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Synthesis and Characterization of Aziridine Complexes of Cobalt(III) and Chromium(III) Designed as Hypoxia-Selective Cytotoxins. X-ray Crystal Structure of *trans*-$[Co(Az)_4(NO_2)_2]Br\cdot 2H_2O\cdot LiBr$

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The synthesis of a series of cobalt(III) and chromium(III) aziridine complexes designed as potential hypoxia-selective anticancer drugs is reported. Direct substitution of an aziridine (Az) ligand for a halide ligand was achieved by reaction of *cis*-$[Co(en)_2Cl_2]Cl$ (en = ethylenediamine), *cis*-$[Co(NH_3)(en)_2Br]Br_2$, or *cis*-$[Co(trien)Cl_2]Cl$ (trien = triethylenetetramine) in neat aziridine, producing *cis*-$[Co(en)_2(Az)Cl]Cl_2$ (**1**), *cis*-$[Co(NH_3)(en)_2(Az)]Br_3$ (**2**), or *cis*-$[Co(trien)(Az)Cl]Cl_2$ (**3**), respectively. *trans*-$[Co(Az)_4(NO_2)_2]Br\cdot 2H_2O\cdot LiBr$ (**4c**) was prepared similarly from $Na_3[Co(NO_2)_6]$. New triflato (trifluoromethanesulfonato) complexes *cis*-$[Co(NH_3)_4(OSO_2CF_3)_2](OSO_2CF_3)$ (**5**), *mer*-$[Co(NH_3)_3(OSO_2CF_3)_3]$ (**6**), and *cis*-$[Co(NH_3)(en)_2(OSO_2CF_3)](OSO_2CF_3)_2$ (**7**) were prepared by treatment of the corresponding halide complexes with neat triflic acid. The triflato ligands in **5** and **7** were substituted by aziridine to give *cis*-$[Co(NH_3)_4(Az)_2]Cl_3$ (**10**) and **2**, respectively, and $[Co(NH_3)_5(Az)]Cl_3$ (**8**), *cis*-$[Co(en)_2(Az)_2]Br_3$ (**9**), and $[Cr(NH_3)_5(Az)](OSO_2CF_3)_3$ (**11**) were produced similarly from known triflato complexes. All the aziridine complexes were fully characterized. In particular, ^1H and ^{13}C NMR spectroscopy allowed complete assignment of the stereochemistry. A single-crystal X-ray analysis showed *trans*-tetrakis(aziridine)dinitrocobalt(III) bromide–lithium bromide dihydrate (**4c**) to crystallize in the orthorhombic space group *Ccca* with cell constants $a = 9.121$ (2) Å, $b = 15.836$ (2) Å, $c = 12.764$ (1) Å, $V = 1836.7$ (5) Å^3, and $Z = 4$. The structure was refined to $R = 0.023$ ($R_w = 0.027$) for 858 reflections with $F_o^2 > 3\sigma F_o^2$. Cyclic voltammetry of **1**, **2**, **4**, **8**, and **10** showed that the Co(III) complexes were reduced to Co(II) species in an irreversible process even at fast scan rates. Testing of the complexes in a hypoxic cell culture indicated facile reduction of the cobalt(III) center and release of aziridine.

Introduction

Transition-metal complexes containing coordinated aziridine were first reported from the research group of Edwards between 1961 and 1968.[1,2] In the intervening period since then there has been little interest in complexes of this small, highly strained heterocycle. The limited development of transition-metal aziridine chemistry may arise in part from the difficulties in working with this volatile and highly toxic substance. The strained, three-membered heterocycle is a highly reactive molecule that readily undergoes ring-opening reactions, particularly under acid conditions. However, once coordinated to an inert metal center such as Co(III) or Cr(III), the reactivity of aziridine toward nucleophiles is much diminished and the heterocycle is stabilized with respect to ring-opening reactions.

We are interested in the use of metal complexes of aziridine as potential hypoxia-selective drugs. The majority of solid tumors (both in humans and experimental animals) contain a proportion of cells that are either chronically or transiently hypoxic due to the immature nature of the neoplastic vasculature and to compression of this by the growing tumor.[3] These cells are particularly resistant to most drugs for a variety of reasons including their quiescent state,[4] reversed transmembrane pH gradient,[5] and inaccessibility to drugs.[6] The refractory nature of such hypoxic cells and the fact that the hypoxic environment is essentially restricted to the tumor since nearly all normal tissue is well perfused provide considerable incentive for the development of drugs that are selectively toxic to such hypoxic cells. For these reasons, there has been recent interest in the design of electrophilic agents that can be activated by oxygen-inhibited cellular reduction processes only in hypoxic environments, for example nitrophenyl carbamates[7] and nitrophenyl mustards.[8] Activation of these compounds depends on oxygen-reversible, one-electron reduction of the nitro group.

Our interest in transition-metal aziridine complexes stems from their potential as a means of selectively targeting hypoxic tumor cells. Free aziridine is a potent alkylating agent and is active toward substrates such as DNA, suggesting applications for aziridine chemistry in cancer chemotherapy. A number of organic molecules containing the aziridine moiety are used as anticancer agents,[9] for example the drug Thiotepa (tris(aziridin-1-yl)phosphine sulfide). This relatively stabilized form of aziridine relies on hydrolysis to release to the potent alkylator aziridinium ion.[10] A possible method for masking the reactivity of small cytotoxic molecules like aziridine is to complex them to suitable metal ions. The widely differing lability of coordination complexes of Co(III) and Co(II), the reduction potential of the Co(III)/Co(II) couple, and the well-established coordination chemistry of cobalt led us to choose this metal for our investigations. Whereas the metal complex in the +III oxidation state is substitutionally inert, one-electron reduction of the complex to the +II state provides an enormous enhancement in lability, resulting in release of the cytotoxic ligand. This is the basis for the hypoxia-selective mechanism. Chromium shares these favorable characteristics and may also be useful for this application. In this paper we explore the preparation and characterization of a series of cobalt(III) aziridine complexes and one example of a Cr(III) complex as potential hypoxia-selective drugs.

We have prepared several of the cobalt aziridine complexes first reported by Edwards, most by modified syntheses. These complexes were originally characterized by elemental analysis and by UV–visible and IR spectroscopy, which were sufficient to confirm the composition, but assignment of the stereochemistry remained incomplete.[1] In addition, we describe the preparation of a number of new cobalt aziridine complexes, some of which have been prepared by displacement of the labile triflato ligand from suitable cobalt precursor complexes. Several of these triflato complexes are reported here for the first time and may be useful

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Table I. Crystallographic Data for *trans*-$[Co(Az)_4(NO_2)_2]Br\cdot 2H_2O\cdot LiBr$ (**4c**)

formula	$C_8H_{24}Br_2CoLiN_6O_6$	Z	4
M_r	526.00	T/°C	22
space group	Ccca (No. 68, origin at $\bar{1}$)	λ/Å	0.71069
a/Å	9.121(2)	μ/cm^{-1}	62.0
b/Å	15.836(2)	transm coeff	0.87–1.00
c/Å	12.764(1)	R^a	0.023
V/Å^3	1836.7(5)	R_w^b	0.027
ρ_{calcd}/g·cm^{-3}	2.91		

$^a R = \sum||F_o| - |F_c||/\sum|F_o|$. $^b R_w = [\sum_w(|F_o| - |F_c|)^2/\sum_w|F_o|^2]^{1/2}$; $w = 2.7813/[\sigma^2(F_o) + 0.000695F_o^2]$.

as precursors for the rational synthesis of other cobalt complexes. All the complexes, which contain one, two, or four aziridine ligands in the coordination sphere, are fully characterized, and ^1H and ^{13}C NMR studies have allowed complete assignment of the stereochemistry. For two complexes, computer simulation of the experimental ^1H NMR spectra has allowed calculation of the non-first-order coupling constants for the aziridine ring protons. In addition the tetrakis(aziridine) complex *trans*-$[Co(Az)_4(NO_2)_2]Br\cdot 2H_2O\cdot LiBr$ has been the subject of an X-ray crystal structure determination. The preparation of a pentaammine chromium aziridine complex is also reported.

