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Synthesis, Characterization and Antitumour Activity of Iron(II) and Iron(III) Complexes of 3- and 5-Substituted Salicylaldehyde Benzoyl Hydrazones

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Abstract

Iron(II) and iron(III) complexes of tridentate ligands derived from various substituted salicylaldehydes and benzoyl hydrazones have been prepared and characterized by elemental analysis, conductance measurements, magnetic susceptibilities (from room temperature down to liquid N_2 temperature), and Mössbauer, electronic and infrared spectral studies. On the basis of these studies the following structures are suggested: monomeric, high-spin, five-coordinate for $Fe(XSBH)SO_4 \cdot H_2O$ (XSBH = substituted salicylaldehyde benzoyl hydrazone, X = H, 3-CH_3O, 3-NO_2, 5-Cl, 5-Br, 5-CH_3 or 5-NO_2); dimeric, high-spin, phenoxide bridged, five-coordinate for Fe(H-SBH)Cl (H-SBH = salicylaldehyde benzoyl hydrazone); and monomeric, high-spin, six-coordinate for $Fe(XSBH)Cl_2 \cdot H_2O$ (X = 3-CH_3O, 3-NO_2, 5-Cl, 5-Br, 5-CH_3 or 5-NO_2). Intermolecular antiferromagnetic exchange interaction is present in the dimeric Fe(XSBH)Cl complex, where the exchange parameter is −7.3 cm^{-1}. The complex exhibits an asymmetrical quadrupole-split doublet in its ^{57}Fe Mössbauer spectra. The asymmetry is found to be temperature dependent with a relatively symmetrical doublet at low temperature. All these complexes have been screened for their antitumour activity against the P388 lymphocytic leukaemia test system in mice and have been found to possess no significant activity at the dosages employed.

Introduction

There are several types of antitumour agents, including the clinically used *cis*-dichlorodiamine Pt(II) (cisplatin) and bleomycin, which have substantial antineoplastic effects in animals and, in some cases, in humans and which may interact with metals as part of their cytotoxic activities against tumour and normal cells: e.g. bis(thiosemicarbazones)(Cu), α-*N*-heterocyclic carboxaldehyde thiosemicarbazones (Cu, Fe), streptonigrin (Fe), adriamycin (Fe), IRRF-159 (Zn), rhodium carboxylates, and cyclopentadienyl titanium and gallium salts [1–8]. Thus, the possibility that the metal complexes may be useful drugs is sufficient for us to focus our attention on metal complexes and metal binding ligands to explore this area.

Aroyl hydrazones have been shown to possess a significant inhibiting effect on DNA synthesis and cell growth in a number of human and rodent cell lines grown in culture [9]. A copper(II) complex of the most potent chelator, salicylaldehyde benzoyl hydrazone (H-SBH), exhibits a more significant inhibitory activity than does H-SBH itself [10]. It has been postulated that inhibition is due to the ability of aroyl hydrazones to penetrate cell membranes and disrupt the intracellular metabolism of essential metal ions [10]. The exact nature of such disruptions, and the extent to which they may be exploited for therapeutic purposes, require much more study including the detailed elucidation of the chemical nature of the complexes formed between biologically active aroyl hydrazones and physiologically important transition metals. This paper describes the synthesis, characterization and antitumour properties of iron(II) and iron(III) complexes of 3- and 5-substituted salicylaldehyde benzoyl hydrazones.

Experimental

Materials

Salicylaldehyde, 3-methoxysalicylaldehyde (*o*-vanillin) and benzoylhydrazide were obtained from the Aldrich Chemical Co., Milwaukee, Wisconsin, and used without further purification. 5-Chlorosalicylaldehyde and 3- and 5-nitrosalicylaldehyde were obtained from the Eastman Chemical Co., Rochester, New York. All other chemicals and solvents were Reagent grade or equivalent.

5-Bromosalicylaldehyde was prepared by adding bromine to an equivalent amount of a cold solution of salicylaldehyde dissolved in glacial acetic acid. 5-Methylsalicylaldehyde was prepared by a modification of the Reimer–Tieman reaction, using *p*-cresol and chloroform in a highly alkaline medium.

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TABLE I. Analytical and Conductance Data of Iron(II) and Iron(III) Complexes of 3- and 5-Substituted Salicylaldehyde Benzoyl Hydrazones

Compound	Colour	Found (%)				Calculated (%)				Λ_M (Ω^{-1} mol^{-1} cm^2)
		C	H	N	Fe	C	H	N	Fe	
Fe(H-SBH)$SO_4 \cdot H_2O$	brown	46.98	3.75	8.00	15.42	47.59	3.68	7.43	15.86	10.35
Fe(3-CH_3OSBH)$SO_4 \cdot H_2O$	brown	41.50	3.50	6.25	12.85	41.00	3.42	6.38	12.76	12.20
Fe(3-NO_2SBH)$SO_4 \cdot H_2O$	dark brown	37.29	2.40	9.10	12.20	37.00	2.64	9.25	12.33	14.54
Fe(5-ClSBH)$SO_4 \cdot H_2O$	reddish brown	38.20	2.90	6.25	12.51	37.88	2.71	6.31	12.63	14.70
Fe(5-BrSBH)$SO_4 \cdot H_2O$	brown	33.89	2.56	5.91	11.60	34.43	2.46	5.74	11.48	13.78
Fe(5-CH_3SBH)$SO_4 \cdot H_2O$	dark brown	42.04	3.68	6.71	13.39	42.55	3.55	6.62	13.24	14.10
Fe(5-NO_2SBH)$SO_4 \cdot H_2O$	dark brown	36.84	2.42	9.40	12.40	37.00	2.64	9.25	12.33	12.90
Fe(H-SBH)Cl	black	50.34	2.92	8.32	17.10	50.99	3.03	8.50	17.00	–
Fe(3-CH_3OSBH)$Cl_2 \cdot H_2O$	dark green	43.07	3.50	6.84	13.47	43.48	3.62	6.76	13.53	14.26
Fe(3-NO_2SBH)$Cl_2 \cdot H_2O$	dark green	38.89	2.91	9.88	13.12	39.16	2.80	9.79	13.05	10.50
Fe(5-ClSBH)$Cl_2 \cdot H_2O$	green	40.52	2.69	6.77	13.44	40.14	2.87	6.69	13.38	14.28
Fe(5-BrSBH)$Cl_2 \cdot H_2O$	black	36.47	2.72	6.00	10.26	36.29	2.59	6.05	12.10	13.90
Fe(5-CH_3SBH)$Cl_2 \cdot H_2O$	dark green	48.38	3.68	7.48	15.31	48.91	3.77	7.61	15.22	14.25
Fe(5-NO_2SBH)$Cl_2 \cdot H_2O$	dark green	40.02	2.74	9.88	13.12	39.16	2.80	9.79	13.05	14.70

