

## Tetracycline Adducts with 3d Metal Perchlorates\*

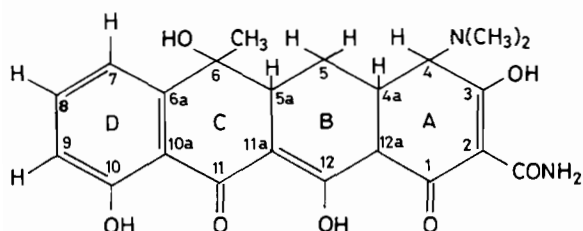
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Tetracycline (tc; I) and substituted derivatives have found wide application in human and veterinary medicine, biology and animal nutrition [2, 3]. It is now established that some of the biological effects of tetracyclines arise from their interactions with metal ions [4]. The affinity of tetracyclines for metal ions is well documented [4–22]. Studies involving formation of tetracycline metal complexes in solution have been most frequently carried out, but a number of solid complexes have been also isolated and characterized, including  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$  [18, 19] and  $\text{Ca}^{2+}$  [22] complexes with anionic  $\text{tc}^-$  of the  $\text{M}(\text{tc}^-)_2(\text{OH}_2)_2$  type [18, 19, 22]. These complexes were precipitated from methanol solutions of tetracycline hydrochloride and  $\text{MCl}_2$ , after adjusting the pH of the combined mixture at 7.4 by adding triethylamine [18, 19, 22]. It was of interest to us to prepare water-free complexes of tc with 3d metal perchlorates, and we felt that a suitable synthetic approach should involve use of a dehydrating agent, such as triethyl orthoformate (teof) [23]. Accordingly, preparative work in this direction was undertaken, and a synthetic procedure similar to that employed by these laboratories for the syntheses of metal perchlorate complexes with purines [24] was used successfully. The present communication deals with the tc adducts we isolated.



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## Experimental

The synthetic procedure employed was as follows: 1.4 mmol hydrated 3d metal perchlorate are dissolved in a mixture of 35 ml ethanol and 15 ml teof, at 40–50 °C. Then, 2.5 mmol tc free base are added to the warm solution and the resultant mixture is refluxed for 24–48 h. Subsequently, the volume of the mixture is reduced by about 50%, by heating under reduced pressure, and the residue is cooled to room temperature. The precipitated complex is separated by filtration, washed with cold anhydrous ethanol and stored *in vacuo* over anhydrous  $\text{CaCl}_2$ . This procedure resulted in the formation of 2:1 tc to metal perchlorate adducts in all but one of the cases investigated, *i.e.*,  $\text{M}(\text{tc})_2(\text{ClO}_4)_3$  ( $\text{M} = \text{Cr}, \text{Fe}$ ) and  $\text{M}(\text{tc})_2(\text{ClO}_4)_2$  ( $\text{M} = \text{Mn}, \text{Fe}, \text{Co}, \text{Ni}, \text{Zn}$ ). The exception was with  $\text{M} = \text{Cu}^{2+}$ , which led to the precipitation of the  $\text{HClO}_4$  complex of tc ( $\text{tcH}^+\text{ClO}_4^-$ ).  $\text{Cu}(\text{tc})_2(\text{ClO}_4)_2$  was prepared by briefly heating a 2:1 molar solution of tc and  $\text{Cu}(\text{ClO}_4)_2$  in ethanol–teof to 60 °C, under stirring, and then allowing the mixture to stand at ambient temperature for 1–2 days. The new metal complexes are characterized by various shades of brown colors, ranging from light ( $\text{M} = \text{Zn}^{2+}$ ) to very dark ( $\text{M} = \text{Cr}^{3+}, \text{Cu}^{2+}$ ) brown, and were obtained in yields of 65–95% with the exceptions of the  $\text{Mn}^{2+}$  and  $\text{Zn}^{2+}$  adducts, for which the yields were 42% and 28%, respectively. The complexes are generally insoluble in ethanol, diethyl ether and water; most complexes are also insoluble in acetone or nitromethane, but those with  $\text{Fe}^{2+}$ ,  $\text{Fe}^{3+}$  and  $\text{Cu}^{2+}$  show limited solubility in these media. Molar conductivities of  $10^{-3}$  M solutions of the latter three adducts in 1:1 (*v/v*) acetone–nitromethane at 25 °C indicate the presence of 1:1 electrolytes [25], *viz.*,  $\Lambda_{\text{M}}, \Omega^{-1} \text{cm}^2 \text{mol}^{-1}$ :  $\text{M} = \text{Fe}^{2+}$  71;  $\text{Fe}^{3+}$  77;  $\text{Cu}^{2+}$  69. Magnetic moments at 300 K are generally normal for high-spin complexes of 3d metal ions [26]:  $\mu_{\text{eff}}, \mu_{\text{B}}$ :  $\text{M} = \text{Cr}^{3+}$  3.86;  $\text{Mn}^{2+}$  5.94;  $\text{Fe}^{2+}$  5.13;  $\text{Fe}^{3+}$  6.20;  $\text{Co}^{2+}$  4.66;  $\text{Ni}^{2+}$  3.41;  $\text{Cu}^{2+}$  1.94. Infrared and solid-state (Nujol mull) electronic spectra were obtained by methods described elsewhere [24, 27].