Experimental Section

Reagents and Physical Measurements. All chemicals were reagent grade and were used as received. Chloroform was dried by distillation from CaH_2 and stored over molecular seives. Anhydrous trifluoromethanesulfonic acid was obtained from 3M. The following compounds were prepared by literature procedures:[11] $[Co(NH_3)_5Cl]Cl_2$,[12] *cis*-$[Co(NH_3)_4(H_2O)Cl]Cl_2$,[13] *cis*-$[Co(NH_3)_4(CO_3)]Cl$,[13] *cis*-$[Co(en)_2(CO_3)]Cl$,[14] *mer*-$[Co(NH_3)_3(H_2O)Cl_2]Cl$,[15] *cis*-$[Co(en)_2(NH_3)Br]Br_2\cdot H_2O$,[16] *cis*-$[Co(trien)Cl_2]Cl$,[17] *trans*-$[Co(en)_2Cl_2]Cl$,[18] $[Co(NH_3)_5(OSO_2CF_3)](CF_3SO_3)_2$,[19] $[Co(en)_2(OSO_2CF_3)_2](CF_3SO_3)$,[19] $[Cr(NH_3)_5(OSO_2CF_3)](CF_3SO_3)_2$.[20] The ion exchange media used were Amberlite IRA 401 (Cl^- form) and Sephadex-SP, C-25 (H^+ form).

Aziridine was prepared from 2-aminoethanesulfonic acid[21] by using a flash distillation modification[22] of the Wenker procedure, and was purified by repeated distillation from NaOH and stored over NaOH in a Schlenk storage flask at 5 °C. *Caution! Aziridine is a volatile* (bp = 56 °C; vapor pressure at 20 °C = 160 torr) *and highly toxic* (LD_{50} = 5 mg·kg^{-1}, orally in rabbits)[23] *substance which must be handled with extreme care.* All reactions involving aziridine were carried out under N_2 by using Schlenk techniques in a well-ventilated fume hood. Transfers of aziridine from the Schlenk storage flask were carried out with gastight syringes. Excess aziridine removed from reaction mixtures was destroyed by treatment with acid, and all contaminated glassware was soaked in an acid bath.

Melting points were determined on a Reichert Kofler apparatus and are uncorrected. Elemental analyses were performed by Dr. R. G. Cunninghame and associates at the University of Otago, Dunedin, New Zealand. UV–visible spectra were recorded on a Varian DMS-100 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 5979 infrared spectrophotometer as KBr disks. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker AM 400 spectrometer. Proton chemical shifts are relative to internal $SiMe_4$ in DMSO-d_6. Carbon chemical shifts are referenced to internal dioxane at 69.27 ppm or acetone at 32.93 ppm, relative to DSS (3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt) in D_2O. Computer simulations of ^1H NMR spectra were performed on a Bruker ASPECT 3000 computer using the PANIC program supplied by Bruker. Cyclic voltammetry was performed on a Princeton Applied Research 173 potentiostat/galvanostat in conjunction with a Model 175 universal programmer. A three-electrode configuration was used with platinum or wax-impregnated graphite working and platinum-coil auxilliary electrodes and a saturated calomel reference electrode in N_2-purged phosphate buffer medium (0.1 mol·L^{-1}) at pH 7.

Table II. Positional Parameters with Estimated Standard Deviations for *trans*-$[Co(Az)_4(NO_2)_2]Br\cdot 2H_2O\cdot LiBr$ (**4c**)[a]

atom	x	y	z
Br	0.75	0.00	0.62901 (3)
Co	0.50	0.75	0.25
N(1)	0.4959 (2)	0.6589 (1)	0.1459 (1)
C(1)	0.6105 (3)	0.5959 (2)	0.1180 (2)
C(2)	0.5591 (4)	0.6558 (2)	0.0386 (2)
N(2)	0.7116 (3)	0.75	0.25
O(1)	0.7813 (2)	0.7641 (1)	0.1683 (1)
O(2)	0.00	0.1232 (2)	0.75
Li	0.00	0.75	0.25
H(1a)	0.577 (4)	0.538 (3)	0.115 (2)
H(1b)	0.708 (4)	0.608 (2)	0.144 (2)
H(2a)	0.491 (4)	0.630 (2)	−0.010 (3)
H(2b)	0.631 (4)	0.706 (3)	0.022 (3)
H(O)	0.929 (4)	0.593 (2)	0.282 (3)
H(N)	0.426 (4)	0.635 (2)	0.151 (3)

[a] Parameters without standard deviations are fixed by crystallographic symmetry.

All diffraction data for the structure determination of *trans*-$[Co(Az)_4(NO_2)_2]Br\cdot 2H_2O\cdot LiBr$ (**4c**) were collected on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Mo Kα (λ = 0.71069 Å) radiation. The structure was solved by using the SHELX-86 and SHELX-76 programs and refined to final residuals R = 0.023, R_w = 0.027. Crystallographic data are given in Table I and positional parameters are given in Table II. Further crystallographic data and details of the structure solution are given in the supplementary material, together with the atomic thermal parameters and the observed and calculated structure factors.

Synthesis. ***cis*-$[Co(en)_2(Az)Cl]Cl_2\cdot H_2O$ (1).** Acid-free *trans*-$[Co(en)_2Cl_2]Cl$ (1.51 g, 5.26 mmol) was stirred in a Schlenk tube under nitrogen while ice-cold aziridine (2.0 mL, 38.6 mmol) was added carefully. The green starting material dissolved immediately to give a dark red viscous solution. Removal of the excess aziridine under reduced pressure gave a red-pink powder, which was filtered, washed well with diethyl ether, and dried in vacuo over P_2O_5. Yield = 1.40 g (93%). Recrystallization by vapor diffusion of ethanol into water afforded large red-purple crystals, mp 218–219 °C. Anal. Calcd for $C_6H_{23}Cl_3CoN_5O$: C, 20.79; H, 6.69; N, 20.21. Found: C, 20.84; H, 7.00; N, 20.05. UV–visible: λ_{max} (ϵ/L·mol^{-1}·cm^{-1}) 522 (74), 363 (81) nm.

***cis*-$[Co(NH_3)(en)_2(Az)]Br_3\cdot EtOH$ (2).** (a) Solid *cis*-$[Co(NH_3)(en)_2Br]Br_2\cdot H_2O$ (0.86 g, 1.90 mmol) was stirred under nitrogen and cooled in a dry ice/acetone bath while aziridine (1.0 mL, 19.32 mmol) was carefully added. The purple solution was warmed to room temperature and stirred for 6 h, after which time a color change to orange was observed. The solution was stirred vigorously while ethanol and diethyl ether were slowly added simultaneously. An orange precipitate formed, which was filtered, washed with ether, and dried in vacuo over P_2O_5 to give an orange powder. Yield = 0.93 g (97%). Recrystallization from water/ethanol yielded small orange crystals of the product.

(b) The addition of aziridine (0.8 mL, 15.45 mmol) to *cis*-$[Co(NH_3)(en)_2(OSO_2CF_3)](CF_3SO_3)_2$ (**7**) (0.31 g, 0.49 mmol) gave *cis*-$[Co(NH_3)(en)_2(Az)](CF_3SO_3)_3$ as an orange powder. Yield = 0.23 g (68%). Purification and counterion metathesis to give the bromide salt (**2**) was effected by chromatography on Sephadex (H^+ form). An orange band containing the product was eluted using 0.3 mol·L^{-1} HBr. The solvent was removed under reduced pressure and the orange residue was recrystallized from water/ethanol to yield small orange crystals, mp > 250 °C. Anal. Calcd for $C_8H_{30}Br_3CoN_6O$: C, 18.30; H, 5.76; N, 16.01. Found: C, 18.46; H, 5.90; N, 16.98. UV–visible: λ_{max} (ϵ/L·mol^{-1}·cm^{-1}) 475 (78), 331 (157) nm.

