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Metal Complexes of Anti-inflammatory Drugs. Part III. Nictindole Complexes of Copper(II) Halides

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Abstract

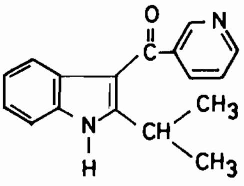
The preparation and properties of the copper(II) halide complexes $CuX_2(NIDOL)_2$ (where $X = Cl$, Br) are reported for the anti-inflammatory drug nictindole (NIDOL). The diffuse reflectance spectra, magnetic moments and electron spin resonance spectra are consistent with a tetragonally distorted pseudo-octahedral environment around the copper(II) ions. The infrared spectra indicate monodentate coordination of the neutral drug to the central metal ion via the nitrogen atom of the pyridine ring.

Introduction

The production of reactive oxygen species by phagocytic cells is now well established as a defence mechanism against bacterial infection [1]. Biological reduction of oxygen occurs by a monovalent pathway to produce initially the superoxide radical anion O_2^- and hydrogen peroxide H_2O_2. If these species are not removed by an efficient scavenger mechanism then ultimately the production of the hydroxyl radical OH and singlet oxygen $^1\Delta gO_2$ results [2]. Reactive oxygen species of this type cannot be readily tolerated by living cells and can cause tissue damage [3]. Under normal circumstances, this is prevented by the superoxide dismutases, a group of enzymes that are able to scavenge superoxide anions and prevent the production of the more reactive hydroxyl radical.

Superoxide dismutases are metalloproteins containing copper and zinc or manganese as the prosthetic group [4]. The superoxide ion scavenging ability of simple copper(II) complexes has also been demonstrated [5]. Recently, a number of investigations have focussed on the complexing of anti-inflammatory drugs to transition metal ions with a view to isolating anti-inflammatory agents with improved potency and less adverse side effects than the parent drug [6].

The majority of clinically useful non-steroidal anti-inflammatory drugs are carboxylic or enolic acids [7]. Nictindole (L-8027; abbreviation NIDOL) is the generic name for the basic compound 2-isopropyl-3-nicotinyl-indole [8] that has recently been under test as a potential anti-inflammatory agent [9]. In this paper, we report the preparation and properties of complexes formed between nictindole and copper(II) halides.



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Experimental

Nictindole was supplied by Sanofi Pharma International (Paris) and was used without further purification. Copper(II) halide salts were of Analar reagent grade.

Preparation of $CuX_2(NIDOL)_2$

Nictindole (1 g; 1 mol equivalent) was dissolved in ethanol (25 cm^3). The resulting yellow solution was added slowly with stirring to a cold solution of the copper(II) halide (0.5 mol equivalent) in ethanol (7.5 cm^3). The resulting mixture was heated over a steam bath to reduce the volume to ~10 cm^3, cooled to room temperature and ethoxyethane (~40 cm^3) added. The resulting precipitate was filtered off under vacuum, washed with cold ethoxyethane and dried at 50 °C.

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Microanalysis

Calc. for $CuCl_2(NIDOL)_2$: C, 61.59; H, 4.83; N, 8.45. Found: C, 60.92; H, 4.42; N, 8.05%. Calc. for $CuBr_2(NIDOL)_2$: C, 54.29; H, 4.26; N, 7.45. Found: C, 53.84; H, 4.28; N, 7.24%.

Physical Measurements

Carbon, hydrogen and nitrogen analyses were performed in the microanalytical laboratory of the University College of North Wales, Bangor. The diffuse reflectance spectra were determined on a Beckmann DK-2A spectrophotometer fitted with a standard reflectance attachment. Infrared spectra (4000–200 cm^{-1}) were recorded on a Perkin-Elmer 580 spectrometer as caesium halide discs while far-infrared spectra (200–40 cm^{-1}) were recorded on a Beckmann F.S. 720 spectrophotometer. Electron spin resonance data was obtained using a Jeol PE-1X instrument operating in the X-band; *g*-factors were measured using a manganese(II) standard. Room temperature magnetic susceptibility measurements were made on powdered samples using a Newport Instruments Gouy balance.

Results and Discussion

Infrared Spectra

4000–400 cm^{-1}

A partial assignment of the absorption bands observed for nictindole and the copper(II) complexes is given in Table I. Nictindole possesses three potential donor sites: (i) pyridine ring nitrogen, (ii) carbonyl oxygen and (iii) indole ring nitrogen. Owing to the disposition of these donor sites in the molecule, nictindole cannot act as a chelating agent. However, one cannot rule out the possibility of two of the coordination sites bonding to different metal ions resulting in polymeric structures.