3- and 5-substituted salicylaldehyde benzoyl hydrazone (XSBH; X = H, 3-CH_3O, 3-NO_2, 5-Cl, 5-Br, 5-CH_3, 5-NO_2) were prepared by the condensation of benzoylhydrazide with aldehydes, according to the reported method [9].

Synthesis of the Complexes

All the iron(II) and iron(III) complexes were prepared by the following general method. To the hot solution of XSBH (1 mmol) in ethanol (25 ml) was added a hot solution of $FeCl_3$ (0.016 g, 1 mmol) or $FeSO_4 \cdot 7H_2O$ (0.027 g, 1 mmol) in ethanol (20 ml), with constant stirring, and the dark-coloured solution mixture was refluxed for 2–3 h. The hot solution was filtered and allowed to stand for 4–5 days at room temperature. The shiny crystals which separated were filtered off, washed with ethanol, then ether, and dried over P_2O_5 under vacuum.

Physical Measurements

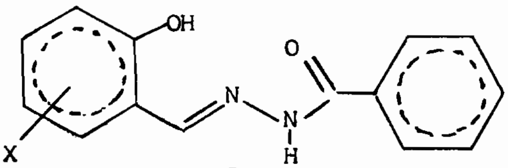
Conductance measurements in ethanol at 10^{-3} M were carried out on a Toshniwal conductivity bridge type CL 01/01. Magnetic measurements were obtained on a standard Gouy balance calibrated with $HgCo(NCS)_4$ [11] from room temperature down to 78 K. Diamagnetic corrections were applied using Pascal's constants [12]. The error limit for the reported magnetic moment is ± 0.05 μ_B. The Fe Mössbauer spectra were obtained on polycrystalline samples by using a constant-acceleration Mössbauer spectrometer which was calibrated with natural α-iron foil. The source was ^{57}Co(Cu) and was at room temperature for all experiments. The low temperature results were measured in a vacuum cryostat with a sample holder which protected the sample from the cryostat vacuum. The Mössbauer results were determined by inspection with an accuracy of ±0.01 mm/s.

The diffuse reflectance spectra were recorded on a Cary-14 spectrophotometer equipped with a reflectance accessory using MgO as the reference. The infrared spectra of the free ligands and their iron(II) and iron(III) complexes were recorded on a Perkin-Elmer 337 spectrophotometer in CsI in the 4000–200 cm^{-1} range.

Iron was estimated in all complexes by EDTA titrimetry using Erichrome Black T as an indicator after destroying the organic part by aqua regia and then conc. H_2SO_4 [13]. Carbon, hydrogen and nitrogen were determined microanalytically at C.D.R.I., Lucknow (Table I).

Results and Discussion

The infrared spectra of free XSBH ligands exhibit ν(N–H) absorption bands at *ca.* 3276s and 3210s cm^{-1} and ν(C=O) at *ca.* 1670s cm^{-1}, indicating that the ligands exist in the *keto* form (**I**) in the solid state. However, in solution and in the presence of metal ions, the compounds probably exist in equilibrium with the tautomeric *enol* form (**Ia**). By the loss of the enolic and phenolic protons tautomer (**Ia**) may act as a doubly charged tridentate ligand coordinating through the phenolic oxygen, the azomethine nitrogen and the carbonyl oxygen atoms. When the hot solution of XSBH in ethanol is refluxed with a solution of ferric chloride or ferrous sulphate heptahydrate, it gives shiny, coloured crystalline solids of the general formula Fe(XSBH)SO$_4$·H$_2$O, Fe(H-SBH)Cl and Fe(XSBH)Cl$_2$·H$_2$O. All these complexes, except Fe(H-SBH)Cl, are soluble in water and in a variety of organic solvents. The molar conductances of the Fe(XSBH)SO$_4$·H$_2$O and Fe(XSBH)Cl$_2$·H$_2$O complexes in ethanol at *ca.* 10^{-3} M, determined at 27 °C, are in the range 10.5–14.7 ohm^{-1} cm^2 mol^{-1}, indicating their non-electrolytic behaviour [14] in solution.



