C_6H_5SH, 108-98-5; 3-NCC_6H_4COCl, 1711-11-1; 5-Ac-2-OHC_6H_3COCl, 108295-15-4; 5-Et-2-$OHC_6H_3CO_2H$, 51-27-4; 2-*n*-PrC_6H_4OH, 644-35-9; 4-MeC_6H_4SH, 106-45-6; 2-Br-4-EtC_6H_3OMe, 99179-98-3; 3-Me-2-$OHC_6H_3CO_2H$, 83-40-9; C_6H_6, 71-43-2; 3-Pr-2-$OHC_6H_3CO_2H$, 22890-52-4; 2-$OHC_6H_4CO_2H$, 69-72-7; 4-MeC_6H_4COCl, 874-60-2; C_6H_5COCl, 98-88-4; 4-ClC_6H_4SH, 106-54-7; 4-ethylphthalic anhydride, 35081-12-0; 4-ethylphenyl 3-cyanobenzoate, 108295-14-3; 2-furoyl chloride, 527-69-5; 4-ethylphenyl 2-furoate, 108319-34-2; 4-ethylphenyl 3-thenoate, 69582-66-7; thiophene, 110-02-1; 4-cyanopyridine, 100-48-1; 2-cyanopyridine, 100-70-9; 2-chlorothiophene, 96-43-5; 1-methylpyrrole, 96-54-8.

Stereocontrolled Syntheses for the Six Diastereomeric 1,2-Dihydroxy-4,5-diaminocyclohexanes: Pt^{II} Complexes and P-388 Antitumor Properties[1]

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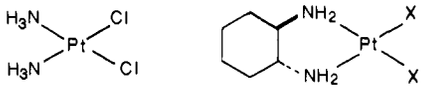
Stereocontrolled syntheses for the six diastereomeric 1,2-dihydroxy-4,5-diaminocyclohexanes **3a–f** from cyclohexene diamines *cis*-**4** and *trans*-**5** are described. Cbz-protected species *cis*-**9** and *trans*-**11**, respectively, served as a source of stable Cbz-protected precursors to these cyclohexanediol diamines (CDD), which were liberated upon catalytic (H_2, Pd/C) hydrogenation. Catalytic osmylation of **9** afforded a mixture of diastereomeric diols **13** and **14**, which served as precursors to cis-anti-cis CDD **3b** and cis-syn-cis CDD **3a**, respectively, whereas osmylation of **11** yielded the expected single product **12**, the precursor to cis-anti-trans CDD **3d**. Epoxidation of olefins **9** and **11** afforded oxiranes **15** and **17**, respectively, which upon acid-catalyzed hydrolysis produced the corresponding Cbz-protected diols **16** and **18**, which served as precursors to CDD trans-anti-cis **3c**, and trans-anti-trans **3e**. Formation of diol **18** from oxirane **17** was accompanied by formation of 2-oxa-4-azabicyclo[3.3.1]nonan-3-one **19**. CDD trans-syn-trans **3f** was prepared from diol **12** via regioselective monoacetylation, yielding **22**, followed by oxidation to afford ketone **24**. Sodium borohydride reduction and acetylation produced diacetate precursor **26**. $Pt^{II}Cl_2$ complexes of five of the diamines (**3a–d,f**) are described, and their activities were compared with cisplatin (**1**) by employing P-388 leukemia implanted CDF_1 mice. The data indicate that stereochemistry of the amino groups on the cyclohexanediamine ligand modulate the expression of toxic effects, and depending upon hydroxyl and amino group stereochemistry, there is a marked effect on complex formation (e.g., Cl_2Pt^{II}-**3e**) and solubility characteristics (e.g., Cl_2Pt^{II}-**3c**). Acetylation of the hydroxyl functions in selected isomers (**28a–c**) rendered the Pt^{II} complexes inactive. A single-crystal X-ray structure of compound **3a** was determined at room temperature and indicated the cis-syn-cis arrangement of the OH and NH_2 groups.

The clinical utility of antineoplastic platinum complexes, typified by cisplatin (**1**), has engendered numerous studies directed toward understanding the unique biological properties exhibited by such species.[2] Additionally, congeners of **1** are desired that do not share its severe nephrotoxicity and emetic potential thereby limiting the effective therapeutic use of the drug.[2b,3] Second-generation organoplatinum compounds include 1,2-diaminocyclohexane-Pt^{II} complexes (**2**),[4] which display less nephrotoxicity, decreased cross resistance with cisplatin, or a somewhat expanded antitumor spectrum when compared to **1**.[2a] Structure–activity studies[4–9] of **2** have focused on the labile ligands which modify aqueous solubility,[10] reactivity in vivo with DNA bionucleophiles[2e–g,i,j] such as the N-7 position of guanine,[2c,d,j] and toxicity.[11] Although numerous efficacious and sometimes water-soluble drugs have been prepared,[4–9] problems[5,12] associated with modification of the leaving group in **2** are exemplified by complexes having inadequate water solubility (**2a**) or chemical instability (**2c,d**), thus producing unacceptable



1

2a, X = Cl
b. X = malonate
c. X = SO_4
d. X = NO_3

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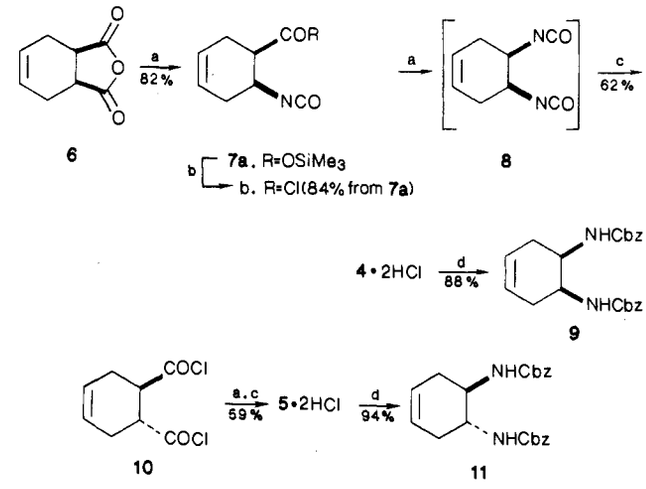
toxicity[11] and/or dosage limitations. Relatively unreactive species such as malonate **2b**, however, generally have reduced toxicity.[12]

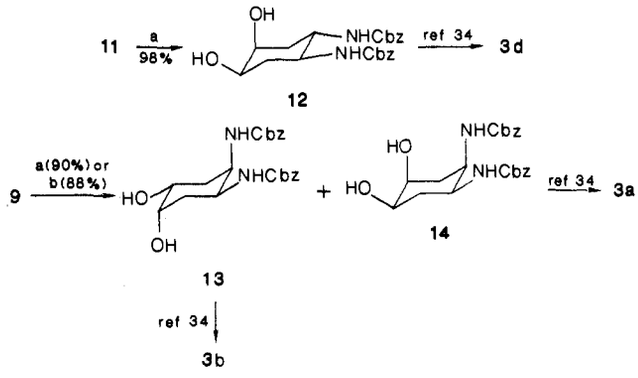
A variety of cyclic, alicyclic, and aromatic primary and secondary mono- and diamines have served as ligands for Pt^{II} [13,14] and Pt^{IV} [13,14] complexes. In contrast, drug development based upon hydroxyl group functionalization of the diaminocyclohexane ring of **2** seems not to have been investigated. Very recently, however, Pt^{II} complexes of amino sugars have been shown to have good activity against sarcoma S-180 in mice.[15] The steric[14] or electronic[16,18] properties of the diamine ligand have been shown[14,16-20] to modulate diffusion, absorption, and/or interaction of the Pt complex with DNA and consequently bioactivity. In this paper, we describe biological studies for five of the six dichloro Pt^{II} complexes and stereocontrolled syntheses for the cyclohexanediol diamine (CDD) ligands **3a–f**. These compounds were prepared in order to assess the effect of hydroxyl group substitution on the physical properties of the complexes and their bioactivity in the P-388 model. For the Cl_2Pt^{II} complexes of stereoisomers **3**, we envisioned[1] that hydroxyl substitution on the cyclohexane ring may intrinsically (or by derivatization) render the organoplatinum species more water soluble than the simple diaminocyclohexane complex, thereby facilitating intravenous administration. We also suggested[1] that such complexes may be less toxic owing possibly to a more facile excretion via the kidney because of enhanced water solubility of the parent drug or a conjugated metabolite. To facilitate discussion, relative stereochemical relationships of substituents are defined beginning with C-1 and proceeding clockwise as follows:

Scheme I[a]

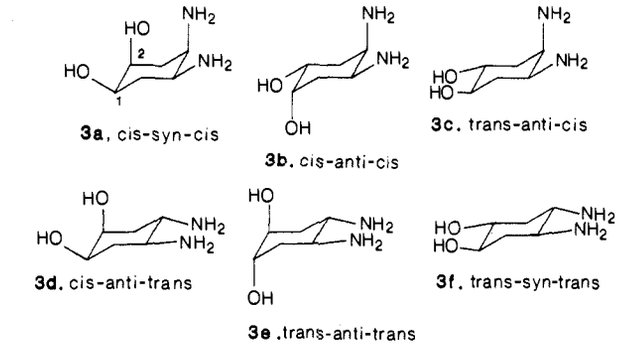


[a] a = Me_3SiN_3, dioxane; b = $SOCl_2$, catalytic DMF, CCl_4; c = concentrated HCl, 35 °C; d = CbzCl, 1,2,2,6,6-pentamethylpiperidine (PMP), aqueous THF, 0 °C.

Scheme II[a]



[a] For a, 1.3:1.0 (13:14); for b, 2.1:1.0. a = *N*-methylmorpholine *N*-oxide (NMO), catalytic OsO_4, aqueous acetone/*t*-BuOH, room temperature 16 h; b = NMO, catalytic OsO_4, aqueous acetone/*t*-BuOH, −20 °C, 5 days.