The particularly low frequency and broadness of the N–H stretching band (3300–2550 cm^{-1}) in the infrared spectra of the free base is indicative of hydrogen bonding. The position of the N–H band is known to be affected by the nature and position of substituents on the pyrrole ring [10]. Electron attracting groups (e.g. C=O) shift the N–H band to lower frequencies and a substituent on the 3-position has a larger effect than the same substituent on the 2-position [11]. Both will affect the position of the stretching band in nictindole. In the two copper(II) complexes the N–H band is present in the region 3250–3300 cm^{-1} indicating that the NH of the indole ring is not coordinated to copper. The reduction in intensity and broadness of the absorption in this region in the complexes compared with the free drug indicates the absence of hydrogen bonding in the chloro-complex and a reduction in hydrogen bonding in the bromo-complex compared with the free drug.

The most striking feature of indole spectra in the carbonyl region is the pronounced shift to lower frequencies which accompanies conjugation with the indole nucleus [12]. Carbonyl frequencies have previously been reported as low as 1618 cm^{-1} for a series of indole carbonyl compounds [11]. The strong band observed at 1635 cm^{-1} in the free ligand and in the region 1615–1625 cm^{-1} for the complexes is consequently assigned to the carbonyl stretch of the ketone group on the indole 3-position. The similarity in the band position in the free ligand and in the complex indicated that the carbonyl group is not involved in coordination to the copper.

Interactions between ring C=C and C=N stretching vibrations of the pyridine ring result in the presence of two strong to medium absorption bands about 100 cm^{-1} apart [13]. These absorptions occur at 1600 cm^{-1} and 1497 cm^{-1} in nictindole with only minor shifts in the complexes.

From a consideration of the infrared spectra, it is suggested that in the copper(II) complexes nictindole acts as a mono-dentate ligand via the pyridine nitrogen atom. The outstanding feature of the infrared spectra is the close similarity between the spectra of the free base and that of the complexes. This is in accord with previous observations on pyridine complexes [14, 15] that, with the exception of relatively minor shifts, the fundamental frequencies of the base are altered little on coordination. This is attributed [15] to back-bonding from the d-orbitals of the metal to the π-electron system of the heterocyclic base.

TABLE I: Infra-red Absorption Bands (4000–400 cm^{-1})[a]

	ν(N–H)	ν(C–H) aromatic	ν(C=O)	Pyridine ring	
				ν(C=N/C=C)	Ring vibrations
NIDOL	3300–2550(br)		1635	1600, 1497	610
$CuCl_2(NIDOL)_2$	3295(sh)	3060	1625	1595, 1460	615
$CuBr_2(NIDOL)_2$	3260(br)	3060	1615	1580, 1460	610

[a]br = broad, sh = sharp.

TABLE II. Infra-red Absorption Bands (400–40 cm^{-1})

	ν(Cu–X)	ν(Cu–N)	Other bands
$CuCl_2(NIDOL)_2$	286 267	248	303, 176, 172
$CuBr_2(NIDOL)_2$	253 235	245	297

400–40 cm^{-1}

The copper(II) complexes of the stoichiometry CuX_2L_2, where X is a halogen and L is pyridine or a 3 or 4-substituted pyridine, exhibit two infrared active ν(Cu–X) bands in the solid state arising from the stretching of the bridging copper–halogen bonds. Corresponding complexes of 2-substituted pyridines, on the other hand, show only one infrar-red active ν(Cu–X) mode, indicating monomeric square-planar structures for these complexes, enforced by the steric requirements of the base [16]. A comparison of the far infrared spectra of the solid copper(II) halide complexes of nictindole shows clearly that there are two bands (X = Cl; 286, 267: X = Br; 253, 235 cm^{-1}) in the spectrum of each arising from a copper–halogen stretching mode (Table II). In the chloro-complex a third band at 176 cm^{-1} is tentatively assigned to the Cu–X in-plane bending mode of the distorted $[CuCl_4]_n$ chain.

Both complexes exhibit a fairly strong band at 247 ± 2 cm^{-1}, which cannot be assigned to a Cu–X mode since its position is too constant nor can it be assigned to a lattice mode as the frequency of the band is considered too high. It seems reasonable therefore to assign this band to the ν(Cu–N) vibration and this assignment is in agreement with previous observations for pyridine complexes [16]. Theoretical predictions indicate that the ν(M–N) mode of pyridine complexes would occur in the 150–200 cm^{-1} region [17]. That the bands assigned to the ν(Cu–N) vibration in the present work are at a somewhat higher frequency than predicted supports the suggestion [16] that there is appreciable back-bonding from the copper(II) ion to the ligand.

Electronic Properties

The electronic spectra of the $CuX_2(NIDOL)_2$ complexes are similar to those reported [18] for CuX_2py_2 in which the copper(II) ion is in a tetragonally distorted pseudo-octahedral environment of four short planar bonds (two Cu–N and two Cu–Cl) and two longer Cu–Cl bonds at right angles to this plane [19]. The reflectance spectra for both complexes consist of a broad, moderately intense absorption and a slightly less intense shoulder (Table III). The ^2E_g and $^2T_{2g}$ states of the octahedral copper(II) ion (d^9) are split under the influence of a tetragonal distortion and the distortion can be such as to cause the three transitions $^2B_1 \rightarrow {}^2B_2$; $^2B_1 \rightarrow {}^2E$ and $^2B_1 \rightarrow {}^2A_1$ to remain unresolved in the spectrum. The position and intensity indicate that the copper(II) ion is in just such a distorted octahedral environment and in the absence of any other bands, it is suggested that all three transitions lie within the single broad absorption band. This assignment is in agreement with the general observation that copper(II) d–d transitions are normally close in energy [20].

