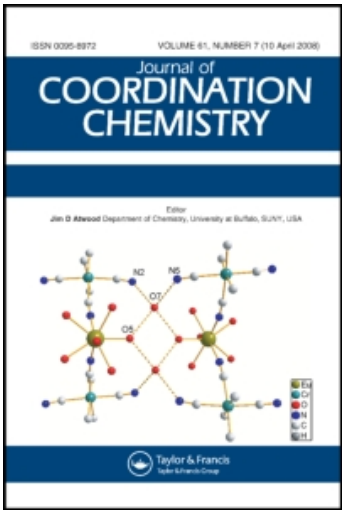


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D. O. Harrison[a]; R. Thomas[a]; A. E. Underhill[a]; F. A. Everall[b]; P. S. Gomm[b]; G. D. Low[b]
[a] Department of Chemistry, University College of North Wales, Bangor, Gwynedd, U.K [b] Department of Chemistry, Rugby School, Rugby, Warwickshire, U.K

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# METAL COMPLEXES OF ANTI-INFLAMMATORY DRUGS. PART II. AZAPROPAZONE COMPLEXES OF IRON(III), COBALT(II), NICKEL(II), COPPER(II) AND ZINC(II)

D.O. HARRISON, R. THOMAS, A.E. UNDERHILL
*Department of Chemistry, University College of North Wales, Bangor, Gwynedd LL57 2UW, U.K.*

and

F.A. EVERALL, P.S. GOMM and G.D. LOW
*Department of Chemistry, Rugby School, Rugby, Warwickshire, U.K.*

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The preparation and properties of the complexes $[Fe(AZAP)_3]$ and $[M(AZAP)_2(H_2O)_2]$ (where M = Co(II), Ni(II), Cu(II), Zn(II)) are reported for the anti-inflammatory drug azapropazone (AZAP). The measured diffuse reflectance spectra and magnetic moments are consistent with a pseudo-octahedral structure for the complexes. The infra-red spectra indicate bidentate coordination of the anionic drug to the central metal ion *via* the enolic oxygen atom of the 3,5-dioxopyrazolidine ring and the nitrogen of the 3-dimethylamino group.



## INTRODUCTION

A large number of organic compounds is in use or under study for the control of musculoskeletal disease. Both steroidal and non-steroidal anti-inflammatory drugs[1] have been developed but recently interest has focused on the use of metallic compounds in treating connective tissue disorders.[2] The copper dependence of rheumatoid arthritis is well established and the observation that copper complexes involving anti-inflammatory drugs can be more effective and involve less gastro-intestinal irritation than the free drug,[3] has stimulated a number of investigations involving drug complexing.[4]

Pyrazolone derivatives have been known for their anti-inflammatory activity for several years.[5] The compound 5-dimethylamino-9-methyl-2-propyl-1H-pyrazolo[1,2-α][1,2,4]benzotriazine-1,3(2H)-dione (approved name azapropazone; abbreviation AZAP) is one such derivative that exhibits analgesic and anti-inflammatory properties comparable with those of aspirin but with a lower incidence of side effects.[6] The chemical properties of this molecule have been studied[7] together with an N.M.R. investigation[8] that suggests the free drug exists in a keto-enol tautomeric equilibrium (Figure 1). In this paper, we report the preparation and properties of complexes formed between azapropazone and some first row transition metals.

## EXPERIMENTAL

Azapropazone dihydrate was supplied by A.H. Robbins Ltd., and was used without further purification. The metal chlorides were of Analar reagent grade with the exception of iron(III) chloride hexahydrate (B.D.H.).

*Preparation of Complexes*

A solution of azapropazone dihydrate (1 mole) was prepared by the slow addition with constant agitation of an aqueous 0.1 M sodium hydroxide solution at 20°. A slight excess of drug was used to exclude excess hydroxide ions. The resulting suspension was filtered to remove excess ligand and the filtrate was added slowly with stirring to a cold aqueous solution of the metal chloride (0.5 mole). The resulting precipitate was filtered, washed with distilled water, and dried at 80°. The complexes were obtained as microcrystalline powders in high yield (>90%).