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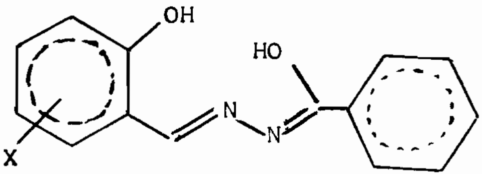
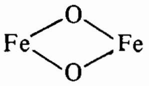


Ia

X = H, 3-CH$_3$O, 3-NO$_2$, 5-Cl, 5-Br, 5-CH$_3$, 5-NO$_2$

The assignments of some of the infrared bands observed in the spectra of the free XSBH ligands and their Fe(II) and Fe(III) complexes are reported in Table II. The infrared spectra of the free ligands exhibit bands at *ca.* 3440s, 3380s and 2800m cm^{-1} which are assigned to ν_{as}(OH), ν_s(OH) and the intramolecular H-bonded hydroxyl group of the phenolic group, respectively [15]. In the spectra of all the Fe(II) and Fe(III) complexes these absorption bands are not observed and the phenolic (C–O) stretching and bending vibrations, observed at *ca.* 1520 and 1280 cm^{-1}, respectively, in the free ligands, are shifted to a higher frequency by about 25 cm^{-1} in the Fe(H-SBH)Cl complex, while in the Fe(XSBH)SO$_4$·H$_2$O and Fe(XSBH)Cl$_2$·H$_2$O complexes these are not much disturbed. The shift of the bands is probably due to the increase in C–O bond strength on extended delocalization of the π system of the azine moiety and strongly suggests the dimeric structure for the Fe(H-SBH)Cl complex, involving phenoxide bridging [16, 17]. This is further confirmed by the appearance of a



ring vibration at 730 cm^{-1} [18, 19].

In the NH stretching region, the high frequency component ν_{as}(NH) remains practically unchanged on coordination, relative to that of the free ligands, while the low frequency component ν_s(NH) is shifted to a high frequency by approximately 50 cm^{-1} in the Fe(XSBH)SO$_4$·H$_2$O and Fe(XSBH)Cl$_2$·H$_2$O complexes. This suggests that the ligands exist in the *keto* form in these complexes [20], as partly confirmed by the high frequency shift of the amide-II ($\Delta\nu$(CN) + δ(NH) $\simeq$ 30 cm^{-1}) and amide-VI ($\Delta\delta$(C=O) $\simeq$ 20 cm^{-1}) and the low frequency shift of amide-I ($\Delta\nu$(C=O) $\simeq$ 40 cm^{-1}) and amide-III ($\Delta\delta$(NH) $\simeq$ 10 cm^{-1}) bands. However, the spectrum of the Fe(H-SBH)Cl complex does not show any characteristic bands of amide and amino groups, indicating that the ligand is coordinated in the *enolic* form [21].

The coordination of the azomethine nitrogen to the Fe(II) and Fe(III) ions is indicated by the shifting of the bands chiefly assigned to the ν(N–N) and ν(C=N) stretching vibrations [22]. The spectra of the complexes show a low frequency shift of ν(N–N) from *ca.* 980 cm^{-1} for ligands to approximately 970 cm^{-1} and ν(C=N) from *ca.* 1630 cm^{-1} to *ca.* 1600 cm^{-1}. These changes in the frequencies of the >C=N–N–C– group are typical of the coordination of the ligands to a metal through the azomethine nitrogen atom.

In the far-infrared spectral region the Fe(XSBH)SO$_4$·H$_2$O complexes exhibit bands at *ca.* 440, 425, 390 and 340 cm^{-1} which are assigned to ν(Fe–O) phenolic, ν(Fe–N), ν(Fe–O)H$_2$O and ν(Fe–O) ketonic, respectively [23]. The monodentate coordination of the sulphate group is indicated by the appearance of a ν(S–O) band at *ca.* 985 cm^{-1} and ν(Fe–OSO$_3$) at *ca.* 250 cm^{-1} in Fe(XSBH)SO$_4$·H$_2$O complexes [24]. The other bands associated with the sulphate group vibrations are obscured by ligand absorption bands. The Fe(H-SBH)Cl complex shows bands at 440s, 418m, 340s and 325 m cm^{-1}, which are assigned to ν(Fe–O) phenolic, ν(Fe–N), ν(Fe–Cl) and ν(Fe–O) enolic vibrations, respectively [23, 25]. On the other hand, in the Fe(XSB)Cl$_2$·H$_2$O complexes the bands are observed at *ca.* 410, 370, 342, 330 and 270 cm^{-1}, which are assigned to ν(Fe–O) phenolic, ν(Fe–O)H$_2$O, ν(Fe–N), ν(Fe–O) ketonic and ν(Fe–Cl) vibrations, respectively [23].

TABLE II. Important Infrared Spectral Data of Iron(II) and Iron(III) Complexes of 3- and 5-Substituted Salicylaldehyde Benzoyl Hydrazones