## Results and Discussion

The  $\nu_{\text{OH}}$ ,  $\nu_{\text{NH}}$  and  $\nu_{\text{CH}} + \nu_{\text{CH}_3}$  absorptions of free tc at 3609, at 3361, 3300 and at 2944, 2930  $\text{cm}^{-1}$ , respectively [19, 28], appear virtually unchanged in the spectra of the new complexes. In an earlier study, a band at 1770–1760  $\text{cm}^{-1}$ , absent from the spectrum of tc hydrochloride [28], was assigned as a C–O–metal mode in the spectra of  $\text{M}(\text{tc}^-)_2(\text{OH}_2)_2$  ( $\text{M} = \text{Co}, \text{Ni}$ ) [19]. It is of interest to mention, in this connexion, that tc free base shows a distinct weak

TABLE I. Infrared Spectra of the New tc Metal Complexes at 500–230 cm<sup>-1</sup>

M <sup>n+</sup>	$\nu_{M-O}$ Bands <sup>a</sup>	tc Bands <sup>b</sup>
Cr <sup>3+</sup>	444m, 333w, 300w	490m, 460m, 370w,b, 244w
Mn <sup>2+</sup>	402w, 391w, 309w, 252w	490m, 460m, 377w, 340w, 240w,sh
Fe <sup>2+</sup>	407w, 390w, 313w, 253w	490m, 450m,b, 380w,b, 345w, 240w,sh
Fe <sup>3+</sup>	435w,b, 328w, 295w	500w,b, 450w,b, 375w, 345w, 242w
Co <sup>2+</sup>	414w, 388w, 316w, 259w	485m, 460w, 370w, 345w, 235w
Ni <sup>2+</sup>	421w, 390w, 319w, 268w	490m, 460m, 372w, 350w,b, 237w
Cu <sup>2+</sup>	427w, 396w, 322w, 273w	485m, 450m,b, 375w, 350w,b, 240w
Zn <sup>2+</sup>	400w,b, 311w, 248w	490m, 450m,b, 378w, 345w

<sup>a</sup>See text for tentative  $\nu_{M-O}$  band assignments.

<sup>b</sup>Free tc bands in the region, cm<sup>-1</sup>: 488s, 456m, 441m, 378m, 356sh, 339w, 327w, 317w, 242w [28].

absorption maximum at 1770 cm<sup>-1</sup>. Free tc IR bands associated with the amide group at ring A, at 1670(vs), 1520(s) and 1247(s), 1226(vs) cm<sup>-1</sup> [28], are shifted to 1650–1630(m or w), 1490–1475(ms) and 1230–1210(s) cm<sup>-1</sup>, respectively, upon metal perchlorate adduct formation. In contrast, the very strong tc  $\nu_{C=O}$  bands at 1611 (ring A) and 1580 (ring C) cm<sup>-1</sup> [28], undergo either positive or negative small frequency shifts, appearing at 1615–1590 and 1590–1575 cm<sup>-1</sup>, respectively, in the spectra of the new complexes. Shifts of the various  $\nu_{C-O}$  modes of the COH groups of tc ( $\nu_{C-O}$  for ring A occurs at 1111 cm<sup>-1</sup>) [28] cannot be detected in the spectra of the new adducts, as they are masked by the strong  $\nu_3(\text{ClO}_4)$  absorptions at 1130–1045 cm<sup>-1</sup> [29, 30]. Both the  $\nu_3$  and  $\nu_4(\text{ClO}_4)$  modes are triply split in the spectra of the tc adducts ( $\nu_3$  at 1130–1110vs, 1100–1070vvs and 1065–1045s;  $\nu_4$  at 655–645m, 630–620s and 620–610s); this is indicative of the simultaneous presence of ionic  $\text{ClO}_4^-$  and unidentate coordinated  $-\text{OClO}_3$  ligands [29, 30]. IR-active  $\nu_1$  and  $\nu_2(\text{ClO}_4)$  are presumably masked by tc absorptions at 949, 938 and 488, 456 cm<sup>-1</sup>, respectively [28]. Tentative  $\nu_{M-O}$  band assignments are given in Table I. The various  $\nu_{M-O}$  bands are assigned as follows, cm<sup>-1</sup>:  $\nu_{M-O(H)-C}$  444–435 for M<sup>3+</sup>; 427–388 for M<sup>2+</sup> [31];  $\nu_{M-OClO_3}$  333–328 for M<sup>3+</sup>; 322–309 for M<sup>2+</sup> [32];  $\nu_{M-O=CNH_2}$  300–295 for M<sup>3+</sup>; 273–248 for M<sup>2+</sup> [33]. Participation of the C=O oxygen of the amido group at C2 of ring A of tc in binding, is favored by the IR evidence discussed above [19]. Chelation of tc can occur by the simultaneous involvement of either the C=O oxygen at C1 or the OH oxygen at C3 of the same ring in coordination. The former possibility is ruled out since the  $\nu_{C=O}$  mode at 1611 cm<sup>-1</sup> does not undergo large shifts to lower wavenumbers in the spectra of the complexes; on the other hand, the presence of metal-sensitive absorptions at 444–388 cm<sup>-1</sup> is consistent with participation of the OH oxygen at C3 in binding [31]. Chelation of tc through the C=O oxygen of the amido group at C2 and the oxygen at C3 of ring A

