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Cadmium Cyclam Complexes: Interconversion of *Cis* and *Trans* Configurations and Fixation of CO_2

Xiangyang Liang, John A. Parkinson, Simon Parsons, Michael Weishäupl, and Peter J. Sadler*

Department of Chemistry, University of Edinburgh, King's Buildings, West Mains Road, Edinburgh EH9 3JJ, U.K.

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There is current interest in the antiviral activity of metal, especially zinc, cyclam (1,4,8,11-tetraazacyclotetradecane) complexes. Their biological activity appears to be dependent on recognition of membrane proteins (viral coreceptors) and therefore on their configurations. Here, we use Cd(II) as a probe for Zn(II) on account of its useful NMR properties. We have prepared and characterized Cd(II) complexes of cyclam, Cd(cyclam)$(ClO_4)_2$ (**1**), Cd(cyclam)-Cl_2 (**2**), and $[Cd_3(cyclam)_3(CO_3)](ClO_4)_4 \cdot 3H_2O$ (**3**), and have identified key markers for various configurations adopted by these complexes under a variety of solution conditions using 1D and 2D ^1H, ^{13}C, ^{15}N, and ^{111}Cd NMR spectroscopy, including Karplus-type analyses of ^1H, ^1H and ^1H, ^{111}Cd coupling constants. These complexes were stable at high pH (>8.2) but dissociated completely on lowering the pH to 5.3. Two major configurations of both **1** and **2** exist in aqueous solution: *trans*-I (*R,S,R,S* at nitrogen) and *cis*-V (*R,R,R,R*). $^3J(^{111}Cd, ^1H)$ coupling constants showed that the five-membered rings of the *trans*-I configuration adopt the eclipsed conformation, and the six-membered rings adopt chair conformations. The X-ray crystal structure of **3** shows that the cation adopts the unusual folded *cis*-I configuration in which all of the N–H bonds are oriented up (or down) in a novel tri-cadmium cluster. This complex contains triply bridged carbonate fixed from atmospheric CO_2. Each Cd(II) is bound by two *cis* oxygen atoms from CO_3^{2-} (Cd–O bond lengths 2.373 and 2.412 Å) and four nitrogen atoms from cyclam (C–N bond lengths 2.270–2.323 Å). The geometry can be described as trigonal bipyramidal with the two donor oxygen atoms occupying one of the apices of the in-plane triangle. In acetonitrile solution, complex **3** gives rise to only one configuration, *trans*-I, with eclipsed five-membered rings, and six-membered rings with chair conformations.

Introduction

Saturated macrocyclic polyamines exhibit new properties beyond those anticipated from mere assemblies of linear polyamines. Cyclam is one of the most commonly studied and used macrocyclic polyamines.[1] It has applications in a wide variety of areas including catalysis, biomimicry, metal recovery, and medicine.[2]

Our interest in cyclams arises from their anti-HIV activity. The bicyclam AMD3100 (the octa-HCl salt of 1-1′-[1,4-phenylenebis(methylene)]-bis(1,4,8,11-tetraazacyclotetradecane)) is a highly potent inhibitor of infection by the human immunodeficiency virus (HIV) and has recently been in phase II clinical trials.[3] Cyclam itself also exhibits significant anti-HIV activity.[4] Zn_2(bicyclam) has a low toxicity and exhibits higher anti-HIV activity than the free ligand.[5] Zn(II) is readily available in the body and may play a key role in the biological activity of the drug. The biological activity of metal cyclam complexes appears to depend on recognition of the membrane receptor protein CXCR4 via specific

* To whom correspondence should be addressed. E-mail: p.j.sadler@ed.ac.uk.

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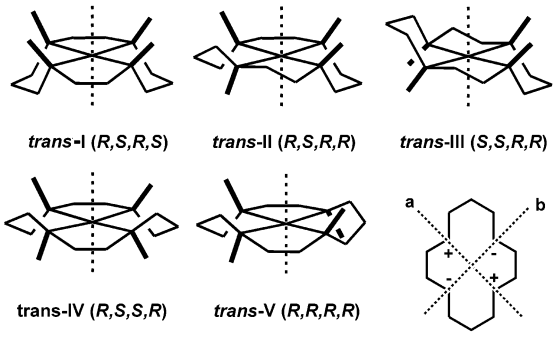

Figure 1. Five possible configurations of metal cyclam complexes, showing the different alignments of the NH protons and chirality at the N atoms. The folding of the *trans*-V configuration along axes *a* or *b* to give the *cis*-V configuration is shown in the bottom right (+ indicates NH proton above the cyclam plane, − below).

interactions with amino acid side-chains such as the carboxylate groups of aspartate and glutamate.[6,7] Such interactions are likely to be highly dependent on cyclam conformation.

Depending on the spatial alignment of the NH protons, there are five possible configurations of metal cyclam complexes: *RSRS*, *RSRR*, *SSRR*, *RSSR*, and *RRRR*, designated *trans*-I to *trans*-V, respectively, in Figure 1. In solution, cyclam complexes can exist as complicated mixtures of isomers in dynamic equilibrium,[8] but few detailed analyses of such equilibria have been previously reported.

In this paper, we study the structure of cadmium cyclam complexes in solution by 1D and 2D solution NMR techniques, and we have determined the X-ray crystal structure of $[Cd_3(cyclam)_3(CO_3)](ClO_4)_4 \cdot 3H_2O$. Our aim is to establish methods for identifying the various configurations of cyclam complexes in solution in view of the potential relationship between cyclam configuration, receptor recognition, and biological activity. We used cadmium for this initial study because, unlike zinc isotopes, which are unfavorable for NMR studies, ^{111}Cd and ^{113}Cd are spin-$^1/_2$ nuclei and are a potential source of structural information in solution via coupling constants and Cd chemical shifts.

Experimental Section

Caution! Perchlorate salts of metal complexes with organic ligands are potentially explosive and should be handled with great care. Only small amounts of these materials were prepared.

Synthesis of Cd(cyclam)$(ClO_4)_2$ (1). Cyclam (50.1 mg, 0.25 mmol) and $Cd(ClO_4)_2 \cdot 6H_2O$ (104.9 mg, 0.25 mmol) were heated under reflux in CO_2-free methanol (10 mL) for 2 h under argon. The volume was reduced (to ca. 4 mL) under reduced pressure until a white precipitate appeared. The precipitate was filtered off and washed with a small amount of methanol under argon to give the product. Yield 83.4 mg (65.2%). Anal. Calcd for $C_{10}H_{24}N_4CdCl_2O_8$: C, 23.48; H, 4.73; N, 10.95%. Found: C, 23.69; H, 4.91; N, 11.07%. Selected IR (KBr, cm^{-1}): 3306 s (NH), 3282 m (NH), 2921 m (CH), 2861 m (CH), 1611 w (NH).