***cis*-$[Co(trien)(Az)Cl]Cl_2\cdot H_2O$ (3).** Reaction of aziridine (1.5 mL, 29.02 mmol) and *cis*-$[Co(trien)Cl_2]Cl$ (0.40 g, 1.29 mmol) by the same method used for **2** gave a hygroscopic red-brown solid (0.28 g). The product was purified by chromatography on Sephadex cation-exchange resin (H^+ form), and was eluted as a red band with 0.2 mol·L^{-1} HCl. The removal of solvent under reduced pressure followed by recrystallization

(11) Abbreviations: Az, aziridine; en, ethylenediamine; trien, triethylenetetramine.
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of the residue from water/ethanol gave large red-purple crystals, mp 241–243 °C. Anal. Calcd for $C_8H_{25}Cl_3CoN_8O$: C, 25.79; H 6.76; N, 18.79. Found: C, 25.95; H, 6.86; N, 18.30. UV–visible: λ_{max} (ϵ/L·mol^{-1}·cm^{-1}) 527 (80), 366 (81) nm.

***trans*-[Co(Az)$_4$(NO$_2$)$_2$]ClO$_4$ (4b) and *trans*-[Co(Az)$_4$(NO$_2$)$_2$]Br·LiBr·2H$_2$O (4c).** Sodium hexanitrocobaltate(III) (0.85 g, 2.09 mmol) and aziridine (1.0 mL, 19.32 mmol) were placed in a stoppered 25 mL round-bottomed flask and kept at room temperature for 8 h with occasional stirring. The flask was then cooled at 5 °C for 1 week. The complex slowly dissolved to give a brown solution, and crystals of sodium nitrite separated. Ethanol (10 mL) was added, allowing $NaNO_2$ and unreacted $Na_3[Co(NO_2)_6]$ to be removed by filtration. The addition of diethyl ether to the brown filtrate afforded *trans*-[Co(Az)$_4$(NO$_2$)$_2$]NO$_2$ (**4a**) as an orange-yellow microcrystalline solid, which was filtered, washed with diethyl ether and dried in vacuo over P_2O_5. Yield = 0.32 g (41%).

Purification of **4a** (60 mg) and counterion metathesis to form the perchlorate salt **4b** was effected by chromatography on Sephadex resin (Na^+ form). The product (**4b**) was eluted rapidly with 0.3 mol·L^{-1} $NaClO_4$. The solvent was removed at reduced pressure until the formation of crystals was apparent. On cooling, fine orange-yellow crystals were deposited, which were collected by filtration, washed with ethanol, and dried in vacuo over P_2O_5. Yield = 48 mg (80%). Anal. Calcd for $C_8H_{20}ClCoN_6O_8$: C, 22.73; H, 4.77; N, 19.88; Cl, 8.39. Found: C, 22.50; H, 4.91; N, 20.15; Cl, 8.35.

Recrystallization and conversion to the bromide salt (**4c**) was achieved by dissolving **4a** (50 mg) in a minimum volume of water, and adding excess lithium bromide (1 g). After the mixture was allowed to stand for a week, large orange crystals of *trans*-[Co(Az)$_4$(NO$_2$)$_2$]Br·2H$_2$O·LiBr (**4c**) formed; mp 131 °C dec. Anal. Calcd for $C_8H_{24}Br_2CoLiN_6O_6$: C, 18.27; H, 4.60; N, 15.97; Br, 30.38. Found: C, 17.78; H, 4.73; N, 15.48; Br, 30.64.

***cis*-[Co(NH$_3$)$_4$(OSO$_2$CF$_3$)$_2$](CF$_3$SO$_3$) (5).** Anhydrous CF_3SO_3H (8 mL) was added to solid *cis*-[Co(NH$_3$)$_4$(H$_2$O)Cl]Cl$_2$ (2.04 g, 8.10 mmol) in a 25-mL three-necked round-bottomed flask. A nitrogen inlet was connected to the reaction flask, which was lowered into an oil bath and heated at 100 °C for 6 h with gentle bubbling of nitrogen. The flask was removed from the oil bath and allowed to cool to room temperature with nitrogen still passing through the solution. The gas flow was disconnected, and the solution was poured into a 400-mL flask. The purple product was precipitated by the slow addition of diethyl ether (200 mL) with stirring. (*Caution*! exothermic process. The addition of ether must be performed slowly with vigorous stirring.) The product was collected on a fine-porosity sintered-glass funnel, initially under gravity and then under suction. The product was washed well with diethyl ether and then briefly air dried. The solid was immediately transferred to a 50-mL round-bottomed flask and refluxed in dry chloroform (20 mL) for 10 min. After filtration and washing with ether, the purple product was ground with a mortar and pestle and dried in a vacuum desiccator over P_2O_5. Yield = 3.72 g (80%). Mp: 140–141 °C. Anal. Calcd for $C_3H_{12}CoF_9N_4O_9S_3$: C, 6.27; H, 2.11; N, 9.76. Found: C, 6.12; H, 2.75; N, 9.18. Compound **5** could also be produced by using [Co(NH$_3$)$_4$(CO$_3$)]Cl as the reagent in the above procedure. However, a lower yield (23%) was obtained.

***mer*-Co(NH$_3$)$_3$(OSO$_2$CF$_3$)$_3$ (6).** Anhydrous CF_3SO_3H (5.0 mL) was cautiously added to recrystallized mer-[Co(NH$_3$)$_3$(H$_2$O)Cl$_2$]Cl (0.80 g, 3.4 mmol) in a 10-mL round-bottomed flask. The reaction was carried out as described for **5** (90 °C, 5 h). The resulting purple powder was dried in vacuo over P_2O_5. Yield = 1.56 g (82%). Mp: >250 °C. Anal. Calcd for $C_3H_9CoF_9N_3O_9S_3$: C, 6.47; H, 1.63; N, 7.54. Found: C, 6.29; H, 1.66; N, 7.42.

***cis*-[Co(NH$_3$)(en)$_2$(OSO$_2$CF$_3$)](CF$_3$SO$_3$)$_2$ (7).** Anhydrous CF_3SO_3H (6.0 mL) was added carefully to solid *cis*-[Co(NH$_3$)(en)$_2$Br]Br$_2$·H$_2$O (1.56 g, 3.45 mmol) in a 10-mL round-bottomed flask and the reaction carried out as described for **5** (105 °C, 4.5 h). The pink product was collected, purified, and dried as above. Yield = 1.59 g (72%). Mp: 192–193.5 °C. Anal. Calcd for $C_7H_{19}CoF_9N_5O_9S_3$: C, 12.43; H, 3.50; N, 10.63. Found: C, 13.08; H, 2.98; N, 10.89.

[Co(NH$_3$)$_5$(Az)]Cl$_3$·0.5H$_2$O (8). Solid [Co(NH$_3$)$_5$(OSO$_2$CF$_3$)](CF$_3$SO$_3$)$_2$ (0.5 g, 0.85 mmol) was stirred in a Schlenk tube under nitrogen, while aziridine (0.9 mL, 17.4 mmol) was carefully added by syringe. There was immediate dissolution to give an orange solution, which was stirred for 1 h. Excess aziridine was removed under reduced pressure. The resulting orange solid was dissolved in methanol, and the triflate salt [Co(NH$_3$)$_5$(Az)](CF$_3$SO$_3$)$_3$ was precipitated as a flocculent orange solid by the slow addition of diethyl ether. The product was collected, washed with ether, and dried in vacuo over P_2O_5. Yield = 0.47 g (87%). Counterion metathesis to form the chloride salt **8** was accomplished by passing an aqueous solution of the crude triflate salt through an anion-exchange column (Cl^- form). The resulting solution was concentrated under reduced pressure and then cooled to 5 °C. Addition of ethanol resulted in the immediate formation of an orange powder, which was removed by filtration, washed with diethyl ether, and dried in vacuo over P_2O_5. The chloride salt **8** was then purified by chromatography on Sephadex resin (H^+ form). The product, an orange band, was eluted with 0.3 mol·L^{-1} HCl. The solvent was removed under reduced pressure, and the orange residue was recrystallized by vapor diffusion of ethanol into water to give orange needles, mp 198–200 °C. Anal. Calcd for $C_2H_{21}Cl_3CoN_6O_{0.5}$: C, 8.07; H, 7.15; N, 27.54. Found: C, 7.94; H, 7.00; N, 27.78. UV–visible: λ_{max} (ϵ/L·mol^{-1}·cm^{-1}) 476 (54), 341 (48) nm.