Compound	ν_{as}(NH)	ν_s(NH)	ν(C=N)	ν(C–O) phenolic	$\nu(\mathrm{Fe}{<}^{\mathrm{O}}_{\mathrm{O}}{>}\mathrm{Fe})$		ν(Fe–O) phenolic	ν(Fe–O) water	ν(Fe–O) ketonic/ enolic	ν(Fe–N)	ν(Fe–Cl)
SBH	3276s	3210m	1630s	1520s	1280s	–	–	–	–	–	–
3-CH_3OSBH	3276s	3210m	1632s	1518s	1280s	–	–	–	–	–	–
3-NO_2SBH	3272s	3212s	1630s	1518s	1280m	–	–	–	–	–	–
5-ClSBH	3270s	3210m	1630s	1520s	1280m	–	–	–	–	–	–
5-BrSBH	3276s	3208s	1628s	1520s	1276m	–	–	–	–	–	–
5-CH_3SBH	3276s	3212m	1632vs	1520m	1278m	–	–	–	–	–	–
5-NO_2SBH	3275s	3210m	1630s	1520s	1276m	–	–	–	–	–	–
Fe(H-SBH)$SO_4 \cdot H_2O$	3280s	3255m	1598m	1517s	1276m	–	440s	390m	340m	425s	–
Fe(3-CH_3OSBH)$SO_4 \cdot H_2O$	3285s	3260m	1596m	1515s	1275w	–	440s	390m	338w	425s	–
Fe(3-NO_2SBH)$SO_4 \cdot H_2O$	3278m	3250m	1600m	1515s	1270w	–	445m	395m	344w	420s	–
Fe(5-ClSBH)$SO_4 \cdot H_2O$	3280s	3255m	1600m	1512s	1270w	–	445m	395m	345w	420m	–
Fe(5-BrSBH)$SO_4 \cdot H_2O$	3280s	3250s	1595m	1515s	1270m	–	440s	390m	345w	418m	–
Fe(5-NO_2SBH)$SO_4 \cdot H_2O$	3276s	3260m	1598w	1515s	1272m	–	446s	390w	340w	418m	–
Fe(5-CH_3SBH)$SO_4 \cdot H_2O$	3276s	3250s	1600m	1515s	1270m	–	445s	388w	340w	425m	–
Fe(H-SBH)Cl	–	–	1595s	1540s	1305m	730s	440s	–	325m	418m	340s
Fe(3-CH_3OSBH)$Cl_2 \cdot H_2O$	3278s	3255s	1600m	1518s	1275m	–	410s	378s	330m	342m	270m
Fe(3-NO_2SBH)$Cl_2 \cdot H_2O$	3276s	3260s	1595m	1515w	1275w	–	412	375s	330m	342m	272m
Fe(5-ClSBH)$Cl_2 \cdot H_2O$	3270m	3255m	1595m	1515m	1280m	–	410	370s	330w	342m	275w
Fe(5-BrSBH)$Cl_2 \cdot H_2O$	3275m	3260m	1600s	1518s	1270m	–	410	370m	335w	341w	270m
Fe(5-CH_3SBH)$Cl_2 \cdot H_2O$	3280s	3250s	1598m	1514vs	1270m	–	414	370w	330w	340w	270w
Fe(5-NO_2SBH)$Cl_2 \cdot H_2O$	3275s	3260m	1598m	1515w	1275m	–	412	370w	330m	340w	275m

TABLE III. Magnetic Susceptibility Data of Iron(II) and Iron(III) Complexes of 3- and 5-Substituted Salicylaldehyde Benzoyl Hydrazones

Compound	Temperature (K)	$10^6 \chi_M'$ (cgsu)	μ_{eff} (μ_B)
Fe(H-SBH)$SO_4 \cdot H_2O$	298.8	11399	5.25
$\theta = -10$ K	260.4	13058	5.25
	208.5	15952	5.20
	190.0	17413	5.19
	145.2	22408	5.16
	106.6	29597	5.10
	94.8	32908	5.08
	78.0	39414	5.06
Fe(3-CH_3OSBH)$SO_4 \cdot H_2O$	298.5	11410	5.25
$\theta = -7.5$ K	258.5	13202	5.26
	210.4	15691	5.18
	188.8	17257	5.15
	140.5	22531	5.09
	108.7	28821	5.08
	95.6	32393	5.06
	78.0	38966	5.03
Fe(3-NO_2SBH)$SO_4 \cdot H_2O$	300.0	11141	5.20
$\theta = -12.5$ K	265.0	12594	5.20
	210.2	15587	5.16
	188.5	16956	5.10
	146.3	21574	5.08
	110.2	28006	5.04
	95.0	32218	5.03
	78.0	38669	5.01
Fe(5-ClSBH)$SO_4 \cdot H_2O$	300.0	11311	5.24
$\theta = -10$ K	259.9	12838	5.20
	210.2	15587	5.16
	192.4	16810	5.13
	150.3	21093	5.09
	98.7	31168	5.04
	78.0	38818	5.02
Fe(5-BrSBH)$SO_4 \cdot H_2O$	298.7	11403	5.25
$\theta = -13$ K	260.3	12819	5.20
	209.5	15638	5.16
	194.3	16649	5.13
	152.2	20675	5.07
	98.7	31048	5.03
	78.0	38818	5.02
Fe(5-CH_3SBH)$SO_4 \cdot H_2O$	299.5	11373	5.25
$\theta = -10$ K	260.4	12814	5.20
	212.3	15435	5.15
	190.5	16781	5.10
	148.7	21151	5.07
	99.5	31044	5.05
	78.0	38966	5.03
Fe(5-NO_2SBH)$SO_4 \cdot H_2O$	300.0	11311	5.24
$\theta = -10$ K	265.5	12523	5.19
	215.4	15100	5.14
	194.6	16433	5.10
	150.2	21025	5.08
	100.3	30804	5.05
	78.0	38818	5.02
Fe(H-SBH)Cl	299.8	13458	5.68
$J = -7.3$ cm^{-1}	250.2	15822	5.62
$g = 2.0$	204.6	18033	5.43
	152.8	22055	5.19
	120.5	25422	4.94
	98.6	28146	4.71
	78.0	31063	4.40
Fe(3-CH_3OSBH)$Cl_2 \cdot H_2O$	300.0	14778	6.00
$\theta = -3$ K	248.9	17758	6.00
	210.2	20959	6.00
	190.0	23136	6.00
	154.2	28264	5.99
	116.0	37105	5.98
	98.7	43466	5.99
	78.0	54031	5.97
Fe(3-NO_2SBH)$Cl_2 \cdot H_2O$	298.0	14827	5.99
$\theta = -5$ K	250.4	17654	6.00
	208.3	21078	5.99
	154.4	28228	5.99
	112.8	38118	5.98
	98.0	43623	5.98
	78.0	54031	5.97
Fe(5-ClSBH)$Cl_2 \cdot H_2O$	299.7	14793	6.00
$\theta = -5$ K	250.3	17661	6.00
	205.6	21418	6.00
	152.8	28423	5.98
	114.3	37757	5.99
	98.7	43188	5.97
	78.0	54031	5.97
Fe(5-BrSBH)$Cl_2 \cdot H_2O$	300.0	14681	5.98
$\theta = -6$ K	250.3	17545	5.98
	207.4	21167	5.99
	148.8	29165	5.98
	110.2	38857	5.97
	97.6	43514	5.96
	78.0	54031	5.97
Fe(5-CH_3SBH)$Cl_2 \cdot H_2O$	300.0	14730	5.99
$\theta = -2$ K	252.4	17517	6.00
	210.6	20852	5.99
	155.5	28034	5.99
	110.6	38846	5.98
	97.4	43740	5.97
	78.0	53860	5.96
Fe(5-NO_2SBH)$Cl_2 \cdot H_2O$	298.8	14837	6.00
$\theta = -3$ K	249.7	17587	5.98
	214.0	20595	6.00
	154.0	28299	5.99
	110.2	38857	5.97
	98.4	43176	5.96
	78.0	53860	5.96