To prepare ^{111}Cd-**1** for NMR studies, ^{111}CdO (2.5 mg, 0.02 mmol, 95.29%; Oak Ridge National Laboratory, TN) was dissolved in a slight molar excess of $HClO_4$ (0.5 M), and the solution was evaporated to dryness under vacuum. H_2O (containing 10% D_2O) was added, followed by cyclam (3.96 mg, 0.02 mmol), to give a sample which was ca. 30 mM in ^{111}Cd-**1**, with a measured pH of 8.7. The ^{1}H NMR spectrum of this sample was identical to that for the unlabeled complex prepared as described previously, except for additional splittings due to ^{1}H, ^{111}Cd couplings, and the presence of ca. 15% of free ligand.

Synthesis of Cd(cyclam)Cl_2 (2). Cyclam (50.1 mg, 0.25 mmol) and $CdCl_2$ (48.3 mg, 0.25 mmol) were heated under reflux in CO_2-free methanol (10 mL) for 2 h under argon. The volume was reduced (to ca. 4 mL) under reduced pressure until a white precipitate appeared. The precipitate was filtered off and washed with a small amount of methanol under argon to give the product. Yield 81.7 mg (85.2%). Anal. Calcd for $C_{10}H_{24}N_4CdCl_2$: C, 31.31; H, 6.31; N, 14.60%. Found: C, 31.03; H, 5.96; N, 14.39%. Selected IR (KBr, cm^{-1}): 3179 s (NH), 2906 m (CH), 2838 s (CH), 1623 w (NH).

Synthesis of $[Cd_3(cyclam)_3(CO_3)](ClO_4)_4 \cdot 3H_2O$ (3). Complex **1** (1 g, 2 mmol) was dissolved in water and left standing in air. After 7 days, colorless crystals of **3** were filtered off and washed with a small amount of methanol. Yield 0.62 g (62%). Anal. Calcd for $C_{31}H_{78}N_{12}Cd_3Cl_4O_{22}$: C, 25.68; H, 5.42; N, 11.59%. Found: C, 26.09; H, 4.83; N, 11.45%. Selected IR (KBr, cm^{-1}): 3431 s, br (OH), 3303 s (NH), 3175 s (NH), 2909 s (CH), 2852 s (CH), 1451 s (CO), 839 m (CO).

Spectroscopic Measurements. Infrared spectra were recorded as KBr pellets in the range 4000−400 cm^{-1} on a Perkin-Elmer Paragon 1000 Fourier transform IR spectrometer. ^{1}H NMR spectra were acquired on either Bruker DMX 500 (^{1}H = 500 MHz) or Varian Unity INOVA (^{1}H = 600 MHz) NMR spectrometers using TBI [^{1}H, ^{13}C, X] or triple resonance [^{1}H, ^{13}C, ^{15}N] probeheads, respectively, and equipped for *z*-field gradients. All data were acquired at a probe temperature of 298 K. ^{1}H chemical shifts were internally referenced to the methyl singlet of TSP (3-trimethylsilylpropionate-d_6) at 0 ppm; ^{13}C chemical shifts were referenced externally also using TSP. All NMR experiments were performed in 10% D_2O/90% H_2O under argon, with **1** at a concentration of 36 mM, pH 7.9, and **2** at a concentration of 47 mM, pH 8.2 unless otherwise stated.

1D ^{1}H NMR data were acquired over a ^{1}H frequency width of 5 kHz into 16K data points (acquisition time = 1.64 s). The water resonance was suppressed by presaturation or via the WATERGATE pulsed-field-gradient sequence.[9] 2D spectra were acquired using standard sequences.[10]

1D ^{111}Cd{^{1}H} NMR data were typically acquired (using a broadband probehead) on a sample of ^{111}Cd-**1** over a ^{111}Cd frequency width of 15.9 kHz (150 ppm) centered at 246 ppm. ^{111}Cd peaks were referenced to 0.1 M $^{111}Cd(ClO_4)_2$ in 90% H_2O/10% D_2O (external). Data were acquired with 100000 transients into 4K complex data points (acquisition time = 0.13 s, delay between pulses 400 ms).

2D [^{1}H, ^{13}C] HSQC NMR data were typically acquired over a ^{1}H frequency width of 5 kHz and a ^{13}C frequency width of 5 kHz (40 ppm) centered at 43 ppm. Data were acquired with 64 transients into 2K complex data points (acquisition time 205 ms) for each of 128 t_1 increments (acquisition time 12.7 ms).

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2D [^{1}H, ^{15}N] HSQC NMR data were acquired over a ^{1}H frequency width of 1 kHz and a ^{15}N frequency width of 250 Hz (5 ppm) centered at 12 ppm. Data were acquired with 240 transients into 2K complex data points for each of 128 t_1 increments.

2D [^{1}H, ^{111}Cd] HSQC NMR data were acquired for ^{111}Cd-**1** over a ^{1}H frequency width of 5 kHz (10 ppm) and a ^{111}Cd frequency width of 2.1 kHz (20 ppm) centered at 244 ppm. 2D [^{1}H, ^{111}Cd] HSQC-TOCSY NMR data were acquired over a ^{111}Cd frequency width of 1 kHz (10 ppm) centered at 246 ppm using a mixing period of 55 ms. Both experiments were adjusted for a $^2J(^1H_N,^{111}Cd)$ coupling of 30 Hz. Data were acquired with 8 transients (4 for HSQC-TOCSY) for each of 128 (64 for HSQC-TOCSY) t_1 increments into 2K complex data points (acquisition time 170 ms). For all inverse 2D experiments, the water resonance was eliminated as part of the coherence selection process.

2D [^{1}H, ^{1}H] *z*-filtered TOCSY data were acquired at 600 MHz for ^{111}Cd-**1** and used for the measurement of ^{1}H/^{111}Cd coupling constants: 4096 complex data points were acquired over an F2 frequency width of 3 kHz (acquisition time = 0.683 s); 16 transients were acquired for each of 2 × 512 t_1 increments in F1 (frequency width = 1.5 kHz). A spin-lock time of 70 ms was employed. Solvent suppression was achieved using WET.[11]

All NMR data were processed using Xwin-nmr (version 2.0, Bruker U.K. Ltd.).