Chemistry. Overall our synthetic plan was based upon oxidative manipulation of the suitably protected diaminocyclohex-4-enes **4** and **5** owing to their anticipated facile and stereospecific preparation.[21-23] Stereocontrolled

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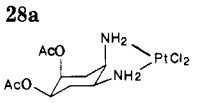
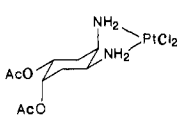
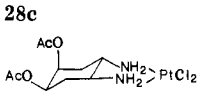
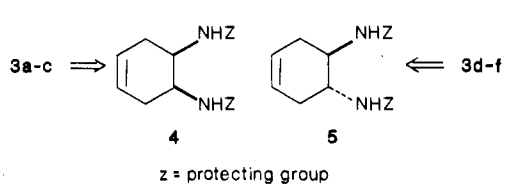
Table I. Comparative Evaluation of Pt^{II} Complexes in P-388 CDF_1 Mice

compound	dose, mg/kg[a]	MST	T/C[b]
cisplatin	6	24.5	249
	3	18.5	188
	1.5	15.5	158
saline		9.8	
Cl_2Pt^{II}-**3a**	40	14.5	138
	20	12.0	114
	10	12.5	119
	5	11.2	106
saline		10.5	
Cl_2Pt^{II}-**3b**	40	16.5	157
	20	14.0	133
	10	12.5	119
	5	11.8	113
saline		10.5	
Cl_2Pt^{II}-**3c** (crude)[c]	80	14.5	141
	60	16.0	155
	40	13.8	134
	20	14.0	136
	10	12.5	121
saline		10.3	
Cl_2Pt^{II}-**3d**	40	3.0	29
	20	4.5	43
	10	12.8	122
	5	12.5	119
saline		10.5	
Cl_2Pt^{II}-**3f**	40	6.0	55
	20	10.8	98
	10	6.0	55
	5	12.5	114
	2.5	12.5	114
saline		11.0	
28a	40	11.3	103
	20	11.3	103
	10	11.1	101
	5	11.0	100
saline		11.0	
28b	40	11.3	102
	20	11.0	100
	10	11.1	101
	5	10.5	95
saline		11.0	
28c	40	12.2	111
	20	12.0	109
	10	11.5	105
	5	10.9	99
saline		11.0	

[a] All drugs injected ip on day 1. [b] Toxic T/C < 85, active T/C > 120. [c] Control experiments using K_2PtCl_4 established that the observed activity was due to the crude CDD-Pt^{II} complex.

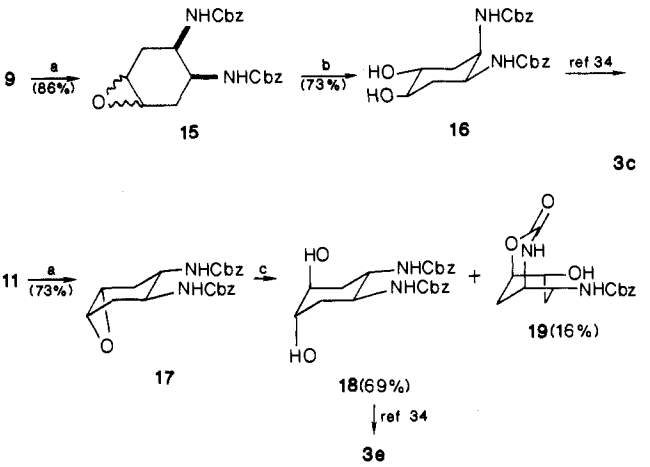
glycol formaton via mild and readily available reagents[24,25] was anticipated to provide the target diol diastereomers **3a–f**.



Stepwise Curtius rearrangement[22] of the respective acyl azides available from anhydride **6** and acid chloride **7b** (Scheme I) followed by subsequent hydrolysis of the bis(isocyanate) **8** afforded *cis*-**4**·2HCl in 50% overall yield. Similarly, bis(acid chloride) **10**[23] was converted to *trans*-**5**·2HCl in 59% net yield. Respective bis(benzyl carbamates) (Cbz ≡ carbobenzoxy)[26] **9** and **11** were desired, since subsequent applications of these CDDs required facile amine deprotection without inorganic byproducts.[27,28] Amine acylation[29] using common organic bases such as triethylamine or pyridine as acid scavengers gave unsatisfactory yields, but application of 1,2,2,6,6-pentamethylpiperidine (PMP)[30,31] in aqueous THF provided bis(Cbz) derivatives **9** and **11** in excellent yield by recrystallization of the crude reaction mixtures. Addition of excess benzyl alcohol[32] to the intermediate bis(isocyanates) afforded the desired diastereomers **9** and **11** in approximately 30% yield, but extensive chromatographic procedures were required to separate desired materials from complex mixtures.

Catalytic osmylation[33] of *trans*-**11** afforded cis-anti-trans diol **12** (98%), which served as a stable source of **3d**[34] (Scheme II; Table II). Similar osmylation of *cis*-**9** at room temperature for 16 h proceeded with little stereocontrol; a 90% yield of a 1.3:1.0 ratio of diol **13** to the sterically more congested isomer **14** was obtained. Glycol formation at −20 °C resulted in a modest increase 2.1:1.0, respectively) in stereoselectivity. Contrary to our expectations, these results indicate that the pseudoaxial carbamate presents only a minor degree of steric impedence to OsO_4 for approach to the system.

Scheme III[a]



[a] a = MCPBA, CH_2Cl_2, room temperature; b = 1% aqueous H_2SO_4, Me_2CO or THF, room temperature, 6 h; c = 1% H_2SO_4, Me_2CO or THF, room temperature, 2 h.

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(34) Bis(Cbz) derivatives of diol diamines **3a–f** were stored until needed as a source of the unprotected compound. Except for trans-anti-trans **3e**, diol diamines were derivatized and characterized as their $Pt^{II}Cl_2$ complexes. Apparently, trans-anti-trans CDD **3e** is primarily oxidized by K_2PtCl_4 although 1% of yellow-green crystals formed. Prior to formation of such complexes, ^1H NMR analysis proved useful for structural analysis of these easily air oxidizable CDD.

Table II. 500-MHz ^1H NMR Resonance Signal (δ) Assignments for CDD Diastereomers **3a–f**

compd	proton no.[a]							
	H_1	H_2	H_{3a}	H_{3e}	H_4	H_5	H_{6a}	H_{6e}
3a	3.75–3.95		1.85–1.98	1.98–2.20	3.52–3.60		1.85–1.98	1.98–2.20
3b	3.86–3.96		1.88–1.96	2.00–2.08	3.89–3.93		1.88–1.96	2.00–2.08
3c	3.72	3.83	1.82	2.07–2.16	3.80	3.67	1.86	2.07–2.16
3d	3.73	3.95	1.68	2.22	3.52	3.42	1.82	2.02
3e	3.52–3.60		1.55–1.63	2.28–2.34	3.43–3.50		1.55–1.63	2.28–2.34
3f	3.89–3.93		1.95–2.02	2.02–2.10	3.60–3.64		1.95–2.02	2.02–2.10

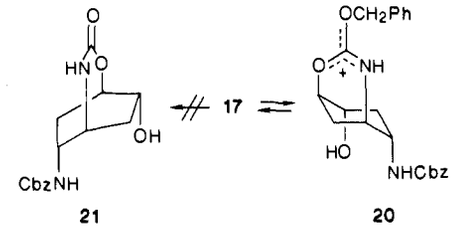
[a] Compounds **3a–f** are numbered by starting with the carbon bearing hydroxyl group as no. 1 in the lower left part of the ring as drawn in the body of the manuscript.

^1H or ^{13}C NMR spectroscopic techniques were not useful for unambiguously distinguishing cis-anti-cis diol **13** from cis-syn-cis diol **14**. However, notable differences in the 500-MHz ^1H spectra of these compounds supported the indicated assignments, which were made in accord with literature precedent.[24] At identical concentrations in acetone-d_6 solution, the NH (δ 6.45) and OH (δ 4.14) proton resonance signals in **14** were downfield relative to those of **13** (δ 6.27 and 3.70, respectively). Intramolecular hydrogen bonding owing to the 1,3-diaxial relationship of OH and NH functions in **14** (also present in its alternate conformation) could account for this downfield shift.[35,36] Furthermore, the NH protons in diol **14** exchange with D_2O at a much faster rate (15 min) than those in **13** (significant exchange not observable after 30 min). Hydroxyl proton exchange with D_2O proceeded equally rapidly for both isomers. Confirmation of the relative stereochemical assignments for these isomers was provided by X-ray analysis of the dichloro Pt^{II} complex of **3a** (derived from **14**), which clearly showed the cis-syn-cis arrangement of OH and NH_2 functions.

Epoxidation of olefins **9** and **11** was effected at room temperature with 2 equiv of freshly purified *m*-chloroperbenzoic acid (MCPBA),[37] and each afforded a single epoxide, **15** (86%) and **17** (73%), respectively (Scheme III). Unlike epoxide **17**, which has a C_2 axis of symmetry and whose 500-MHz ^1H NMR spectrum is first order (Experimental Section), **15** displayed a deceptively simple spectrum with insufficiently resolved two-proton resonance signals at δ 3.85 (H-3 and H-4), 3.2 (H-1 and H-6), and 2.35 (H-2e and H-5e) to permit determination of stereochemistry.

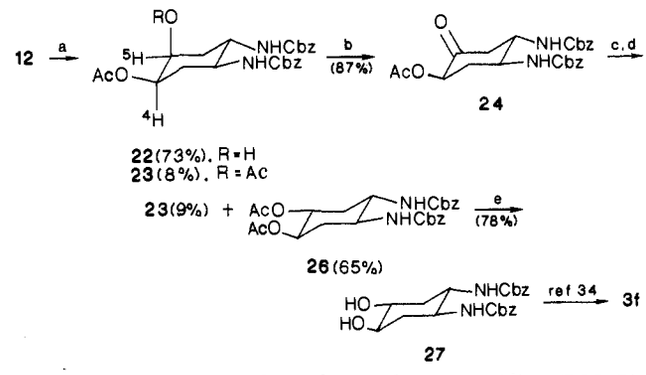
Acid-catalyzed hydrolysis (Scheme III) of epoxides **15** and **17** at room temperature afforded trans-anti-cis diol **16** (73%) and trans-anti-trans diol **18** (69%), respectively, which in turn served as stable precursors to diol diamines **3c** and **3e**. Formation of **18** from oxirane **17** was accompanied by formation of bicyclic compound **19** (16%). The ratio of **18** to **19** was unchanged at temperatures between 0 and 65 °C. Treatment of oxirane **17** with glacial HOAc in the presence[38] or absence[39] of NaOAc, or with H_2O_2/HCO_2H,[40] mainly afforded carbamate **19** with only a trace of diol **18**.