***cis*-[Co(en)$_2$(Az)$_2$]Br$_3$·H$_2$O (9b).** Powdered *cis*-[Co(en)$_2$(OSO$_2$CF$_3$)$_2$](CF$_3$SO$_3$) (0.20 g, 0.33 mmol) was stirred in a Schlenk tube under nitrogen and cooled in a dry ice/acetone bath while aziridine (0.5 mL, 9.66 mmol) was added slowly. The reaction mixture changed color from purple to orange on warming to room temperature. After the mixture was stirred for 2 h, ethanol and diethyl ether were added to precipitate the triflate salt *cis*-[Co(en)$_2$(Az)$_2$](CF$_3$SO$_3$)$_3$ (**9a**) as a brown solid. Counterion metathesis to form the bromide salt (**9b**) was achieved by the application of an aqueous solution of the triflate salt to an Amberlite anion-exchange column (Br^- form). The resulting solution was concentrated under reduced pressure. The addition of ethanol and cooling on ice caused a pale orange powder to precipitate. The product was filtered, washed with diethyl ether, and dried in vacuo over P_2O_5. Yield = 82 mg (48%). Recrystallization by vapor diffusion of ethanol into water yielded bright orange crystals of the product, mp 190–191 °C. Anal. Calcd for $C_8H_{28}Br_3CoN_6O$: C, 18.37; H, 5.40; N, 16.07. Found: C, 19.07; H, 5.65; N, 15.76. UV–visible: λ_{max} (ϵ/L·mol^{-1}·cm^{-1}) 475 (97), 335 (146) nm.

***cis*-[Co(NH$_3$)$_4$(Az)$_2$]Cl$_3$·0.5H$_2$O (10).** Solid *cis*-[Co(NH$_3$)$_4$(OSO$_2$CF$_3$)$_2$](CF$_3$SO$_3$) (**5**) (1.12 g, 1.95 mmol) was stirred in a Schlenk tube under nitrogen while aziridine (0.6 mL, 11.6 mmol) was added by syringe. The purple starting material dissolved immediately to give an orange solution. The excess aziridine was removed under reduced pressure to give an orange-brown oil. The oil was dissolved in methanol, and upon addition of diethyl ether, an orange powder precipitated, which was filtered rapidly, washed with diethyl ether, and dried in vacuo over P_2O_5. Yield = 0.95 g (86%). Recrystallization from hot acetone/ethanol gave the triflate salt *cis*-[Co(NH$_3$)$_4$(Az)$_2$](CF$_3$SO$_3$)$_3$ as an orange microcrystalline material. Purification and conversion to the chloride salt **10** was achieved by chromatography on Sephadex cation-exchange resin (H^+ form). An initial pink band was eluted slowly with 0.2 mol·L^{-1} HCl and more rapidly with 0.3 mol·L^{-1} HCl. An orange band also eluted in 0.3 mol·L^{-1} HCl, but more slowly than the pink band. The solvent was removed under reduced pressure, and the orange residue was recrystallized by vapor diffusion of ethanol into water to give the product (**10**) as orange needles, mp >250 °C. Anal. Calcd for $C_4H_{23}Cl_3CoN_6O_{0.5}$: C, 14.62; H, 7.06; N, 25.58. Found: C, 14.18; H, 7.11; N, 25.57. UV–visible: λ_{max} (ϵ/L·mol^{-1}·cm^{-1}) 479 (68), 343 (61) nm.

[Cr(NH$_3$)$_5$(Az)](CF$_3$SO$_3$)$_3$ (11). [Cr(NH$_3$)$_5$(OSO$_2$CF$_3$)](CF$_3$SO$_3$)$_2$ (0.20 g, 0.342 mmol) was placed in a Schlenk tube and cooled in a dry ice/ethanol bath (−72 °C). Aziridine (0.5 mL, 9.66 mmol) was added with stirring, and the solution was allowed to warm slowly to room temperature. The color changed rapidly from red-pink to yellow-orange. After the mixture was stirred at room temperature for 5 min, ether (10 mL) was added dropwise with vigorous stirring, and a yellow-orange microcrystalline solid formed. This was washed with ether and dried in vacuo over P_2O_5. Yield = 0.19 g (89%). Anal. Calcd for $C_5H_{20}CrF_9N_6O_9S_3$: C, 9.57; H, 3.21; N, 13.39. Found: C, 11.16; H, 3.43; N, 13.09.

Results and Discussion

Syntheses. The simplest approach to the synthesis of cobalt aziridine complexes is to stir a preformed cobalt(III) coordination complex or a cobalt(III) salt in neat aziridine. (The heterocycle is a liquid with a boiling point of 56 °C.) This results in substitution of one or more ligands in the precursor complex by aziridine ligands. The rather low substitutional lability of cobalt(III) means that reaction times can be long, depending on the substrate, and for some potential precursor complexes, this route is unsuccessful. Using as substrates *cis*-[Co(en)$_2$Cl$_2$]Cl, *cis*-[Co(NH$_3$)(en)$_2$Br]Br$_2$, *cis*-[Co(trien)Cl$_2$]Cl, and Na$_3$[Co(NO$_2$)$_6$], we produced the aziridine complexes *cis*-[Co(en)$_2$(Az)Cl]Cl$_2$ (**1**) (93% yield), *cis*-[Co(NH$_3$)(en)$_2$(Az)]Br$_3$ (**2**) (97%), *cis*-[Co(trien)(Az)Cl]Cl$_2$ (**3**) (62%), and trans-[Co(Az)$_4$(NO$_2$)$_2$]NO$_2$ (**4a**) (41%), respectively, by this method.

The complexes were isolated from the reaction mixture either by removal of the aziridine solvent, or by precipitation from aziridine solution by addition of ethanol/ether. Purification was

Table III. IR Data (cm^{-1})[a]

compound no.	compound formula	ν(NH)[b]	δ(NH)[c]	δ(Az)[c]	other bands[d]
1	*cis*-$[Co(en)_2(Az)Cl]Cl_2$	3150	1620	893	
2	*cis*-$[Co(NH_3)(en)_2(Az)]Br_3$	3120	1578	891	
3	*cis*-$[Co(trien)(Az)Cl]Cl_2$	3100	1593	885	
4a	*trans*-$[Co(Az)_4(NO_2)_2]NO_2$	3188	1633	882	$\nu_{as}(NO_2)$ 1417 m $\nu_s(NO_2)$ 1271 s
5	*cis*-$[Co(NH_3)_4(OSO_2CF_3)_2]CF_3SO_3$	3200	1610		$\nu(CF_3SO_3)$(coord) 1400 s $\nu(CF_3SO_3)$(ionic) 1260 s $\nu(CF_3)$ 1180 s $\nu(SO_3)$ 1037 s
6	*mer*-$Co(NH_3)_3(OSO_2CF_3)_3$	3320, 3240	1612		$\nu(CF_3SO_3)$ (coord) 1332 s $\nu(CF_3)$ 1243 s $\nu(SO_3)$ 1019 s
7	*cis*-$[Co(NH_3)(en)_2(OSO_2CF_3)](CF_3SO_3)_2$	3200	1600		
8	$[Co(NH_3)_5(Az)]Cl_3$	3220	1620	897	$\rho(NH_3)$ 851 m
9	*cis*-$[Co(en)_2(Az)_2]Br_3$	3100	1592	889 s	
10	*cis*-$[Co(NH_3)_4(Az)_2Cl_3$	3130	1610	892	$\rho(NH_3)$ 851 m
	cis-$[Co(NH_3)_4(Az)_2](CF_3SO_3)_3$	3280	1610	892	$\nu(CF_3SO_3)$(ionic) 1250 s $\rho(NH_3)$ 858 m
11	$[Cr(NH_3)_5(Az)](CF_3SO_3)_3$[e]	3250	1625	896	$\nu(CF_3SO_3)$ (ionic) 1255 s $\nu(CF_3)$ 1180 s $\nu(SO_3)$ 1025 s

[a] All data recorded as KBr pellet. [b] All bands broad. [c] All bands of medium intensity unless specified otherwise. [d] Intensity: m, medium; s, strong. [e] Data recorded as Nujol mull.

effected by recrystallization and/or cation-exchange chromatography. Since the concentration of H^+ used to elute a cation from Sephadex resin is related to the charge on the cation (a +1 cation is eluted by 0.1 mol·L^{-1} [H^+], a +2 cation by 0.2 mol·L^{-1} [H^+], etc.), this latter procedure confirmed the net charge on each cobalt cation. In addition, a perchlorate salt of complex **4** (**4b**) was prepared by cation exchange chromatography of **4a**, using $NaClO_4$ to elute the new salt **4b**. A bromide salt (**4c**) resulted from recrystallization of **4a** in the presence of LiBr.