Carbonate Binding to Complex 1. $Na_2{}^{13}CO_3$ was dissolved in 90% H_2O/10% D_2O to give a 40 mM solution in the presence of TSP. Stepwise addition of a concentrated solution of **1** was made to this solution to give $^{13}CO_3{}^{2-}$/**1** ratios from 1/0.2 to 1/3.5 in 10 steps. $^{13}C\{^1H\}$ NMR spectra were acquired at 150 MHz (512 transients, 31.44 kHz sweep width, 25216 data points, 0.4 s acquisition time) after each addition of **1**. An estimate of the binding constant for 1/1 carbonate binding to complex **1** was obtained by fitting the data in Figure 6 using the program Origin (version 5.0, Microcal Software, Inc.). In a similar experiment, Na_2CO_3 was added stepwise to a solution of **1** (16 mM in 90% H_2O/10% D_2O) to give molar ratios of **1**/$^{13}CO_3{}^{2-}$ of 1/0.5, 1/1, 1/2, 1/4, and ^{1}H NMR spectra were acquired after each addition.

pH Titration. Complex **1** was dissolved in CO_2-free 90% H_2O/10% D_2O. The pH was adjusted to 12.1 with 0.1 M NaOH in the NMR tube, and the back-titration was carried out from 12.1 to 5.3 by addition of 0.1 M $HClO_4$. Values of pH were measured with a Corning 145 pH meter equipped with a microcombination electrode (Aldrich) calibrated with Aldrich standard buffers (pH 4, 7, and 10). No correction was made for deuterium isotope effects. All experiments were performed on samples saturated with argon.

NMR Spin Simulations. Spin system simulations were carried out using the program Spinworks (version 1.1, Kirk Marat, University of Manitoba, 1999).

Molecular Modeling. A molecular model for the *trans*-I configuration of Cd(II) cyclam was built using the program Sybyl (version 6.3, Tripos Inc.) on the basis of the *cis*-I configuration in the crystal structure of **3**.

Crystallography. The crystal data and refinement parameters for **3** are summarized in Table 1. Colorless needles developed along (001) with other faces along the (110) and ($\bar{1}$10) directions. Data were collected with Mo Kα radiation on a Stoë Stadi-4 diffractometer equipped with an Oxford Cryosystems low-temperature device. An absorption correction was applied by Gaussian integration following refinement of the crystal dimensions against a set of ψ-scan (Stoë X-shape,[12] μ = 1.435 mm^{-1}, T = 0.915−0.937).

Table 1. Crystal Data and Refinement Parameters for Complex **3**

formula	$C_{31}H_{78}Cd_3Cl_4N_{12}O_{22}$
M	1309.95
cryst syst	rhombohedral
space group	$R\bar{3}$
a/Å	23.142(2)
b/Å	23.142(2)
c/Å	17.500(4)
β/°	90
U/Å^3	8116.6(19)
Z	6
T/K	150(2)
D_c/Mg m^{-3}	1.608
μ/mm^{-1}	1.435
unique data	2341
obsd data	1401
R (R')	0.0660 (0.1444)

The structure was solved by direct methods (SIR92[13]) and refined by full-matrix least-squares against F^2 (Shelxl97[14]). The perchlorate anions centered on Cl2 and Cl3 are disordered about a $\bar{3}$ special position, and that centered on Cl1 is orientationally disordered in the ratio 70:30 with a common Cl position; equivalent Cl−O and O···O distances were restrained to be similar. H-atoms were placed in calculated positions on C-atoms. The positions of H-atoms attached to O1W (water of crystallization) could not be calculated unambiguously and were therefore not placed at all. All non-H atoms with the exception of the minor-occupancy O-atoms in perchlorate-1 were refined anisotropically. Standard data relating to the X-ray crystal structure of complex **3** have been deposited in the Cambridge Data Centre with CCDC reference number 182196.

Results

Three Cd(II) cyclam complexes were prepared: the perchlorate complex **1**, the chloride complex **2**, and the carbonate complex **3**, the latter being obtained from **1** via fixation of atmospheric CO_2. The structures of these complexes were studied by IR and NMR spectroscopy and, for **3**, by X-ray crystallography.

IR Spectroscopy. N−H stretching vibrations occur at 3306 and 3208 cm^{-1} for **1** and 3303 and 3175 cm^{-1} for **3**. A single intense N−H stretching vibration at 3179 cm^{-1} for **2** was observed. Complex **3** exhibits carbonate-related IR absorption bands at 1451 and 839 cm^{-1} as in carbonato complexes of other metal ions.[15,16]

^{1}H, ^{13}C, ^{15}N, and ^{111}Cd NMR of 1 in Aqueous Solution. The ^{1}H NMR spectrum of **1** acquired immediately after dissolving the sample in 10% D_2O/90% H_2O is shown in Figure 2a and did not change over a period of more than 2 weeks at ambient temperature. Few signals were cleanly resolved, and in order to overcome this problem and to fully assign the ^{1}H NMR spectrum, 2D homonuclear [^{1}H, ^{1}H] TOCSY and DQFCOSY NMR data sets and natural abundance 2D heteronuclear [^{1}H, ^{13}C] and [^{1}H, ^{15}N] HSQC NMR data sets were acquired.

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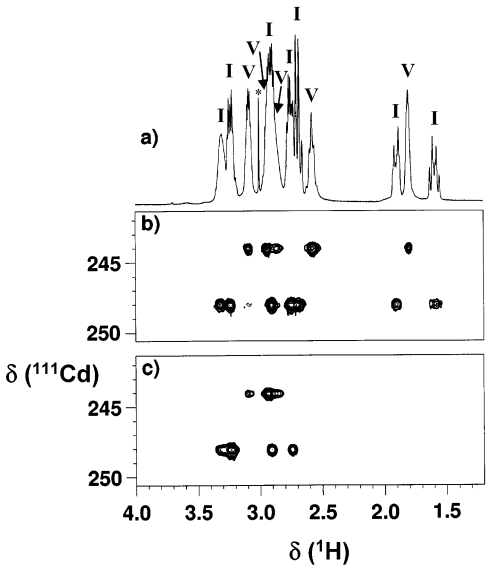

Figure 2. (a) ^{1}H NMR spectrum of complex **1**. Resonances for the *trans*-I configuration are designated I and resonances for *cis*-V are designated V. Asterisk indicates free ligand. (b) 2D [^{1}H, ^{111}Cd] HSQC-TOCSY NMR spectrum of ^{111}Cd-**1**. (c) 2D [^{1}H, ^{111}Cd] HSQC NMR spectrum of ^{111}Cd-**1**. Connectivities to the minor ^{111}Cd resonance at 219 ppm (not shown) are very weak. All samples were dissolved in 10% D_2O/90% H_2O.