Formation of the bicyclo[3.3.1] system **19** is proposed to arise from putative intermediate **20**, which results from intramolecular diaxial opening of epoxide **17** by urethane oxygen. This pathway (eq 1) should be favored over an



alternative intramolecular mode of epoxide cleavage which would lead to the bicyclo[3.2.2] skeleton **21**, even though transition states leading to each are allowed processes.[41] However, ^1H NMR double resonance experiments could not distinguish between these regioisomers. Correlation of long-range H–C couplings (COLOC)[42] carried out on the debenzylated oxazanonanone derived from **19** clearly established carbamate **19** as the product. Correlation between the proton resonance signals at δ 3.78 and 4.55 with the carbonyl resonance signal at 156 indicated that these proton signals could be assigned to H-5 and H-1, respectively. Observation of a similar three-bond J_{C-H} correlation between the resonance signals for H-1 and C-5 (δ 46) and H-5 and C-1 (δ 75) can only take place in the debenzylated bicyclo[3.3.1] product derived from **19**.

Scheme IV[a]



[a] a = 1.1 equiv of Ac_2O, 4-(dimethylamino)pyridine (DMAP), THF, −25 °C, 24 h; b = 2.5 M Cr^{6+}, acetone, ice bath, 2 h; c = $NaBH_4$, THF, EtOH, −78 °C, 1 h; d = Ac_2O, DMAP, Et_3N, room temperature, 1 h; e = K_2CO_3, MeOH, 1 h, heat, 1.5 h.

The synthesis of **3f** was achieved from cis-anti-trans diol **12** (Scheme IV). Regioselective acetylation [1.1 equiv of Ac_2O with 4-(dimethylamino)pyridine as catalyst] in THF at −25 °C furnished monoacetate **22** (73%) contaminated with diacetate **23** (8%) (independently prepared from **12** in 92% yield by using excess Ac_2O at room temperature). Anticipated equatorial acetylation[43] in **22** was confirmed

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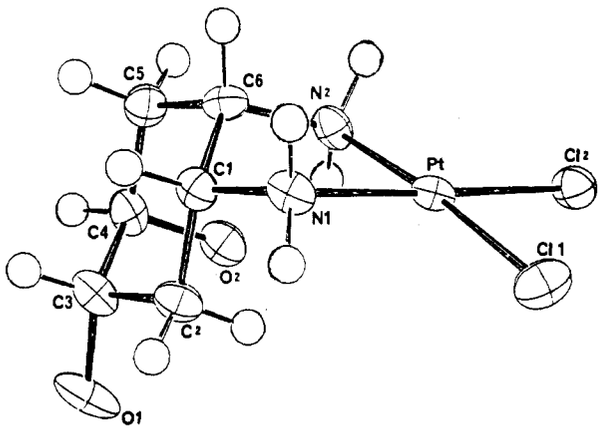

Figure 1. ORTEP drawing with 50% probability thermal ellipsoids for the non-hydrogen atoms in **3a**. The hydrogen atoms are drawn with an artificial radius and are labeled according to the attached carbon atoms.

by ^{1}H NMR analysis. Decoupling of equatorial hydrogen H-5 (δ 4.5) (α to the OH group in **22**) revealed the requisite axial–equatorial and diaxial coupling constants of 5 and 12 Hz between H-4 (δ 5.10) and the C-3 methylene protons. Jones oxidation of alcohol **22** afforded keto acetate **24** (87%). Reduction ($NaBH_4$) and acetylation afforded diacetates **26** (65%) and **23** (9%), which were separated by crystallization. Deacetylation of **26** (MeOH, K_2CO_3) afforded diol **27**, a stable precursor to CDD **3f**.[34]

CDD **3a–f** formed hygroscopic salts. The free amines were characterized by 500-MHz ^{1}H NMR spectroscopy (Table II) and/or by conversion in situ to their Pt^{II} complexes prepared by treatment with K_2PtCl_4. Hydroxylated diamine ligands were platinated[19] following catalytic N-debenzylation of the corresponding bis(*N*-Cbz) species. A single-crystal X-ray structure determination of **3a** (Figure 1) was necessary to unambiguously differentiate this diastereomeric ligand from **3b**. This analysis also showed a water molecule to be hydrogen bonded within the crystal lattice. Four of the six CDD provided pure complexes [Cl_2Pt^{II}-**3a**·H_2O (37%), Cl_2Pt^{II}-**3b**·H_2O (43%), Cl_2Pt^{II}-**3d**·H_2O (73%), Cl_2Pt^{II}-**3f**·H_2O (61%)], all of which were obtained as sparingly water soluble monohydrates. Curiously, the trans-anti-cis and trans-anti-trans diastereomers **3c** and **3e**, respectively, did not afford crystalline Pt^{II} derivatives. In the case of the former, we suspect that the complex formed, but the compound could not be purified by crystallization from the crude highly water soluble yellow solid obtained following removal of solvent. Nevertheless, the impure "complex" was examined for antitumor activity. For **3e**, which forms <5% complex, there is an apparent preference for an alternate reaction pathway. After 24h, the reaction mixture was dark green-black and contained a fine black powder, indicative of amine oxidation by Pt^{II}. At risk of violation of the Curtin-Hammett principle, possibly the rate of diaxial diamine oxidation competes favorably with platination since the two cyclohexane conformers may not rapidly interconvert owing to a relatively more stable intramolecular diequatorial dihydroxy H-bond. Clearly, further work is necessary to substantiate this possibility.

The Pt^{II} complexes of acetate esters **28a** (49%) and **28b** (65%) (Table I) were prepared from bisacetylated **14** and **13**, respectively, as possible lipid-soluble prodrug analogues. Thus, reaction of **9** with a catalytic amount of OsO_4/*N*-methylmorpholine *N*-oxide followed by acetylation [Ac_2O, 4-(dimethylamino)pyridine] affords bisacetylated **14** and **13** in 80% net yield. Debenzylation and platination afforded **28a** and **28b**, respectively. Similarly, diol **12** afforded bisacetylated **12** (92%), which upon debenzylation and platination yielded **28c** (73%).

Biological Results and Discussion

Antineoplastic evaluation of the dichloro Pt^{II} complexes was carried out in vivo by employing CDF_1 mice, seven per group implanted with P-388 acute lymphocytic leukemia. The compounds were administered in a single intraperitoneal dose 24 h after the intraperitoneal implantation of 10^6 P-388 tumor cells. Analysis of antitumor activity was carried out according to NCI protocol by comparing the median survival time (MST) of the treated groups vs. the MST of the untreated control groups, expressed as a percentage (T/C). Cisplatin served as a positive control (Table I).

Pt^{II} complexes of CDD ligands **3a–c** having cis amino groups were the most efficacious of the five diastereomers tested, but none of these materials was more potent than cisplatin. CDD Pt^{II} complexes **3d** and **3f** having trans amino functions were more toxic than complexes **3a–c**. Previously, *cis*-1,2-diaminocyclohexane–Pt^{II} analogues were shown to have lower host toxicity and a better therapeutic index against Sarcoma 180[7] than optically active trans species **2**, but both trans analogues were more efficacious than the corresponding cis isomer against L-1210 and P-388.[44]

The possibility that poor lipid solubility was a primary determining factor resulting in reduced antitumor activity of the CDD Pt^{II} complexes led us to test selected bis(acetates) **28a–c**. However, these acetylated derivatives were devoid of both antitumor activity and host toxicity at the dose employed. Possibly these data reflect poor diffusion of these insoluble materials limiting drug access to vital macromolecular targets in the host animal or in P-388 cells housed in the peritoneal cavity.

Clearly, these compounds have an attenuated antitumor activity in this limited series relative to that exhibited by cisplatin. Amino group stereochemistry, at least in the P-388 model, most influences host toxicity. Additionally, the relative stereochemistry of the amino and hydroxyl functions can markedly affect complex formation or lack thereof (e.g., Cl_2Pt^{II}-**3e**) as well as solubility characteristics (e.g., Cl_2Pt^{II}-**3c**). The significant H-bonding network observed in the crystal structure of Cl_2Pt^{II}-**3a** (Figure 3, Experimental Section) likely competes for water of solvation, thus rendering this compound sparingly soluble in this solvent. These observations shall be important in future drug development since previous attempts to improve the water solubility of complexes of the type **2** focused on the nature of the leaving group.[7,14] No further work with these specific complexes is planned at this time since all systems studied were less effective P-388 leukemia than cisplatin or stereoisomers of **2a**.[14]

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded with a Beckman Model 4230 spectrophotometer. Nuclear magnetic resonance spectra were recorded by using either a Bruker WP-80 or HX-90E 300-MHz or 500-MHz spectrometer. Me_4Si ($CDCl_3$, Me_2SO, acetone, or pyridine) or TSP (D_2O) were used as internal standards. Chemical shifts are reported on the δ scale with peak multiplicities as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets. THF was freshly distilled from Na/benzophenone ketyl. Dioxane was distilled first from CaH_2 and then from Na/benzophenone ketyl. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

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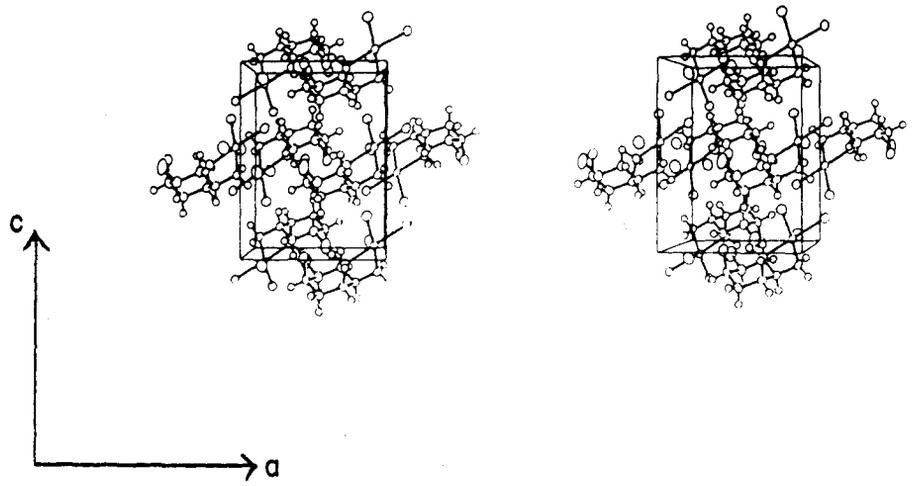

Figure 2. Stereodrawing of the unit cell for **3a**. The *b*-axis points into the plane of the page.

