Pergamon

0277-5387(94)00427-7

Polyhedron Vol. 14, No. 12, pp. 1641–1646, 1995

0277-5387/95 $9.50+0.00

SYNTHESIS AND CHARACTERIZATION OF CATIONIC BIS-AZIRIDINE COBALT(III) COMPLEXES CONTAINING SCHIFF BASE LIGANDS

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(*Received* 23 *August* 1994; *accepted* 5 *October* 1994)

Abstract—The syntheses of cationic bis-aziridine (Az) complexes, $[Co(SB)(Az)_2]Cl$, where SB is a Schiff base ligand (SB = acacen, salen, salpn, hapen, happn or saloph) by oxidation of cobalt(II) in basic solution containing the ligands are described. A corresponding series of methylamine complexes $[Co(SB)(CH_3NH_2)_2]Cl$ was also prepared (SB = acacen, salen, salpn, hapen or saloph). Both series of complexes were characterized by ^1H NMR spectroscopy, while the aziridine complexes and selected methylamine complexes were also investigated by ^{13}C NMR spectroscopy.

As part of our interest in the preparation of cobalt (III) complexes containing cytotoxic ligands,[1,2] we prepared several series of cobalt(III) aziridine complexes containing ammonia, amine or glyoximato ancillary ligands.[3,4] We have now extended this work to the synthesis of a set of new cationic cobalt (III) bis-aziridine complexes containing dianionic, tetradentate Schiff base ligands. One other report of the synthesis of cobalt(III) aziridine complexes has been made.[5]

Aziridine is a volatile, toxic and highly reactive molecule. During the development of synthetic routes to new aziridine complexes, it is useful to optimize reaction conditions using a less toxic and reactive ligand as an analogue of aziridine. In the present study, methylamine was used for this purpose, and a parallel series of cationic cobalt(III) bis-methylamine complexes containing the same Schiff base ligands are also reported here. Several of the methylamine complexes have been described in the older literature,[6,7] but without the full NMR spectroscopic characterization which is presented here.

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer Model 597 spectrometer using Nujol mulls between KBr discs. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker AM400 spectrometer operating at 400 and 100 MHz, respectively. Microanalyses were carried out by Dr R. Cunninghame and associates at the Department of Chemistry, University of Otago. Aziridine, prepared by published procedures,[8,9] was purified by repeated distillation from NaOH and was stored under N_2 over NaOH at 5 C. **CAUTION**: Aziridine is a highly toxic and volatile substance. All reactions involving aziridine were carried out under N_2 using Schlenk techniques in a well-ventilated fumehood. All aziridine residues were decomposed by treatment with aqueous HCl. The Schiff base ligands H_2acacen, H_2salen, H_2salpn, H_2hapen, H_2happn or H_2saloph were prepared from the reaction of the appropriate aldehyde or ketone and diamine in a 2:1 ratio in ethanol. The

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bis-methylamine complexes were prepared essentially as described below for the bis-aziridine complexes, except a methanolic solution of methylamine was used in place of aziridine.

Synthesis of [Co(acacen)$(Az)_2$]Cl

H_2acacen (0.12 g, 5 mmol) was dissolved in hot MeOH (30 cm^3) and solid KOH (0.56 g, 10 mmol) was added, followed by a solution of $CoCl_2 \cdot 6H_2O$ (1.19 g, 5 mmol) in hot MeOH (25 cm^3). A gelatinous green–brown precipitate rapidly formed. Aziridine (1.04 cm^3, 20 mmol) was then added with stirring, followed by H_2O_2 (2.8 cm^3 of a 3% aqueous solution, 2.5 mmol). This caused the rapid dissolution of the precipitate and the resulting mixture was left to stand at room temperature for 18 h. The dark brown precipitate which had formed was collected by filtration, washed with cold MeOH and hexane and recrystallized from hot MeOH. Yield

Table 1. ^{1}H NMR data for aziridine and methylamine complexes[a]