The direct substitution procedure above is effective for precursor complexes containing chelating polyamine ligands in the coordination sphere. It was also sucessful for $Na_3[Co(NO_2)_6]$ as the substrate, but not for other cobalt(III) complexes containing nitro ligands. When simple ammine complexes of cobalt(III), $[Co(NH_3)_xCl_y]^{(3-y)+}$, were stirred in neat aziridine, no substitution of aziridine for either ammine or chloro ligands occurred. These results indicated that the direct substitution procedure is limited in scope, and in order to prepare complexes containing both aziridine and ammine ligands, an alternative route was developed. Transition-metal complexes containing the very labile triflato ($CF_3SO_3^-$) ligand have proved to be useful as synthetic precursors to a variety of new complexes that have eluded synthesis by other means.[24] A precursor complex containing chloro or bromo ligands is stirred in neat triflic acid (CF_3SO_3H). The HCl or HBr byproduct is flushed out during the reaction, and then ether is added to precipitate the substitutionally labile triflato complex. These complexes are often moisture sensitive, capable of substituting H_2O for the coordinated triflato ligands even in the solid state. The mild conditions required for substitution of the triflato ligand are especially suitable for substitution by reactive ligands like aziridine.

We prepared by this method three new triflato species for use as potential precursors to aziridine complexes. Complexes *cis*-$[Co(NH_3)_4(OSO_2CF_3)_2](OSO_2CF_3)$ (**5**) (80% yield), *mer*-$[Co(NH_3)_3(OSO_2CF_3)_3]$ (**6**) (82%), and *cis*-$[Co(NH_3)(en)_2(OSO_2CF_3)](OSO_2CF_3)_2$ (**7**) (72%) were prepared by this route from *cis*-$[Co(NH_3)_4Cl_2]Cl$, *mer*-$[Co(NH_3)_3(OH_2)Cl_2]Cl$, and *cis*-$[Co(NH_3)(en)_2Br]Br_2$, respectively. The new triflato complexes were characterized by elemental analysis and IR spectroscopy but proved to be too reactive in solution to allow NMR studies.

The complete characterization of the new triflato complexes and assignment of the stereochemistry result from the formation of aziridine derivatives by replacement of each labile triflato ligand by the heterocycle. This rapid, exothermic reaction is best effected by cooling a solid sample of the triflato complex in a dry ice/acetone bath under a nitrogen atmosphere, followed by slow addition of excess aziridine. The mixture is allowed to warm slowly to room temperature, by which time the reaction is complete. After removal of aziridine and isolation of the crude triflate salt the final purification and conversion to the chloride or bromide salt was effected by cation-exchange chromatography.

The known complexes $[Co(NH_3)_5(OSO_2CF_3)](OSO_2CF_3)_2$ and *cis*-$[Co(en)_2(OSO_2CF_3)_2](OSO_2CF_3)$[19] and the new complexes **5** and **7** were used as precursors to the aziridine complexes $[Co(NH_3)_5(Az)]Cl_3$ (**8**) (87% yield), *cis*-$[Co(en)_2(Az)]Br_3$ (**9b**) (58%), *cis*-$[Co(NH_3)_4(Az)_2]Cl_3$ (**10**) (86%), and *cis*-$[Co(NH_3)(en)_2(Az)]Br_3$ (**2**) (68%), respectively. This route was an alternative synthesis of complex **2**, while complex **9b** had been previously reported, prepared by direct substitution of aziridine on *cis*-$[Co(en)_2Br_2]Br$.[1] The neutral triflato complex **6** exhibited solubility properties different from those of the cationic species. The reaction with aziridine, in an attempt to produce the *tris*-(aziridine) species, was highly exothermic and did not result in tractable products.

In one further example of the use of triflato complexes as precursors to aziridine-containing species, the chromium(III) complex $[Cr(NH_3)_5(OSO_2CF_3)](OSO_2CF_3)_2$[20] was treated with aziridine under similar conditions to produce $[Cr(NH_3)_5(Az)](OSO_2CF_3)_3$ (**11**) (88%).

Satisfactory elemental analyses were obtained for complexes **1–11**, and UV–visible data were recorded for each complex. The visible absorption maxima of all the aziridine complexes prepared are given in the Experimental Section. Each complex exhibits the two characteristic ligand field bands typical of low-spin cobalt(III) complexes.

IR Spectroscopy. The reactive triflato complexes **5–7** can only be characterized in triflic acid solution or in the solid state. Although every band associated with the triflato moiety in the IR spectrum cannot be unequivocally assigned, there are characteristic absorptions that allow differentiation of coordinated triflato ligands and ionic triflate counterions.[19a,24] The band at 1270 cm^{-1} has been assigned to $\nu[SO_3(E)]$ in ionic $CF_3SO_3^-$ as the Ag^+ salt, and is observed to shift to near 1380 cm^{-1} for a monodentate-coordinated triflato ligand.[24] Complex **5** shows $\nu[SO_3(E)]$ values at 1260 cm^{-1} for the free anion and at 1400 cm^{-1} for the coordinated ligand. The neutral complex **6** shows only $\nu[SO_3(E)]$ values at 1332 cm^{-1} associated with the coordinated ligand (Table III). The presence of the intact aziridine ligand

(24) Lawrance, G. A. *Chem. Rev.* **1986**, *86*, 17.

Table IV. ^{1}H NMR Data (400 MHz, DMSO-d_6)[a]

compound		aziridine			ethylenediamine	
no.	formula	CH	NH	NH_3	CH	NH
4a	*trans*-$[Co(Az)_4(NO_2)_2]NO_2$	1.26 (m, 8 H) 2.18 (m, 8 H)	3.94 (br p, 4 H) $^3J_{HH}$ = 6.1 Hz			
	trans-$[Co(Az)_4(NO_2)_2]NO_2$[b]	1.46 (br d, 8 H) 2.33 (br d, 8 H) $^3J_{HH}$ = 3.6 Hz				
8	$[Co(NH_3)_5(Az)]Cl_3$	1.74 (m, 2 H) 1.91 (m, 2 H)	4.30 (br p, 1 H) $^3J_{HH}$ = 6.7 Hz	3.75 (s, 3 H, trans to Az) 3.79 (s, 12 H, cis to Az)		
10	*cis*-$[Co(NH_3)_4(Az)_2]Cl_3$	1.82 (m, 4 H) 1.97 (m, 4 H)	4.57 (br p, 2 H) $^3J_{HH}$ = 6.7 Hz	3.78 (s, 6 H, trans to Az) 3.87 (s, 6 H, cis to Az)		
9a	*cis*-$[Co(en)_2(Az)_2](CF_3SO_2)_3$	1.60 (br d, 1 H) 1.70 (br d, 1 H) $^3J_{HH}$ = 5.6 Hz 2.21 (m, 2 H)	3.81 (br p, 2 H) $^3J_{HH}$ = 6.7 Hz		2.59 (m, 4 H) 2.50[c] (4 H)	4.32 (br, 2 H) 4.65 (br, 4 H) 5.21 (br, 2 H)
2	*cis*-$[Co(NH_3)(en)_2(Az)]Br_3$	1.81 (m, 2 H) 2.02 (m, 2 H)	3.92 (br p, 1 H) $^3J_{HH}$ = 6.3 Hz	3.64 (s, 3 H)	2.63 (br, 4 H) 2.72 (br, 4 H)	4.61 (br, 1 H) 4.79 (br, 1 H) 5.04 (br, 2 H) 5.23 (br, 1 H) 5.46 (br, 2 H) 5.61 (br, 1 H)
1	*cis*-$[Co(en)_2(Az)Cl]Cl_2$	1.70 (m, 1 H) 1.76 (m, 1 H) 1.84 (m, 1 H) 1.91 (m, 1 H)	4.22 (br p, 1 H) $^3J_{HH}$ = 6.7 Hz		2.42 (br, 1 H) 2.50[c] (1 H) 2.62 (br, 2 H) 2.70 (br, 4 H)	4.56 (br, 1 H) 4.85 (br, 1 H) 5.26 (br, 2 H) 5.66 (br, 2 H) 5.99 (br, 1 H) 6.11 (br, 1 H)

[a] All data given in ppm relative to TMS (tetramethylsilane) in DMSO-d_6 or DSS (3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt) in D_2O. Br = broad; d = doublet; p = pentet; m = multiplet; s = singlet. [b] D_2O solvent. [c] Obscured by solvent peak.