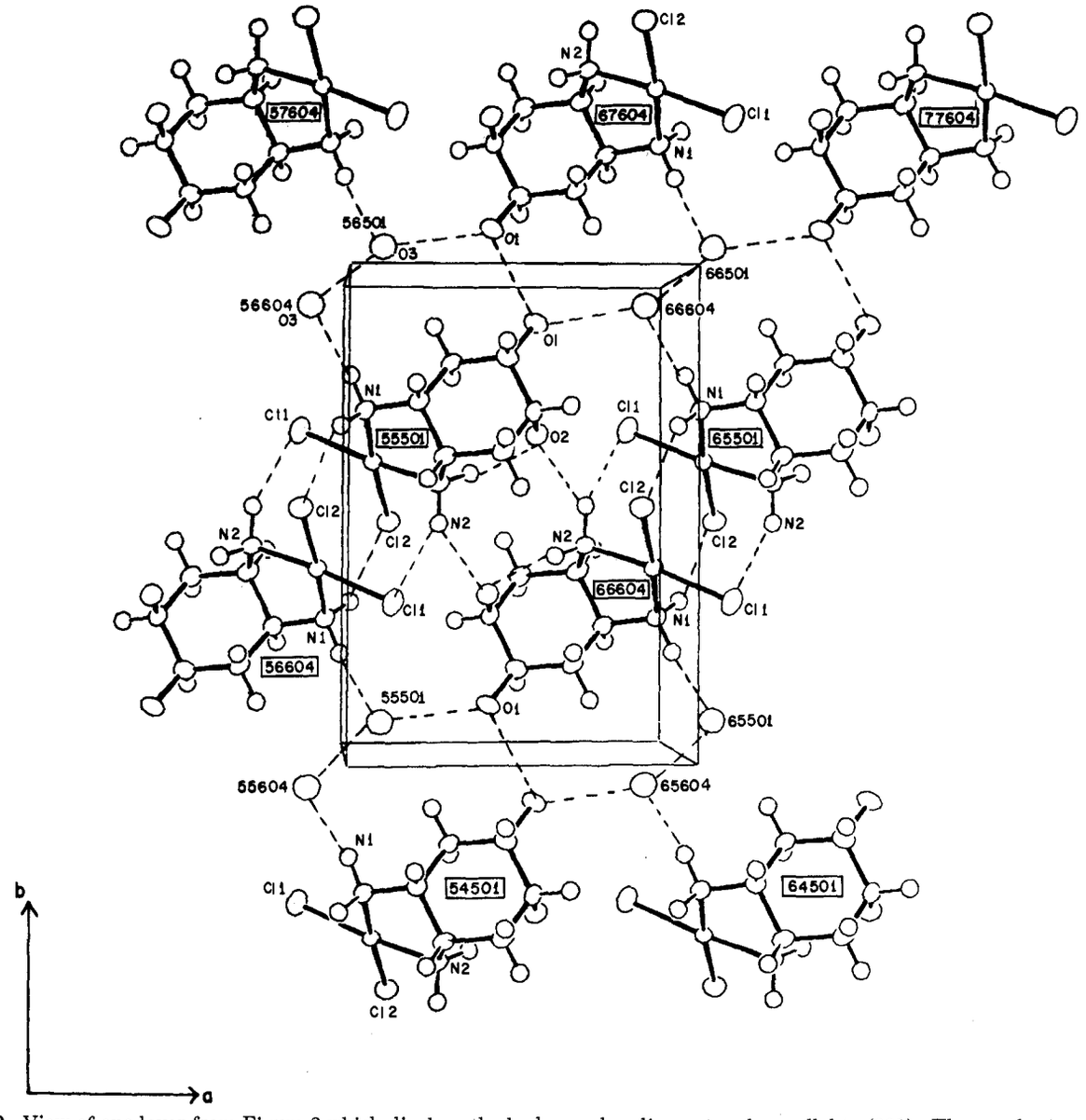

Figure 3. View of one layer from Figure 2 which displays the hydrogen bonding network parallel to (001). The numbering scheme used to define each molecule is the atom designator code as described in the ORTEP program (ORTEP II, C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, TN, 1976). The symmetry operator numbers are defined as 1 = x,y,z and 4 = $\bar{x},\bar{y},\bar{z}$.

Diastereomeric 1,2-Dihydroxy-4,5-diaminocyclohexanes 3a–f. Deprotection of the Respective Cbz-Protected Diol Diamines. The respective Cbz-protected diamines (100 mg, 0.242 mmol; **12** → **3d**, **13** → **3b**, **14** → **3a**, **16** → **3c**, **18** → **3e**; **27** → **3f**) were dissolved in 5 mL of MeOH. Catalyst (10% Pd/C; 20 mg) was added and the bottle alternately evacuated (H_2O aspirator)

and refilled to 20 psi with H_2 five times. The suspension was shaken under 20 psi of H_2 for 2 h. Following filtration (Celite), the colorless filtrate was concentrated in vacuo routinely affording >90% of the free diamines **3a–f**, whose NMR spectra are recorded in Table II.

***cis*-4-Cyclohexene-1,2-diamine Dihydrochloride (4·2HCl).** Acid chloride **7b** (12.61 g, 68 mmol) was dissolved in 40 mL of dry dioxane under argon in an oven-dried 250-mL round-bottom flask. Trimethylsilyl azide (Me_3SiN_3) (11.03 g, 95 mmol) was added at room temperature by pipette to the stirred solution, which was subsequently heated to 80–85 °C in an oil bath. **Caution**: Vigorous N_2 evolution began within 5–10 min (remove heating bath) and continued for 20–30 min. Reheating to 80 °C may be necessary to ensure completion of rearrangement. The reaction was cooled to 35–40 °C and diluted with 25 mL of Me_2CO.

Concentrated HCl (17 mL) was added cautiously through the top of the condenser. Stirring was continued until CO_2 formation ceased (ca. 30 min). The precipitate was filtered and washed with Me_2CO and Et_2O, providing 7.5 g (60%) of the diamine salt as a white powder: mp 255–265 °C; IR (KBr) 2800 and 1460 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 5.62 (deceptively simple t, 2 H, olefinic), 3.75–3.9 (m, 2 H, methines), 2.0–2.6 (m, 4 H, methylenes). Anal. ($C_6H_{14}N_2Cl_2$) C, H, N, Cl.

***trans*-4-Cyclohexene-1,2-diamine Dihydrochloride (5·2HCl).** Trans bis(acid chloride) **10** (4.7 g, 23 mmol) was dissolved in 10 mL of dry dioxane under argon in an oven-dried 50-mL round-botton flask. Me_3SiN_3 (5.85 g; 50 mmol) was added by pipet at room temperature and the reaction carried out and worked up as for 4·2HCl with 15 mL of Me_2CO followed by cautious addition of 7 mL of concentrated HCl. The precipitate was collected by filtration and washed with Me_2CO and Et_2O, affording 2.6 g (61%) of white powder: mp >280 °C (lit.[21] mp >320 °C); IR (KBr) 2820, 1600, and 1515 cm^{-1}; NMR (90 MHz, D_2O) δ 5.6–5.7 (m, 2 H, olefinic), 3.6–3.8 (m, 2 H, methines), 2.0–2.7 (m, 4 H, methylenes). Anal. ($C_6H_{14}N_2Cl_2$) C, H, N, Cl.

Trimethylsilyl *cis*-6-isocyanato-3-cyclohexene-1-carboxylate (7a) was prepared according to the method of Kricheldorf.[22] *cis*-1,2,3,6-Tetrahydrophthalic anhydride (**6**, Aldrich, recrystallized from toluene, 15.0 g, 99 mmol) was dissolved in 90 mL of dry dioxane under argon in an oven-dried 250-mL round-botton flask. Me_3SiN_3 (16.0 g, 138 mmol) was added by pipet to the stirred solution held at room temperature. The gently stirring solution was immersed in an oil bath preheated to 80–85 °C. N_2 evolution ceased after 30–45 min. The solution was cooled to 35–40 °C and concentrated in vacuo (bath temperature <35 °C) to a slightly yellow oil, which was purified by distillation under reduced pressure to furnish 19.36 g (82%) of a colorless liquid: bp 80–84 °C (0.4 torr) [lit.[22] bp 82–84 °C (0.4 torr)]; IR (neat) 2250 and 1720 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 5.5–5.9 (m, 2 H, olefinic), 4.2–4.3 (m, 1 H, H-6), 2.5–2.8 (m, 1 H, H-1), 2.3–2.5 (m, 4 H, methylenes), 0.3 (s, 9 H, $SiMe_3$).

***cis*-6-Isocyanato-3-cyclohexene-1-carbonyl chloride (7b)** was prepared by a modification of the method of Kricheldorf[22] wherein use of a catalytic amount of DMF provided an improved yield at lower temperature: Trimethylsilyl ester **7a** (19.36 g, 81 mmol) was dissolved in 40 mL of CCl_4. DMF (10 drops) was added followed by freshly distilled $SOCl_2$ (15.18 g, 113 mmol). The reaction mixture was heated to 40–50 °C in an oil bath. Gas evolution began within 5–10 min. The temperature of the reaction mixture was maintained at ca. 50 °C until the infrared absorption at 1720 cm^{-1} (ester) had disappeared (30–45 min). The solution was cooled to room temperature and concentrated in vacuo to a viscous yellow liquid, which was distilled under reduced pressure to furnish 12.61 g (84%) of **7b** as a colorless liquid: bp 60–62 °C (0.15 torr) [lit.[22] bp 70–72 °C (0.2 torr)]; IR (neat) 2260 and 1790 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 5.5–5.9 (m, 2 H, olefinic), 4.4–4.5 (m, 1 H, H-6), 3.0–3.2 (m, 1 H, H-1), 2.4–2.6 (m, 4 H, methylenes). This compound was used immediately for the next reaction.