The μ_{eff} values for Fe(II) and Fe(III) complexes have been measured as a function of temperature and are detailed in Table III. The magnetic moments of Fe(XSBH)$SO_4 \cdot H_2O$ complexes are almost independent of temperature, ranging from 5.25–5.20 μ_B at *ca.* 298 K to 5.06–5.02 μ_B at 78 K. These values are significantly lower than that of six-coordinate

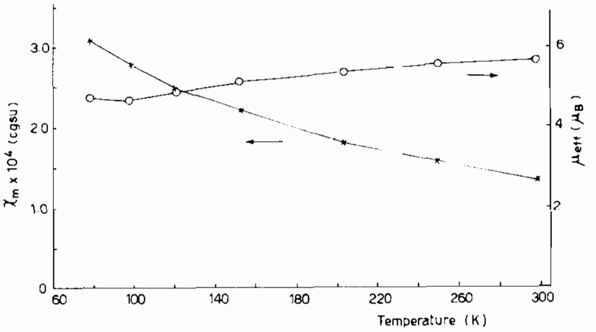


Fig. 1 Magnetic susceptibility (χ_m) and effective magnetic moment (μ_{eff}) *vs.* temperature for Fe(H-SBH)Cl.

complexes ($\mu_{eff} = 5.50\ \mu_B$) [26] and are consistent with those reported for five-coordinate iron(II) complexes [27]. The presence of axial ligands in the five-coordination sphere would generate a large splitting of the $^5T_2$ state (of O_h origin), thereby reducing the orbital contribution to μ_{eff}. The magnitude and temperature-independence of the magnetic moments strongly suggest the absence of antiferromagnetic interaction and contributions from terms other than the ground term $^5A_{1g}/(t_{2g}{}^3\,e_g{}^2)$ in Fe(XSBH)$Cl_2 \cdot H_2O$ complexes [28].

The Fe(H-SBH)Cl complex has an effective magnetic moment of 5.68 μ_B at room temperature, indicating the presence of high-spin iron(III) ions. As the temperature is lowered, this μ_{eff} value decreases to 4.40 μ_B at 78 K. Plots of magnetic data for this complex are illustrated in Fig. 1. This behaviour is an indication of an intermolecular antiferromagnetic exchange interaction between the two $S = 5/2$ ions in the dimeric complex [29]. Such an exchange interaction between two $S = 5/2$ ions can be largely accounted for with an isotropic exchange spin Hamiltonian of the form $\hat{H} = -2J\hat{S}_1 \cdot \hat{S}_2$, where S_i is the spin operator on each of the two metal centres and J is the exchange parameter, which is a gauge of the magnitude of the interaction. An exchange-coupled, $S_1 = S_2 = 5/2$, complex has electronic states with a total spin of $S' = 5,4,3,2,1$ and 0. It is the characteristic of such an interacting ferric dimer that, even for a weak interaction, the variation in Boltzmann distribution over the S' states as a function of temperature is gradual and has an effect even at high temperatures. Thus, even a weak antiferromagnetic exchange interaction can influence the μ_{eff} values at room temperature and this could partially explain why the observed value is below the spin-only value of 5.9 μ_B.

The variable-temperature magnetic susceptibility data for Fe(H-SBH)Cl were fitted to the theoretical equation [30] to give $J = -7.3$ cm^{-1} and $g = 2.0$. The theoretical fits to both the μ_{eff} and χ_m *vs.* temperature curves are indicated in Fig. 1 as solid lines. It can be seen that the fits are reasonable, which verifies the suggestion that there is an antiferromagnetic interaction present in the dimeric complex. It is interesting to note that the magnitude of the interaction is very close to that found for Fe(salen)Cl (salen = *N,N'*-ethylenebis(salicylideneiminate) [31]. Thus, the antiferromagnetic interaction is a reflection of the details of the electronic structure of the bridged species and does not depend simply on metal–metal distance.

