The NMR resonance at 15 ppm, assigned to these bridging protons, disappears on addition of D_2O to the sample while all other resonances remain unchanged. This downfield chemical shift value is consistent with the trend observed for various bridging O--H--O protons in α-amine oxime complexes.[29] The positive FAB mass spectrum of **3** shows both the molecular ion at m/z 590/592 and the protonated molecular ion at m/z 591/593. When acidic (0.1 N DCl/D_2O) deuterated glycerol is used as the FAB matrix, the deprotonated molecular ion at m/z 589/591 is shifted to m/z 590/592. As this ion is most likely formed by the loss of an exchanged deuterium, the results are consistent with the presence of two exchangeable hydrogens. Positive FAB mass spectra allow a similar interpretation showing a 2 Da shift for the less intense M^+ parent.[15]

The long distance of the uncapped oxygen triangle (3.83 Å) precludes any hydrogen bonding between the two flanking oxygen atoms and apparently also precludes further capping by boron for, as previously mentioned, attempts to "force" the introduction of a second cap were unsuccessful.

One other tris(dioxime) Tc complex, **8**, was reported previously.[30] The technetium is seven-coordinate, bound to three DMG groups and a bridging oxygen atom. The oxygen atoms on one end of *two* of the DMG groups and the lone oxygen atom are joined through a Sn cap. Unlike the BATO complexes, however, the third DMG group is transversely disposed and not joined to the cap (Figure 4). Although these compounds are unique as monocapped vicinal dioxime complexes, seven-coordinate technetium(III) compounds have previously been reported with a variety of ligands. (See, for example, ref 31-33.)

Lability of the Halogen. The lability of the halogen ligand is predicted by X-ray photoelectron spectroscopy data,[34] which imply a charge separation in the Tc-Cl bond. The range of Cl $2P_{3/2}$ binding energies of technetium compounds is about 195.7 (Cl^-) to 198.2 eV (covalent Cl). An intermediate value, 197.1 eV, was found for both **2** and **4**. The halogen can be readily exchanged for another halogen or for hydroxide. The bromo complexes can be converted to the chloro complexes by stirring with excess chloride, either 1 M HCl or NaCl, in acetonitrile/water. In the presence of added base, the hydroxide derivative is obtained. Heating reduces to minutes the time required for reaction. Alternatively, the use of Ag^+ to abstract the bromide ion and subsequent addition of chloride ion under acidic conditions (HCl) result in quantitative conversion. Ag^+ may also be used to abstract the halide under basic conditions, to give the hydroxide derivative.

Attempts to remove the halogen and form a monocapped (or biscapped) hexacoordinate BATO complex were not successful. The use of Ag^+ to abstract the halogen gave only a monocapped hydroxide derivative, even when excess boronic acid was added to favor the formation of a biscapped complex.

Conclusion

A new family of technetium complexes has been isolated. The Tc(III) is surrounded by three dioxime molecules capped on one end by a boron-alkyl group. The dioxime oxygen atoms at the other, uncapped, end of the molecule are involved in hydrogen bonding with two protons. A halogen, which is easily exchanged for another halide or hydroxide, is also bonded to the seven-coordinate technetium atom. Structural distortions due to the presence of this halogen probably preclude the addition of a second boron cap.

These BATO complexes are prepared by template synthesis; consequently, a large number of complexes can be examined in vivo simply by changing the components of the ligand system. This is much easier than "traditional" preparations of ^{99m}Tc radiopharmaceuticals where pertechnetate and a reducing agent are added to a preformed ligand and the preparation of a different radiopharmaceutical first requires the synthesis of a new ligand.

The single cap of the BATO compounds also represents a distinct advantage in the study of radiopharmaceutical compounds, for better control and organ targeting of the ^{99m}Tc complex can be achieved by introducing only a single modification (the boron R group), as opposed to the multiple modifications that are introduced when derivatized bi- or tridentate ligands are bound to the technetium.

Acknowledgment. We wish to thank Dr. S. Jurisson and Dr. K. Linder for helpful discussions. We are grateful to Dr. Linder for experimental assistance.

Supplementary Material Available: Tables SI-SIII, SV-SVII, and SIX-XI, listing bond distances and angles and thermal parameters for **1**, **3**, and **5**, and Table SXIII, listing calculated hydrogen atom coordinates for **3** (18 pages); Tables SIV, SVIII, and SXII, listing observed and calculated structure factors for **1**, **3**, and **5** (33 pages). Ordering information is given on any current masthead page.