Bis(phenylmethyl) *cis*-4-Cyclohexene-1,2-diylbis(carbamate) (9). Dihydrochloride 4·2HCl (2.35 g, 13 mmol) was dissolved in 40 mL of THF and 5.0 mL of distilled H_2O and cooled in an ice bath. 1,2,2,6,6-Pentamethylpiperidine (PMP; 7.87 g, 58 mmol) was added by pipet. After 10 min, a cold (0 °C) solution of benzyl chloroformate (4.34 g, 25 mmol) in 10 mL of THF was added dropwise over 15 min. Vigorous stirring was maintained for 1 h at ice-bath temperature. The reaction mixture was diluted with 100 mL of EtOAc and washed with 3 × 10 mL of 10% HCl solution. The acidic aqueous layer was back-extracted with 3 × 20 mL of EtOAc. The combined organic layers were washed with 3 × 25 mL of brine, dried ($MgSO_4$), and concentrated in vacuo, affording a viscous, faintly yellow oil, which was purified by flash chromatography (petroleum ether/EtOAc, 3:1), providing the biscarbamate **9** as a thick colorless liquid. The liquid was induced to solidify when treated with Et_2O/hexane, affording 4.25 g (88%) of a white powder, mp 80–81 °C, which resisted further recrystallization: IR (KBr) 3380, 3360, 1720, and 1680 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 7.34 (s, 10 H, aromatic), 5.60 (m, 2 H, olefinic), 5.2–5.4 (m, 2 H, NH), 5.09 (s, 4 H, benzylic), 3.9–4.2 (m, 2 H, methines), 2.4–2.7 (m, 2 H, pseudoequatorial methylenes), 1.8–2.2 (m, 2 H, pseudoaxial methylenes). Anal. ($C_{22}H_{24}N_2O_4$) C, H, N.

***trans*-4-Cyclohexene-1,2-dicarbonyl Dichloride (10).**[23] Freshly distilled fumaryl dichloride (3.7 g, 24 mmol) was dissolved in 10 mL of dry Et_2O in an oven-dried 2-neck 50-mL round-bottom flask fitted with a gas inlet and dry ice Dewar condenser. The stirred solution was cooled to ca. −50 °C (dry ice/CH_3CN). Butadiene (ca. 3 mL) was condensed into the flask and the cooling bath removed. Within 25–30 min the exothermic reaction ceased. After an additional 10 min, the excess butadiene and solvent were removed in vacuo to furnish 4.7 g (ca. 95%) of the Diels–Alder adduct as a colorless liquid, which was used immediately without further pruification: IR (neat) 3140 and 1785 cm^{-1}.

Bis(phenylmethyl) *trans*-4-cyclohexene-1,2-diylbis(carbamate) (11) was prepared in 94% yield from **5**·2HCl by using methodology identical with that used for the synthesis of the corresponding cis isomer. The white solid obtained after chromatography was recrystallized from toluene/hexane, affording fine white needles: mp 144–145 °C; IR (KBr) 3320 and 1685 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 7.3 (s, 10 H, aromatic), 5.67 (d, 2 H, NH, J = 2.6 Hz), 5.07 (s, 4 H, benzylic), 3.6–3.9 (m, 2 H, methines), 2.3–2.7 (m, 2 H, pseudoequatorial methylenes), 1.8–2.2 (m, 2 H, pseudoaxial methylenes). Anal. ($C_{22}H_{24}N_2O_4$) C, H, N.

Bis(phenylmethyl) (1α,2β,4α,5α)-(4,5-Dihydroxy-1,2-cyclohexanediyl)bis(carbamate) (12). Olefin 11 (2.0 g, 5.3 mmol) was added to a mixture of Me_2CO (40 mL), distilled H_2O (3 mL), and *t*-BuOH (2 mL). *N*-methylmorpholine *N*-oxide (NMO) monohydrate (0.8 g, 5.9 mmol) and OsO_4 (0.009 g, 0.036 mmol) in CCl_4 were added, and the reaction mixture was stirred at room temperature under dry argon for 16 h. Me_2CO (50 mL) was added, and the white precipitate dissolved. Solid $NaHSO_3$ (ca. 0.2 g) was added, and the mixture was stirred for 15 min. The suspension was filtered, and the filtrate was concentrated in vacuo, providing a tan solid, which was purified on silica gel by eluting with $CHCl_3/Me_2CO$, 1:1, affording 2.13 g (98%) of white solid: mp 172–173 °C; IR (KBr) 3460 (sh), 3320, 1690, 1070, and 1025 cm^{-1}; NMR (500 MHz, pyridine-d_5) δ 8.40 (d, 1 H, aromatic, J = 8 Hz), 8.04 (d, 1 H, aromatic, J = 8 Hz), 7.30–7.40 (m, 4 H, aromatic), 7.20–7.30 (m, 4 H, aromatic), 6.31 (s, 1 H, NH), 6.24 (s, 1 H, NH), 5.31 ($H_{A'}$ of A'B' q, 1 H, benzylic, J = 12.6 Hz), 5.29 ($H_{B'}$ of A'B' q, 1 H, benzylic, J = 12.6 Hz), 5.22 (H_A of AB q, 1 H, benzylic, J = 12.9 Hz), 5.19 (H_B of AB q, 1 H, benzylic, J = 12.9 hz), 4.65–4.72 (m, 1 H, H-2), 4.35–4.38 (m, 1 H, H-4), 4.16–4.26 (m, 1 H, H-1), 4.00–4.08 (m, 1 H, H-5), 2.63 (deceptively simple d, 1 H, H-3e, J = 12.5 Hz), 2.48–2.60 (m, 2 H, H-6a and H-6e), 1.84 (deceptively simple t, 1 H, H-3a, J = 12 Hz). Anal. ($C_{22}H_{26}H_2O_6$) C, H, N.

Bis(phenylmethyl) (1α,2α,4β,5β)-(4,5-Dihydroxy-1,2-cyclohexanediyl)bis(carbamate) (13) and Bis(phenylmethyl) (1α,2α,4α,5α)-(4,5-Dihydroxy-1,2-cyclohexanediyl)bis(carbamate) (14). Olefin **9** (2.00 g, 5.3 mmol) was dissolved in 16 mL of Me_2CO, 3.2 mL of distilled H_2O, and 2.1 mL of *t*-BuOH at room temperature NMO monohydrate (0.80 g, 5.9 mmol) and OsO_4 (0.0091 g, 0.036 mmol) in 0.91 mL of CCl_4 were added, and stirring was continued under argon for 16 h. Excess OsO_4 was decomposed by addition of ca. 0.2 g of $NaHSO_3$. The suspension was stirred for 15–20 min and filtered through $MgSO_4$. The filtrate was concentrated in vacuo, affording a tan solid. Chromatography over 120 g of silica gel using $CHCl_3/Me_2CO$, 3:2, as eluant afforded 1.14 g (52%) of **13**, mp 142–144 °C, and 0.86 g (39%) of **14**, mp 157–158 °C, in a ratio of 1.3:1.0, respectively. For **13**: IR (KBr) 3460 (br), 1715, 1680, 1080, and 1020 cm^{-1}; NMR (500 MHz, acetone-d_6) δ 7.3–7.35 (m, 10 H, aromatic), 6.27 (br s, 2 H, NH), 5.05 (s, 4 H, benzylic), 4.16–4.19 (m, 2 H, H-4 and H-5), 3.95–3.97

(m, 2 H, H-1 and H-2), 3.70 (d, 2 H, OH, exch with D_2O, J = 3.9 Hz), 1.86–1.97 (m, 4 H, methylenes). Anal. ($C_{22}H_{26}N_2O_6$) C, H, N. For 14: IR (KBr) 3380, 3320, 1710, 1700, 1100, and 1035 cm^{-1}; NMR (500 MHz, acetone-d_6) δ 7.28–7.40 (m, 10 H, aromatic), 6.3–6.5 (br s, 2 H, NH), 5.06 (s, 4 H, benzylic), 4.14 (s, 2 H, OH, exch with D_2O), 3.8–4.1 (br m, 4 H, methines), 1.9–2.0 (m, 2 H, equatorial methylenes), 1.81 (deceptively simple d, 2 H, axial methylenes, J_{gem} = 13 Hz). Anal. ($C_{22}H_{26}N_2O_6$) C, H, N.

Epoxidation of 9 (15). Olefin **9** (1.4 g, 3.8 mmol) was dissolved in 15 mL of CH_2Cl_2 at room temperature, and $NaHCO_3$ (0.31 g, 3.8 mmol) was added. *m*-Chloroperoxybenzoic acid (MCPBA, freshly purified, 0.63 g, 7.8 mmol) in 10 mL of CH_2Cl_2 was added dropwise over 10 min to the vigorously stirred suspension. After 3 h, EtOAc (50 mL) was added, and the solution was washed with 3 × 15 mL portions of 10% $NaHSO_3$ and 5% $NaHCO_3$ solutions and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, affording a colorless oil. Four hours following addition of 25 mL of Et_2O, colorless needles (1.09 g) were collected by filtration. Flash chromatography of the mother liquor (petroleum ether/Me_2CO, 3:1) provided an additional 0.18 g of product (mp 107–108.5 °C) for a combined yield of 1.27 g (86%): IR (KBr) 3420, 3300, 1725, 1690, and 1320 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.29–7.35 (m, 10 H, aromatic), 5.57 (d, 2 H, NH, J = 6.4Hz), 5.10 (H_A of AB q, 2 H, benzylic, J = 12 Hz), 5.06 (H_B of AB q, 2 H, benzylic, J = 12 Hz), 3.85 (deceptively simple dd, 2 H, H-3 and H-4, J = 6 and 13 Hz), 3.21 (s, 2 H, H-1 and H-6), 2.35 (deceptively simple d, 2 H, H-2e and H-5e, J = 13 Hz), 2.02 (dd, 2 H, H-2a and H-5a, J = 7 and 13 Hz). Anal. ($C_{22}H_{24}N_2O_5$) C, H, N.