*Physical Measurements*

Diffuse reflectance spectra were determined using a Beckmann DK2A spectrophotometer fitted with a standard refletance attachment. Infrared spectra (4000–400 $cm^{-1}$) were recorded on a Perkin-Elmer 225 spectrophotometer in Nujol mulls or KBr discs. Room temperature magnetic measurements on powdered samples were made on a Newport Instruments Gouy balance using mercury tetrathiocyanatocobalt(II) as calibrant.

## RESULTS AND DISCUSSION

*Infra-red Spectra*

Table I lists and compares the infra-red spectra for free azapropazone dihydrate and the metal complexes. The bands in the drug spectrum are well reproduced in the spectra of the complexes with only minor shifts or splittings. The assignments of the various bands, without being rigorous, have been made by a direct comparison between the spectrum of coordinated azapropazone and that of the free base.

Azapropazone is known from N.M.R. studies[8] to exist in the keto-enol tautomeric forms shown in the Figure and as a result a sharp O-H stretching band is expected for the free enol form of the drug.[9] The drug molecule is supplied as the dihydrate and the broadness of the OH-stretching band (3000–3500 $cm^{-1}$) in the free drug spectrum is indicative of hydrogen bonding. Analyses of the metal complexes show them to be hydrated and in all the spectra a broad absorption is observed in the region 3000–3500 $cm^{-1}$ indicating tht some water molecules are hydrogen bonded. In all cases heating the complexes to ≥100° prior to infrared examination in KBr discs caused a marked

TABLE I
Infrared absorption bands[a] ($cm^{-1}$) for the ligand and complexes.

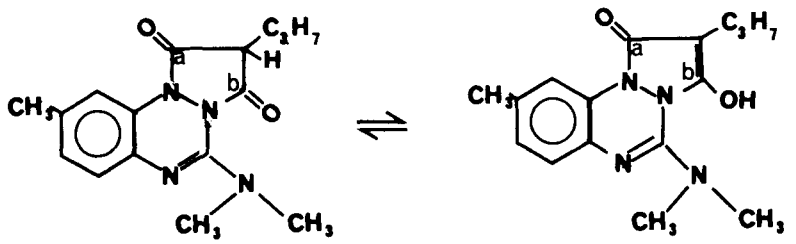
| | O-H (str) | $N-CH_3$ | C=O (a) | C=O (b) | C=N |
|---|---|---|---|---|---|
| AZAP | 3000–3500 b | 2800 sh | 1700 s | 1660 | 1590 |
| $Fe(AZAP)_3 \cdot 7H_2O$ | 3000–3500 b | 2850 | 1700 | 1640 | 1590 |
| $Co(AZAP)_2 \cdot 6H_2O$ | 3000–3500 b | 2850 | 1700 | 1650 | 1590 |
| $Ni(AZAP)_2 \cdot 5H_2O$ | 3000–3500 b | 2850 | 1700 | 1650 | 1590 |
| $Cu(AZAP)_2 \cdot 3H_2O$ | 3000–3500 b | 2870 | 1700 | 1650 | 1590 |
| $Zn(AZAP)_2 \cdot 7H_2O$ | 3000–3500 b | 2870 | 1700 | 1640 | 1590 |

[a]b = broad, sh = shoulder, s = strong

reduction in intensity and in some cases the disappearance of the broad absorption in this region. The absence of a sharp O-H absorption in the spectra of these dehydrated samples is indicative of metal attachment as an anionic ligand *via* the enolic oxygen atom.

The free ligand has two bands assigned to carbonyl groups. The sharp band at 1700 $cm^{-1}$ is assigned to the $\nu$(C=O) vibration of the non-tautomeric carbonyl group (see Figure, structure position (a)) while the absorption at 1660 $cm^{-1}$ is assigned to the vibration of the tautomeric carbonyl group in position (b) of the 3,5-dioxo-pyrazolidine ring system. The 1660 $cm^{-1}$ band is seen to shift consistently to lower frequencies in the complexes, consistent with metal attachment *via* the oxygen atom. The carbonyl absorption at 1700 $cm^{-1}$ and the absorption observed at 1590 $cm^{-1}$ assigned to the C=N stretch are uneffected by complexing.

An absorption is expected at 2800 $cm^{-1}$ arising from the $\nu(N\text{-}CH_3)$ vibration of the tertiary amine group. In the free drug this is observed as a shoulder on the broad O-H absorption whereas in the dehydrated metal complexes the same band is observed as a sharp, moderately intense band, at 2850–2870 $cm^{-1}$.