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Chemistry of Bis(platinum) Complexes. Formation of Trans Derivatives from Tetraamine Complexes

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Some chemistry of bis(platinum) complexes, and particularly the formation of complexes of the general formula $[\{trans\text{-}PtCl_2(NH_3)\}_2H_2N(CH_2)_nNH_2]$, is reported. The complexes contain both platinum coordination spheres in the trans configuration and are derived from the doubly bridged tetraamine complexes $[\{cis\text{-}Pt(NH_3)_2(H_2N(CH_2)_nNH_2)\}_2]Cl_4$. These latter complexes are derived in turn from $[PtCl_2(NH_3)_2]$ by reaction with the appropriate diamine in aqueous solution. A further set of tetraamine complexes may be prepared by the reaction of aqueous ammonia with $[\{cis\text{-}PtCl_2(NH_3)\}_2H_2N(CH_2)_nNH_2]$, giving $[\{Pt(NH_3)_3\}_2H_2N(CH_2)_nNH_2]Cl_4$. The complexes were characterized by IR and NMR (^1H, ^{13}C, ^{195}Pt) spectroscopy and elemental analyses. Kinetic measurements of the initial reaction of bis(platinum) complexes in DMSO indicate that the complexes are kinetically more reactive than their monomer analogues. The mechanism of the formation of the trans derivatives is discussed.

Bis(platinum) complexes containing two units of the antitumor drug Cisplatin, *cis*-$[PtCl_2(NH_3)_2]$, are of both chemical and biological interest, and their synthesis and initial DNA-binding properties have been reported.[1] Monomeric platinum-amine

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complexes represent the series $[PtX_{4-n}(am)_n]^{(n-2)+}$ (X = halide, am = amine), and we have begun to develop an analogous chemistry as part of our studies on the properties of bis(platinum) complexes. This paper reports on the synthesis and characterization of further bis(platinum) complexes containing tetraamine, $Pt(am)_4$, and *trans*-$PtX_2(am)_2$ coordination spheres.

Experimental Section

Starting Materials and Physical Methods. The complexes *cis*-$[PtCl_2(NH_3)_2]$ and $K[PtCl_3(NH_3)]$ were prepared by the methods of Dhara[2] and Abrams[3] respectively. All diamines were purchased as their hydrochloride salts and used without further purification. IR spectra were obtained as KBr disks on Nicolet FT6000 series and Perkin-Elmer 1430 spectrophotometers. UV/visible spectra were run on a Perkin-Elmer Lambda 4B instrument. NMR spectra were run on Bruker 250- and 270-MHz spectrometers. ^{195}Pt NMR spectra (250 MHz) were run in either mixtures of DMA/acetone-d_6 or D_2O with respect to a Na_2PtCl_6 solution in D_2O as external reference. Samples were run at a pulse width of 15 μs and a sweep width of 30 kHz. Shifts are positive to lower shielding. ^{13}C and ^1H NMR spectra are relative to TSS (sodium 3-(trimethylsilyl)propanesulfonate). Conductivity was measured on a YSI Model 34 (Fisher) conductance unit in H_2O. Analyses were by Robertson Laboratories, Madison, NJ. The kinetic experiments were performed with 2.5 mM solutions of the cis or trans complex dissolved in DMSO. The increase in the absorption at 257 nm was monitored, and kinetic data were abstracted from the initial part of the plot, which obeyed the relationship $kt = -\ln (A_t - A_0)/A_0$.

Preparation of Complexes. **[{*cis*-$PtCl_2(NH_3)$}$_2$$H_2N(CH_2)_4NH_2$] (Complex I).** To $K[PtCl_3(NH_3)]$ (1.9 g, 5.3 mmol) suspended in 130 mL of MeOH was added a solution of 1,4-diaminobutane dihydrochloride (0.43 g, 2.7 mmol) dissolved in 65 mL of MeOH and 5 mL of Et_3N. After the mixture was stirred for 24 h, the precipitated compound was filtered, washed with water and EtOH, and dried. The solid was recrystallized from DMA/0.1 N HCl to give the pale yellow product, yield 60%. Anal. Calcd for $C_4H_{18}N_4Cl_4Pt_2$: C, 7.33; H, 2.77; N, 8.56; Cl, 21.68. Found: C, 7.64; H, 2.87; N, 8.56; Cl, 21.54.

[{$Pt(NH_3)_3$}$_2$$H_2N(CH_2)_4NH_2$]$Cl_4$ (Complex II). To complex I (0.654 g, 1 mmol) suspended in 10 mL of water at 60–70 °C was added slowly concentrated NH_4OH (30%, 0.5 mL, 4 mmol). The mixture was stirred for approximately 1 h or until colorless. (If after 30 min the solution is still yellow, excess NH_4OH may be added.) The colorless liquid was filtered upon cooling and evaporated to 1-mL volume. EtOH was added and the solution cooled at −3 °C. The precipitated product was filtered and recrystallized from H_2O/EtOH; yield 85%. Anal. Calcd for $C_4H_{30}N_8Cl_4Pt_2$: C, 6.65; H, 4.19; N, 15.51. Found: C, 6.68; H, 4.15; N, 15.38.