	H(2)	H(3)	H(4)	H(5)	H(7)	H(7′)	H(8)	H(9)	H(10)	Amine ligand	
Aziridine complexes										CH_2 (*syn*)	CH_2 (*anti*)
[Co(acacen)$(Az)_2$]Cl	2.28	5.09				2.08	3.63			1.10	1.51
	s	s				s	s			br d	br d
										(3.5)	—
[Co(salen)$(Az)_2$]Cl[b]	7.24	7.43	6.75	7.43	8.28		4.04			1.20	1.48
	d	m	t	m	s		s			br d	br d
	(8.8)		(7.3)							(3.9)	(3.9)
[Co(salpn)$(Az)_2$]Cl	7.22	7.37	6.76	7.37	7.89		3.82	2.43		1.32	1.62
	d	m	t	m	s		br p	br t		br d	br d
	(8.1)		(7.3)				(6)	(6)		—	—
[Co(hapen)$(Az)_2$]Cl	7.29	7.37	6.77	7.76		2.88	4.08			1.15	1.40
	d	t	t	d		s	s			br d	br d
	(8.4)	(7.6)	(7.5)	(8.2)						(4.1)	(4.1)
[Co(happn)$(Az)_2$]Cl	7.24	7.31	6.79	7.66		2.73	3.83	2.39		1.31	1.50
	d	t	t	d		s	t	br p		br d	br d
	(8.3)	(7.6)	(7.4)	(8.1)			(6.9)	(6.9)		(4.4)	(4.4)
[Co(saloph)$(Az)_2$]Cl	7.36	7.53	6.84	7.63	8.85			7.59	8.27	1.04	1.41
	d	t	t	d	s			dd	m	br d	br d
	(8.5)	(7.8)	(7.3)	(8.1)				—	—	(3.7)	(3.7)
Methylamine complexes										CH_3	NH_2
[Co(acacen)$(CH_3NH_2)_2$]Cl	2.25	5.14				2.10	3.62			1.58	2.86
	s	s				s	s			t	br q
										(6.4)	(6.4)
[Co(salen)$(CH_3NH_2)_2$]Cl	7.26	7.44	6.77	7.44	8.26		4.05			1.56	3.29
	d	m	t	m	s		s			t	br q
	(8.4)	[c]	(7.0)	[c]						(6.5)	(6.5)
[Co(salpn)$(CH_3NH_2)_2$]Cl	7.23	7.39	6.74	7.33	7.82		3.94	2.28		1.72	3.94
	d	t	t	d	s		br m	br p		t	br m
	(8.5)	(7.7)	(7.3)	(7.8)			[c]	(3.9)		(6.1)	[c]
[Co(hapen)$(CH_3NH_2)_2$]Cl	7.30	7.40	6.79	7.79		2.86	4.09			1.50	3.11
	d	t	t	d		s	s			t	br q
	(8.3)	(7.4)	(7.6)	(8.3)						(6.3)	(6.3)
[Co(saloph)$(CH_3NH_2)_2$]Cl	7.34	7.52	6.84	7.63	8.85			7.58	8.26	1.45	3.28
	d	t	t	d	s			dd	dd	t	br q
	(8.6)	—	(7.4)	(8.0)				—	—	(6.5)	(6.5)

[a] Data recorded in D_2O and referenced to internal DSS [3-(trimethylsilyl)-1-propanesulphonic acid, sodium salt]. Coupling constants in Hz given in parentheses. Multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

[b] Referenced using internal dioxane (3.75 ppm downfield from DSS).

[c] Overlapping peaks.

0.93 g, 46%. Found: C, 46.9; H, 7.3; N, 13.7. Calc. for $C_{16}H_{28}ClCoN_4O_2 \cdot 0.5H_2O$: C, 46.7; H, 7.1; N, 13.6%. IR (Nujol): ν(C=N) = 1610 cm^{-1}, δ(Az) = 890 cm^{-1}.

Synthesis of [Co(salen)(Az)$_2$]Cl

This complex was prepared as described for the acacen analogue using H_2salen (1.34 g, 5 mmol), KOH (0.28 g, 5 mmol), $CoCl_2 \cdot 6H_2O$ (0.59 g, 2.5 mmol), aziridine (0.78 cm^3, 15 mmol) and H_2O_2 (1.4 cm^3 of a 3% aqueous solution, 1.25 mmol). Yield 0.20 g, 18%. Found: C, 51.6; H, 5.5; N, 12.0. Calc. for $C_{20}H_{24}ClCoN_4O_2 \cdot H_2O$: C, 51.7; H, 5.6; N, 12.0%. IR (Nujol): ν(C=N) = 1625 cm^{-1}, δ(Az) = 890 cm^{-1}.