Bis(phenylmethyl) (1α,3α,4β,6α)-7-Oxabicyclo[4.1.0]heptane-3,4-diylbis(carbamate) (17). Olefin 11 (500 mg, 1.4 mmol) was treated with MCPBA in $NaHCO_3$-buffered CH_2Cl_2 for 4 h at room temperature as described for the preparation of **15**. Flash chromatography afforded epoxide **17** as a white solid, which was recrystallized from CCl_4, yielding 380 mg (73%) of fine white needles: mp 168–169 °C; IR (KBr) 3300, 1685, and 1290 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 10 H, aromatic), 4.99–5.10 (m, 5 H, 4 benzylic and 1 NH), 4.84 (s, 1 H, NH), 3.71–3.74 (m, 1 H, H-4), 3.53–3.57 (m, 1 H, H-3), 3.21 (s, 1 H, H-1), 3.13 (deceptively simple t, 1 H, H-6, J = 4 Hz), 2.55 (deceptively simple dd, 1 H, H-5e, J = 2 and 15 Hz), 2.46 (deceptively simple dt, 1 H, H-2e, J = 4, 10, and 15 Hz), 1.83 (deceptively simple dd, 1 H, H-2a, J = 10 and 15 Hz), 1.74 (ddd, 1 H, H-5a, J = 2, 10, and 15 Hz). Anal. ($C_{22}H_{24}N_2O_5$) C, H, N.

Bis(phenylmethyl) (1α,2α,4α,5β)-(4,5-Dihydroxy-1,2-cyclohexanediyl)bis(carbamate) (16). Method A. Epoxide **15** (300 mg, 0.76 mmol) was dissolved in 4 mL of THF at room temperature. Two milliliters of 1% (v/v) aqueous H_2SO_4 was added and the reaction mixture stirred for 6 h at room temperature. The solution was diluted with 25 mL of EtOAc and extracted with 2 × 5 mL portions of 5% $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography ($CHCl_3$/Me_2CO, 3:2) to furnish 231 mg (74%) of the trans diol as a white solid: mp 141–142 °C; IR (KBr) 3360, 1735, 1680, and 1065 cm^{-1}; NMR (500 MHz, pyridine-d_5) δ 8.06 (d, 1 H, NH, J = 8 Hz), 7.95 (br s, 1 H, NH), 7.35–7.43 (m, 4 H, aromatic), 7.22–7.31 (m, 6 H, aromatic), 5.12–5.27 (m, 4 H, benzylic), 4.51–4.63 (m, 1 H, H-4), 4.40–4.51 (m, 1 H, H-2), 4.05–4.18 (m, 1 H, H-1), 2.41–2.60 (m, 2 H, H-3e and H-6e), 2.18–2.30 (m, 1 H, H-6a), 2.01–2.16 (m, 1 H, H-3a). Anal. ($C_{22}H_{26}N_2O_6$) C, H, N.

Method B. Epoxide **15** (300 mg, 0.76 mmol) was dissolved in a mixture of 5 mL of dry THF and 1 mL of distilled deionized H_2O. Nafion-H (35–60 mesh powder; 60 mg) was added, and the reaction mixture was heated at reflux with vigorous stirring for 36 h. The reaction mixture was cooled, and the catalyst was removed by filtration. The filtrate was concentrated in vacuo, affording a clear oil, which was purified as in method A to furnish 264 mg (84%) of diol **16**.

Bis(phenylmethyl) (1α,2β,4α,5β)-(4,5-Dihydroxy-1,2-cyclohexanediyl)bis(carbamate) (18) and Phenylmethyl (1α,5α,6β,8β)-(8-Hydroxy-3-oxo-2-oxa-4-azabicyclo[3.3.1]non-6-yl)carbamate (19). Epoxide **17** (50 mg, 0.13 mmol) was dissolved at room temperature in 1.5 mL of Me_2CO with stirring. Aqueous H_2SO_4 (1% v/v, 0.5 mL) was added and the solution stirred at room temperature for 2 h. Solid $NaHCO_3$ was added to pH 7 (pH paper). The reaction mixture was concentrated, affording a white solid, which was purified by preparative TLC (silica gel, two developments with $CHCl_3$/Me_2CO, 3:2), yielding 6 mg (16%) of the bicyclic compound **19**, mp 214–215 °C, and 36 mg (69%) of diol **18**, mp 171–172 °C. For **19**: IR (KBr) 3420, 3300, 1735, 1680, and 1065 cm^{-1}; NMR (500 MHz, pyridine-d_5) δ 8.91 (s, 1 H), 7.43 (d, 2 H, J = 7 Hz), 7.30–7.35 (m, 2 H), 7.27 (d, 1 H, J = 7 Hz), 6.94 (d, 1 H, J = 7.6 Hz), 5.31 (H_A of AB q, 1 H, benzylic, J = 12.3 Hz), 5.25 (H_B of AB q, 1 H, benzylic, J = 12.3 Hz), 4.64–4.70 (m, 1 H), 4.32–4.38 (m, 1 H), 4.22–4.30 (m, 1 H), 3.90–3.96 (m, 1 H), 2.71 (deceptively simple d, 1 H, J = 13.8 Hz), 2.32 (deceptively simple dt, 1 H, J = 3.9, 4.5, and 14 Hz), 1.82 (deceptively simple d, 1 H, J = 15 Hz), 1.74 (deceptively simple d, 1 H, H-7a, J = 13.8 Hz). Anal. ($C_{15}H_{18}N_2O_5$) C, H, N. For **18**: IR (KBr) 3360, 3290, 1685, and 1035 cm^{-1}; NMR (270 MHz, acetone-d_6) δ 7.28–7.33 (m, 10 H, aromatic), 6.15 (d, 2 H, NH, J = 7 Hz), 5.02 (s, 4 H, benzylic), 4.01 (d, 2 H, OH, exch with D_2O, J = 3 Hz), 3.80–3.88 (m, 4 H, methine), 1.90–1.97 (m, 4 H, methylene). Anal. ($C_{22}H_{26}N_2O_6$) C, H, N.

Bis(phenylmethyl) (1α,2β,4α,5α)-[4-(Acetyloxy)-5-hydroxy-1,2-cyclohexanediyl]bis(carbamate) (22) and Diacetate 23. Diol **12** (1.0 g, 2.42 mmol) was dissolved in 50 mL of THF and cooled to −25 °C in dry ice/CCl_4. Et_3N (0.27 g, 2.4 mmol), (dimethylamino)pyridine (DMAP; 0.03 g, 0.24 mmol), and Ac_2O (0.27 g, 2.66 mmol) were added. After standing for 24 h in the freezer at −25 °C, the solution was concentrated to afford a white solid, which was partitioned between EtOAc (100 mL) and 5% HCl solution (20 mL). The organic layer was washed with 20 mL of dilute HCl and 2 × 20 mL portions of brine and dried (Na_2SO_4). Concentration furnished a white solid, which was crystallized from $CHCl_3$ to afford 0.61 g of the hydroxy acetate **22** as a white solid, mp 199–201 °C. Flash chromatography (Et_2O) of the mother liquor gave 0.095 g (8%) of **23** and another 0.204 g of **22** for a total yield of 73%. For **22**: IR (KBr) 3520, 3310, 1720, 1680, 1265, and 1030 cm^{-1}; NMR (500 MHz, pyridine-d_5) δ 8.55 (s, 1 H, aromatic), 8.21 (s, 1 H, aromatic), 7.39 (dd, 4 H, aromatic, J = 7 and 18 Hz), 7.20–7.30 (m, 4 H, aromatic), 6.84 (s, 1 H, NH), 5.34 (H_A of AB q, 1 H, benzylic, J = 12.6 Hz), 5.28 ($H_{A'}$ of A'B' q, 1 H, benzylic, J = 12.7 Hz), 5.22 ($H_{B'}$ of A'B' q, 1 H, benzylic, J = 12.7 Hz), 5.18 (H_B of AB q, 1 H, benzylic, J = 12.6 Hz), 5.10 (deceptively simple dt, 1 H, H-4, J = 5 and 12 Hz), 4.7–4.8 (m, 1 H, H-1), 4.50–4.53 (m, 1 H, H-5), 4.2–4.3 (m, 1 H, H-2), 2.55–2.67 (m, 2 H, H-3a and H-6e), 2.40–2.48 (m, 1 H, H-3e), 1.80–1.90 (m, 4 H, OAc and H-6a). Anal. ($C_{24}H_{28}N_2O_7$) C, H, N.

Bis(phenylmethyl) (1α,2β,4α,5α)-[4,5-Bis(acetyloxy)-1,2-cyclohexanediyl]bis(carbamate) (23). Diol **12** (350 mg, 0.845 mmol) was dissolved in 20 mL of THF and cooled in an ice bath. Et_3N (171 mg, 1.69 mmol), DMAP (21 mg, 0.169 mmol), and Ac_2O (345 mg, 3.38 mmol) were added. The reaction mixture was allowed to warm slowly to room temperature. After 22 h the solution was evaporated to dryness. The residual white solid was dissolved in 25 mL of EtOAc and washed with 2 × 10 mL portions each of 5% HCl solution and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to an oil. Upon addition of Et_2O (10 mL) and hexane (5 mL), small white rosettes formed slowly. After standing for 2 h, the crystals (349 mg) were collected by filtration. Preparative TLC (Et_2O) of the mother liquor afforded an additional 40 mg, for a total of 392 mg (92%): mp 122–123 °C; IR (KBr) 3360, 3300, 1740, 1690, and 1250 cm^{-1}; NMR (80 MHz, $CDCl_3$) δ 7.29 (s, 10 H, aromatic), 4.7–5.3 (m, 8 H, benzylic, NH, H-4, and H-5), 3.4–3.9 (m, 2 H, H-1 and H-2), 1.5–2.3 (m, 10 H, methylene and OAc). Anal. ($C_{26}H_{30}N_2O_8$) C, H, N.