[{*cis*-$Pt(NH_3)_2(H_2N(CH_2)_4NH_2)$}$_2$]$Cl_4$ (Complex III). *cis*-$[PtCl_2(NH_3)_2]$ (0.6 g, 2 mmol) was suspended in 20 mL of water, 1,4-diaminobutane (0.177 g, 2 mmol) was added, and the mixture was stirred at 60 °C for 1–1.5 h. Then the solution was filtered and evaporated to 1-mL volume. After this solution stood for 1 day at 3 °C, the product precipitated out and was filtered, washed with EtOH, and dried. The complex is recrystallized from H_2O/EtOH; yield 68%. Anal. Calcd for $C_8H_{36}N_8Cl_4Pt_2$: C, 12.38; H, 4.67; N, 14.43. Found: C, 12.34; H, 4.55; N, 14.28.

[{*trans*-$PtCl_2(NH_3)$}$_2$$H_2N(CH_2)_4NH_2$] (Complex IV). Complex III (0.5 g, 0.64 mmol) was dissolved in 2 mL of H_2O, and 50 mL of 6 N HCl was added. The solution was allowed to react at 60–70 °C for 6–8 h with constant stirring. After this time the yellow solid that precipitated was filtered off, washed with water and acetone, and dried in vacuo; yield 45%. Complex V is isolated from the filtrate. Complex IV was recrystallized from DMA/0.1 N HCl. Anal. Calcd for $C_4H_{18}N_4Cl_4Pt_2$: C, 7.33; H, 2.77; N, 8.56; Cl, 21.68. Found: C, 7.41; H, 2.72; N, 8.40; Cl, 21.88.

***trans*-[$PtCl_2(NH_3)(H_2N(CH_2)_4NH_3)$]Cl (Complex V).** This complex was isolated by evaporating the above filtrate to an oil, adding 30 mL of EtOH, and stirring for 30 min. The yellow solid was filtered off, washed with EtOH, and dried. The complex may be recrystallized from H_2O/EtOH. Anal. Calcd for $C_4H_{16}N_2Cl_3Pt$: C, 11.79; H, 3.96; N, 10.31; Cl, 26.09. Found: C, 12.05; H, 3.82; N, 10.02; Cl, 25.91.

[$PtCl_2(H_2N(CH_2)_4NH_2)$] (Complex VI). $[K_2PtCl_4]$ (0.415 g, 1 mmol) was dissolved in 10 mL of H_2O, and 1,4-diaminobutane (0.088 g, 1 mmol) was added dropwise to the solution. After 2 h of stirring the yellow solid was filtered off, washed with H_2O, and dried; yield 27%. Anal. Calcd for $C_4H_{12}N_2Cl_2Pt$: C, 13.57; H, 3.42; N, 7.91; Cl, 20.02. Found: C, 13.42; H, 3.23; N, 8.10; Cl, 20.08.

[$Pt(NH_3)_2(H_2N(CH_2)_4NH_2)$]$Cl_2$ (Complex VII). To complex VI (0.354 g, 1 mmol) suspended in 10 mL of H_2O was added slowly concentrated NH_4OH (30%, 0.25 mL, 2 mmol). The mixture was stirred for approximately 1 h until colorless. The solution was then evaporated to 1-mL volume, and EtOH was added and cooled to −3 °C. The product was filtered off and washed with EtOH; yield 90%. Anal. Calcd for $C_4H_{18}N_4Cl_2Pt$: C, 12.38; H, 4.67; N, 14.43. Found: C, 12.67; H, 4.58; N, 14.19.

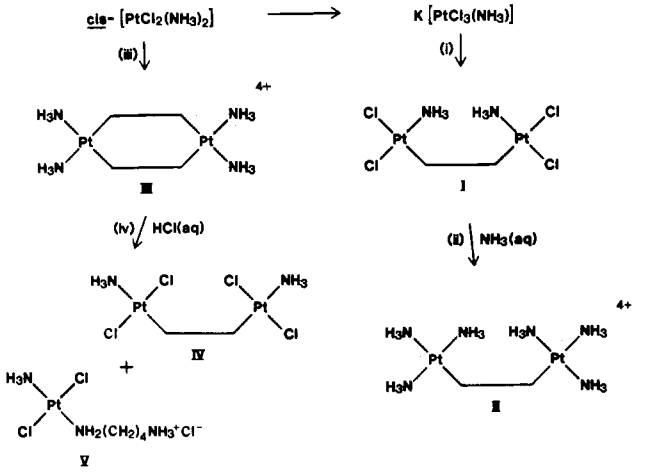

Figure 1. Synthetic scheme for formation and interconversion of bis(platinum) complexes for monomeric precursors. Note that the bridging symbol is simplified for clarity and refers to any diamine bridge, independent of chain length. Reaction numbers are discussed in the text.