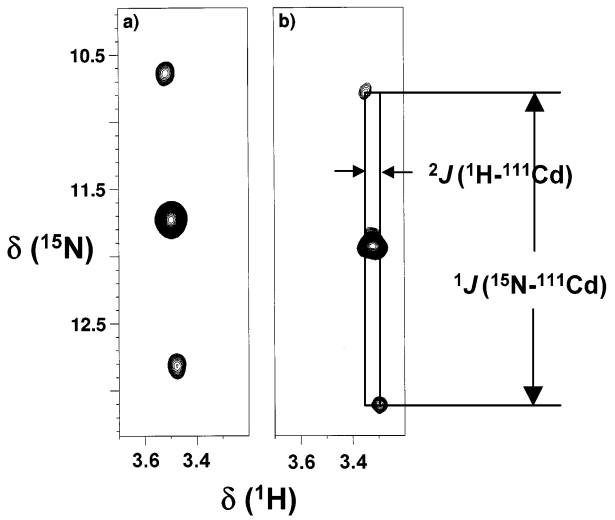

Figure 3. (a) 2D [^{1}H, ^{15}N] HSQC NMR spectrum of complex **2** and (b) 2D [^{1}H, ^{15}N] HSQC NMR spectrum of complex **1**, in 10% D_2O/90% H_2O.

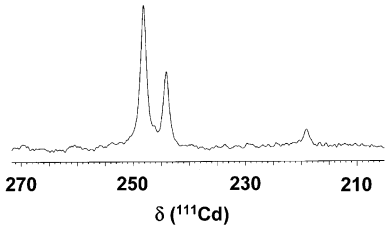

Figure 4. 1D ^{111}Cd{^{1}H} NMR spectrum of ^{111}Cd-**1** in 10% D_2O/90% H_2O.

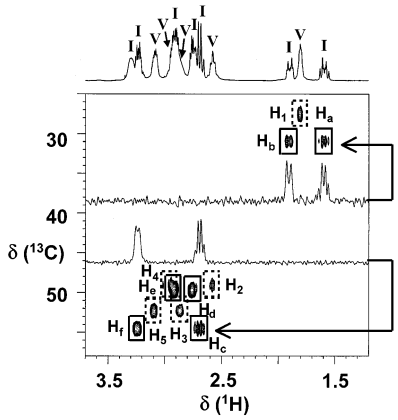

Figure 5. 2D [^{1}H, ^{13}C] HSQC NMR spectrum of complex **1** in 10% D_2O/90% H_2O. Resonances (H_a−H_f) for the *trans*-I configuration are designated by solid boxes, and resonances (H_1−H_5) for the *cis*-V configuration are designated by dashed boxes. 1D slices are shown for the two ^{13}C shifts of the six-membered rings (N*CH*$_2$*CH*$_2$*CH*$_2$N).

Two doublets of triplets (1.59 ppm, H_a, and 1.90 ppm, H_b) couple to one another (Figure S1). The presence of two spin systems is revealed by 2D [^{1}H, ^{1}H] TOCSY NMR data (Figure S2). Within the first spin system (labeled I), H_a couples to H_b and to H_c (2.69 ppm), H_b couples to H_f (3.23 ppm), and H_c and H_f couple to one another. H_e (2.91 ppm) and H_d (2.75 ppm) also couple to one another and to the broad signal at 3.31 ppm, which additionally correlates strongly with H_c. The second spin system (labeled V) is composed of 5 signals: H_1 (1.81 ppm) couples to H_3 (2.86 ppm) and H_5 (3.09 ppm); H_3 and H_5 couple to one another; H_2 (2.58 ppm) couples to H_4 (2.94 ppm), both of which are also associated with H_3 and H_5 via TOCSY correlations.

The 2D [^{1}H, ^{15}N] HSQC NMR spectrum of **1** in 90% H_2O/10% D_2O (Figure 3b) showed one broad signal (δ^1H/^{15}N: 3.31/11.91). This was accompanied by two satellite signals, arising from the presence of $^{111/113}$Cd at natural abundance (^{111}Cd, 12.81%; ^{113}Cd, 12.22%): ^1J(^{15}N, $^{111/113}$Cd) = 118 Hz; ^2J(^1H_N, $^{111/113}$Cd) = 27 Hz. Only spin system I (H_a−H_f) showed TOCSY correlations to the N*H* signal; spin system V (H_1−H_5) showed no relationship to the N*H* signal nor to any of the signals H_a−H_f, leading to the speculation that the two identified spin systems arise from two different configurations (I and V) of Cd(II) cyclam. Supporting evidence for this came from ^{111}Cd-edited NMR data.

The 1D ^{111}Cd{^{1}H} NMR spectrum acquired for ^{111}Cd-**1** (Figure 4) showed three major ^{111}Cd peaks at 248, 244, and 219 ppm with relative peak areas of 1:0.5:0.1, respectively. The latter minor species was not observed in 1D ^{1}H and 2D NMR spectra. The 2D [^{1}H, ^{111}Cd] HSQC NMR spectrum showed seven ^{1}H/^{111}Cd correlations (Figure 2c): four ^{1}H signals correlated with the major ^{111}Cd resonance at 248 ppm, and three ^{1}H signals correlated with the lower intensity ^{111}Cd resonance at 244 ppm. The 2D [^{1}H, ^{111}Cd] HSQC-TOCSY NMR data (Figure 2b) confirmed the presence of the two spin systems (and hence two major configurations of **1**) identified from the 2D [^{1}H, ^{1}H] TOCSY NMR data. The 2D [^{1}H, ^{13}C] HSQC NMR spectrum also reflects this, showing cross-peaks corresponding to the 11 ^{1}H NMR signals described previously and 6 ^{13}C NMR signals (Figure 5; Table 5). Geminal pairs of protons were identified thus: for configuration I, H_a/H_b (δ ^{13}C 31.12), H_c/H_f (δ ^{13}C 54.53), H_d/H_e (δ ^{13}C 49.73), and for configuration V, H_2/H_4 (δ ^{13}C 49.08), H_3/H_5 (δ ^{13}C 52.29). Because all protons except N*H* belong to geminal pairs in this complex, the remaining cross-

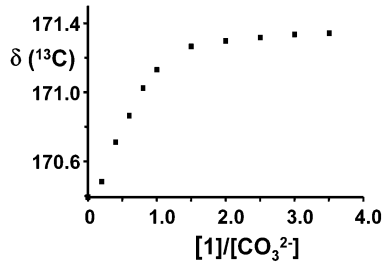

Figure 6. Plot of ^{13}C chemical shift of $^{13}CO_3^{2-}$ versus the molar ratio of **1**/$Na_2{}^{13}CO_3$ at pH 11. A computer best fit to these data gave log $K = 2.6 \pm 0.3$ for a 1:1 complex.

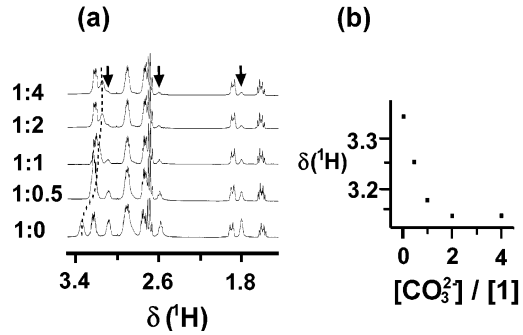

Figure 7. (a) ^1H NMR spectrum of complex **1** before and after addition of various amounts of Na_2CO_3 in 10% D_2O/90% H_2O, pH 9. (b) Plot of NH ^1H NMR chemical shift versus the molar ratio of Na_2CO_3/**1**.

peak for configuration V, H_1 (δ $^1H/^{13}C$ 1.81/27.68), corresponds to two equivalent protons.