Synthesis of [Co(salpn)(Az)$_2$]Cl

This complex was prepared as described for the acacen analogue using H_2salpn (1.42 g, 5 mmol), KOH (0.56 g, 10 mmol), $CoCl_2 \cdot 6H_2O$(1.19 g, 5 mmol), aziridine (1.04 cm^3, 20 mmol) and H_2O_2 (2.8 cm^3 of a 3% aqueous solution, 2.5 mmol). Yield 0.18 g, 8%. Found: C, 53.8; H, 5.8; N, 11.9. Calc. for $C_{21}H_{26}ClCoN_4O_2 \cdot 0.5H_2O$: C, 53.7; H, 5.8; N, 11.9%. IR (Nujol): ν(C=N) = 1620 cm^{-1}, δ(Az) = 895 cm^{-1}.

Synthesis of [Co(hapen)(Az)$_2$]Cl

This complex was prepared as described for the acacen analogue using H_2hapen (1.48 g, 5 mmol), KOH (0.56 g, 10 mmol), $CoCl_2 \cdot 6H_2O$ (1.19 g, 5 mmol), aziridine (1.04 cm^3, 20 mmol) and H_2O_2 (2.8 cm^3 of a 3% aqueous solution, 2.5 mmol). Yield 1.02 g, 43%. IR (Nujol): ν(C=N) = 1600 cm^{-1}, δ(Az) = 890 cm^{-1}.

Synthesis of [Co(happn)(Az)$_2$]Cl

This complex was prepared as described for the acacen analogue using H_2happn (1.56 g, 5 mmol), KOH (0.56 g, 10 mmol), $CoCl_2 \cdot 6H_2O$ (1.19 g, 5 mmol), aziridine (1.04 cm^3, 20 mmol) and H_2O_2 (2.8 cm^3 of a 3% aqueous solution, 2.5 mmol). Yield 1.65 g, 68%. IR (Nujol): ν(C=N) = 1595 cm^{-1}, δ(Az) = 890 cm^{-1}.

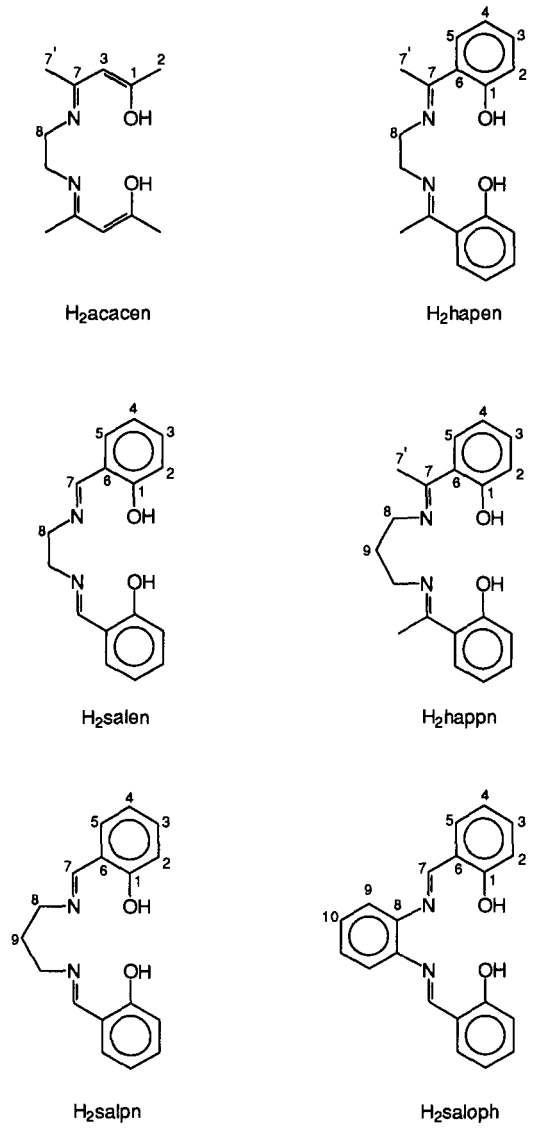
Synthesis of [Co(saloph)(Az)$_2$]Cl

This complex was prepared as described for the acacen analogue using H_2saloph (1.58 g, 5 mmol), KOH (0.56 g, 10 mmol), $CoCl_2 \cdot 6H_2O$ (1.19 g, 5 mmol), aziridine (1.04 cm^3, 20 mmol) and H_2O_2 (2.8 cm^3 of a 3% aqueous solution, 2.5 mmol). Yield 0.50 g, 20%. Found: C, 55.5; H, 5.0; N, 10.9. Calc. for $C_{24}H_{24}ClCoN_4O_2 \cdot 1.5H_2O$: C, 55.2; H, 5.2; N, 10.7%. IR (Nujol): ν(C=N) = 1605 cm^{-1}, δ(Az) = 895 cm^{-1}.