Results and Discussion

The bis(platinum) complexes initially reported contain both Pt coordination spheres in the *cis*-$[PtX_2(am)_2]$ configuration (bis(cis-platinum)). This is because the method of synthesis, employing $K[PtCl_3(NH_3)]$, results in displacement of Cl cis to the NH_3 in the starting material (reaction i, Figure 1).

$$2K[PtCl_3(NH_3)] + H_2N(CH_2)_4NH_2 \rightarrow [\{cis\text{-}PtCl_2(NH_3)\}_2H_2N(CH_2)_4NH_2]$$
I

In view of the extensive comparisons between the DNA binding and antitumor activity of *cis*- and *trans*-$[PtCl_2(NH_3)_2]$ an interesting question is what the biological activity of a complex with both Pt coordination spheres in the trans configuration would be, in comparison with both the bis(cis) complexes and the cis and trans monomers. We therefore set out to prepare the bis(trans-platinum) complexes. The chemistry of bis(platinum) complexes to be presented is outlined in Figure 1, and for greater clarity we will discuss in detail only the 1,4-butanediamine case. The synthetic schemes are applicable to higher homologues, and these results will be summarized in a separate section.

Bis(platinum) Tetraamine Complexes. Monomeric *trans*-$[PtCl_2(NH_3)_2]$ is usually prepared from the tetrammine complex:

$$cis\text{-}[PtCl_2(NH_3)_2] \xrightarrow{NH_3(aq)} [Pt(NH_3)_4]Cl_2 \xrightarrow{HCl(aq)} trans\text{-}[PtCl_2(NH_3)_2]$$

This route was explored for bis(platinum) complexes. Two sets of tetraamine complexes, which we distinguish as types II and III (corresponding to structures in Figure 1), were in fact prepared. Tetraamine bis(platinum) complexes of type II are easily prepared by reaction of the bis(cis) complexes with NH_3(aq) following reaction ii of Figure 1. The characterization of the highly water-soluble complex is given in Table I. In type II complexes the substitution of amine by chloride can however occur in any of three different positions (there are three distinct coordinated amines: the diamine NH_2, NH_3 trans to the diamine, NH_3 trans to NH_3). In the first two cases bridge cleavage will occur, and attempts to prepare bis(trans) complexes did not give clean

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Table I. Spectroscopic Data for Bis(platinum) and Related Complexes[a]

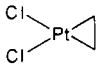
complex	IR, cm^{-1} ν(NH)	ν(PtCl)	other signif bands	NMR, δ, ppm $\delta(^1H)$	$\delta(^{13}C)$	δ(Pt)
I	3238, 3186	326, 318	1580 (m), 1300 (s), 800 (m)	1.62, 2.54		-2163
II	3200 (s, vbr)		1600 (m), 1350 (m), 1210 (m, sh), 1040 (w), 975 (w), 880 (m, br)	1.72, 2.74	30.2, 48.5	-2644
III	3160 (s, bvr)		1580 (m), 1480, 1380 (w), 1330 (s), 1210 (w), 1040 (w), 985 (w), 825 (br)	1.71, 2.74, (2.1, 2.9)	30.3, 48.8	-2683
IV	3280, 3235, 3195	340	1560 (m), 1460, 1370, 1295 (s), 1195 (s), 1050 (m), 985 (w), 790 (m), 680 (w)	1.63, 2.68		-2167
V	3290 (sh), 3245, 3200	335	1580, 1515 (s), 1470, 1450 (m), 1280 (s), 1210 (m), 1135, 1115 (m), 1020 (w), 918 (w), 870, 790 (w), 675 (w), 500, 440 (w)	1.8, 2.72 (t), 3.1	47.8, 42.0, 29.6, 26.8	-2132
VII	3150 (s, bvr)		1620, 1450 (m, br), 1400, 1345 (m), 1190 (w), 1150 (w), 1090 (m), 980, 985 (w), 850 (w, br), 510 (m)	2.04, 2.88 (t, 48.6)	28.4, 48.7	-2675

[a] Conditions as in the Experimental Section. IR spectra were taken as KBr disks. NMR spectra were recorded in DMF-d_7 (^1H) or DMA/acetone-d_6 (^{195}Pt) for I and IV and D_2O for all other samples. NMR peaks are multiplets except as noted (t = triplet; numbers in parentheses refer to Pt–H satellites).