*Diffuse-reflectance Spectra*

The reflectance spectrum of the ligand exhibits a number of low intensity absorption bands that are considered to be infrared overtones, together with a shoulder at 22,222 $cm^{-1}$ that forms part of the charge transfer band. These features are common to all the spectra of the metal complexes with the shoulder increasing in intensity (Table II). This is probably due to some forbidden transition in the ligand that is enhanced on complexing to a metal.

TABLE II
Diffuse reflectance spectra[a] and room temperature magnetic moments

| | $\mu_{eff}$ (BM) | Ligand field parameters ($cm^{-1}$) | | | $D_q$ ($cm^{-1}$) |
|---|---|---|---|---|---|
| $Fe(AZAP)_3 \cdot 7H_2O$ | 3.95 | $\nu$ 10526 (0.15) | | | |
| $Co(AZAP)_2 \cdot 6H_2O$ | 5.00 | $\nu_1$ 6452 (0.40) | | $\nu_3$ 15503 (0.55) | 806 |
| $Ni(AZAP)_2 \cdot 5H_2O$ | 3.4 | $\nu_1$ 7140 (0.18) | $\nu_2$ 8510 (0.19) | $\nu_3$ 14600 (0.23) | 851 |
| $Cu(AZAP)_2 \cdot 3H_2O$ | 1.8 | $\nu$ 14084 | | | 1408 |

[a]Figures in parenthesis represent intensity of the band on the arbitrary Beckmann scale.

The diffuse reflectance spectrum for the $Fe(AZAP)_3$ complex is similar to that of the free ligand spectrum and to the spectrum of $Zn(AZAP)_2$ except for a very broad, low intensity absorption at 10,526 $cm^{-1}$. The absence of appreciable absorption at lower energy than the charge transfer edge is consistent with a pseudo-octahedral environment about the $Fe^{3+}$ ion. As iron(III) has a $d^5$ electronic configuration, the ground state in the high spin complex is 6S and since there are no other sextet energy levels, all transitions are spin forbidden and therefore extremely weak.[10] The observed magnetic moment of 3.95 BM is rather low for a high spin octahedral iron(III) complex.[11]

The low intensities and the positions of the absorption bands in the reflectance spectra of $Co(AZAP)_2 \cdot 6H_2O$, $Ni(AZAP)_2 \cdot 5H_2O$ and $Cu(AZAP)_2 \cdot 3H_2O$ indicate an essentially pseudo-octahedral stereochemistry (Table 2). The complex $Co(AZAP)_2 \cdot 6H_2O$ has a magnetic moment of 5.00 BM which lies within the range normally observed for octahedral cobalt(II) complexes.[11] The reflectance spectrum consists of two absorption bands, the first at 6452 $cm^{-1}$ and a second centred at 15503 $cm^{-1}$ but resolved into two peaks at 15152 $cm^{-1}$ and 15873 $cm^{-1}$. The band at 6452 $cm^{-1}$ is assigned (assuming pseudo-octahedral symmetry for convenience) to the $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ ($\nu_1$) transition. The band system centred at 15503 $cm^{-1}$ probably arises from the $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ ($\nu_3$) transition in octahedral symmetry which is known to be split in complexes of $D_{4h}$ symmetry or less. The transition $^4T_{1g}(F) \rightarrow {}^4A_{2g}(\nu_2)$ in octahedral symmetry is spin allowed but known to be weak.[12] Using the relationship $\nu_2 = \nu_1 + 10\ D_q$ the $\nu_2$ band would be expected to occur at about 14500 $cm^{-1}$, which is very close to the lower energy peak (15152 $cm^{-1}$) of the double-peaked $\nu_3$ absorption. Thus the $\nu_2$ is probably obscured by the strong $\nu_3$ band system.