The magnetic moments (1.84 μ_B (Cl); 1.74 μ_B (Br)) fall within the range normally observed for mononuclear complexes having little interaction between copper(II) centres. The ESR spectrum of the chloro-complex consists of a line shape characteristic of a complex with two g-values and with $g_\parallel > g_\perp$ [21]. This, together with the magnitude of the lowest g-value indicates an elongated tetragonal environment for the copper(II) ion and a $d_{x^2-y^2}$ orbital as the ground state [22]. The bromo-complex exhibits an isotropic ESR spectrum with a g_{iso} of 2.083.

All the measurements discussed above are consistent with the $CuX_2(NIDOL)_2$ complexes possessing a polymeric halogen bridged structure with the nictindole coordinated via the pyridine ring nitrogen.

TABLE III. Electronic Properties[a]

	μ_{eff} (M_B)	Ligand field parameters (cm^{-1})	Dq (cm^{-1})	Electron spin resonance	
$CuCl_2(NIDOL)_2$	1.84	13333 (0.76), 11765 (sh; 0.74)	1333	$g_\parallel$ $g_\perp$	2.215 2.008
$CuBr_2(NIDOL)_2$	1.74	11765 (0.72), 12500 (sh; 0.71)	1176	g_{iso}	2.083

[a]Figures in parenthesis represent intensity of the band on the arbitrary Bechmann scale: sh = shoulder.

References

1 B. M. Babior, *N. Engl. J. Med., 298,* 721 (1978); B. Halliwell, *Cell. Biol. Int. Rep., 6,* 529 (1982).
2 B. Halliwell and J. M. C. Gutteridge, *Biochem. J., 219,* 1 (1984).
3 J. M. McCord, *Science, 185,* 529 (1974).
4 J. A. Fee, J. Piesach and W. B. Mims, *J. Biol. Chem., 256,* 1910 (1981).
5 R. Brigelius, R. Spottl, W. Bors, E. Lengfelder, M. Saran

and U. Weser, *FEBS Lett.*, *47*, 72 (1974); L. R. de Alvare, K. Goda and T. Kimura, *Biochem. Biophys. Res. Commun.*, *69*, 687 (1976).

6 D. O. Harrison, A. E. Underhill, J. K. Fletcher, P. S. Gomm and F. Holloway, *Polyhedron*, *4*, 681 (1985).

7 J. G. Lombardino, *Ann. Rep. Med. Chem.*, *13*, 167 (1978).

8 G. Rosseels, M. Peiren, J. Matteazzi, G. Wouters and M. Prost, *Bull. Soc. Chim. Belg.*, *84*, 263 (1975).

9 C. Deby, M. Descamps, F. Binon and Z. M. Bacq, *C.R. Soc. Biol.*, *165*, 2465 (1971); M. Descamps, H. Inion, H. de Vogelaer, R. Charlier, M. Colot and M. Vandamme, *Chim. Thér.*, *2*, 173 (1973).

10 J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, S. Eardley, B. E. Jennings and A. Robinson, *J. Chem. Soc.*, 2227 (1957).

11 F. Millich and E. I. Becker, *J. Org. Chem.*, *23*, 1096 (1958).

12 A. H. Soloway and S. L. Friess, *J. Am. Chem. Soc.*, *73*, 5000 (1951).

13 G. Socrates, 'Infrared Characteristic Group Frequencies', Wiley, New York, 1980.

14 R. Hulme, G. J. Leigh and I. R. Beattie, *J. Chem. Soc.*, 366 (1960).

15 A. I. Popov, J. C. Marshall, F. N. Stute and W. B. Person, *J. Am. Chem. Soc.*, *83*, 3586 (1961).

16 M. Goldstein, E. F. Mooney, A. Anderson and H. A. Gebbie, *Spectrochim. Acta*, *21*, 105 (1965).

17 L. P. Bicelli, *Ann. Chim. (Rome)*, *48*, 749 (1958).

18 E. Konig and H. L. Schläfer, *Z. Phys. Chem.*, *26*, 371 (1960).

19 J. D. Dunitz, *Acta Crystallogr.*, *10*, 307 (1957).

20 O. G. Holmes and D. S. McClure, *J. Chem. Phys.*, *26*, 1686 (1957).

21 H. Elliott, B. J. Hathaway and R. C. Slade, *J. Chem. Soc. A*, 1443 (1966); B. J. Hathaway, I. M. Procter, R. C. Slade and A. A. G. Tomlinson, *J. Chem. Soc. A*, 2219 (1969).

22 C. J. Ballhausen, 'Introduction to Ligand Field Theory', McGraw, New York, 1962, p. 134.