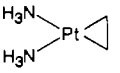
products by this method, elemental analyses indicating the presence of monomeric species (see also discussion below).

To circumvent this problem, a further series of bis(platinum) tetraamine complexes was prepared by the reaction of diamines with *cis*-$[PtCl_2(NH_3)_2]$ (reaction iii of Figure 1). Characterization data are also given in Table I. In the specific case of 1,4-butanediamine the possibility of chelate, rather than bridge, formation was eliminated by the independent preparation of appropriate complexes containing chelated 1,4-butanediamine and a comparison of conductivity and spectral data (see below).

$$[PtCl_2(H_2N(CH_2)_4NH_2)] + NH_3(aq) \longrightarrow [Pt(NH_3)_2(H_2N(CH_2)_4NH_2)]Cl_2$$



VI



VII

Formation of $[\{trans\text{-}PtCl_2(NH_3)\}_2H_2N(CH_2)_nNH_2]$. Type III tetraamine complexes have the advantage over the type II class that there are now only two distinct amines and, even if one bridge is cleaved, the other remains intact, preserving the bis(platinum) structure. Reaction with HCl (reaction iv, Figure 1) gives the desired trans complexes, which precipitate from solution and were characterized by elemental analysis and IR, ^1H NMR, and ^{195}Pt NMR spectroscopy. The reaction, however, is still not simple. Upon separation of the precipitate, evaporation of the mother liquor gives a yellow product whose elemental analysis and spectroscopic properties are consistent with the formulation *trans*-$[PtCl_2(NH_3)(H_2N(CH_2)_4NH_3)]Cl$ (V), containing one end of the diamine coordinated to Pt and the other end protonated.

The presence of this product is perfectly consistent with known chemistry. Complexes of this type have in fact been briefly reported,[4] and a similar species, *trans*-dichlorobis(ethylenediamine hydrochloride)platinum, formed by the ring opening of chelated ethylenediamine has also been prepared.[5] The kinetics of the opening, and subsequent closing, of the chelate ring in $[PtCl(Me_2SO)(H_2N(CH_2)_nNH_2)]^+$ (n = 2–4) have been studied and the complexes resulting from ring opening, *cis*-$[PtCl_2(Me_2SO)(H_2N(CH_2)_nNH_3)]Cl$, isolated.[6,7] These complexes are therefore analogous to complex V, with both platinated and protonated diamine. As expected, ring closing is much slower for the 1,4-butanediamine (seven-membered ring) case then for the ethylenediamine and bis(platinum) (five- and six-membered rings, respectively) cases in the pH range 4.8–6.3. Bridge cleavage of complexes II and III and the formation of complex V may therefore also be expected.

The formation of IV and V may be understood by consideration of the possible mechanism of attack of Cl^- on complex III. Assuming independent attack of one chloride on both platinum atoms, there is almost equal probability of attack on all amines. The reaction conditions of large chloride excess and the reaction time involved also means that the reaction would be very difficult to control to give a more specific attack. Thus, the final products are dictated by both the distribution of the initial substitution and the Cl trans influence. Figure 2 shows all possible combinations of the first chloride ion attack on each Pt atom of the bis(platinum) complexes. In principle, eight combinations, derived from attack on either independent amine of one Pt atom and the four (now distinct) sites of attack on the second Pt, are possible. Combinations i, ii, iv, and v may be considered as resulting from attack on the bridging diamine of one Pt followed by the four independent sites of the second platinum. Combinations iii and vi are obtained if we begin with the NH_3. There are only six unique possibilities distinguishable because combinations i and v are degenerate, being formed whether one starts with the NH_3 or diamine NH_2. The second chloride on each platinum automatically substitutes trans to the first one. Thus only the two final products shown are