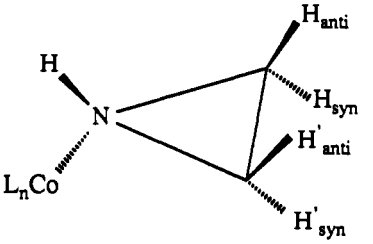
Table V. ^{13}C NMR Data (100 MHz, D_2O)[a]

compound			other ligand	
no.	formula	aziridine		
4a	*trans*-$[Co(Az)_4(NO_2)_2]NO_2$	25.29		
8	$[Co(NH_3)_5(Az)]Cl_3$	24.62		
10	*cis*-$[Co(NH_3)_4(Az)_2]Cl_3$	24.84		
9a	*cis*-$[Co(en)_2(Az)_2](CF_3SO_2)_3$	25.87, 25.91	en	46.07, 47.92
2	*cis*-$[Co(NH_3)(en)_2(Az)]Br_3$	25.46, 25.65	en	46.31, 47.03, 47.48, 47.59
1	*cis*-$[Co(en)_2(Az)Cl]Cl_2$	23.97, 25.19	en	47.01, 47.33, 47.44, 47.83
3	*cis*-$[Co(trien)(Az)Cl]Cl_2$[b]	23.75, 25.33	trien	45.61, 46.31, 57.58, 58.49, 58.75, 60.28

[a] All chemical shifts given in ppm relative to DSS at 0 ppm. Dioxane or acetone was used as internal reference. [b] Major isomer only.

in **1–4** and **8–11** was confirmed in the IR spectrum by a characteristic medium–strong band at ca. 890 cm^{-1}, which is assigned to a deformation of the aziridine ring (Table III).[25] However assignment of the stereochemistry and confirmation of the coordination sphere was unequivocally determined by ^{1}H and ^{13}C NMR spectroscopy (except in the case of the paramagnetic Cr(III) complex **11**). These data are given in Tables IV and V, respectively.

NMR Spectroscopy. The symmetry of the coordinated aziridine ring and the stereochemistry of the cobalt complex must be considered when the NMR spectra are interpreted. 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). Within each set, the two protons are magnetically inequivalent. Thus H_{syn} and H'_{syn} are chemically equivalent but magnetically inequivalent, and the same is true for H_{anti} and H'_{anti}. However the ^{1}H NMR spectrum of aziridine in the condensed phase or in solution shows only one line corresponding to all four CH protons, a result of rapid inversion at nitrogen,[26] which has been ascribed to NH proton exchange.[27] In contrast, the BH_3 adduct of aziridine shows one multiplet for H_{syn} and a second for H_{anti}, indicating that inversion at nitrogen is much slower on the NMR time scale.[28] The multiplets exhibit different splitting patterns, primarily due to the different NH–H_{syn} and NH–H_{anti} coupling constants.



In all the cobalt complexes discussed here, two multiplets are seen for the CH protons of coordinated aziridine, even in the highly symmetrical complexes $[Co(NH_3)_5(Az)]Cl_3$ (**8**) and $[Co(Az)_4(NO_2)_2]NO_2$ (**4a**), confirming that inversion at nitrogen is suppressed on coordination to cobalt (Figure 1a). The four protons exhibit non-first-order coupling, and each is also coupled to the NH proton as evidenced by the splitting of the resonance arising from this proton. The ^{1}H NMR spectrum shows two complex multiplets (ca. 1.2–2.2 ppm), corresponding to two H_{syn} and two H_{anti} protons, and one broadened pentet (ca. 3.9–4.6 ppm) arising from the single NH proton. In all the complexes containing more than one aziridine moiety, these ligands are found in chemically equivalent environments; thus, this pattern is seen for all of the complexes **1–5**, **8**, **9a**, and **10**. Exchange of the NH proton in D_2O results in loss of the resonance near 4 ppm, but preserves the H_{syn}

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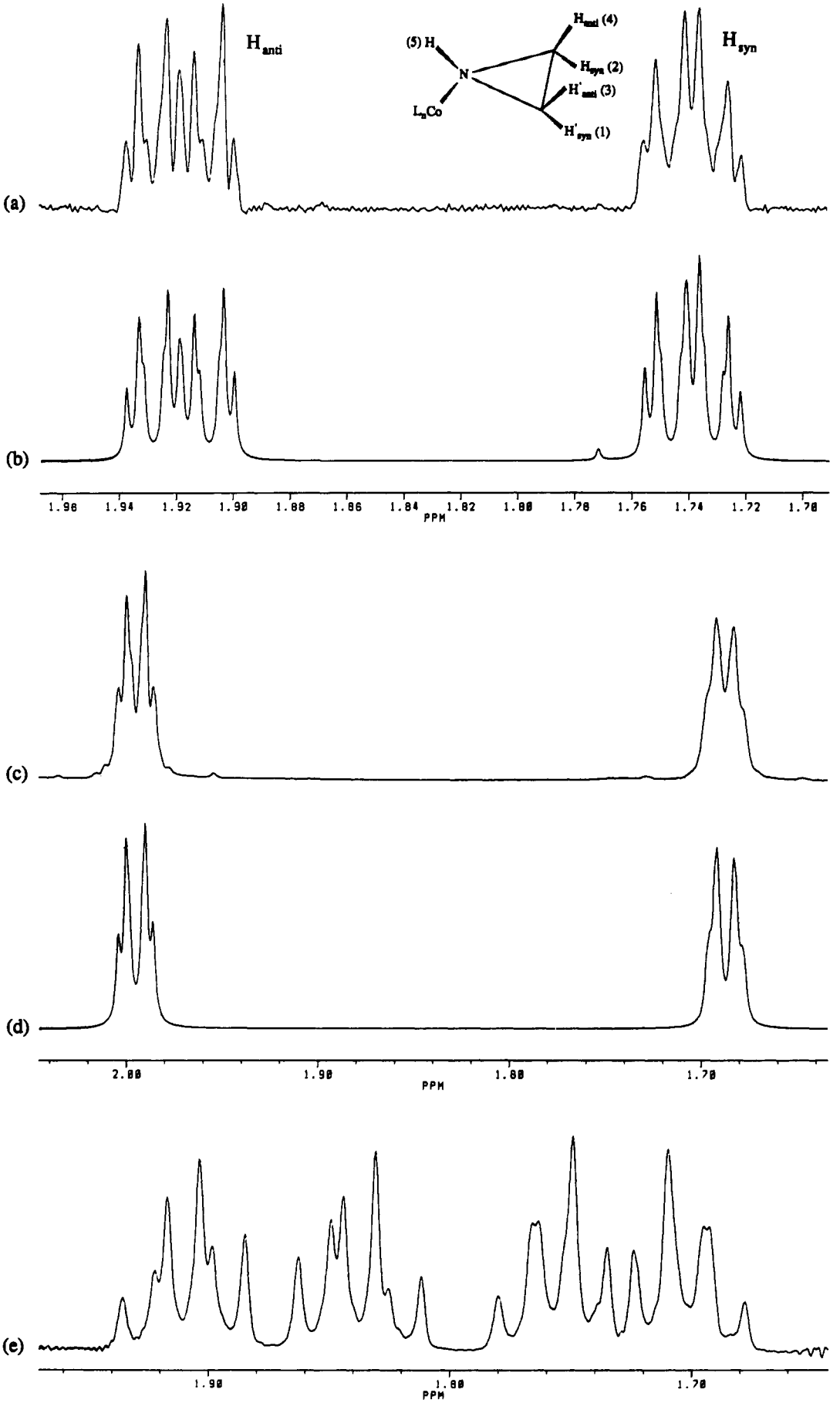