was previously proposed for the  $\text{M}(\text{tc}^-)_2(\text{OH}_2)_2$  (M = Co, Ni) complexes [19].

The UV bands of tc at 220, 271 and 360 nm [22] appear at 208–218, 265–282 and 366–372 nm, respectively, in the spectra of the metal complexes. Occasional splittings of some of these bands are observed (doublets at 270–273 and 292–310 nm for M = Fe<sup>2+</sup>, Co<sup>2+</sup>, Ni<sup>2+</sup> and a doublet at 345–370 nm for M = Cr<sup>3+</sup>). Strong charge-transfer absorption, extending to ca. 550 nm is observed in the spectra of the new complexes. The d–d transition maxima favor coordination number six for the M<sup>3+</sup> and five for the M<sup>2+</sup> complexes [34–37], i.e., nm: M = Cr<sup>3+</sup> <sup>4</sup>A<sub>2g</sub>(F) → <sup>4</sup>T<sub>1g</sub>(F) 450s,b; → <sup>4</sup>T<sub>2g</sub>(F) 545ms, 630m, 685m (Dq = 1613 cm<sup>-1</sup>); Fe<sup>2+</sup> 700mw,b, 805mw,b, 940w,b, 1380w,vb; Co<sup>2+</sup> 455m,b, 507m,sh, 620w, 705w,b, 810w,b, 965w, 1375w,b, 1875vw,b; Ni<sup>2+</sup> 482s,b, 560m,sh, 630m,sh, 718w,sh, 835w,sh, 977w, 1280w,b, 1860vw,b; Cu<sup>2+</sup> 503vs, 548vs,b, 650s,vb, 920w,vb. These coordination numbers are also compatible with the IR  $\nu_{M-O}$  band assignments for the O-binding sites of tc and the  $-\text{OClO}_3$  ligand [31–33].

On the basis of the spectral, magnetic and conductance data discussed, the new complexes are formulated as  $[\text{M}(\text{tc})_2(\text{OClO}_3)_2]\text{ClO}_4$  (M = Cr, Fe) and  $[\text{M}(\text{tc})_2(\text{OClO}_3)]\text{ClO}_4$  (M = Mn, Fe, Co, Ni, Cu, Zn), involving MO<sub>6</sub> and MO<sub>5</sub> chromophores, respectively. Each tc ligand acts as bidentate chelating, binding through the C=O oxygen of the amide group at C2 and the OH oxygen at C3 of ring A [19]. More detailed characterization work is in progress and will appear in a future paper.

## References

- 1 C. M. Mikulski, J. Fleming, D. Fleming and N. M. Karayannis, *Abstracts, XXIV ICCO*, Athens, Greece, Aug. 24–29, 1986.
- 2 D. L. J. Clive, *Q. Rev.*, 435 (1968).
- 3 W. Dürckheimer, *Angew. Chem., Int. Ed. Engl.*, 14, 721 (1975).