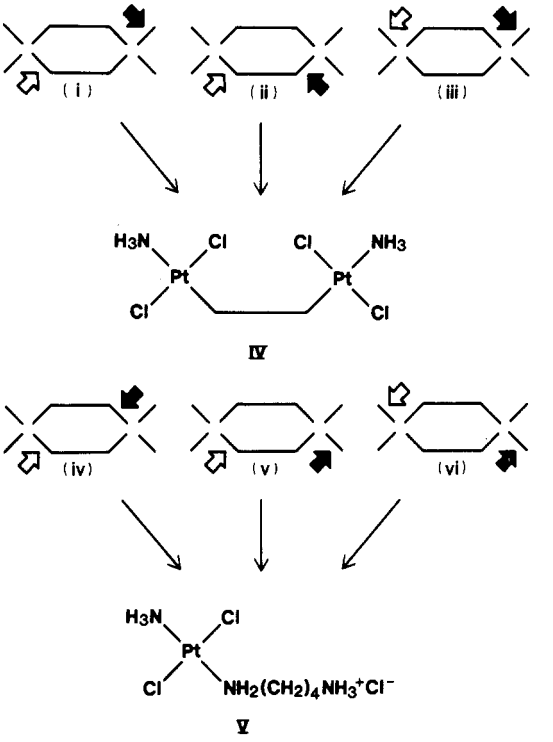


Figure 2. Mechanism of formation of $[\{trans\text{-}PtCl_2(NH_3)\}_2H_2N(CH_2)_nNH_2]$ and *trans*-$[PtCl_2(NH_3)(H_2N(CH_2)_nNH_3)]Cl$ by chloride displacement of amine from tetraamine precursors. The arrows signify the initial chloride attack on the platinum atoms of complex III (see Figure 1), giving in total eight possible combinations. The attack of the second chloride ion on each Pt must be trans to the first, thus giving the final products represented.

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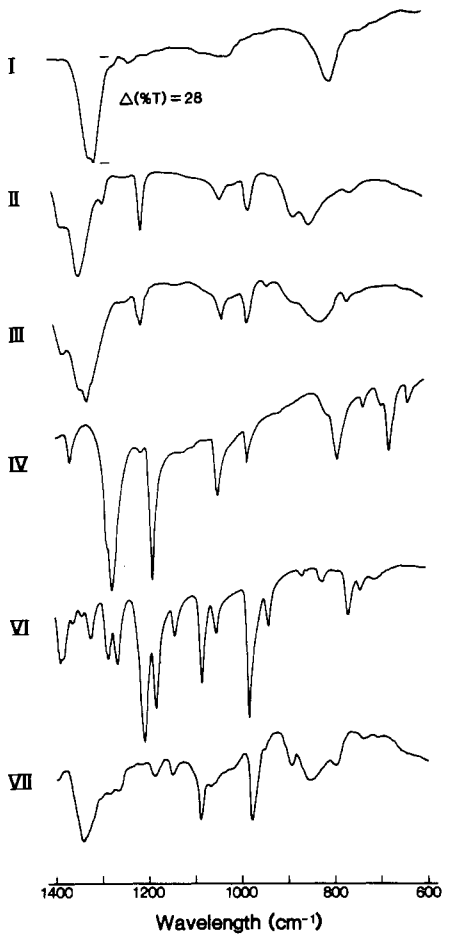

Figure 3. IR spectra of bis(platinum) complexes and monomeric analogues (complex numbering as in Figure 1).

possible and our isolation and structure assignment of these products is perfectly consistent.

The failure to get a good reaction with complex II may now be easily understood in these terms. The bis(trans) complex IV can only be formed by attack on the pair of mutually trans amines. All other possibilities lead to the formation of either *trans*-$[PtCl_2(NH_3)_2]$ or complex V. Confirming our interpretations, we isolated complex V (IR, ^1H NMR spectra compared with those of the authentic sample) from the mother liquor of the reaction of complex II with HCl.

Spectroscopic Data. Infrared spectra for chelating and bridging 1,4-butanediamine have been briefly reported for $[PtCl(Me_2SO)(H_2N(CH_2)_4NH_2)]^+$ and $[\{trans\text{-}PtCl_2(Me_2SO)\}_2(H_2N(CH_2)_4NH_2)]$.[8] In a qualitative manner the bridging diamine gives much simpler spectra, and broad peaks are observed in contrast to the sharp peaks of the chelate. This is shown for the complexes under discussion here in Figure 3 and is a useful diagnostic for the presence of bridging diamine. The broadness of these bands may possibly be explained by the fact that there are many more conformations possible for a bridging diamine than for a chelate form and the various contributions of these could result in combination leading to broadening. Table I summarizes the principal bands. Complex I is characterized by broad IR bands at 1300 and 800 cm^{-1}, the higher frequency band being at least twice as strong. Clear differences between complexes I and IV are found in the ν(NH) region, where the trans isomer shows a distinctive three-band pattern in comparison to the two broad bands associated with I. The 1400–600-cm^{-1} region of the IR spectrum contains bands associated with the diamine skeletal vibrations. We note that the bands of IV appear more intense than those of I despite the similarity in structure.

The monomeric compound VII is analytically indistinguishable from the tetraamine complex III, and the correct assignment of the structure of III is important for the mechanism of formation of the bis(trans) species. Both IR and NMR spectra of III are radically different from those of VII. Further, conductivity data in water (not shown) show that complexes II and III behave as 4:1 electrolytes instead of the 2:1 electrolyte behavior of VII. The IR spectra of the tetraamine complexes II and III are typical of a bridging diamine.