Figure 1. (a) Experimental (400 MHz, DMSO-d_6) and (b) simulated (line width = 1.3 Hz) ^{1}H NMR spectra of the aziridine CH protons in $[Co(NH_3)_5(Az)]Cl_3$ (**8**). Coupling constants (Hz) are as follows: J_{15},J_{25} = 6.1; J_{35},J_{45} = 7.8; J_{34} = 4.4; J_{12} = 4.3; J_{14},J_{23} = 5.7; J_{13}, J_{24} = −1.6. (c) Experimental (400 MHz, DMSO-d_6/D_2O) and (d) simulated (line width = 1.0 Hz) ^{1}H NMR spectra of D_2O-exchanged **8**. (e) Experimental (400 MHz, DMSO-d_6) ^{1}H NMR spectrum of the aziridine CH protons in $[Co(en)_2(Az)Cl]Cl_2$ (**1**).

and H_{anti} distinction. The two upfield multiplets are retained but simplify considerably and become much more similar in form (Figure 1c).

The aziridine resonances in the ^1H NMR spectrum of $[Co(NH_3)_5(Az)]Cl_3$ (**8**) (Figure 1a) were simulated by using the PANIC program. The simulated spectrum (Figure 1b) shows good agreement with the experimental spectrum, allowing assignment of the six coupling constants required to characterize this spin system. The experimental spectrum of the D_2O-exchanged sample (Figure 1c) could then be simulated simply by setting the coupling constants involving the NH proton equal to zero. Better areement with the experimental spectrum is obtained if a small $ND-H_{syn}$ coupling constant (0.6 Hz) is retained (Figure 1d). This results in the slight broadening of the upfield peak (H_{syn}) in Figure 1c,d. The two aziridine H_{anti} protons in complex **8** are assigned to the downfield resonance at 1.91 ppm, and the upfield resonance at 1.74 ppm is assigned to the two H_{syn} protons.

The four aziridine CH resonances of the less symmetrical complex $[Co(en)_2(Az)Cl]Cl_2$ (**1**) are shown in Figure 1e. Simulation of these resonances permitted calculation of the 10 necessary coupling constants.[29] Again, the downfield resonances (1.91, 1.81 ppm) are assigned as H_{anti} and H'_{anti}, and the upfield resonances (1.76, 1.70 ppm) are assigned as H_{syn} and H'_{syn}.

The assignment of the H_{syn} (with respect to cobalt) protons upfield of the H_{anti} protons is difficult to confirm experimentally. It was not possible to observe unambiguously a through-space NOE enhancement between the NH proton and either the H_{syn} or the H_{anti} proton. However, in both free and N-substituted aziridines, the CH protons syn to the NH or N substituent have been assigned upfield of the anti protons.[26] If the bulky cobalt substituent in an aziridine complex is considered to have a comparable effect on the chemical shifts to the *N*-alkyl substituent in a free *N*-alkylaziridine, then these assignments are consistent. However, the possible effect of the magnetic anisotropy of the cobalt atom on the chemical shifts of the syn and anti protons may complicate this argument. Thus the assignments of the aziridine CH protons are tentative.

In the highly symmetrical complexes **4a**, **8**, and **10**, only a single resonance is seen in the ^{13}C NMR spectra for the aziridine carbon atoms, consistent with rapid rotation about the Co–N bond on the NMR time scale. For the less symmetrical complexes, the aziridine carbon atoms become chemically inequivalent and two resonances are seen. Thus ^{13}C NMR is a good probe for the symmetry of the aziridine coordination environment. For example, a single aziridine carbon peak appears in the ^{13}C NMR spectrum of *cis*-$[Co(NH_3)_4(Az)_2]Cl_3$ (**10**), in contrast to the two peaks (separated by only 0.04 ppm) observed for the aziridine carbon atoms in *cis*-$[Co(en)_2(Az)_2]Br_3$ (**9**), reflecting the lowered symmetry in the complex containing chelating ligands.

In $[Co(NH_3)_5(Az)]Cl_3$ (**8**), the NH_3 protons appear as two broad resonances at 3.79 and 3.75 ppm in a 4:1 ratio, corresponding to the ammine ligands cis and trans to the aziridine ligand, respectively. The ^{13}C NMR spectrum of **8** shows a single peak for the aziridine ligand at 24.62 ppm. Complex **8** is the only complex for which there is only one possible stereoisomer. For the other complexes (**1–5**, **9a**, and **10**) the stereochemistry can be assigned from an analysis of the ^1H and ^{13}C NMR spectra. For example, the cis configuration of $[Co(en)_2(Az)Cl]^{2+}$ (**1**) is apparent from the existence of four peaks for the ethylenediamine ligands in the ^{13}C NMR spectrum. The more symmetrical trans isomer would be expected to show only a single peak corresponding to the four CH_2 groups. As a result of the lowered symmetry of the cis isomer, the two carbon atoms of the aziridine ligand are chemically differentiated and appear as two peaks (23.97 and 25.19 ppm), and four multiplets are observed in the ^1H NMR spectrum arising from the four chemically different CH protons of the aziridine ligand (Figure 1e). The tetrakis(aziridine) complex

(29) Coupling constants for the aziridine ring protons in $[Co(en)_2(Az)Cl]Cl_2$ (**1**) are as follows (refer to diagram in Figure 1): $J_{15} = 6.2$; $J_{25} = 6.5$; $J_{35} = 7.5$; $J_{45} = 7.8$; $J_{12} = 6.3$; $J_{34} = 7.4$; $J_{14} = 6.0$; $J_{23} = 6.0$; $J_{13} = -0.1$; $J_{24} = -0.3$ Hz.

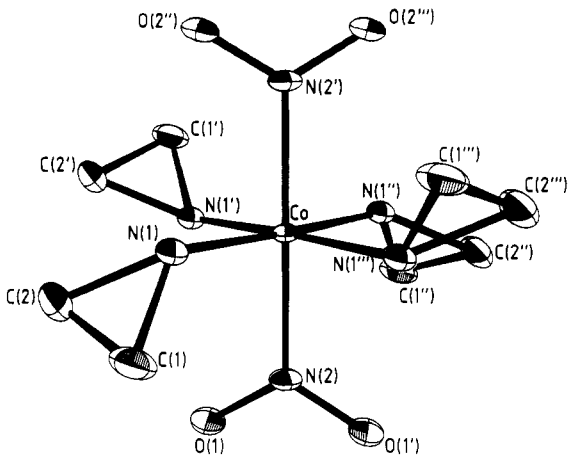

Figure 2. Geometry and atom numbering for the $[Co(Az)_4(NO_2)_2]^+$ cation in $[Co(Az)_4(NO_2)_2]Br\cdot 2H_2O\cdot LiBr$ (**4c**).

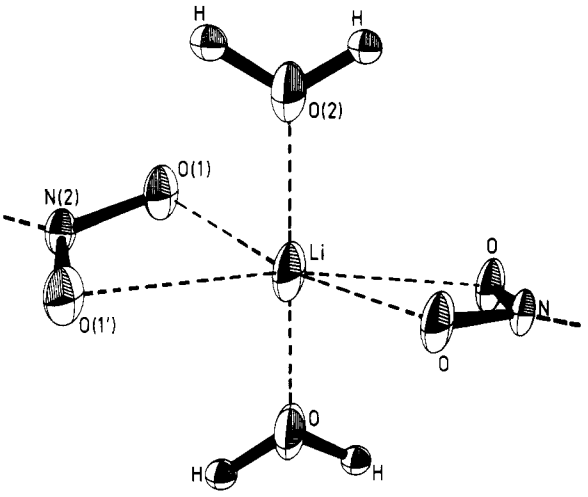

Figure 3. Environment about the Li^+ ion in $[Co(Az)_4(NO_2)_2]Br\cdot 2H_2O\cdot LiBr$ (**4c**).