The electronic spectrum of nickel(II) compounds of $D_{4h}$ symmetry and a triplet ground state has been discussed.[13] The $^3T_{2g}$ and $^3T_{1g}(F)$ levels in $O_h$ symmetry are split in $D_{4h}$ symmetry into $^3B_{2g}$ and $^3E_g$, and $^3A_{2g}$ and $^3E_g$ respectively. Consequently, for the nickel(II) ion in $D_{4h}$ symmetry, four absorption bands are expected in the region 7000–18000 $cm^{-1}$, whereas only two should be observed if the symmetry is $O_h$. The general features of the $Ni(AZAP)_2 \cdot 5H_2O$ spectrum suggest $D_{4h}$ symmetry and on this basis, the band at 7140 $cm^{-1}$ is assigned to the $^3B_{1g} \rightarrow {}^3E_g$ absorption, that at 8510 $cm^{-1}$ to the $^3B_{1g} \rightarrow {}^3B_{2g}$ absorption and the 14600 $cm^{-1}$ band to the $^3B_{1g} \rightarrow {}^3A_{2g}$ absorption. The room temperature magnetic moment of 3.4 BM is at the top of the range normally observed for octahedral nickel(II) complexes but it has been shown[14] that tetragonal complexes may have moments as high as 3.5 BM.

The reflectance spectrum of $Cu(AZAP)_2 \cdot 3H_2O$ consists of a very broad, low intensity band with a maximum at 14085 $cm^{-1}$. The position, band shape and intensity indicate that the copper(II) ion is in a distorted octahedral environment. The effect of a tetragonal distortion on an octahedral copper(II) ion is to split the $^2E_g$ and $^2T_{2g}$ states so that as the energy of the $^2A_1$ state increases a situation may arise in which this state is sufficiently close to the $^2E$ and $^2B_2$ states for the three transitions not to be resolved in the spectrum.[15] In the absence of any other bands in the $Cu(AZAP)_2 \cdot 3H_2O$ spectrum, it is concluded that all three transitions lie within the single broad envelope centred at 14085 $cm^{-1}$. This assignment is in agreement with the general observation[16] that copper(II) d-d transitions are normally close in energy. The magnetic moment (1.8 BM) falls within the range normally observed for mononuclear complexes having no major interaction between copper(II) centres.

Azapropazone is a complex heterocyclic system with a number of possible oxygen or nitrogen coordination sites. The structure of azapropazone suggests that bidentate metal attachment *via* the carbonyl oxygen of the 3,5-dioxopyrazolidine ring (position b) and the nitrogen of the 3-dimethylamino group could result in six-membered chelate systems. N.M.R. investigations[8] suggest that keto-enol tautomerism occurs in the free drug molecule. Consequently, the possibility arises of forming neutral inner complexes

TABLE III
Analyses of the azapropazone complexes

| | Found (%) | | | Required (%) | | |
|---|---|---|---|---|---|---|
| | C | H | N | C | H | N |
| $Fe(AZAP)_3 \cdot 7H_2O$ | 53.19 | 6.92 | 15.58 | 53.39 | 6.58 | 15.57 |
| $Co(AZAP)_2 \cdot 6H_2O$ | 49.91 | 6.98 | 14.54 | 50.20 | 6.54 | 14.64 |
| $Ni(AZAP)_2 \cdot 5H_2O$ | 51.78 | 6.50 | 15.02 | 51.41 | 6.43 | 14.99 |
| $Cu(AZAP)_2 \cdot 3H_2O$ | 53.38 | 7.03 | 15.51 | 53.67 | 6.15 | 15.65 |
| $Zn(AZAP)_2 \cdot 7H_2O$ | 48.18 | 6.34 | 14.00 | 48.65 | 6.59 | 14.19 |

by bidentate attachment of the drugs to the metal ions, as anionic species.

In the present investigation we are utilising the fact that base displaces the tautomeric equilibrium to the enol form and produces the enolate anion by proton removal. Mixing solutions of the transition metal chloride salts and the water soluble sodium enolate, in the correct molar ratio, causes the neutral inner complexes to precipitate in high yield.

Elemental analysis indicates that the drug molecule remains uneffected by the mildly basic conditions and that the complexes contain two moles of drug to one mole of divalent metal ion (general formula $M(AZAP)_2$ where M = Co(II), Ni(II), Cu(II), Zn(II)) or three moles of drug to one mole of trivalent metal ion (general formula $M(AZAP)_3$ where M = Fe(III)).