The ^1H NMR spectra of complexes I and IV in DMF-d_7 show only broad peaks attributable to the CH_2 resonances, indicative of unhindered rotation around the backbone. The NMR spectrum of complex II in D_2O shows two broad peaks with no fine structure at δ 1.72 (central $-CH_2CH_2-$) and 2.74 (amine–CH_2). Complex III shows analogous peaks at δ 1.71 and 2.74, along with a small broad peak at δ 2.90 and a doublet of similar intensity centered at δ 2.1. Further, the δ 2.74 peak begins to show some fine structure. In contrast, $[Pt(NH_3)_2H_2N(CH_2)_4NH_2]Cl_2$ (VII) shows a sharp peak at δ 2.04 and a 1:4:1 triplet (^3J(Pt–H) = 48.6 Hz) centered at δ 2.88 (cf. ethylenediamine protons in $[Pt(NH_3)_2(en)]^{2+}$ at δ 2.66, J = 41.5 Hz[9]). We note that the satellites due to three-bond Pt–H coupling are not observed for bis(platinum) complexes at the field strength employed. The ^{13}C NMR spectra for III and VII also show different chemical shifts. Comparison of all data for VII and III show clearly the differences in the two species and support the structure assignment of III as a bis(platinum) complex with two diamine bridges.

Complex III represents a large 14-membered ring system, formed by both diamines and the two Pt atoms, and it is likely that the conformations of the diamine will be more restricted in this case than in complex II, as any conformational changes involve simultaneous changes in both diamines. Model studies show that for unsubstituted diamines there is little restriction to rotation around the diamine backbone but this could become a factor upon substitution of the backbone. The minor peaks observed in the ^1H NMR spectrum of III disappear upon raising the temperature of the sample with a concomitant broadening of the major peaks. We interpret this behavior as an indication of some conformational preferences in these compounds. A fuller investigation of the dynamic behavior of these compounds will be reported separately.

The ^1H NMR spectrum of V shows three sets of resonances, with two distinct peaks at δ 3.06 and 2.71, as expected due to the chemical inequivalence of the $-NH_2CH_2-$ protons. The broad multiplet centered at δ 1.77 is presumably due to the central $-CH_2CH_2-$ protons, which are not distinguished. The ^{13}C NMR spectrum, on the other hand, shows four well-defined peaks at δ 47.8, 42.0, 29.60, and 26.8, corresponding to the four independent carbon atoms. These may be assigned (C atom italicized) to $Pt-NH_2-\mathit{C}H_2$, $\mathit{C}H_2NH_3^+$, $Pt-NH_2-CH_2\mathit{C}H_2$, and $\mathit{C}H_2CH_2NH_3^+$, respectively. The free 1,4-butanediamine dihydrochloride shows two peaks at δ 41.64 and 26.51, and two peaks are also observed for complexes II, III, and VII.

The ^{195}Pt NMR chemical shifts of all complexes are consistent with the proposed structures. The very similar shifts of complexes III and VII reflect their identical chemical environments, and their upfield shift in comparison to II is consistent with the differences between NH_3 and RNH_2 (cf. $[Pt(NH_3)_4]^{2+}$ in D_2O at −2580 ppm[10]). Spectra for all chloro complexes were run in DMA/acetone-d_6, and the spectra for the tetraamine complexes were run in deuterated water. Previous samples of the chlorides were run in DMF-d_7, and ^1H NMR spectra are routinely run in this solvent, but to avoid possible dissociation over the longer scan times the non-protonic DMA is preferred.

Higher Homologues. The spectral data for all complex types (I–IV, Figure 1) with n = 5 and n = 6 chain lengths are very similar to those discussed above and allow identical structural assignments. Thus, the synthetic scheme developed is a general one. Pertinent data for the cis and trans isomers of $[\{PtCl_2(NH_3)\}_2H_2N(CH_2)_nNH_2]$ (n = 5, 6) are given in Table II.

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Table II. Characterization Data for the New Bis(platinum) Complexes $[\{PtCl_2(NH_3)\}_2H_2N(CH_2)_nNH_2]$ ($n > 4$)[a]

		anal. calcd (found)				IR, cm^{-1}		NMR, δ, ppm	
geom	n	% C	% H	% N	% Cl	ν(NH)	ν(PtCl)	δ(^{1}H)	δ(^{195}Pt)
cis	5	9.0 (8.9)	3.0 (2.8)	8.4 (8.3)	21.2 (21.2)	3200 (br) 3125 (sh)	330, 310	2.70 (m, 2) 1.69 (m, 2) 1.32 (m, 1)	−2170
trans	5	9.0 (9.1)	3.0 (2.9)	8.4 (8.3)	21.2 (21.3)	3278 3238 3202	339	2.68 (m, 2) 1.61 (m, 2) 1.31 (m, 1)	−2177
cis	6	10.6 (10.7)	3.2 (3.2)	8.2 (8.4)	20.6 (20.3)	3200 (br) 3140 (sh)	326 (br)	2.69 (t) 1.68 (m) 1.38 (m)	−2172
trans	6	10.6 (10.3)	3.2 (3.0)	8.2 (7.9)	20.6 (20.7)	3280 3230 3195	340	2.67 (t) 1.72 (m) 1.35 (m)	−2166

[a] All conditions as per Table I and Experimental Section. Numbers in parentheses in the ^{1}H NMR data refer to the relative integration of peaks in the $n = 5$ complexes.