RESULTS AND DISCUSSION

The new cationic bis-aziridine Schiff base compounds [Co(SB)(Az)$_2$]Cl (SB = acacen, salen, salpn, hapen, happn or saloph) were prepared as the chloride salts by hydrogen peroxide oxidation of cobalt(II) in the presence of the required ligands. The Schiff base ligands are shown schematically below. When the Schiff base and cobalt(II) chloride are mixed in basic solution, a brown–red gelatinous precipitate of the cobalt(II) Schiff base complex forms immediately. This redissolves upon coordination of aziridine and oxidation to cobalt(III) by hydrogen peroxide. The products are red–brown in colour and are isolated by crystallization from the reaction mixture followed by recrystallization from methanol. All of the aziridine complexes were characterized by IR and ^{1}H and ^{13}C NMR spectroscopy, and by elemental analysis for SB = salen, salpn, saloph and acacen. For two of the compounds, where SB = hapen and happn, satisfactory elemental analyses could not be obtained. The formulation of these complexes was confirmed by comparison of their spectroscopic data with that of the other four bis-aziridine Schiff base complexes. In particular, the elemental analysis data for the two compounds are not consistent with aziridine loss before analysis. The NMR spectra of the complexes show no uncomplexed aziridine and are consistent with coordination of two aziridine ligands per complex, indicating that the poor analysis data do not result from decomposition of the complexes through loss of aziridine.

In order to establish suitable conditions for the preparation of the aziridine complexes, a series of bis-methylamine complexes, [Co(SB)(MeNH$_2$)$_2$]Cl (SB = salen, salpn, saloph, acacen, hapen or happn), were prepared. These complexes were characterized by comparison with the data given in the literature (for SB = acacen[6] and salen[6,7]), by ^{1}H NMR and by ^{13}C NMR for selected complexes. ^{1}H and ^{13}C NMR data for both the aziridine and methylamine complexes are given in Tables 1 and 2, respectively.



Scheme 1.

Aziridine is a volatile and highly reactive molecule that readily undergoes ring-opening reactions, particularly under acidic conditions. This required that the reactions be carried out under sufficiently basic conditions to preclude ring-opening. Each neutral Schiff base ligand releases two protons upon coordination to cobalt. For this reason the Schiff base ligands were deprotonated by treatment with a stoichiometric amount of KOH before addition of aziridine to the reaction mixture. Only a modest excess (two-fold) of aziridine is used in order to minimize exposure to unreacted aziridine during work-up and also to ensure use of the minimum amount of this toxic material, which is not commercially available.

Once coordinated to cobalt(III), the hazard posed by aziridine is reduced, primarily due to the lack of volatility of the complexes, but also due to

Table 2. ^{13}C NMR data for aziridine and methylamine complexes[a]

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(7′)	C(8)	C(9)	C(10)	Amine ligand
Aziridine complexes												
[Co(acacen)(Az)$_2$]Cl	180.62	27.20	97.63				171.96	24.37	55.10			22.08
[Co(salen)(Az)$_2$]Cl[b]	164.79	116.02	135.18	122.25	135.77	118.01	168.18		57.92			20.03
[Co(salpn)(Az)$_2$]Cl	167.54	119.13	137.01	124.70	138.25	122.40	172.09		58.71	27.78		24.02
[Co(hapen)(Az)$_2$]Cl[c]	167.41	118.61	133.81	125.91	136.69	123.48	177.79	22.31	56.83			22.73
[Co(happn)(Az)$_2$]Cl	166.31	114.33	131.09	123.19	132.54	123.62	174.31	19.02	47.85	24.91		21.40
[Co(saloph)(Az)$_2$]Cl[d]	168.51	119.41	139.03	125.21	139.88	120.14	163.24		145.56	119.60	131.96	22.56
Methylamine complexes												
[Co(salpn)(CH$_3$NH$_2$)$_2$]Cl	165.97	119.03	137.57	124.25	138.74	120.11	173.51		63.19	28.82		30.49
[Co(hapen)(CH$_3$NH$_2$)$_2$]Cl	168.16	118.91	134.00	126.08	136.86	123.03	179.09	22.49	57.18			29.49

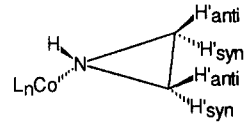
[a] Data recorded in D_2O and referenced to internal DSS [3-(trimethylsilyl)-1-propanesulphonic acid, sodium salt], except where noted.
[b] Referenced to internal dioxane (66.6 ppm downfield from DSS).
[c] Recorded in DMSO-d_6 solvent and referenced to internal TMS.
[d] Chemical shifts of C(2), C(9) and C(3), C(5) are very close and assignments within each pair could not be determined.