Table VI. Bond Distances (Å) and Angles (deg) with Estimated Standard Deviations for *trans*-$[Co(Az)_4(NO_2)_2]Br\cdot 2H_2O\cdot LiBr$ (**4c**)

	Bond Distances[a]		
Co–N(1)	1.959 (2)	C(1)–C(2)	1.463 (4)
Co–N(2)	1.930 (2)	O(1)–N(2)	1.241 (2)
N(1)–C(1)	1.486 (4)	Li–O(1)	2.262 (2)
N(1)–C(2)	1.486 (3)	Li–O(2)	2.003 (2)
	Bond Angles		
N(1)–Co–N(2)	91.1 (1)	C(1)–N(1)–C(2)	59.0 (2)
N(1)–Co–N(1')	94.6 (1)	N(1)–C(1)–C(2)	60.5 (2)
N(1)–Co–N(1'')	177.8 (2)	N(1)–C(2)–C(1)	60.5 (2)
Co–N(1)–C(1)	129.8 (2)	Co–N(2)–O(1)	120.8 (1)
Co–N(1)–C(2)	129.9 (2)	O(1)–N(2)–O(1')	118.4 (3)

[a] Bonds to hydrogen atoms range from 0.96 to 1.04 Å.

4a exhibits only one peak at 25.29 ppm in the ^{13}C NMR spectrum, indicative of a highly symmetrical complex with the four aziridine ligands occupying the equatorial positions in the octahedral complex. This geometry was confirmed by an X-ray crystal structure determination of the bromide salt, *trans*-$[Co(Az)_4(NO_2)_2]Br$ (**4c**).

Description of the Structure. Crystals of **4c** were prepared by slow recrystallization of the nitro salt (**4a**) from an aqueous solution containing excess lithium bromide. The crystals of *trans*-$[Co(Az)_4(NO_2)_2]^+$ (space group *Ccca*) possess a bromide counterion and in addition contain a lithium bromide and two molecules of H_2O of crystallization per molecule of **4c**. This formulation was confirmed by elemental analysis. A drawing of the cobalt cation and a view showing the coordination sphere about the lithium atom are given in Figures 2 and 3, respectively, each

with the atom-labeling scheme. Bond lengths and angles are given in Table VI.

The coordination geometry about cobalt is a tetragonally distorted octahedron. The aziridine nitrogen atoms alternate 0.024 (6) Å above and below the plane drawn through the center of the cobalt atom and perpendicular to the N(2)–Co–N(2′) bond axis. When the nitrogen atom is above this plane, the aziridine ring is directed downward, and when the nitrogen atom is below the plane, the aziridine ring is directed upward. The cobalt atoms are located in special positions of high 222 symmetry at which three orthogonal C_2 axes intersect. One axis is coincident with the N(2)–Co–N(2′) bond axis. The other C_2 axes are perpendicular to this axis: one bisects the N(1)–Co–N(1′) bond angle and the other bisects the N(1)–Co–N(1‴) bond angle. This high symmetry renders the two nitro ligands equivalent, and a single N–O bond length of 1.241(2) Å is observed. The four aziridine ligands are also equivalent, and one set of C–C, C–N, Co–N(Az), and Co–N(NO_2) bond lengths are sufficient to describe the structure (Table VI).

The staggering of the aziridine rings above and below the equatorial plane means there is no C_4 axis coincident with the N(2)–Co–N(2′) bond axis, and two pairs of bond angles are observed about the cobalt atom. The N(1)–Co–N(1′) and N(1″)–Co–N(1‴) bond angles are 94.6 (1)°, while the N(1)–Co–N(1‴) and N(1′)–Co–N(1″) bond angles are 85.4 (1)°. Intermolecular forces will play a part in this difference, but the dominant effect is more likely to be the intramolecular steric interaction arising from the nitro groups that lie in the plane bisecting the N(1)–Co–N(1′) and N(1″)–Co–N(1‴) bond angles. This may explain why these bond angles are the larger of the pair.

The bond lengths for the coordinated aziridine in complex **4c** can be compared with those found for free aziridine in the gas phase[30] and for other transition-metal aziridine complexes. The C–C bond length (1.480 Å) for aziridine vapor is significantly longer than the C–C bond length of 1.463 (4) Å observed in **4c**. This C–C bond length shortening on complex formation was also observed in the tetraaziridine complexes *trans*-[$Rh(Az)_4I_2$]I (1.36 (5) Å)[30] and [$Cu(Az)_4$](NO_3)$_2$ (1.40 (4) Å).[30] The high standard deviations in two further structures of aziridine complexes, the cis and trans isomers of $Pt(Az)_2Cl_2$,[31] preclude direct comparison with **4c**.

The lithium cation present in the crystals of **4c** is surrounded by six oxygen atoms in a pseudooctahedral geometry (Figure 3) and is located on a special position of 222 symmetry. Four oxygen atoms, in "equatorial" positions with an Li–O distance of 2.262 (2) Å, derive from two nitro ligands coordinated to different cobalt centers. Two water molecules occupy the "axial" positions (Li–O = 2.003 (2) Å). No close interatomic contacts are observed about the bromide ions, the closest approaching being N(1) at 3.37 Å.

Electrochemistry. An impetus for preparing these complexes was the possibility of reductive activation of the cobalt center in hypoxic tumor cells. For this reason the electrochemical behavior of the aziridine complexes was investigated. Kinetically inert low-spin cobalt(III) complexes undergo a one-electron electrochemical reduction, which is usually irreversible. This is ascribed to rapid ligand substitution at the labile cobalt(II) center.[32] Cyclic voltammetry of the aziridine complexes **1**, **2**, **4a**, **8**, and **10** in aqueous solution showed that, as expected, the Co(III) complexes were reduced to Co(II) species in an irreversible process even at the fastest scan rate (v = 1 V·s^{-1}). No reoxidation was observed up to the solvent limit consistent with formation of [$Co(H_2O)_6$]$^{2+}$ ($E°$ = 1.81 V) upon reduction. The E_{pc} values (V) measured for these complexes (**1**, −0.53; **2**, −0.73; **4a**, −0.34; **8**, −0.57; **10**, −0.39 V at v = 0.01 V·s^{-1}) were proportional to ln v, shifting to more negative potentials with increasing scan rate over the range v = 0.01–1.00 V·s^{-1}. This observation is consistent with either electrochemical or chemical irreversibility. A reference compound [$Co(en)_3$]$^{3+}$ gave similar values for E_{pc} (−0.55 V) measured by cyclic voltammetry and $E_{1/2}$ (−0.52 V) measured by polarography.[33] Thus the E_{pc} values measured for the aziridine complexes can be considered similar to polarographic $E_{1/2}$ values, and the relative order of the reduction potentials can be assumed from the experimental data. Due to the kinetic nature of the reduction potential, few conclusions can be drawn.

The cobalt aziridine complexes were designed to undergo reduction by a biological reductant as the means of drug activation in hypoxic tumor cells. Qualitative experiments in buffered solution (pH = 7.2) using ascorbate ion as the reductant showed that aziridine was released from the cobalt complexes **2**, **8**, and **10**, as detected by a colorimetric test for aziridine.[34] Neither L-cystine nor L-cysteine were effective as reductants. Preliminary testing of the cobalt complexes in cell culture for antitumor activity and hypoxic selectivity showed that while a baseline cobalt(III) complex, [$Co(NH_3)_6$]Cl_3, containing no aziridine ligands was nontoxic, the aziridine-containing complexes were almost as toxic as free aziridine, indicating facile biological reduction of the cobalt(III) center and release of aziridine.[35] The cell culture studies were carried out in open wells in a hypoxic chamber, and unequivocal quantitative data could not be obtained as the volatile free aziridine released from the complexes led to cross contamination of the wells. However, these studies did serve to establish the feasibility of release of a cytotoxic ligand from cobalt(III) upon biological reduction in an hypoxic environment. A series of second-generation cobalt(III) complexes containing much less volatile cytotoxic ligands has been prepared, for which quantitative biological data has been obtained.[35]

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Supplementary Material Available: Tables of crystallographic data and atomic thermal parameters (2 pages); a table of observed and calculated structure factors (2 pages). Ordering information is given on any current masthead page.

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