Inorganica Chimica Acta, 108 (1985) L7–L9

Theophylline Adducts with some Divalent 3d Metal Perchlorates*

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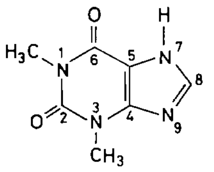
Received April 19, 1985

Theophylline (tpH; 1,3-dimethylxanthine; I) has been studied in recent years as a model of guanine-metal ion interactions [2, 3]. As the pyrimidine ring nitrogens (N(1), N(3)) are blocked by methyl substituents, the sites available for binding of tpH to metal ions are the imidazole nitrogens (N(7), N(9)), the carbonyl oxygens (O(2), O(6), although the former is severely sterically hindered), and, possibly, the C(8) carbon. The weakly acidic proton of neutral tpH is bound to N(7) in the solid [4], while protonation at N(9) can occur under relatively acidic conditions [5, 6]. The majority of the theophylline metal complexes prepared so far have been isolated under basic reaction conditions and were found to exhibit metal ion binding at N(7) [5]. Thus, several complexes involving terminal unidentate N(7)-bonded neutral tpH [7–9] or the anionic theophyllinato (tp$^-$) ligand [10–13] were elucidated by means of crystal structure determinations. On the other hand, use of the somewhat sterically hindered (due to the presence of the methyl substituent at N(3)) N(9) site for binding of theophylline to metal ions occurs [5] only when the metal complexes are prepared under sufficiently acidic conditions, as to preclude ionization at N(7) [14], or when N(7) is blocked by prior metal ion coordination [15, 16]. The crystal structure determinations of two complexes prepared from acidic solutions revealed the presence of N(9)-bonded terminal tpH [17, 18], while the presence of bidentate bridging N(7), N(9)-bonded tp$^-$ was invoked in order to rationalize the formation of a trimeric Pt^{4+} complex [15]. More recently, elucidation of the structure of (β-methoxyethyl)(theophyllinato)Hg(II) revealed that this compound consists of molecules of $[Hg(CH_2CH_2OCH_3)(tp)]$ with C-bonded etheric and N(7)-bonded tp$^-$ groups (bond lengths: Hg–C 2.13; Hg–N(7) 2.08 Å), linked into a three-dimensional network by weak intermolecular Hg––O (methoxyethyl) and Hg––N(9) (tp$^-$) interactions of 2.89 and 2.91 Å, respectively [16]. Bridging of tp$^-$ through N(7), N(9) was also postulated for $[(CH_3Hg)_2tp]NO_3$ [5], whose interaction with additional CH_3HgNO_3, under conditions leading to C(2) substitution in N-methylimidazole [19] and C(8) substitution in xanthosine [20] and inosine [21], did not result in C(8) substitution [5]. In this respect, theophylline resembles unsubstituted imidazole, which does also not demonstrate carbon-methylmercury bond formation under similar conditions [5]. Finally, the presence of chelating O(6), N(7)-bonded tp$^-$, involving however weak Cu–O(6) interaction (bond lengths of 2.919–3.340 Å), was established for a number of Cu^{2+} complexes with this ligand [14, 22].



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During earlier work in these laboratories, we prepared and characterized a 2:1 adduct of tpH with $Cu(ClO_4)_2$, which is apparently tetrahedral with two unidentate N(7)-bonded tpH and two unidentate $-OClO_3$ terminal ligands [23]. This complex was relatively difficult to isolate and was synthesized by refluxing a 2:1 molar mixture of tpH and Cu^{2+} salt in ethanol–triethyl orthoformate (teof) for 10 days, reducing the volume of the solution, dissolving the viscous residue in acetone, and allowing the acetone to evaporate; the semi-solid residue was gradually solidified to a hard, glassy green material upon desiccation *in vacuo* [23]. When we attempted to extend our studies to adducts of tpH with other 3d metal(II) perchlorates (M = Mn, Fe, Co, Ni, Zn), the same synthetic method failed to produce solid complexes, but the following alternate method was successful in most cases, and proved to be also suitable for the preparation of $Cu(tpH)_2(ClO_4)_2$ in green crystalline powder rather than glassy solid form: 1.2 mmol hydrated metal perchlorate is dissolved in a mixture of 35 ml ethyl acetate and 15 ml teof, 2.5 mmol tpH are added, and the resultant mixture is refluxed for 6 h or until no further significant change in appearance is noted. After cooling to ambient temperature, 15–20 ml anhydrous diethyl ether are added to the mixture and the volume is then reduced at low heat to about 20 ml. The solid residue is separated by filtra-

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*Presented in part at the 189th National meeting of the American Chemical Society [1].

0020-1693/85/$3.30

tion, washed with 30 ml diethyl ether and stored *in vacuo* over anhydrous $CaSO_4$. Well-defined solid complexes of the types $M(tpH)_2(ClO_4)_2$ (M = Mn, white, yield 47.2%; M = Cu, green, yield 90%; M = Zn, cream white, yield 65.8%) and $Ni(tpH)_2(ClO_4)_2 \cdot 2H_2O$ (light green, yield 74.6%) were isolated and are the subject of this letter. With M = Co, a purple solid, which is extremely moisture-sensitive, producing an orange colored hydrate immediately upon exposure to the atmosphere, was obtained in good yield, whilst in the case of Fe^{2+} a brown oily complex was isolated. The latter complexes appear to be also 2:1 adducts of tpH and metal salt, but were not obtained in sufficiently pure form for characterization studies. Work aimed at their purification is in progress, and it is anticipated that a paper covering the whole series of 3d M^{2+} (M = Mn, Fe, Co, Ni, Cu, Zn) as well as some M^{3+} (M = Cr, Fe) perchlorate adducts with tpH will be published in the near future.