The complexes and the parent drug molecule analyse as hydrates (Table III). The broad infrared absorption between 3000–3500 $cm^{-1}$ that can be reduced on heating suggests that some water molecules are only weakly bonded. Water molecule attachment is not unexpected in view of the many potential hydrogen bonding sites on the drug molecule. The absence of a sharp O-H absorption in the infrared spectra of heated complexes, supports the suggestion that complexing occurs *via* the enolic oxygen atom of the 3,5-dioxopyrazolidine ring.

Although it is not clear from the infrared evidence that the nitrogen atom of the 3-dimethylamino group completes the chelate attachment, it would seem likely both from theoretical considerations and from the fact that diffuse reflectance spectroscopy suggests a basically octahedral environment around the central metal ion. The electronic spectra of the complexess indicate a pseudo-octahedral structure due to the asymmetry of two nitrogen and four oxygen ligands around the divalent metal ions and three nitrogen and three oxygen ligands around the iron(III) centre. The complexes are probably better formulated as $[M(AZAP)_2(H_2O)_2] \cdot xH_2O$ for the cobalt(II), nickel(II), copper(II) and zinc(II) compounds and as $[Fe(AZAP)_3] \cdot 7H_2O$ for the iron(III) compound. The reflectance spectra of the divalent metals are not consistent with those expected[17] for a *cis*-octahedral $C_{2v}$ complex. The structure is therefore most likely to be *trans*-octahedral $D_{4h}$ with two azapropazone anionic ligands coordinated in the xy plane *via* the N-atom of the 3-dimethylamino group and the *O*-atom of the enolate group with two water molecules completing the six-coordinate structure. The remaining water molecules are thought to be hydrogen bonded to the drug molecules.

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REFERENCES


1. S. Wong, *Ann. Rep. Med. Chem.*, **10,** 172 (1975); Y.-H. Chang, *Ann. Rep. Med. Chem.*, **11,** 138 (1976). J.G. Lombardino, *Ann. Rep. Med. Chem.*, **13,** 167 (1978).
2. B.M. Sutton, *Ann. Rep. Med. Chem.*, **14,** 321 (1979).
3. J.R.J. Sorenson, *Prog. Med. Chem.*, **15,** 211 (1978).
4. J.R.J. Sorenson, *J. Med. Chem.*, **19,** 135 (1976); D.H. Brown, W.E. Smith, J.W. Teape and A.J. Lewis, *J. Med. Chem.*, **23,** 729 (1980).
5. M.W. Whitehouse, *Prog. Drug Research*, **8,** 321 (1965).
6. F.D. Hart, 'Drug Treatment of the Rheumatic Diseases', M.T.P. Press Ltd., International Medical Publishers (1978).
7. G. Mixich, *Helv. Chim. Acta*, **51,** 532 (1968).
8. H. Fenner and G. Mixich, *Arzneim. -Forsch (Drug Res.)*, **23,** 51 (1973).
9. G. Socrates, 'Infrared Characteristic Group Frequencies', Wiley-Interscience Publications (1980).
10. C.K. Jorgensen, 'Absorption Spectra and Chemical Bonding in Complexes', Addison-Wesley Publishing Co., Inc., Reading, Mass. (1962).
11. B.N. Figgis and J. Lewis, *Prog. Inorg. Chem.*, **6,** 37 (1964).
12. S. Koide, *Phil. Mag.*, **4,** 243 (1959).
13. G.R. Brubaker and D.H. Busch, *Inorg. Chem.* **5,** 2114 (1966); D.M.L. Goodgame, M. Goodgame, M.A. Hitcham and M.J. Weeks, *J. Chem. Soc. (A)*, 1769 (1966); D.M.L. Goodgame, M. Goodgame and M.J. Weeks, *J. Chem. Soc. (A)*, 1125 (1967).
14. A.B.P. Lever, *Inorg. Chem.*, **4,** 763 (1965).
15. E. Konig and H.L. Schlafer, *Z. Phys. Chem.*, **26,** 371 (1960).
16. O.G. Holmes and D.S. McClure, *J. Chem. Phys.*, **26,** 1686 (1957); D.W. Smith, *Inorg. Chem.*, **5,** 2236 (1966).
17. B.J. Hathaway and A.A.G. Tomlinson, *Coord. Chem. Rev.*, **5,** 1 (1970).