Titration of Complex 1 with $^{13}CO_3^{2-}$. In a separate series of NMR experiments, the perchlorate complex **1** was added to a solution of 40 mM $Na_2{}^{13}CO_3$ in 10% D_2O/90% H_2O at pH 11. At this pH, the complex exists predominantly as a single configuration (*trans*-I, see Discussion), and carbonate is fully deprotonated (pK_1, 10.29; pK_2, 6.35).[17] Ten separate additions of **1** were made to the $Na_2{}^{13}CO_3$ solution to give $Na_2{}^{13}CO_3$/**1** molar ratios from 1/0.2 to 1/3.5. The solution was readjusted to pH 11 using 0.1 M NaOH after every addition of the complex. Addition of aliquots of **1** to $^{13}CO_3^{2-}$ resulted in a gradual shift (fast exchange regime) of the ^{13}C resonance of $^{13}CO_3^{2-}$ from 170.4 to 171.33 ppm with an apparent end point at a 1:1 molar ratio (Figure 6). From these data, a binding constant for 1:1 complex formation of log $K = 2.6 \pm 0.3$ was determined.

In a reverse titration, ^1H NMR spectra of **1** were acquired in the presence of increasing quantities of Na_2CO_3 at pH 9, to give **1**/Na_2CO_3 molar ratios of 1/0.5, 1/1, 1/2, and 1/4. The N*H* resonance for **1** in the absence of Na_2CO_3 appeared at 3.31 ppm. At increasing CO_3^{2-} concentrations, the N*H* resonance gradually shifted to lower frequency, reaching an apparent end point at a 1:1 molar ratio. The reduction in the intensity of the ^1H NMR signals H_1-H_5 with simultaneous growth of signals H_a-H_f showed that configuration V converts almost entirely to configuration I under these conditions (Figure 7). Although the ratio of configurations is strongly pH dependent, this effect appears to be due to the presence of Na_2CO_3, given that the solution was readjusted to pH 9.

Effect of pH on Complex 1 Studied by ^1H NMR. The ^1H NMR spectrum of the perchlorate complex **1** in 90% H_2O/10% D_2O was strongly pH-dependent (Figure S3). Only three sharp ^1H NMR peaks (3.11, 3.02, and 1.90 ppm) were observed at pH 5.3, corresponding to the free ligand. No peaks for free ligand were observed at pH > 8.2; at pH 12.1, integration showed that 94% of complex **1** existed in configuration I, and 6% as configuration V. When the pH was lowered from 12.1 to 8.2, free ligand peaks gradually appeared, which accounted for 6% of the total cyclam, with the proportion of configuration V increasing to 39%. The process was reversible by lowering or raising the pH.

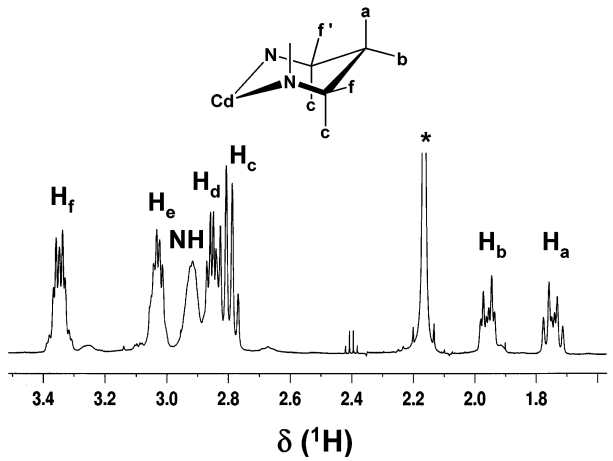

Figure 8. ^1H NMR spectrum of complex **3** in CD_3CN and the labeling scheme for protons in the six-membered ring (chair conformation). Asterisk indicates CHD_2CN.

Solution NMR Analysis of Complex 3. The solution configuration of **3** was studied in CD_3CN. Organic solvents have been used previously to retain CO_3^{2-} bound to a complex in solution.[18] The ^1H NMR spectrum of **3** was acquired immediately after dissolving crystals of **3** in acetonitrile (Figure 8). The 1D ^1H NMR spectrum is similar to that of **1** in H_2O, but it consists of only a single set of resonances. 2D [^1H, ^1H] COSY NMR data revealed the presence of three spin systems (Figure S4). Within the first spin system, resonance a (1.74 ppm) couples to b (1.96 ppm) and to c (2.79 ppm) and weakly to f (3.34 ppm). Resonance b couples strongly to f and weakly to c. In the second spin system, d (2.84 ppm) couples to e (3.02 ppm). The third spin system is composed of three minor peaks corresponding to the free cyclam ligand (m, n, and o: 3.20, 3.13, 1.99 ppm, respectively). Subsequent ^1H NMR spectra acquired on the same sample at later times showed that the signals m−o had increased in intensity, indicating the release of free ligand with time. Minor cross-peaks were also observed and may arise from a second species.

High resolution, first-order resonances for H_a and H_b allowed direct measurement of coupling constants. The spectrum was also simulated. The ^1H NMR resonance for H_a consists of a doublet of triplets of triplets (Figure S5d), the result of coupling to H_b, H_c, and H_f with coupling constants of 16.3, 11.1, and 1.6 Hz, respectively. The H_b ^1H NMR resonance is also a doublet of triplets of triplets (Figure

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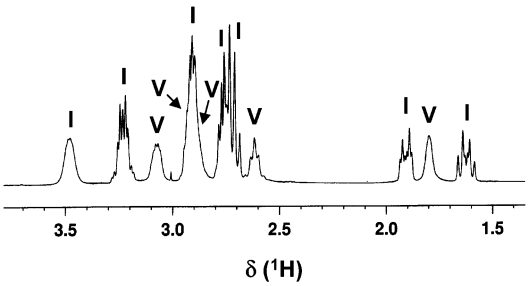

Figure 9. ^{1}H NMR spectrum of complex **2** in 10% D_2O/90% H_2O. Resonances assigned to the *trans*-I configuration are designated I, and resonances for the *cis*-V configuration are designated V. For assignments, see Table 5.