The ^{57}Fe Mössbauer spectra of Fe(II) and Fe(III) complexes have been measured at room temperature and 78 K and the spectral data are reported in Table IV. The observed chemical isomer shift values, δ, relative to natural iron foil, which are sensitive to both the oxidation state and the spin state of the iron, and the quadrupole splitting values, ΔE_Q, in Fe(XSBH)SO_4H_2O are of the magnitude expected for distorted, high-spin, five-coordinate iron(II) complexes [32]. The large ΔE_Q values for the Fe(XSBH)$SO_4 \cdot H_2O$ complexes are most probably caused by large contributions of like sign from both the non-spherical electron distribution and the ligand-field dissymmetry [33]. The contribution to ΔE_Q from the non-spherical d-electron distribution will depend on the nature of the ground state. Under a tetragonal distortion the $^5T_2$-state (of O_h symmetry) is split into $^5B_2$- and $^5T_2$-states. The magnitude of contributions to ΔE_Q from a 3d electron in either a $^5B_2$ or a ^5E ground state are equal, but the electric field gradients associated with these two states are of opposite signs. The results of the magnetically perturbed Mössbauer spectrum of a five-coordinate complex imply that the ground state is $^5B_2$, contrary to the ordering of the one-electron d-orbitals expected from crystal field theory, for both the square-pyramidal or trigonal-bipyramidal geometries [34]. From this result it is assumed that the ground state in Fe(XSBH)$SO_4 \cdot H_2O$ complexes is $^5B_2$.

The ^{57}Fe Mössbauer spectra were obtained for all iron(III) complexes; the spectral parameters are reported in Table IV. The spectra of Fe(H-SBH)Cl and Fe(XSBH)$Cl_2 \cdot H_2O$ (X = 3-CH_3O) are illustrated in Figs. 2 and 3, respectively. Essentially identical spectra to Fe(3-CH_3O·SBH)$Cl_2 \cdot H_2O$ were observed for the remaining iron(III) complexes. The observed isomer shift, δ, and quadrupole splitting, ΔE_Q, values of the Fe(XSBH)$Cl_2 \cdot H_2O$ complexes are of the magnitude expected for monomeric, high-spin, six-coordinate iron(III) complexes, whereas these values suggest a dimeric, high-spin ($S = 5/2$), five-coordinate structure for the Fe(H-SBH)Cl complex [32]. The larger quadrupole splitting in the Fe(H-SBH)Cl complex is most probably due to the larger electric field gradient at the nucleus resulting from the open coordination site. The observed asymmetry in the intensity of the two quadrupole lines, which is apparent in Fig. 2 of the Fe(H-SBH)Cl complex, is typical of complexes of this type [31, 32, 35].

TABLE IV. Mössbauer Spectral Data for Iron(II) and Iron(III) Complexes

Compound	Temperature (K)	ΔE_Q (mm/s)	δ[a] (mm/s)	Γ_1[b] (mm/s)	Γ_2[b] (mm/s)
Fe(H-SBH)$SO_4\cdot H_2O$	78	3.98	1.13	0.28	0.30
	RT[c]	3.84	1.00	0.26	0.29
Fe(3-CH_3OSBH)$SO_4\cdot H_2O$	78	3.98	1.14	0.29	0.34
	RT	3.88	1.00	0.26	0.28
Fe(3-NO_2SBH)$SO_4\cdot H_2O$	78	4.00	1.14	0.29	0.34
	RT	3.86	1.00	0.26	0.30
Fe(5-ClSBH)$SO_4\cdot H_2O$	78	3.99	1.10	0.30	0.34
	RT	3.89	0.98	0.30	0.30
Fe(5-BrSBH)$SO_4\cdot H_2O$	78	4.00	1.12	0.28	0.29
	RT	3.85	1.02	0.24	0.26
Fe(5-CH_3SBH)$SO_4\cdot H_2O$	78	4.00	1.10	0.28	0.32
	RT	3.86	1.00	0.24	0.26
Fe(5-NO_2SBH)$SO_4\cdot H_2O$	78	3.98	1.14	0.30	0.33
	RT	3.85	1.04	0.26	0.28
	4.2	1.45	0.55	0.17	0.17
Fe(H-SBH)Cl	78	1.44	0.52	0.20	0.20
	RT	1.40	0.42	0.30	0.28
Fe(3-CH_3OSBH)$Cl_2\cdot H_2O$	78	0.50	0.44	0.28	0.30
	RT	0.50	0.32	0.26	0.28
Fe(3-NO_2SBH)$Cl_2\cdot H_2O$	78	0.52	0.45	0.30	0.30
	RT	0.50	0.30	0.26	0.27
Fe(5-ClSBH)$Cl_2\cdot H_2O$	78	0.54	0.42	0.26	0.32
	RT	0.52	0.30	0.25	0.25
Fe(5-BrSBH)$Cl_2\cdot H_2O$	78	0.50	0.40	0.28	0.32
	RT[c]	0.50	0.35	0.25	0.24
Fe(5-CH_3SBH)$Cl_2\cdot H_2O$	78	0.54	0.42	0.30	0.30
	RT	0.50	0.30	0.26	0.28
Fe(5-NO_2SBH)$Cl_2\cdot H_2O$	78	0.54	0.40	0.29	0.30
	RT	0.52	0.34	0.26	0.28

[a] Relative to natural iron foil. [b] Full width at half-maximum for low velocity line (Γ_1) and high-velocity line (Γ_2). [c] Room temperature.

Although this asymmetry could result from partial orientation of sample crystallites in the sample container, as observed for $Fe_2(CO)_9$ [36], this seems unlikely because the asymmetry tends to decrease with decreasing temperature.

Goldanski *et al.* [37] and Karyagin [38] suggested that the intensity asymmetry in quadrupole split lines results from the anisotropy of the recoil-free fraction of the iron nucleus in the reduced symmetry site and is predicted to decrease with decreasing temperature [39]. Furthermore, the linewidth of the component lines is expected to remain unchanged at a given temperature, while the relative peak areas of the two lines should differ. For the Fe(H-SBH)Cl complex, the best fit of the spectral data is obtained when the areas of the two quadrupole split lines are set equal. Hence, it appears that the line intensity asymmetry is not consistent with that expected from the Goldanski–Karyagin effect.