The infrared spectral features of the four complexes herein discussed are as follows: the Ni^{2+} complex exhibits the ν_{OH} mode of coordinated water at 3420 cm^{-1} [24], while the spectra of the other three complexes are devoid of ν_{OH} bands. In the ν_{NH} region [23, 25, 26], all the complexes show a distinct sharp band at *ca.* 3120 and four broad maxima at *ca.* 2850, 2730, 2700 and 2650 cm^{-1}. A band at 3120 cm^{-1} in $Hg(tpH)Cl_2$ has been attributed to the N(7)–H mode and led to the conclusion that tpH in this adduct is N(9)-bonded [27]. However, our experience is that the 2:1 adducts of not only tpH, but also theobromine (tbH; 3,7-dimethylxanthine) and caffeine (caf; 1,3,7-trimethylxanthine), with $Cu(ClO_4)_2$ show an IR band at *ca.* 3120 cm^{-1} [23], while the free bases are characterized by the following maxima in the same region, cm^{-1}: tpH 3120 ($\nu_{NH} + \nu_{CH}$) [25, 27]; tbH 3150 (ν_{NH}), 3112 (ν_{CH}); caf 3108 (ν_{CH}) [26, 28]. Hence, the appearance of the band at 3120 cm^{-1} in the spectra of the new complexes does not necessarily indicate that N(7) is protonated and not involved in coordination. Terminal unidentate tpH can bind either through N(7) or through N(9) in the form of the N(9)–H or N(7)–H tautomer, respectively [13], and since our synthetic procedure does not involve acidic conditions, it is much more likely that the new complexes contain N(7)-bonded tpH (*vide supra*) [5, 14]. Coordination through an imidazole nitrogen in the new complexes is substantiated by sizeable shifts and occasional splittings of several $\nu_{C=C} + \nu_{C=N}$ (1620–1550 cm^{-1}) and ring (1500–1200 cm^{-1}) vibrations of free tpH [23, 29–32]. The $\nu_{C=O}$ modes of the ligand (1713, 1668 cm^{-1}) undergo little change in the spectra of the metal complexes, appearing at 1715–1705 and 1682–1662 cm^{-1}, so that participation of C=O oxygens of tpH in coordination can be ruled out [23, 29–32]. Significant differences are observed in the ν_3 and $\nu_4(ClO_4)$ regions between the spectra of the Ni^{2+}, Cu^{2+} or Zn^{2+} complexes, which exhibit doublets in both regions (M = Ni 1133, 1079 and 629, 621; M = Cu 1112, 1047 and 639, 617; M = Zn 1106, 1077 and 621, 609 cm^{-1}), and that of the Mn^{2+} complex, which shows five-fold splitting of each of these modes (1128, 1099, 1079, 1060, 1046 and 655, 626, 619, 604, 598 cm^{-1}). These features are interpreted in terms of exclusively unidentate coordinated $-OClO_3$ ligands for M = Ni, Cu, Zn and both unidentate $-OClO_3$ and bidentate $=O_2ClO_2$ ligands for M = Mn [33, 34]. Metal–ligand band assignments are consistent with coordination number four for M = Cu, Zn ($\nu_{Cu-O}(OClO_3)$ 338; ν_{Cu-N} 303, 279; $\nu_{Zn-O}(OClO_3)$ 323; ν_{Zn-N} 289, 278 cm^{-1}), five for M = Mn (ν_{Mn-O}(perchlorato) 309 (broad), ν_{Mn-N} 254, 240 cm^{-1}) and six for M = Ni (ν_{Ni-O}(aqua) 397, $\nu_{Ni-O}(OClO_3)$ 301, ν_{Ni-N} 253, 228 cm^{-1}) [23, 29, 35–40]. As reported previously [23], the Cu^{2+} complex exhibits a room temperature magnetic moment of 2.02 μB, and its main d–d transition maximum at 807 nm, which is compatible with a distorted tetrahedral symmetry [23, 30, 35, 41–43]. Hence, the Cu^{2+} and Zn^{2+} adducts are formulated as tetrahedral of the $[M(tpH)_2(OClO_3)_2]$ type with two terminal N(7)-bonded tpH and two terminal $-OClO_3$ ligands. The Mn^{2+} complex, which has a μ_{eff} of 6.11 μB at 298 K, attains coordination number five by involvement of two terminal N(7)-bonded tpH, one terminal unidentate $-OClO_3$ and one bidentate chelating $=O_2ClO_2$ ligand in coordination; the complex is of the $[Mn(tpH)_2(OClO_3)(O_2ClO_2)]$ type. Finally, the Ni^{2+} complex has a μ_{eff} of 3.13 μB (298 K) and its d–d transition band spectrum is compatible with a low symmetry hexacoordinated configuration ($^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ 431; $\rightarrow {}^3T_{1g}(F)$ 640, 717; $\rightarrow {}^3T_{2g}(F)$ 993, 1171 nm; Dq = 923 cm^{-1}) [35–38]. This complex is apparently of the $[Ni(tpH)_2(OH_2)_2(OClO_3)_2]$ type, involving two of each of the following terminal unidentate ligands: N(7)-bonded tpH, aqua and $-OClO_3$. More detailed characterization studies of the complexes herein reported will appear in a future paper, as already mentioned.

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