Table 2. ^3J and ^2J (^{1}H, ^{1}H) Coupling Constants (Hz) and Corresponding Torsion Angles (deg) for the Six-Membered Rings of Complex **3**

	$^3J(H_a, H_c)$	$^3J(H_a, H_f)$	$^3J(H_b, H_c)$	$^3J(H_b, H_f)$	$^2J(H_a, H_b)$	$^2J(H_c, H_f)$
simulated	11.0	1.5	1.3	5.7	16.3	12.6
measured	11.1	1.6	1.4	5.7	16.3	
			Torsion Angle			
NMR[a]	164	69	81	39		
X-ray[b]	164	78	81	37		

[a] Torsion angles were calculated using the expression $^3J(^1H, ^1H) = 13.89 \cos^2 \phi_{HH} - 0.98 \cos \phi_{HH} + \sum\Delta\chi_i\{1.02 - 3.4 \cos^2(\zeta_i\phi + 14.9|\Delta\chi_i|)\}$; $\Delta\chi_i$ takes the values 0.97 and 0.196 for C_1 and C_2, respectively. $\zeta_i = \pm 1$ according to the definition of position and negative substituents.[20−22] [b] Torsion angles in the X-ray crystal structure of **3**.

Table 3. $^3J(^{111}Cd, ^1H)$ Coupling Constants (Hz) and Corresponding Torsion Angles (deg) for ^{111}Cd-**1**

	six-membered ring		five-membered ring	
	$^3J(H_c, ^{111}Cd)$	$^3J(H_f, ^{111}Cd)$	$^3J(H_d, ^{111}Cd)$	$^3J(H_e, ^{111}Cd)$
coupling constant (measured)	1.6	27.4	14.0	15.3
		Torsion Angle		
NMR[a]	66	134	115	118
measured[b]	65	177	121	123

[a] Calculated using the expression $^3J(^{111}Cd, ^1H) = 36 \cos^2 \phi - 13 \cos \phi + 1$.[23] [b] Torsion angles measured from a model for *trans*-I based on *cis*-I in the crystal structure of **3**.

S5c), the result of coupling to H_a, H_c, and H_f with coupling constants of 16.3, 1.4, and 5.7 Hz, respectively.

Solution NMR Studies of Complex 2. ^{1}H, ^{13}C, and ^{15}N NMR data were also acquired for the chloride complex **2** in 10% D_2O/90% H_2O (Figures 3a and 9). The NMR data are summarized in Table 5.

Conformational Analysis of Complexes 1 and 3. For **3**, ^3J (^{1}H, ^{1}H) coupling constants were derived from spin system simulations for signals a, b, c, and f (Figure S5; Table 2). For ^{111}Cd-**1**, a fully ^{111}Cd-coupled [^{1}H, ^{1}H]-2D TOCSY NMR spectrum was used to measure $^3J(^1H, ^{111}Cd)$ coupling constants (Table 3).

Extension of the standard Karplus equation[19] by Haasnoot et al.[20] has permitted broader applications. The H−C−C−H fragment in the rings under study carries two non-hydrogen substituents. In this case, the generalized Karplus equation takes the form shown in eq 1,

$$^3J(^1H, ^1H) = 13.89 \cos^2 \phi_{HH} - 0.98 \cos \phi_{HH} + \sum\Delta\chi_i\{1.02 - 3.4 \cos^2(\zeta_i\phi + 14.9|\Delta\chi_i|)\} \quad (1)$$

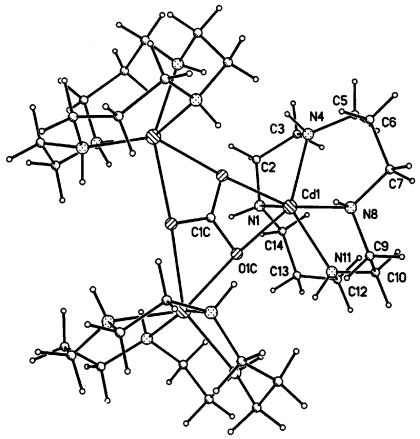

Figure 10. X-ray crystal structure of the cation of complex **3** together with the atom numbering scheme.

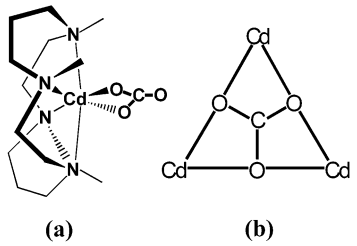

Figure 11. Schematic illustrations of (a) the *cis*-I configuration and (b) the mode of carbonate coordination, in the crystal structure of **3**.

in which ϕ_{HH} is the Klyne−Prelog defined[21] proton−proton torsion angle, and $\Delta\chi_i$ denotes the differences in electronegativity between the substituent S_i and hydrogen on the Huggin's scale[22] corrected for the influence of β substituents;[20] ζ_i takes on a value of +1 or −1 according to the orientation of the substituent S_i with respect to the coupling proton on the same carbon atom.[20]

The only reported Karplus-type correlation between the $^3J(^1H,^{111}Cd)$ coupling constants appears to be that established for cysteine C^β protons and $H^\beta-C^\beta-S^\gamma-Cd$ dihedral angles in proteins.[23] This takes the form shown in eq 2.

$$^3J(^{111}Cd, ^1H) = 36 \cos^2 \phi - 13 \cos \phi + 1 \quad (2)$$

The coupling constants $^3J(^{111}Cd, ^1H)$ for ^{111}Cd-**1** and $^3J(^1H, ^1H)$ for **3** were used to calculate torsion angles based on eqs 1 and 2. Calculated torsion angles and experimentally measured coupling constants are listed in Tables 2 and 3.

X-ray Crystal Structure of $[Cd_3(cyclam)_3(CO_3)](ClO_4)_4 \cdot 3H_2O$ (3). Complex **3** contains carbonate fixed from atmospheric CO_2. The crystal structure of the cation is shown in Figure 10, together with the atomic numbering scheme, and is illustrated schematically in Figure 11a. Selected bond lengths and angles are listed in Table 4. The complex

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Table 4. Selected Bond Distances (Å) and Angles (deg) for **3**

Cd(1)−N(4)	2.270(12)
Cd(1)−N(11)	2.311(12)
Cd(1)−O(1C)	2.373(7)
Cd(1)−N(8)	2.289(12)
Cd(1)−N(1)	2.323(12)
Cd(1)−O(1C)#1[a]	2.412(7)
N(4)−Cd(1)−N(11)	124.5(4)
N(4)−Cd(1)−N(1)	79.9(5)
N(11)−Cd(1)−N(1)	89.7(5)
N(8)−Cd(1)−N(11)	77.3(5)
N(8)−Cd(1)−N(1)	156.7(4)

[a] #1 $-x + y, -x, z$.

contains three independent $\{Cd(cyclam)\}^{2+}$ units. Each unit has a distorted octahedral geometry of the *cis*-CdO_2N_4 type. Each Cd ion is bound to four nitrogens of cyclam with bond lengths for Cd(1)−N(1), Cd(1)−N(4), Cd(1)−N(8), and Cd(1)−N(11) of 2.323(12), 2.270(12), 2.289(12), and 2.311(12) Å, respectively. Two oxygens of the carbonate anion occupy axial positions with Cd−O bond lengths of 2.373 and 2.412 Å. Pairwise bidentate combinations of the three carbonate oxygens join the three $\{Cd(cyclam)\}^{2+}$ units to form a C_3 symmetric arrangement. In each unit, because of the cis coordination of carbonate, cyclam is folded. The configuration of each cyclam unit is *cis*-I (*R,S,R,S*; Figure 1).