The effect of magnetic relaxation on the asymmetry of the quadrupole split Mössbauer absorption bands has been discussed in detail by Blume [40] and by Blume and Tjon [41]. By treating magnetic relaxation as a fluctuating internal magnetic field, these authors showed that asymmetric quadrupole absorptions will result if the spin-relaxation rate is of the same magnitude as the Larmor precessional frequency of the Mössbauer nucleus in the internal hyperfine field generated by unpaired electron spins. For iron with an ^6S free-ion ground state, magnetic relaxation will occur mainly through spin–spin relaxation, and spin–lattice relaxation can in general be ignored. If electronic spin–spin relaxation is the primary relaxation mechanism, the line asymmetry

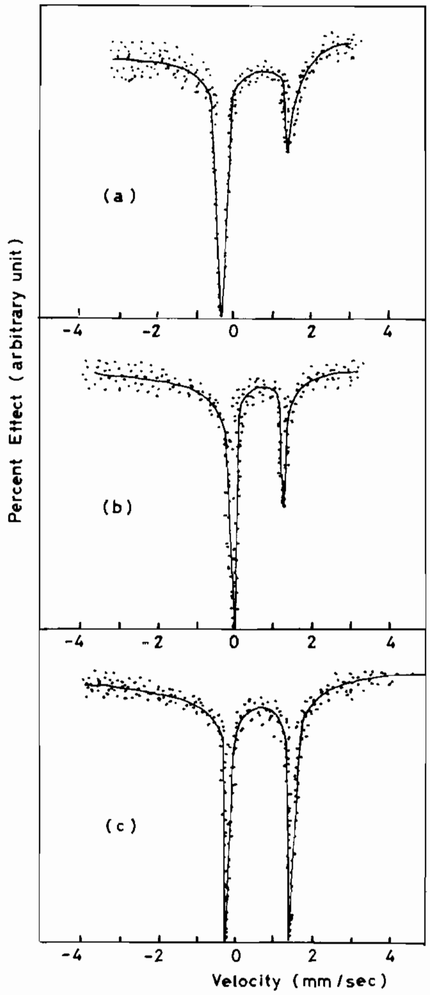


Fig. 2. Mössbauer spectrum of Fe(H-SBH)Cl at (a) 298 K, (b) 78 K and (c) 4.2 K.

will depend on the concentration of the paramagnetic ions and will be essentially independent of temperature. In addition, the linewidths of the asymmetric quadrupole split lines are not expected to be the same in the presence of magnetic relaxation [40]. For an exchange-interacting iron(III) dimer at 4.2 K, most of the molecules are in the diamagnetic $S = 0$ state; there is no hyperfine field and the asymmetric quadrupole absorption is symmetric. At higher temperatures, other dimer states $S' \neq 0$ are populated and slow relaxation of the spins results in a magnetic hyperfine broadening and asymmetrical quadrupole lines. That is why $[Fe(salen)Cl]_2$ ($J = -7.5$ cm^{-1}) [42] gives symmetrical quadrupole split lines at *ca.* 6 K [43], whereas for $[Fe(salen)]_2O$ ($J = -95$ cm^{-1}) [29] they are at 80 K [44]. Buckley *et al.* [45] have shown that the interactions in these types of molecules are intermolecular in nature. Hence, it appears that the asymmetry in the quadrupole split lines and its temperature dependence in the Fe(H-SBH)Cl complex is most likely due to intermolecular spin–spin relaxation.

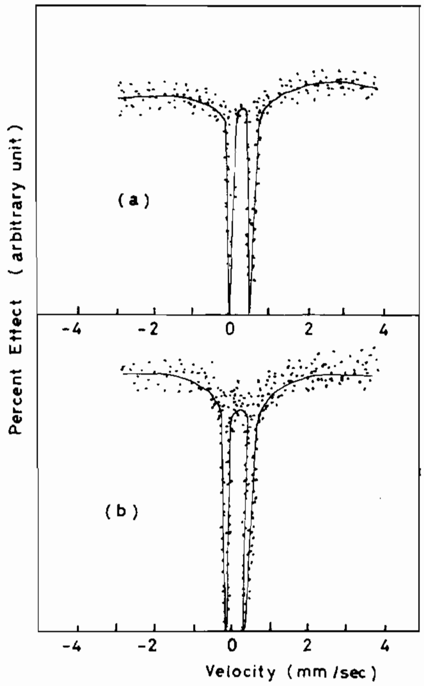


Fig. 3. Mössbauer spectrum of $Fe(XSBH)Cl_2 \cdot H_2O$ (X = 3-CH_3O) at (a) 298 K and (b) 78 K.

In the UV region (400–200 nm), the free ligands, XSBH, exhibit absorption bands at *ca.* 41 670, 38 460 and 31 750 cm^{-1} which are assigned to n → σ*, π → π* and n → π* transitions, respectively [46]. The high absorption by the ligands masks any splitting of the bands and only the slight wavelength and intensity variations are significant in the iron(II) and iron(III) complexes. The spectra of the complexes are dominated by the ligand absorption bands.

In the visible-near IR region, the $Fe(XSBH)SO_4 \cdot H_2O$ complexes exhibit two broad ligand field absorption bands at *ca.* 5400 and 9000 cm^{-1} which can be assigned to the $^5A_1$- and $^5B_1$-states derived from the splitting of the ^5E spectroscopic term in the tetragonal ligand field [27]. It is apparent that the splitting of the ^5E excited state is of the order of *ca.* 4000 cm^{-1}, indicating a highly distorted ligand field in these complexes. The iron(II) complexes also exhibit a very strong, broad band at *ca.* 21 000 cm^{-1} which is assigned to the $Fe(t_{2g} \rightarrow \pi^*)XSBH$ transition [47].

