temperature magnetic moments, suggesting some sort of bridged polymeric structures may be present, a situation which has been proposed for metal-guanine complexes [10], as well as other metal ion–purine adducts [22, 23].

No metal sensitive theophylline bands are noticed in $CuTp_2Cl_2$ and $CuTp_2Br_2 \cdot H_2O$, but prominent M–Cl (302, 288 cm^{-1}) and M–Br (250, 230 cm^{-1}) stretching can be assigned. These compounds form an isomorphous pair, and their low frequency vibrational spectra point to their having a similar distorted tetrahedral coordination geometry. This type of geometry has been reported for other metal–purine complexes containing copper, including Cu(9-methyladenine)Br_2 [24] and [Cu(adenineH)Br_2]Br_2 [25]. Goldstein *et al.* [26] examined the low frequency spectra of CuX_2L_2, where X = Cl or Br and L = pyridine, 2-methyl- and 2-ethylpyridine, 2,6-dimethylpyridine, and quinoline. They concluded that bulky ligands such as quinoline in MX_2L_2 complexes prevent halogen bridging to adjacent MX_2L_2 molecules thereby ruling out a distorted octahedral structure. Theophylline probably acts in a similar manner; a distorted tetrahedral stereochemistry around copper would minimize steric interactions and also give rise to the observed M–Cl and M–Br doublets. The data do not rule out the possibility that theophylline could bridge metal centers, thereby giving rise to polymer formation similar to the above complexes.

The copper, zinc, and cadmium theophylline complexes containing ammonia or water are isomorphous, probably possessing local distorted tetrahedral stereochemistry with long range ligand bridging to form polymers. This is supported by the spectral similarities to tetrahedral $ZnTp_2en$ and by the slightly low ambient temperature magnetic moments of the copper compounds. Polymer formation cannot be ruled out for $CuTp_2$ and for $CuTp_2Cl_2$ and $CuTp_2Br_2 \cdot H_2O$ as well; the low magnetic moment of $CuTp_2$ suggests that extensive magnetic exchange interactions have occurred in comparison to the above complexes, while $CuTp_2Cl_2$ and $CuTp_2Br_2 \cdot H_2O$ are isomorphous and appear to possess a local distorted tetrahedral coordination.

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