Discussion

Solution NMR Analysis of 1. Only the *trans*-I and *trans*-III configurations can give rise to six nonequivalent proton resonances, two of which correspond to the central methylene of the six-membered rings. Because the *trans*-I configuration is considered to be a better fit for larger metal ions (vide infra), species I is likely to correspond to the *trans*-I configuration. The *trans*-IV and *trans*-V configurations have five nonequivalent protons and give rise to five proton resonances, one of which corresponds to the central methylene protons of the six-membered rings. The *cis*-V configuration is strain-free and can exist as two equivalent states in fast exchange on the NMR time scale with averaging of the ^{1}H chemical shifts for the central methylene group. We assign species V to the *cis*-V configuration.

For the six-membered rings, the large difference between two $^3J(^1H, ^{111}Cd)$ couplings (27.4 Hz, torsion angle $^{111}Cd-N-C-H_f$, and 1.6 Hz, torsion angle $^{111}Cd-N-C-H_c$) results from H_c being axial and H_f being equatorial in a six-membered ring with a chair conformation. On the basis of eq 2, the torsion angles $^{111}Cd-N-C-^1H_f$ and $^{111}Cd-N-C-^1H_c$ were calculated to be 134° and 66°, respectively (Table 3). The latter value is similar to that determined from both the crystal structure (*cis*-I configuration) and from a model (*trans*-I configuration), but the former value departs from the expected value of 180° by ca. 45°. This is probably because eq 2 was established on the basis of Cd−S−C−H spin systems in proteins[23] and requires modification for our Cd−N−C−H system in the region 120−180°. Unfortunately, too few data are available to establish a new equation for Cd−N−C−H systems. The $^3J(H_d, ^{111}Cd)$ and $^3J(H_e, ^{111}Cd)$ couplings are very similar (14.0 and 15.3 Hz, respectively), indicating that the five-membered ring is either in rapid equilibrium between two gauche configurations or adopts the eclipsed conformation. In either case, the *trans*-I configuration for **1** in solution differs significantly from that in the crystal structure of complex **3**.

The best-fit M−N bond length for metal coordination to cyclam is 2.06 Å.[24] Such a distance corresponds to a metal with an ionic radius of ca. 0.65−0.7 Å.[24] Because of the flexibility of the cyclam ring, smaller metal ions (ionic radius < 0.75 Å, mainly those of the first row transition metal series) ensure that the cyclam ring adopts the most stable configuration, *trans*-III.[25] With increasing ionic radius, metal ions no longer fit the cyclam cavity well. For example, Hg(II) (1.10 Å) cyclam exists in the *trans*-I configuration in which the metal lies above the cyclam plane,[24] and Pb(II) (1.21 Å) cyclam adopts a *cis*-V configuration.[26] On this basis, it is likely that Cd(II) (0.97 Å) cyclam adopts the *trans*-I rather than *trans*-III configuration. The crystal structure of **3** shows that cadmium cyclam can also adopt the *cis*-I configuration when an additional chelating ligand is bound.

In the *trans*-IV and *trans*-V configurations, because of conformational constraints of the macrocycle, both six-membered rings adopt skew-boat conformations in which the central methylene has two equivalent hydrogens. Possessing higher energy, the skew-boat conformation is not stable. The *trans*-V configuration can fold about diagonals a or b (Figure 1) to form the more common *cis*-V configuration, in which case the six-membered rings exist in a chair conformation, and the five-membered rings in a gauche conformation. The two forms represented in Figure 1 can interconvert rapidly, resulting in the averaging of NMR parameters. Such rapid interconversions on the NMR time scale have been observed for a number of nickel(II) complexes.[27] We did not observe an N*H* NMR signal for the *cis*-V configuration, which may be related either to the interconversion process or to fast exchange with the solvent.

From the ^{13}C NMR titration of $^{13}CO_3^{2-}$ with **1** (Figure 6), and the reverse ^1H NMR titration (Figure 7), it can be concluded that carbonate coordinates to Cd(II) cyclam in aqueous solution. It appears that a 1:1 pyramidal complex $[Cd(cyclam)CO_3]$ is formed with an axially coordinated carbonate anion and cyclam in the *trans*-I configuration.

Effect of pH on Complex 1. Complex **1** is stable only at high pH. At pH < 8.2, dissociation of Cd(II) from cyclam was observed. Free ligand began to appear at pH 8.2, and the complex had dissociated completely by pH 5.3. The *cis*-V configuration converts to *trans*-I with increasing pH, and *trans*-I dominates at highly basic pH. This process is

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Table 5. ^{1}H NMR Chemical Shifts (δ) for Complexes **1**, **2**, and **3** in Various Solvents

				δ, assignment						
complex	solvent	config		NCH_2CH_2N		NCH_2CH_2CH_2N		NCH_2CH_2NCH_2N		NH
1	D_2O/H_2O	*trans*-I	^{1}H	2.91	2.75	3.23	2.69	1.90	1.59	3.31
			^{13}C	49.73		54.53		31.12		
			^{15}N							11.91
			^{111}Cd				248			
		cis-V	^{1}H	2.94	2.58	3.09	2.86	1.81		*a*
			^{13}C	49.08		52.29		27.68		
			^{111}Cd				244			
2	D_2O/H_2O	*trans*-I	^{1}H	2.91	2.77	3.23	2.72	1.91	1.62	3.48
			^{13}C	49.69		54.43		31.05		
			^{15}N							11.72
		cis-V	^{1}H	2.93	2.62	3.07	2.86	1.80		*a*
			^{13}C	49.65		51.95		27.52		
3	CD_3CN	*trans*-I	^{1}H	3.02	2.84	3.34	2.79	1.96	1.74	2.92

[a] Not observed, presumably broadened by exchange.

reversible. Isomerization of *cis*-V to *trans*-I requires the successive inversion of two amine nitrogens via an intermediate *trans*-II configuration (see Figure 1). Base-catalyzed isomerization may occur either by intermolecular attack by hydroxide involving formation of an hydroxo complex, or by intramolecular attack by coordinated hydroxide at the sec-NH centers of the complex.[28] The reverse isomerization and/or dissociation can also be catalyzed by H^+.