The $Fe(XSBH)Cl_2 \cdot H_2O$ complexes exhibit a single broad intense band at *ca.* 26 250 cm^{-1} which is assigned to the $Fe(eg \rightarrow \pi^*)XSBH$ transition. In addition to the charge-transfer band, the Fe(H-SBH)Cl complex also exhibits a single band at 11 000 cm^{-1} which can be assigned to a ligand field transition. A similar absorption has also been observed in the electronic spectrum of other five-coordinate iron(III)

TABLE V. Antitumour Activity of Iron(II) and Iron(III) Complexes of 3- and 5-Substituted Salicylaldehyde Benzoyl Hydrazones

Compound	Dose (mg/kg)	Weight difference (*T* − *C*) (%)	*T*/*C* (%)
H-SBH	400.00	0.3	95
	200.00	−1.0	105
	100.00	−1.7	112
Fe(H-SBH)$SO_4 \cdot H_2O$	400.00	−0.7	88
	200.00	−1.0	88
	100.00	−0.1	TOXIC
Fe(H-SBH)Cl	240.00	−1.2	TOXIC
	120.00	−1.5	86
	60.00	−0.1	88
3-NO_2SBH	400.00		TOXIC
	200.00	−1.2	98
	100.00	−0.5	110
Fe(3-NO_2SBH)$SO_4 \cdot H_2O$	400.00	−1.3	86
	200.00	−1.6	88
	100.00		TOXIC
Fe(3-NO_2SBH)$Cl_2 \cdot H_2O$	400.00	−2.4	90
	200.00	−1.0	95
	100.00	−0.5	100
3-CH_3OSBH	400.00		TOXIC
	200.00	−1.5	97
	100.00	−1.0	90
Fe(3-CH_3OSBH)$SO_4 \cdot H_2O$	400.00	−2.0	86
	200.00	−1.0	90
	100.00	−0.4	95
Fe(3-CH_3OSBH)$Cl_2 \cdot H_2O$	400.00	−2.5	88
	200.00	−1.2	85
	100.00	−1.0	86
5-ClSBH	400.00	−2.5	90
	200.00	−1.0	90
	100.00	−0.5	85
Fe(3-ClSBH)$SO_4 \cdot H_2O$	400.00	−1.5	88
	200.00	−1.0	85
	100.00	−0.5	90
Fe(3-ClSBH)$Cl_2 \cdot H_2O$	400.00	−2.4	95
	200.00	−1.7	86
	100.00	−1.0	90
5-BrSBH	240.00	−2.2	90
	120.00	−0.9	88
	60.00	−0.3	94
Fe(5-BrSBH)$SO_4 \cdot H_2O$	240.00	−3.6	99
	120.00	−2.2	86
	60.00	−1.1	95
Fe(5-BrSBH)$Cl_2 \cdot H_2O$	400.00	−1.6	TOXIC
	200.00	−1.3	TOXIC
	100.00	−0.6	TOXIC
5-CH_3SBH	240.00	−2.0	88
	120.00	−1.0	90
	60.00	−0.5	92
Fe(5-CH_3SBH)$SO_4 \cdot H_2O$	240.00	−3.0	86
	120.00	−2.1	90
	60.00	−1.0	85

(continued)

TABLE V. *(continued)*

Compound	Dose (mg/kg)	Weight difference (*T* – *C*) (%)	*T*/*C* (%)
Fe(5-CH_3SBH)$Cl_2 \cdot H_2O$	240.00	–2.5	98
	120.00	–1.0	105
	60.00	–0.5	96
5-NO_2SBH	240.00	–3.5	89
	120.00	–2.5	92
	60.00	–1.0	105
Fe(5-NO_2SBH)$SO_4 \cdot H_2O$	240.00	–3.2	86
	120.00	–1.5	88
	60.00	–1.0	95
Fe(5-NO_2SBH)$Cl_2 \cdot H_2O$	240.00	–2.5	90
	120.00	–1.0	86
	60.00	–0.5	95

complexes [15, 31]. Although the absorption observed at 11 000 cm^{-1} cannot be assigned properly, it seems to be a common feature of five-coordinate iron(III) complexes [40].

Antitumour Activity

The antitumour activity of the Fe(II) and Fe(III) complexes was determind at the National Cancer Institute (NCI), Bethesda, MD., by the standard screening procedure (*cf.* instruction 14) in the P388 lymphocytic leukaemia test system. The P388 lymphocytic leukaemia screen was carried out on CD_2F_1 (CDF_1) mice (female). On day 0, 1×10^6 ascites cells were injected intraperitoneally (ip). The drugs were suspended in saline with Tween-80 and administered ip once daily with the indicated dose (Table V), beginning on day 1 and ending on day 5. Six mice were used per test compound and a *T*/*C* of greater than 125% was considered significant activity against P388 tumour growth.

All the compounds were evaluated for antitumour activity against the P388 lymphocytic leukaemia test system in mice, and the screening data are reported in Table V. All the complexes do not show significant activity and are toxic at the doses used. This is a surprising finding as metal chelates of aroyl hydrazones, particularly copper(II) chelates, have been shown to be potent inhibitors of DNA synthesis and cell growth in a variety of human and rodent cell lines grown in culture [9, 10]. The antitumour activity of free XSBH ligands is not enhanced by coordination (Table V) with iron(II) and iron(III) ions.

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