Analytical data for the intermediate tetraamine complexes were also in agreement with the calculated values.

Reactivity of Bis(platinum) Complexes. The distinct IR and NMR spectra confirm the differences in the cis and trans isomers, and these are further distinguished by the Kurnakov test—as with the simple monomers only the cis complex gives a yellow coloration upon reaction with thiourea (tu). For *cis*- and *trans*-$[PtCl_2(NH_3)_2]$ the color differences are due to formation of the yellow $[Pt(tu)_4]^{2+}$ adduct upon reaction with the cis isomer (strong trans-labilizing group results in amine loss) and the white $[Pt(NH_3)_2(tu)_2]^{2+}$ adduct upon reaction with the trans isomer.[11] The yellow solution from the reaction of I with tu is identical with $[Pt(tu)_4]^{2+}$ formed from *cis*-$[PtCl_2(NH_3)_2]$, and thus in our case amine displacement in the presence of excess thiourea seems to occur with bridge cleavage. This evidence further strongly supports the structural assignments.

The ^{1}H NMR spectra of I and IV in DMSO show peaks at approximately 3.54 ppm indicative of Pt-bound DMSO.[12] The ready solvolysis of antitumor platinum complexes in DMSO has been appreciated for some time now,[13] and attention has been drawn more recently to problems this may induce in the interpretation of biological data obtained in this solvent.[14] Examination of the kinetics of DMSO solvolysis by UV/vis spectroscopy showed that the kinetics were initially first order. These initial rates of solvolysis in DMSO at 30 °C were calculated at 1.58×10^{-3} and 2.3×10^{-2} s^{-1} for the bis(cis) and bis(trans) complexes compared to 1.35×10^{-4} and 9.1×10^{-4} s^{-1} for *cis*- and *trans*-$[PtCl_2(NH_3)_2]$, respectively. Thus, the bis(platinum) complexes are more reactive than their monomer analogues, and this is a general feature we are encountering in other aspects of their chemistry. As expected, due to the greater trans-labilizing effect of chloride over that of the amine, the solvolysis of the trans complex is faster than that of the cis.

Conclusions

The chemistry of bis(platinum) complexes has been expanded to include two series of tetraamine complexes and the complex with both platinum coordination spheres in the trans configuration. We are actively engaged in studying the biological activity of these species, and all the complexes discussed here are of interest in this respect. A major feature of the structure–activity relationships of platinum antitumor complexes is that only the cis isomer is active whereas the trans complex is not, although both bind to DNA.[15] The prevailing consensus is that the formation of an intrastrand link, accessible only to the cis isomer, is responsible for this difference. In principle, bis(trans) complexes could form an intrastrand link by monodentate binding of both Pt atoms to the same strand. Surprisingly, and somewhat disappointingly, the bis(trans) complexes do not appear to show enhanced cytotoxicity with respect to the trans monomer.[16] Clearly, it is not the intrastrand link per se but rather the conformational distortion that the binding induces (e.g. kinking or bending[17]) which leads to manifestation of the biological effects. The differences in DNA binding, and the conformational changes induced, of the bis(platinum) species with respect to the cis and trans monomers and the correlation of this DNA binding with cytotoxicity are being explored.

Preliminary biological data show that there is a variation of cytotoxicity with chain length in bis(platinum) complexes and modification of the backbone can be expected to alter this further. The pair of tetraamine complexes can be useful models for DNA binding because they represent large cations—one flexible (II) and the other relatively rigid (III). Cations such as $[Co(NH_3)_6]^{3+}$ can dramatically alter DNA conformation by electrostatic interactions,[18] and indeed, the cobalt complex is one of the most effective agents in inducing the B → Z conformational transition.[19] The complex $[Pt(NH_3)_4]^{2+}$ only interacts weakly with polynucleotides,[20] with a very slight increase in T_m, but we can now compare the differences with the bis(tetraamine) complexes and study the effect of the chain length and flexibility of the backbone. We can predict that chain length may be more critical for complex III because of the fixed distance between the two coordination spheres.

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