suppression of the usual reactivity of aziridine. The cobalt(III) aziridine complexes can thus be handled with no special precautions. Aziridine can still be released by reduction to cobalt(III), which we have shown for other cobalt(III) aziridine complexes can occur in mammalian cell culture.[3] Free aziridine is a potent alkylating agent, reacting via nucleophilic attack by a suitable electrophile, leading to ring-opening. If the electrophile is a nucleobase from DNA, the ring opening sequence leads to aminoethyl alkylation of the DNA, and this event is the origin of the toxic and mutagenic properties of aziridine. While coordinated to a metal, the ring-opening reactivity of aziridine is suppressed and the toxic alkylation sequence is prevented.

The presence of intact aziridine ligands in the bis-aziridine complexes was confirmed by a characteristic medium strong band near 890 cm^{-1} in their IR spectra, which is assigned to δ(Az), a deformation of the coordinated aziridine ring.[10] In addition, ν(N—H) of the coordinated aziridine ligands ranged between 3350 and 3420 cm^{-1}. Bands resulting from vibrations of the coordinated Schiff base ligands were also observed. It has previously been recognized[11] that the assignment of the IR spectra of Schiff base ligands, both free and complexed, is difficult due to the complexity of the spectra and the extensive coupling of vibrational modes present. A study of ^{15}N labelled *N*-aryl-salicylideneimines and their copper(II), zinc(II) and cobalt(II) complexes, though, has allowed a number of assignments to be made with some confidence. Three bands are observed in the range 1550–1660 cm^{-1}, which have been assigned to ν(C=C) ν(C=N) and ν(C=N), though clearly all are extensively coupled. The higher energy ν(C=N) band was found to shift consistently *ca* 20 cm^{-1} to lower energy upon coordination.[12] A similar shift in this band to lower energy was observed for the complexes in this study. For example, $[Co(happn)(Az)_2]^+$ has ν(C=N) = 1595 cm^{-1}, while for the free ligand ν(C=N) = 1610 cm^{-1}. The positions of these ν(C=N) bands in addition to the δ(Az) bands are reported in the Experimental section.

The ^1H and $^{13}C\{^1H\}$ NMR spectra of the aziridine complexes are consistent with an aziridine : Schiff base ratio of 2 : 1. The two aziridine ligands in each complex are equivalent and the Schiff base ligands retain idealized D_{2h} symmetry. This indicates that the complexes have adopted *trans* geometry, with the Schiff base ligands occupying the equatorial sites and the aziridine ligands in equivalent *trans* axial positions. In addition, the aziridine ligands are rotating freely on the NMR time scale.

The two pairs of chemically equivalent protons



on the aziridine ring are defined as H_{syn} and H_{anti} (where H_{syn} is on the same side of the aziridine ring as the cobalt atom). Inversion at nitrogen is suppressed on coordination of aziridine to cobalt.[3] N—H exchange, which appears to be the dominant mechanism for inversion in uncoordinated aziridine,[13] is greatly retarded due to the unavailability for protonation of the lone pair on nitrogen. The H_{syn} and H_{anti} protons exhibit non-first-order coupling and appear as two multiplets with different splitting patterns, primarily due to the different NH–H_{syn} and NH–H_{anti} coupling constants in the AA′MM′X spin system. The aziridine CH resonances are assigned by comparison with those in the cobalt(III) aziridine complexes containing amine ligands, with the H_{syn} resonance appearing upfield of the H_{anti} resonance.[3] Exchange of the NH proton of the coordinated aziridine ligand in D_2O results in simplification of the H_{syn} and H_{anti} multiplets, which become identical in form (A_2X_2 spin system). In the methylamine complexes, coupling of the methylamine CH_3 group to the NH_2 protons is observed, even when D_2O is the solvent, indicating that the methylamine NH protons are much slower to exchange than are the aziridine NH protons.

The two carbons atoms of the coordinated aziridine are equivalent and give rise to only one resonance in the ^{13}C NMR spectra due to free rotation about the Co—N_{Az} bond and the symmetric nature of the Schiff base ligands. The Schiff base ligand ^1H and ^{13}C NMR assignments given in Tables 1 and 2 were based on previous NMR studies of Schiff base complexes.[14–17]

Acknowledgement—D.C.W. is grateful to the Cancer Society of New Zealand for financial support.

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