Bis(phenylmethyl) (1α,2β,4β)-[4-(Acetyloxy)-5-oxo-1,2-cyclohexanediyl]bis(carbamate) (24). The pure hydroxy acetate **22** (632 mg, 1.38 mmol) was dissolved at room temperature in 40 mL of Me_2CO and cooled in an ice bath. Jones reagent (1.7 mL of a solution diluted to 2.5 M in Cr^{6+}) was added dropwise. The reaction mixture was stirred for 2 h at ice-bath temperature. 2-Propanol was added to destroy the excess oxidant, and the Cr salts were removed by filtration. The filtrate was concentrated to ca. 5 mL in vacuo and partitioned between EtOAc (50 mL) and H_2O (10 mL). The organic layer was washed with 10 mL of H_2O and 2 × 10 mL of brine and dried (Na_2SO_4). Concentration in vacuo afforded a white solid, which was purified by flash chromatography ($CHCl_3$/Et_2O, 1:1) to afford 547 mg (87%) of **24**: mp

163–164 °C; IR (KBr) 3350, 3280, 1765, 1745, 1720, 1690, 1230, 1060, and 1040 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.3 (s, 10 H, aromatic), 5.2–5.3 (m, 1 H, H-4), 5.0–5.15 (m, 4 H, benzylic), 4.0–4.1 (m, 1 H, H-2), 3.75–3.85 (m, 1 H, H-1), 2.85 (dd, 1 H, H-6e, J = 3 and 11 Hz), 2.50–2.56 (m, 1 H, H-3e), 2.45 (deceptively simple t, 1 H, H-6a, J = 13 Hz), 2.12 (s, 3 H, OAc), 1.72 (deceptively simple q, 1 H, H-3a, J = 13 and 25 Hz). Anal. ($C_{24}H_{26}N_2O_7$) C, H, N.

Bis(phenylmethyl) (1α,2β,4β,5α)-[4,5-Bis(acetyloxy)-1,2-cyclohexanediyl]bis(carbamate) (26). Keto acetate **24** (250 mg, 0.551 mmol) was dissolved in THF (8 mL) and absolute EtOH (2 mL) and cooled to −78 °C. $NaBH_4$ (total of 12.5 mg; 0.330 mmol) was added in three portions every 10 min. After 1 h at −78 °C, the solution was concentrated in vacuo to furnish a white solid, which was partitioned between EtOAc (25 mL), THF (5 mL), and 5 mL of H_2O. The organic layer was washed with 5 mL of H_2O and dried (Na_2SO_4). Concentration in vacuo afforded a white solid, which was dissolved in 10 mL of THF and cooled in an ice bath. Et_3N (110 mg, 1.10 mmol), DMAP (13 mg, 0.110 mmol), and Ac_2O (168 mg, 1.65 mmol) were added. The reaction mixture was allowed to warm slowly to room temperature and after 1 **h** was concentrated in vacuo to furnish a white solid. $CHCl_3$ (25 mL) was added, and the solution was washed with 3 × 5 mL of 5% HCl solution and 2 × 10 mL of brine and dried (Na_2SO_4). The solvent was removed in vacuo and the white solid crystallized from $CHCl_3/CCl_4$ to provide 135 mg of the product. Preparative TLC ($CHCl_3/Et_2O$, 5:1, 2 developments) of the mother liquor furnished 24 mg (9%) of **24** and another 30 mg of **26** for a total of 165 mg (65%): mp 220–221 °C; IR (KBr) 3320, 1730, 1680, 1290, 1250, 1240, 1070, and 1020 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 10 H, aromatic), 5.01–5.09 (m, 6 H, 2 NH and 4 benzylic), 4.89–4.91 (m, 2 H, H-4 and H-5), 3.58–3.66 (m, 2 H, H-1 and H-2), 2.39 (deceptively simple d, 2 H, H-3e and H-6e, J = 12 Hz), 2.01 (s, 6 H, 2 OCH_3), 1.43 (deceptively simple d, 2 H, H-3a and H-6a, J = 11 Hz). Anal. ($C_{26}H_{30}N_2O_8$) C, H, N.

Bis(phenylmethyl) (1α,2β,4β,5α)-(4,5-Dihydroxy-1,2-cyclohexanediyl)bis(carbamate) (27). Diacetate **26** (100 mg, 0.201 mmol) was suspended in 7 mL of MeOH at room temperature. K_2CO_3 (61 mg, 0.442 mmol) was added, and the reaction mixture was heated to reflux (diacetate dissolves). After 1 h the reaction was cooled to room temperature and stirred for another 1.5 h. The solvent was removed in vacuo, affording a white solid, which was recrystallized from $MeOH/H_2O$, affording 65 mg (78%) of diol **27**: mp 197–198 °C; IR (KBr) 3400 (sh), 3300, 1680, 1280, 1240, 1065, and 1030 cm^{-1}; NMR (500 MHz, pyridine-d_5) δ 8.30 (s, 2 H, aromatic), 7.37 (d, 4 H, aromatic, J = 7.2 Hz), 7.2–7.3 (m, 4 H, aromatic), 6.64 (s, 2 H, NH), 5.30 (H_A of AB q, 2 H, benzylic J = 12.6 Hz), 5.21 (H_B of AB q, 2 H, benzylic, J = 12.8 Hz), 4.19–4.26 (m, 2 H, H-4 and H-5), 3.93 (deceptively simple d, 2 H, H-1 and H-2, J = 9.5 Hz), 2.76 (deceptively simple d, 2 H, H-6e and H-3e, J = 12.7 Hz), 1.9–2.0 (m, 2 H, H-6a and H-3a). Anal. ($C_{22}H_{26}N_2O_4$) C, H, N.

Platinum complexes 3a–d,f were prepared from the appropriate bis(Cbz)-protected CDD (100 mg, 0.24 mmol) by addition to a suspension of 20 mg of 10% Pd/C in 5 mL of MeOH. The Parr bottle was alternately evacuated (water aspirator) and refilled five times to 20 psi with H_2 gas. The suspension was shaken at room temperature for 2 h under 20 psi of H_2. The catalyst was removed by filtration and the filtrate concentrated in vacuo to afford a clear oil. Distilled deionized H_2O (5 mL) was added followed by K_2PtCl_4 (100 mg, 0.24 mmol). The flask was swirled to dissolve the salt, stoppered, covered with foil, and allowed to stand for 24 h.

(*SP*-4,2-(1α,2α,4α,5α))-Dichloro(4,5-dihydroxy-1,2-cyclohexanediamine-*N*,*N*′)platinum (Cl_2Pt^{II}-3a) was collected by filtration and recrystallized from H_2O, affording 45 mg (43%) of yellow-green cubes. Anal. ($C_6H_{14}N_2O_2PtCl_2 \cdot H_2O$) C, H, N, Pt, Cl.

(*SP*-4,2-(1α,2α,4β,5β))-Dichloro(4,5-dihydroxy-1,2-cyclohexanediamine-*N*,*N*′)platinum (Cl_2Pt^{II}-3b) was collected by filtration and recrystallized from $H_2O/MeOH$, affording 38.7 mg (37%) of yellow crystals. Anal. ($C_6H_{14}N_2O_2PtCl_2 \cdot H_2O$) C, H, N, Pt, Cl.

(*SP*-4,2-(1α,2α,4β,5α))-Dichloro(4,5-dihydroxy-1,2-cyclohexanediamine-*N*,*N*′)platinum (Cl_2Pt^{II}-3c). After 24 h at room temperature, H_2O was removed by lyophilization and the residue washed with Me_2CO to afford 107 mg of yellow-orange powder, which was dried under reduced pressure. This material was used within 24 h for antitumor testing.

(*SP*-4,2-(1α,2β,4α,5α))-Dichloro(4,5-dihydroxy-1,2-cyclohexanediamine-*N*,*N*′)platinum (Cl_2Pt^{II}-3d) was collected by filtration and recrystallized from H_2O, affording 69 mg (69.5%) of bright yellow powder. Anal. ($C_6H_{14}N_2O_2PtCl_2 \cdot H_2O$) C, H, N, Pt, Cl.

(*SP*-4,2-(1α,2β,4β,5α))-Dichloro(4,5-dihydroxy-1,2-cyclohexanediamine-*N*,*N*′)platinum (Cl_2Pt^{II}-3f) was collected by filtration and recrystallized from H_2O, affording 62 mg (62%) of small bright yellow needles. Anal. ($C_6H_{14}N_2O_2PtCl_2 \cdot H_2O$) C, H, N, Pt, Cl.

Bis(phenylmethyl) (1α,2α,4β,5β)-[4,5-Bis(acetyloxy)-1,1-cyclohexanediyl]bis(carbamate) (Bisacetylated 13) and Bis(phenylmethyl) (1α,2α,4α,5α)-[4,5-Bis(acetyloxy)-1,2-cyclohexanediyl]bis(carbamate) (Bisacetylated 14). Olefin **9** (1.00 g, 2.6 mmol) was treated with OsO_4 and *N*-methylmorpholine *N*-oxide as described previously. The crude reaction mixture was suspended in ice-cold $CHCl_3$ (40 mL). Et_3N (532 mg, 5.3 mmol), DMAP (96 mg, 0.79 mmol), and Ac_2O (1.07 g, 11 mmol) were added respectively. The reaction mixture was allowed to warm slowly to room temperature. After 5.5 h, the solution was washed with 3 × 10 mL portions each of 5% HCl solution and brine and dried (Na_2SO_4). The solution was concentrated in vacuo and the mixture purified by flash chromatography ($CHCl_3/Et_2O$, 5:1) to afford 320 mg of bisacetylated **14** and 356 mg of bisacetylated **13**, plus 370 mg of a mixture, for a total of 1.05 g (80%). For bisacetylated **14**: mp 84–86 °C; IR (KBr) 3300, 1730, 1705, 1250, 1235, 1055, and 1030 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 7.34 (s, 10 H, aromatic), 5.0–5.2 (m, 8 H, benzylic, NH, H-4, and H-5), 4.0–4.3 (m, 2 H, H-1 and H-2), 1.7–2.1 (m, 10 H, methylene and 2 CH_3). For bisacetylated **13**: mp 129–130 °C; IR (KBr) 3300, 1730, 1690, 1245, 1055, and 1020 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 7.33 (s, 10 H, aromatic), 5.0–5.5 (m, 8 H, benzylic, NH, H-4, and H-5), 3.9–4.1 (m, 2 H, H-1 and H-2), 1.8–2.1 (m, 10 H, methylene and 2 CH_3). Anal. (mixture of isomers; $C_{26}H_{30}N_2O_8$) C, H, N.