- 4 M. Brion, L. Lambs and G. Berthon, *Inorg. Chim. Acta*, **123**, 61 (1986) and refs. therein.
- 5 A. Albert, *Nature*, **172**, 201 (1953); A. Albert and C. W. Rees, *Nature*, **177**, 433 (1956).
- 6 J. C. van Meter, A. Spector, J. J. Oleson and J. H. Williams, *Proc. Soc. Exp. Biol. Med.*, **81**, 215 (1952).
- 7 A. K. Saz and R. B. Slie, *J. Am. Chem. Soc.*, **75**, 4626 (1953).
- 8 K. H. Ibsen and A. R. Urist, *Proc. Soc. Exp. Biol. Med.*, **109**, 797 (1962).
- 9 J. T. Doluisio and A. N. Martin, *J. Med. Chem.*, **6**, 16, 20 (1963).
- 10 J. L. Colaizi, A. M. Knevel and A. N. Martin, *J. Pharm. Sci.*, **54**, 1425 (1965).
- 11 L. J. Benet and J. E. Goyan, *J. Pharm. Sci.*, **54**, 983 (1965).
- 12 T. F. Chin and J. L. Lach, *Am. J. Hosp. Pharm.*, **32**, 625 (1975).
- 13 E. C. Newman and C. W. Franck, *J. Pharm. Sci.*, **65**, 1728 (1976).
- 14 M. Saiki and F. W. Lima, *J. Radioanal. Chem.*, **36**, 435 (1977); **50**, 77 (1979).
- 15 S. T. Day, W. G. Crouthamel, L. C. Martinelli and J. K. H. Ma, *J. Pharm. Sci.*, **67**, 1518 (1978).
- 16 K. Taguchi, *Chem. Pharm. Bull.*, **8**, 205, 212, 217 (1960).
- 17 T. V. Alykova, *Antibiotiki*, **17**, 353 (1972).
- 18 W. A. Baker, Jr. and P. M. Brown, *J. Am. Chem. Soc.*, **88**, 1314 (1966).
- 19 B. Jeżowska-Trzebiatowska, J. O. Dziągiewski and P. Głowacki, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **27**, 223 (1979).
- 20 P. Mikelens and W. Levinson, *Bioinorg. Chem.*, **9**, 421 (1978).
- 21 A. H. Caswell and J. D. Hutchison, *Biochem. Biophys. Res. Commun.*, **43**, 625 (1971).
- 22 J.-C. Mani and G. Foltran, *Bull. Soc. Chim. Fr.*, 4141 (1971).
- 23 P. W. N. M. van Leeuwen and W. L. Groeneveld, *Inorg. Nucl. Chem. Lett.*, **3**, 145 (1967).
- 24 A. N. Speca, C. M. Mikulski, F. J. Iaconianni, L. L. Pytlewski and N. M. Karayannis, *Inorg. Chem.*, **19**, 3491 (1980).
- 25 W. J. Geary, *Coord. Chem. Rev.*, **7**, 81 (1971).
- 26 B. N. Figgis and J. Lewis, *Prog. Inorg. Chem.*, **6**, 37 (1964).
- 27 N. M. Karayannis, C. M. Mikulski, M. J. Strocko, L. L. Pytlewski and M. M. Labes, *Inorg. Chim. Acta*, **8**, 91 (1974).
- 28 J. O. Dziągiewski, J. Hanuza and B. Jeżowska-Trzebiatowska, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **24**, 307 (1976).
- 29 B. J. Hathaway and A. E. Underhill, *J. Chem. Soc.*, 3091 (1961); B. J. Hathaway, D. G. Holah and M. Hudson, *J. Chem. Soc.*, 4586 (1963).
- 30 A. E. Wickenden and R. A. Krause, *Inorg. Chem.*, **4**, 404 (1965); S. F. Pavkovic and D. W. Meek, *Inorg. Chem.*, **4**, 1091 (1965); M. E. Farago, J. M. James and V. C. G. Trew, *J. Chem. Soc. A*, 820 (1967).
- 31 C. M. Mikulski, L. S. Gelfand, L. L. Pytlewski, J. S. Skryantz and N. M. Karayannis, *Inorg. Chim. Acta*, **21**, 9 (1977).
- 32 J. R. Ferraro and A. Walker, *J. Chem. Phys.*, **42**, 1273, 1278 (1965).
- 33 B. B. Kedzia, P. X. Armendarez and K. Nakamoto, *J. Inorg. Nucl. Chem.*, **30**, 849 (1968).
- 34 W. Byers, A. B. P. Lever and R. V. Parish, *Inorg. Chem.*, **7**, 1835 (1968).
- 35 I. Bertini, P. Dapporto, D. Gatteschi and A. Scozzafava, *Inorg. Chem.*, **14**, 1639 (1975).
- 36 M. Ciampolini and N. Nardi, *Inorg. Chem.*, **5**, 41, 1150 (1966); **6**, 445 (1967).
- 37 M. Ciampolini and G. P. Speroni, *Inorg. Chem.*, **5**, 45 (1966).