Solution NMR Analysis of Complex 3. The exchange behavior of the NH resonance at 2.92 ppm and the appearance of three resonances from the free ligand indicate that this cadmium complex is unstable in CD_3CN. Two ^{1}H NMR spin systems exist for this complex in solution. For H_a, the largest coupling constant of 16.3 Hz can be assigned to a geminal coupling, while couplings of 11.1 and 1.6 Hz can be assigned to vicinal couplings. The large coupling of 11.1 Hz ($^3J_{HaHc}$) indicates a trans-diaxial relationship between H_a and H_c. The H_b ^{1}H NMR resonance is also a doublet of triplets of triplets (Figure S5c), the result of coupling to H_a, H_c, and H_f with coupling constants of 16.3, 1.4, and 5.7 Hz, respectively. The largest splitting also results from a geminal coupling, and the absence of other large splittings indicates that H_b and H_f bear an equatorial relationship to one another. These observations are consistent with a six-membered ring in the chair conformation. However, in the crystal structure, the ligand is folded into a *cis*-I geometry. It therefore seems likely that the weaker Cd−O bond between carbonate and each monocyclam unit breaks and carbonate becomes a μ_3-CO_3^{2-} bridged unit binding to three Cd(II) ions through each of three O atoms, as is typical of Zn(II) complexes with macrocyclic polyamines (e.g., cyclen).[29] Each monocyclam unit of **3** adopts the *trans*-I configuration in CD_3CN.

The torsion angles for the six-membered rings of **3** in CD_3CN determined from ^{1}H NMR data are close to those found in the crystal structure (Table 2). The six-membered rings therefore adopt a chair conformation. In the crystal structure, the five-membered rings adopt the gauche conformation, but the NMR data for **3** in solution indicate an eclipsed conformation for these rings. This can be explained in one of two ways. Either the five-membered rings exercise pseudorotational mobility and average their couplings, giving the appearance of an eclipsed conformation, or the five-membered rings are locked in an eclipsed conformation in the same way as the six-membered rings are locked in the chair conformation.

Crystal Structure of 3. Carbonate can adopt a variety of different coordination modes, as summarized by Einstein and Willis.[30] Complex **3** and the trinuclear Gd(III) complex, $Na_2[\{Gd(DO3A)\}_3CO_3]$ (DO3A = 1, 4, 7-tri(carboxymethyl)-1, 4, 7, 10-tetraazacyclododecane), contain carbonate bound in a bidentate mode to each of three metal ions which form an equilateral triangle, as shown in Figure 11b.[31]

The very sharp bite angle O(1)−Cd−O(2) of 55.5(4)° for complex **3** is similar to that for $[Cd(O_2COH)(Me_4[14]aneN_4)](ClO_4)$ (54.2°).[32] The angle N(4)−Cd−N(11) (124.5(4)°) is closer to the 120° value expected for a trigonal bipyramidal structure than that for the hydrogencarbonate complex (128.9°).[32] The other N−Cd−N angles are normal and lie in the range 77−90°, because the rigidity of the macrocycle causes narrow bite angles for the five-membered chelate rings. Complex **3** may be considered as trigonal bipyramidal with the two donor oxygen atoms occupying an apex of the in-plane triangle.

$Na_2[\{Gd(DO3A)\}_3CO_3]$ differs from complex **3** in that Gd(III) is coordinated to each oxygen of the three carboxylate arms in the *N*-substituted cyclen in addition to four nitrogens and two carbonate oxygens. As far as we are aware, complex **3** is the only known crystal structure of a cadmium complex containing unsubstituted cyclam and the only known crystal structure of an unsubstituted cyclam complex with a *cis*-I configuration.

Conclusions

The biological activity of metal (especially zinc) cyclam complexes[4,33] is likely to be related to their configurations in

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solution because specific binding of cyclams to the coreceptor CXCR4 appears be involved in blocking the entry of HIV into white blood cells.[7] However, the determination of cyclam configurations in solution is a difficult problem especially because a mixture of species can be present. We have investigated the use of Cd as a substitute for Zn to help probe solution structures of metal cyclam complexes. Cadmium has more favorable NMR properties ($I = {}^1/_2$ for ^{111}Cd and ^{113}Cd), although Cd cyclam (log K 11.7)[34] is less stable than Zn cyclam (log K 15.5).[35]

We have synthesized cadmium cyclam perchlorate (**1**), chloride (**2**), and carbonate (**3**) complexes and have made a detailed analysis of the solution configurations of Cd(II) cyclam in solution using NMR spectroscopy. Assignments of ^{1}H, ^{13}C, ^{15}N, and ^{111}Cd NMR signals were made for aqueous or CD_3CN solutions using 1D and 2D methods. Complexes **1** and **2** both exist as equilibrium mixtures of *cis*-V and *trans*-I configurations in aqueous solution and were stable only at high pH. As the pH was decreased below 8.2, dissociation of free ligand was observed, and the complexes dissociated completely by pH 5.3. $^{111/113}$Cd$-^1$H coupling constants were used to derive Karplus-type conformational information about the chelate rings. The only previous application of this procedure appears to be that for Cd thiolate proteins.[23] For the *trans*-I configuration, the $^3J(^{111}\text{Cd}, ^1\text{H})$ coupling constants for ^{111}Cd-**1** in aqueous solution were similar (14.0 and 15.3 Hz), consistent with eclipsed conformations for the five-membered rings. This contrasts with the diverse $^3J(^{111}\text{Cd}, ^1\text{H})$ coupling constants (1.6 and 27.4 Hz) associated with the six-membered rings of the *trans*-I configuration which adopt chair conformations.

Exposure of complex **1** to the atmosphere led to formation of the novel carbonate-bridged tri-cadmium complex **3**, in which cyclam adopts the unusual *cis*-I configuration with all the N−H bonds oriented in the same direction. NMR data show that complex **3** in CD_3CN exists as only one species, the *trans*-I configuration, with eclipsed conformations for the five-membered rings. The torsion angles calculated using an extension of the standard Karplus relation indicate that the six-membered rings adopt conformations in solution close to those in the crystal structure (chair conformations).

These studies of Cd cyclam complexes have allowed us to characterize the *trans*-I and *cis*-V configurations by NMR spectroscopy. This has enabled us to carry out similar NMR studies for Zn cyclam complexes (to be reported elsewhere). For Zn cyclam in aqueous solution, in addition to the *trans*-I and *cis*-V configurations, we have detected the *trans*-III configuration, which becomes dominant because Zn(II) is a smaller metal ion than Cd(II) and is a better fit for the cyclam ring cavity.

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Supporting Information Available: Crystallographic information (CIF). Figures S1−S5 showing 2D [^{1}H, ^{1}H] COSY, TOCSY NMR spectra and pH dependence of the ^{1}H NMR spectrum for complex **1** and 2D [^{1}H, ^{1}H] COSY and experimental and simulated ^{1}H NMR spectra for complex **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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