(*SP*-4,2-(1α,2α,4α,5α))-Dichloro[4,5-Bis(acetyloxy)-1,2-cyclohexanediamine-*N*,*N*′]platinum (28a). Bisacetylated **14** (100 mg, 0.20 mmol) was added to a suspension of 10% Pd/C in 5 mL of MeOH. The bottle was alternately evacuated (H_2O aspirator) and refilled to 20 psi with H_2 gas. The suspension was shaken under 20 psi for 2 h at room temperature. The catalyst was filtered and the filtrate concentrated in vacuo to afford a clear oil. The residue was dissolved in 5 mL of distilled deionized H_2O, and K_2PtCl_4 (80 mg, 0.20 mmol) was added. The flask was swirled to dissolve the salt, stoppered, and covered with foil. After standing at room temperature for 24 h, the yellow precipitate was filtered and washed with 5% HCl solution, Me_2CO, and Et_2O to afford 64 mg (65%) of **28a**. Anal. ($C_{10}H_{18}N_2O_4PtCl_2$) C, H, N, Pt, Cl.

(*SP*-4,2-(1α,2α,4β,5β))-Dichloro[4,5-Bis(acetyloxy)-1,2-cyclohexanediamine-*N*,*N*′]platinum (28b). Bisacetylated **13** (100 mg, 0.20 mmol) was treated as described for the synthesis of **28a**. The brown precipitate was washed with 5% HCl solution, Me_2CO, and Et_2O to afford 49 mg (49%) of **28b**. Anal. ($C_{10}H_{18}N_2O_4PtCl_2$) C, H, N, Pt, Cl.

(*SP*-4,2-(1α,2β,4α,5α))-Dichloro[4,5-bis(acetyloxy)-1,2-cyclohexanediamine-*N*,*N*′]platinum (28c). Bis(acetate) **23** (100 mg, 0.20 mmol) was treated as described for the synthesis of **28a**. The bright yellow precipitate was washed with 5% HCl solution, Me_2CO, and Et_2O to afford 73 mg (73%) of **28c** as a bright yellow powder. Anal. ($C_{10}H_{18}N_2O_4PtCl_2$) C, H, N, Pt, Cl.

X-ray Crystallographic Analysis. Crystals of complex **3a** are clear, yellow, rectangular rods with well-formed faces. Preliminary examination of the diffraction pattern on a Syntex P1 diffractometer indicated a monoclinic crystal system with systematic absences $0k0$, $k = 2n + 1$ and $h0l$, $l = 2n + 1$. These absences uniquely determine the space group as $P2_1/c$. The unit cell constants a = 8.489 (2) Å, b = 11.948 (2) Å, c = 11.006 (2) Å, and β = 91.02 (1)° were determined by the least-squares fit of the diffractometer setting angles for 25 reflections in the 2θ range 20–30 °C with Mo Kα radiation (λ(K$\bar{\alpha}$) = 0.71069 Å).

Intensities were measured by the θ–2θ scan technique on the Syntex P1 diffractometer. The data were corrected for Lorentz

Table III. Crystallographic Details for $Pt^{II}Cl_2$-**4a**

formula	$[Pt(C_6H_{14}N_2O_2)Cl_2]\cdot H_2O$
formula wt, amu	430.20
space group	$P2_1/c$
a, Å	8.489 (2)
b, Å	11.948 (2)
c, Å	11.006 (2)
β, deg	91.02 (1)
vol, Å^3	1116
Z	4
density (calcd), g/cm^3	2.56
bounding planes[a]	(011), [0.144]; (100), [0.166]; (1$\bar{1}$0), [0.211]; ($\bar{1}\bar{1}$0), [0.227]; (0$\bar{1}$1), [0.230]; (001), (00$\bar{1}$2)
crystal size	0.14 mm × 0.17 mm × 0.23 mm
linear abs coeff, cm^{-1}	131.7
transmission factors	0.143–0.239
temp	19 °C
2θ limits	$4° \le 2\theta \le 55°$
scan speed	2.0–24.0 deg/min in 2θ
background time/scan time	0.5
scan range	(Kα_1 − 1.0)° to (Kα_2 + 1.1)°
data collected	$+h,+k,\pm l$
unique data	2575
unique data, with $F_o^2 > 3\sigma(F_o^2)$	2105
final number of variables	127
$R(F)$[b]	0.028
$R_w(F)$[b]	0.031
error in observation of unit weight, e	1.56

[a] The number of brackets is the distance in millimeters between the Friedel pairs of the preceding form. [b] $R(F) = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w(F) = \sum[w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$ with $w = 1/\sigma^2(F_o)$.

and polarization effects and put onto an absolute scale by means of a Wilson plot.[45] Six standard reflections were measured after every 100 reflections during the course of data collection and indicated no problem with crystal decay.

The position of the platinum atom was determined by the Patterson method. Standard Fourier methods were used to locate the remainder of the non-hydrogen atoms. The presence of a water molecule of solvation was detected at this point. The SHELX-76 package[46] was used for all full-matrix least-squares refinements. Isotropic refinement of the non-hydrogen atoms converged to an R factor of 0.072. An absorption correction was then applied by means of the Gaussian grid method with an 8 × 8 × 8 grid. Isotropic refinement on the absorption-corrected data set then converged to an R factor of 0.063.

After one cycle of anisotropic refinement, the hydrogen atoms bonded to carbon atoms were located on a difference electron density map. Only one hydrogen atom bonded to each nitrogen atom could be found; the positions of the hydrogen atoms bonded to oxygen atoms, including the oxygen of the water molecule, were uncertain. Consequently, the hydrogen atoms bonded to carbon and nitrogen atoms were included in the model as fixed contributions in calculated positions, C–H = 1.00 Å and N–H = 1.00 Å, and with isotropic thermal parameters calculated as 1.0 Å^2 larger than the equivalent isotropic thermal parameter of the bonded carbon or nitrogen atom. Hydrogen atoms bonded to oxygen atoms were not included in the model. The final refinement cycle resulted in aggreement indices of $R = 0.028$ and $R_w = 0.031$ (based on F) for the 2105 unique intensities with $F_o^2 > 3\sigma(F_o^2)$ and the 127 variables (anisotropic non-hydrogen atoms and hydrogen atoms fixed). It was necessary to eliminate the following strong reflections from the final refinement cycles because of probable extinction effects: (100), (011), (111), (2$\bar{2}$1), (1$\bar{2}$1), (202), (1$\bar{1}$2), and (302). The two largest peak heights in the final difference electron density map are both located near the Pt atom and are 1.8e/Å^3; the third-largest peak height is 0.88 e/Å^3. Neutral atom scattering factors for the platinum, chlorine, oxygen, nitrogen, and carbon atoms[47] and for the hydrogen atoms[48] are from the usual sources. Anomalous dispersion corrections to the scattering factors for the non-hydrogen atoms were included in the calculations. Further crystallographic details appear in Table III. Final positional and thermal parameters for the non-hydrogen atoms are listed in Table IV.[49] Bond lengths and bond angles are displayed in Table V.[49] Tables of calculated hydrogen atom positions and structure factors ($10|F_o|$ vs. $10|F_c|$) have been deposited as supplementary material.[49]

The ORTEP drawing for this molecule along with the numbering scheme is shown in Figure 1. The cyclohexane ring is in the chair conformation, and the like substituents on this ring are cis, i.e., the amino groups are cis with respect to each other and the hydroxyl groups are cis with respect to each other.

A stereodrawing of the unit cell in Figure 2 shows the packing arrangement for this structure. The geometry about the platinum atom is square planar, and the molecules are packed together in the crystal as dimers such that the square planes are stacked to give a short Pt–Pt distance of 3.37 Å. Both intra- and intermolecular hydrogen bonding are important in this structure, and a list of short contacts is given in Table VI. The molecules within each dimer unit are centrosymmetrically related, and this arrangement facilitates hydrogen-bonding interactions of the N–H···Cl type within the dimer unit: N-1···Cl-2^i is 3.35 Å, while N-2···Cl-1^i is 3.53 Å. This arrangement is common for *cis*-diaminedichloroplatinum(II) complexes and has been previously noted.[50]

The water molecules of solvation serve to link dimer units together through a hydrogen-bond network such that layers are formed parallel to (001). One such layer is shown in Figure 3 viewed down the c-axis. Within this network are hydrogen bonds between the diaminocyclohexane ring (dach) and the water of solvation, N-1···O-3^i, O-1···O-3^{ii}, water-to-water contacts, O-3···O-3^{iv}, and dach-to-dach contacts, O-1···O-1^{iii}. There is also a second network between dimer units, which involves hydrogen bonds of the type N-2···O-2 and N-2···O-2^{ii}.

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Supplementary Material Available: Tables IV–VII giving positional and thermal parameters, bond lengths and bond angles, and selected short intra- and intermolecular distances for $Pt^{II}Cl_2$-**3a** (4 pages); Table VIII giving observed and calculated structure factors for $Pt^{II}Cl_2$-**3a** (9 pages). Ordering information is given on any current masthead page.

(45) The programs used for data reduction are from the CRYM crystallographic computing package (Duchamp, D. J.; Trus, B. L.; Westphal, B. J. California Institute of Technology, Pasadena, CA, 1964) and modified by G. G. Christoph at the Ohio State University, Columbus, OH.
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(49) Microfilm edition as supplementary material (structure factors in microfiche edition only).
(50) Lock, C. J.; Speranzini, R. A.; Zvagulis, M. *Acta Cryst* **1980**, *B36*, 1789–1793 and references cited therein.